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Platform Session

Monday July 3, 2006
12:00–13:30
Hall 1
Platform Session
Drug Therapy I

001
A RANDOMISED OPEN-LABEL COMPARISON OF THE EFFICACY, TOLERABILITY, AND HORMONAL EFFECTS OF SODIUM VALPROATE AND LAMOTRIGINE MONOTHERAPY IN NEWLY-DIAGNOSED EPILEPSY

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Purpose: This study was designed to compare monotherapy with sodium valproate (VPA) and lamotrigine (LTG) in patients with newly diagnosed epilepsy.

Method: A total of 226 untreated patients (116 male) with a recent diagnosis of epilepsy (60 idiopathic generalised epilepsy, 149 localisation-related epilepsy, 17 unclassified) were randomised to receive either VPA or LTG as monotherapy. Median age was 35 years (range 13–80 years). Patients were followed-up at six-weekly intervals and remained in the study until reaching a predetermined end point (12 month seizure-freedom; intolerable side-effects including idiosyncratic reaction; lack of efficacy despite adequate dosing).

Results: Twenty-nine patients were excluded from the analysis (24 lost to follow-up, 3 withdrawn consent, 1 protocol violator, 1 non-epileptic attack). A total of 197 patients reached an end point, with 126 (63%) becoming seizure-free for a minimum period of 12 months on initial monotherapy. Of these, 64 took VPA (67% of VPA completers; median dose = 1000 mg, range 600–3000 mg) and 62 took LTG (60% of LTG completers; median dose = 200 mg, range 100–700 mg). Thirty-eight patients (24 VPA, 14 LTG) experienced intolerable side effects, while a further 33 (18 VPA, 15 LTG) failed to report acceptable efficacy despite adequate dosing. There were no significant changes in mean (±SEM) serum concentrations of testosterone ($p = 0.225$), SHBG ($p = 0.201$), or androstenedione ($p = 0.394$) in either patient group at 6 months after initiation of therapy.

Conclusion: These findings suggest that there is little (if any) difference in the efficacy, tolerability, or hormonal effects of VPA or LTG monotherapy in the treatment of newly diagnosed epilepsy.

002
MULTICENTRE RANDOMISED CONTROLLED TRIAL COMPARING STANDARD AND NEW ANTIEPILEPTIC DRUGS (SANAD)

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Purpose: There is a paucity of randomised controlled trials (RCTs) that inform a choice among antiepileptic drugs, and existing trials have largely failed to examine longer term effectiveness. SANAD assesses these longer term outcomes.

Method: SANAD is a multicentre, UK based, unblinded RCT recruiting patients over the age of 5 years, requiring antiepileptic drug monotherapy. SANAD has 2 arms. Patients for whom carbamazepine was the standard drug (arm A) were randomised to carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. Patients for whom valproate was the standard drug (arm B) were randomised to valproate, lamotrigine or topiramate. Recruitment commenced in 1999, ended 2005, and follow up ended in 2005. Outcomes included time to the following events: withdrawal of allocated treatment, 12 month remission from seizures, first seizure, as well as adverse events, quality of life and cost effectiveness.

Results: 2443 patients were recruited, for whom we have 7799 patient years follow up, 95% of the maximum possible. 1721 patients entered arm A, 378 were allocated carbamazepine, 377 gabapentin, 378 lamotrigine, 210 oxcarbazepine and 378 topiramate. The mean age was 38.3 yrs, 55% were male and 89% were classified as having a partial epilepsy syndrome. 716 patients entered arm B, 238 were allocated valproate, 239 lamotrigine and 239 topiramate. The mean age was 25.5 yrs, 60% were male, and 62% were classified as having an idiopathic generalised epilepsy syndrome. Full clinical results will be presented.

Conclusion: Large multicentre studies examining the longer term effects of antiepileptic drugs, such as SANAD, are required to inform clinical practice.

003
AN INTERNATIONAL MULTICENTER DOUBLE-BLIND DOUBLE-DUMMY RANDOMISED TRIAL COMPARING LAMOTRIGINE AND SLOW-RELEASE CARBAMAZEPINE FOR TREATING NEWLY DIAGNOSED EPILEPSY IN THE ELDERLY

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Purpose: To compare lamotrigine (LTG) and slow-release carbamazepine (CBZ) in the treatment of newly diagnosed epilepsy in the elderly.

Method: Patients aged >65 years with a history of two or more unprovoked partial and/or tonic–clonic seizures received LTG ($n = 93$) or CBZ ($n = 91$) in a randomised double-blind 40-week trial. Target dose was 100 mg/day for LTG and 400 mg/day for CBZ; dose escalation was 4 weeks and dose adjustments according to response were permitted.

Results: In the LTG group, 68 patients (73%) completed the trial compared with 61 (67%) in the CBZ group (not significant). Time to withdrawal from any cause did not differ between groups ($p = 0.34$). The number of subjects who completed the study and were seizure-free during weeks 4–40 was 37 (40%) in the LTG group and 46 (50%) in the CBZ group. Adverse events leading to withdrawal occurred in 26 (28%) CBZ-treated subjects and 15 LTG-treated subjects (16%). The Liverpool Adverse Event Profile (AEP) score showed a non-significant advantage for LTG.

Conclusion: LTG and CBZ showed comparable effectiveness, with a trend for higher seizure-free rates for CBZ and better tolerability for LTG. Acknowledgment: Supported by GlaxoSmithKline.

004
EFFICACY OF LEVETIRACETAM MONOTHERAPY: RANDOMISED DOUBLE-BLIND HEAD-TO-HEAD COMPARISON WITH CARBAMAZEPINE-CR IN NEWLY DIAGNOSED EPILEPSY PATIENTS WITH PARTIAL ONSET OR GENERALISED TONIC–CLONIC SEIZURES

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Purpose: Sustained seizure freedom (SF) without side effects remains the epilepsy treatment goal. New broad spectrum, well tolerated AEDs at least comparably effective to older AEDs in newly diagnosed patients are still required. This study aimed to demonstrate the noninferiority of levetiracetam (LEV) *vs* carbamazepine controlled-release (CBZ-CR) in achieving 6 month SF in newly diagnosed partial onset or generalised tonic-clonic seizure (GTCS) patients, excluding idiopathic generalised epilepsy (IGE).

Method: Phase III, randomised, double-blind, noninferiority design (non-inferiority limit −15%). Newly or recently diagnosed epilepsy patients (confirmed/suspected localisation-related), ≥2 seizures in preceding year (≥1 in preceding 3 months), no epilepsy treatment for 6 months, received LEV 1000 mg/day or CBZ-CR 400 mg/day following 3 weeks uptitration. Doses were maintained for 6 months evaluation or until next seizure (doses increased to LEV 2000 mg/CBZ-CR 800 mg/day; if needed, to LEV 3000 mg/CBZ-CR 1200 mg/day). Six months SF was followed by 6 months maintenance treatment.

Results: ITT and PP populations included 576 (285 LEV; 291 CBZ-CR) and 472 (237 LEV; 235 CBZ-CR) patients respectively. Six months SF (PP) was achieved in: LEV 73.0% *vs* CBZ-CR 72.8%; absolute treatment differences 0.2% (95% 2-sided CI: −7.8–8.2%). Twelve months SF rates; LEV 56.6%; CBZ-CR 58.5% (95% 2-sided CI of the difference: −10.8 –7.2%). Fewer LEV patients reported adverse events causing drug discontinuation or dose change (16.1% LEV *vs* 23.0% CBZ-CR; p = 0.046).

Conclusion: LEV was effective as first-line monotherapy in newly diagnosed patients with partial onset seizures or GTCS with similar SF rates at 6 and 12 months to CBZ-CR with better tolerability. UCB supported.

005

CONSEQUENCES OF WITHDRAWAL OF ANTIEPILEPTIC MEDICATION ON SEIZURE RELAPSE AND COGNITIVE FUNCTION: A RANDOMISED, PLACEBO CONTROLLED, DOUBLE BLINDED STUDY (THE AKERSHUS WITHDRAWAL STUDY)

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Purpose: The aim of this study was to assess the possibility and consequences of withdrawal of antiepileptic drugs (AEDs) in a double blind design in a selected group of patients who had been seizure free for more than two years.

Method: The study was prospective, randomised, placebo controlled and double blinded. Epilepsy patients (18–67 yrs) on monotherapy were included. Exclusion criteria were: juvenile myoclonus epilepsy (JME), poly pharmacy, paroxysmal epileptiform activity in patients with primarily generalised epilepsy, two prior withdrawal attempts, pregnant or seeking pregnancy, mental retardation, progressive neurological disease, co-medication (except post menopausal hormone substitution, ASA and thyroxin) or other serious disease which may influence the health status of the patient in the study period. Each patient was followed for 12 months or until seizure relapse. Seizure relapse or acute diseases were criteria for breaking the code. The patients went through a set of investigations prior to and after intervention (withdrawal/not withdrawal).

Results: One hundred sixty-nine patients were included in the study. One hundred fifty were randomised and were included in the final analysis. In the withdrawal group (placebo group) 10 patients experienced seizures while 5 patients did so in the group continuing medication (p = 0.14). The percentage of patients scoring normal on all subscales in the neuropsychological test battery increased from 12% to 29% in the withdrawal group and this improvement was significantly better compared to the nonwithdrawal group (p = 0.005).

Conclusion: The vast majority of selected seizure free epilepsy patients remain seizure free one year after discontinuation of medication. The neuropsychological scores improved significantly in the withdrawal group.

006

UNCONTROLLED SEIZURES AFTER DISCONTINUATION OF ANTIEPILEPTIC DRUG TREATMENT IN SEIZURE-FREE PATIENTS WITH CHILDHOOD-ONSET EPILEPSY: A LONG-TERM POPULATION-BASED STUDY

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Purpose: The long-term outcome of seizure recurrence after planned discontinuation of antiepileptic drugs (AEDs) in seizure-free patients is not well known. We studied seizure recurrence and its outcome following reinstituted treatment.

Method: We carried out a prospective long-term population-based study of 242 patients.

Results: Seizure recurrence after AED discontinuation was seen in 43 (36%) of 120 patients. Thirty-two of the 43 patients with a relapse elected not to restart AEDs. Reinstitution of AEDs after recurrence was implemented in 11 of 43 patients leading to 5-year terminal remission (5YTR) in 3 patients, only 10–19 years after restarting treatment. In the other 8 patients, 5YTR was never achieved, and 5 of the 8 did not enter a 5-year remission. Factors associated with failure to reach 5YTR after treatment of recurrence were symptomatic aetiology, and partial epilepsy.

Conclusion: Discontinuation of AEDs in seizure-free patients is associated with seizure recurrence(s) in 1 of 3 patients, and development of drug resistant epilepsy following treatment of recurrence in 8 of 11 patients or delayed control in a further 3 patients, mostly in those with symptomatic and/or partial epilepsy. These risks need to be considered, although there is no evidence that discontinuation was responsible for poor treatment outcome of recurrence.

Monday July 3, 2006
12:00–13:30
Hall 5A
Platform Session
Adult Epileptology I

007

FACIAL DISPLAY OF EMOTIONS DURING EPILEPTIC SEIZURES

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Purpose: To investigate the emergence of emotional display during temporal versus frontal lobe seizures (TLS, FLS).

Method: Three independent observers reviewed presurgical video-EEG recordings of 477 seizures, in 84 patients with drug-resistant epilepsy (45 temporal/39 frontal), analysing the topography of the ictal discharge and the ictal modifications of facial expression, suggesting emotions (FEE). The pattern of facial activation underwent FACS (facial action coding system) analysis. The presence of coherent emotional motor/acoustic behaviour and of a subjective feeling has been alsobreak investigated.

Results: All the six fundamental emotions were observed, with the same muscular pattern of facial activation during FLS and TLS. Negative emotions, particularly fear, were most represented. The prevalence of FEE was similar in FLS (68%) versus TLS (67%); right-sided ictal discharge was observed more frequently (59%). Association of FEE with emotional motor/acoustic behaviours occurred in 21% of seizures and in 13% an emotional experience was referred. Despite the similar prevalence of ictal FEE in both genders, there was male predominance in facial display of rage and a female predominance in referring a subjective emotional feeling and/or in manifesting coherent motor behaviours related to FEE, especially in case of ictal fear.

Conclusion: A coherent pattern of FEE and emotional behaviour can equally emerge during FLS and TLS, with a slight right prevalence of the ictal discharge, confirming the hemispheric right specialisation for emotion. Gender dimorphism expressing and/or referring fear and rage, could reflect either inborn or socio-behavioural differences.

008

THE CONTRIBUTION OF HIPPOCAMPAL DEVELOPMENTAL MALFORMATION TO EPILEPTOGENICITY: AN INTRACRANIAL SEEG STUDY

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Purpose: To assess the epileptogenicity of hippocampal formations (HF) with developmental changes (Baulac et al., Ann Neurol 1998;44:223) through SEEG.

Method: Seventy-three patients with focal epilepsy who underwent at least bilateral temporal lobe SEEG evaluation between 1995–2005 were studied, and divided in 3 groups based on MRI findings: Group 1 ($n = 17$ patients) with malformed HFs ($n = 27$), Group 2 ($n = 25$) with atrophic hippocampus ($n = 34$) and Group 3 ($n = 31$) with normal hippocampi. To assess the epileptogenicity of the malformed HF, we compared the interictal (IEA) and ictal epileptiform activity in limbic structures. We also analysed epileptogenicity of other temporal and extratemporal ($n = 39$ patients) structures.

Results: In the limbic and extratemporal neocortical structures, IEA was recorded equally in all groups. All patients with malformed HF (Group 1*)* showed neocortical temporal IEA, but fewer in Group 2 (76%, $p = 0.034$) and Group 3 (58%, $p = 0.001$). Limbic seizure onsets were more frequent in malformed HF and atrophic hippocampi compared to normal hippocampi (63 and 82 vs 37%, $p = 0.021$ and $p < 0.0001$). Regional temporal seizure onsets occurred more often in Group 1 (65%) than Group 3 (32%, $p = 0.031$) but not differently from Group 2 (44%). Extratemporal seizure onsets were equal in all groups. Temporal lobe resection only led to unfavourable outcome (Engel's class III–IV) in Groups 1 (6/9 patients) and 3 (12/18) compared to Group 2 (4/18, $p = 0.019$ and $p = 0.009$).

Conclusion: This study demonstrates that malformed HFs generate epileptic activity, but in association with widespread epileptogenicity, as most patients show neocortical temporal or extratemporal epileptic discharges and poor outcome only after temporal lobe surgery.

009

DISTRIBUTION OF TEMPORAL LOBE EPILEPTIC SEIZURES OVER THE DAY DURING VIDEO-EEG

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Purpose: Some epileptic seizures have a characteristic temporal distribution, occurring mainly in a specific day/night pattern or period of the sleep–wake cycle. Our aim was to determine the patterns in seizure frequency among patients with temporal lobe epilepsy (TLE) during video-EEG.

Method: From 190 video-EEGs, we selected patients with temporal lobe seizures (TLS) and retrospectively analysed the time when seizures occurred. Each seizure was classified according to the time of occurrence and grouped into 3×8 hour ''bins,'' which we called "afternoon" (12 to 8 p.m.),"night" (8 p.m. to 4 a.m.) and "morning" (4 a.m. to 12 p.m.).

Results: There were 95 reports with TLS and in 75 of these the time of occurrence was registered. We analysed 323 seizures. Each patient had an average of 4.3 seizures (1–17). 148 seizures (48.8%) occurred in the afternoon, 77 (23.8%) at night and 98 (30.3%) in the morning. On average each patient had 2.0 seizures in the afternoon, 1.0 at night and 1.3 in the morning. The difference night/afternoon and morning/afternoon was significant ($p < .05$). We also noticed that, from the 38 patients that had more than 2 seizures in one of the considered periods, 22 of them (57.9%) had them in the afternoon.

Conclusion: The distribution of seizures during the day/night period was clearly unequal. It was during the afternoon that most seizures occurred and that most patients had multiple seizures. This observation suggests the existence of a circadian mechanism regulating the occurrence of TLE seizures.

010

UNILATERAL CEREBRAL POLYMICROGYRIA WITH IPSILATERAL CEREBRAL HEMIATROPHY

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Purpose: There are sporadic reports on unilateral polymicrogyria with ipsilateral hemiatrophia cerebri. Hayakawa et al. (2002) reported on 6 children with this condition associated with epilepsy, spastic hemiparesis and mental retardation. The authors suggested the disorder could constitute a new clinical entity calling it "hemimicrocephaly." The aim of the study was to delineate clinical, electrophysiological, neuropsychological and imaging features of unilateral cerebral polymicrogyria with ipsilateral cerebral hemiatrophy.

Method: Four patients (2 m/2 w) aged from 23 to 31 years (mean 27.5) were evaluated at the Epilepsy outpatient clinic of the Innsbruck University Hospital for Neurology. All subjects underwent clinical, electrophysiological, neuropsychological and high resolution MRI assessment.

Results: All patients were born full term without any significant perinatal event and exposure to intrauterine infection. None suffered from birth asphyxia or ischemic injury. Two patients had closely related parents; 2 had a positive family history of epilepsy. All had delayed developmental milestones and were mentally retarded. All patients suffered from congenital nonprogressive spastic hemiparesis, more prominent in upper extremity. All had epilepsy with seizure onset ranging from 3 to 17 years (mean 7.5), two had intractable seizures. Two patients had local epileptogenic activity on interictal EEG. All patients showed unilateral, right side cerebral polymicrogyria associated with ipsilateral hemiatrophia cerebri. Polymicrogyria involved frontal, temporal and parietal lobes; the occipital region was relatively spared. Sylvian fissure was hypoplastic in all subjects.

Conclusion: The evaluated patients showed homogenous clinical and neuroimaging characteristics. We support the idea that the disorder could constitute a new clinical entity. It might have an underlying genetic cause.

011

EPILEPSY AND SCHIZENCEPHALY

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Purpose: Four patients affected by schizencephaly were analysed to show the relationship between anatomic brain malformation, electroencephalographic and clinical findings.

Method: The schizencephaly was diagnosed by means of MRI (3 cases) or CT scan (1 case). These patients were selected from 589 patients (out-inpatients) who had been seen and registered at Epilepsy Center of our Service of Neurology, last year (January–December 2005). The 4 patients (3 male and 1 female) were aged 18–42 years. In these patients we evaluated disease history, age and modality of seizure onset, clinical course of epilepsy and electroclinical and neuroradiological features. MRI scans were performed in 3 cases and CT scan in 1 case. Interictal EEGs during wakefulness according to the 10–20 International System was recorded for all patients.

Results: One patient had a convulsion in hyperthermia at age 24 months, and 2 patients had convulsions without hyperthermia during childhood. One patient has moderate spastic hemiparesis; more invalid the upper limb, contra lateral to the cleft. Two patients have moderate psychomotor delay and the other 2 only a mild delay. All these patients

have simple or complex partial seizures followed by secondary generalisation. The interictal EEG recordings show focal abnormalities, slow wave, consistent with the cleft location in 2 patients; bilateral frontal discharges of spike-wave complexes D > S in 1 patient and left anterior isolated spikes in the last patient. They are treated with AED in polytherapy, and all of them have shown drug resistance. Three patients have right temporoparietal, open clefts. One patient has also an arachnoideal cyst in the posterior fossa.

Conclusion: Schizencephaly causes neurological impairment, drug resistant secondary generalised seizures and mainly focal discharges on EEG records.

012

DIFFERENCES BETWEEN FEMALE PATIENTS WHO DO AND DO NOT REPORT SEXUAL ABUSE IN A POPULATION OF PATIENTS WITH PSYCHOGENIC NONEPILEPTIC SEIZURES

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Purpose: To investigate differences between female patients with PNES who do and do not report antecedent sexual abuse.

Method: In a consecutive series of 177 patients seen at a PNES clinic.

Results: In a consecutive series of 131 female patients seen at a PNES clinic, 60 reported sexual abuse. Female patients reporting sexual abuse had a higher rate of depression ($p < .001$), self harm ($p = .001$, suicide attempt ($p < .001$), personality disorder ($p = .001$) and previous mental health service referral ($p < .001$). They were more likely to have flashbacks during attacks ($p < .001$) and urinary incontinence during attacks ($p = .001$). Reported nocturnal attacks and injury were more common in the abused group ($p = 0.012$ and 0.020, respectively).

Conclusion: We found some striking differences between abused and nonabused female patients with PNES. These differences may have implications for our understanding of causation of PNES, and for treatment.

Monday July 3, 2006
12:00–13:30
Hall 5B
Platform Session
Epilepsy Surgery I

013

FRAMELESS STEREOTACTIC ROBOT-GUIDED PLACEMENT OF DEPTH ELECTRODES FOR STEREOELECTROENCEPHALOGRAPHY IN PRESURGICAL ASSESSMENT OF CHILDREN WITH REFRACTORY PARTIAL EPILEPSY

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Purpose: To present our experience with frameless stereotactically placed depth electrodes in presurgical evaluation of children with drug-resistant partial seizures.

Method: A total of 738 multilead electrodes were placed with the aid of a Robot-guided MRI-based stereotactic system (Schaerer-Mayfield Neuromate) in 83 children (2.8 to 18 years, mean 9.4). Each monitoring included 6 to 14 electrodes (mean 9) for a period of 2 to 17 days (mean 7).

Results: Twelve children underwent monitoring of a single lobe, 43 of 2, 26 of 3, and 2 children of 4 lobes; 6 had a bilateral recording. MRI was negative in 8 patients (10%). Further studies (PET, SPECT, fMRI, WADA testing, foramen ovale recording) were performed prior to the stereoelectroencephalography (S-EEG) in several cases. We performed electrode stimulations in order to map motor and/or language cortex, and in order to induce seizures. Beside 3 electrode breaks during removal, there were no other surgery-related complications. Having identified the epileptogenic zone, we proposed tailored resection in 69 cases, 1 child had a hemispherotomy instead. In 13 children (16%), SEEG results precluded resective surgery. To date, 57 children underwent surgery; histopathology revealed cortical developmental malformation in 29, glioneural tumour in 13, hippocampal sclerosis in 7 (+ neocortical dysplasia in 5), ischemic alteration in 3, and was negative in 5 cases.

Conclusion: Depth recording remains essential in evaluating the indication and extension of focal resection, particularly in children. Our frameless technique is safe and well tolerated, with no related morbidity in this large series.

014

SURGICAL TREATMENT OF OCCIPITAL LOBE EPILEPSY

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Purpose: Occipital lobe epilepsy (OLE) accounts for a small percentage of extratemporal epilepsies and few large series have been reported. Preoperative findings, surgical strategies, pathologic basis and postoperative outcome for OLE remain to be elucidated.

Method: From a prospective epilepsy surgery database established in 1990, a group of 44 patients with occipital lobe involvement were found. Charts, surgical reports, MRI and pathology data were reviewed, and patients with temporal or parietal involvement were excluded. Seizure outcome was classified according to Engel's score (I–IV).

Results: Twenty-nine patients with pure OLE were found, comprising 9.9% of 292 patients undergoing operation for extratemporal epilepsies. Most (83%) had complex partial seizures, and 69% had generalised seizures. All patients revealed a lesion on MRI and underwent occipital lesionectomies, 6 patients with additional MST. Histopathology revealed 9 gliotic scars (31%), 7 gangliogliomas (24%), 7 vascular malformations (24%), 5 dysplasias (17%) and one low-grade ependymoma (3%). Visual field deficits were present in 11 patients preoperatively (38%), and 6 patients (21%) showed new and 3 patients (10%) aggravated visual field deficits after surgery. After a mean follow-up of 38 months, 21 patients became seizure-free (72% Engel I), 2 had rare seizures (7% Engel II), 3 improved more than 75% (10.5% Engel III), and 3 had no worthwhile improvement (10.5% Engel IV).

Conclusion: Pure OLE is a rare but significant cause of extratemporal epilepsy. Satisfactory results (Engel I or II) were obtained in 79% of patients in our series. Postoperative visual field deficits occur in a significant proportion of patients.

015

MULTIPLE SUBPIAL TRANSECTIONS: SAFETY AND EVOLUTION OF 30 PATIENTS

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Purpose: Multiple subpial transections (MST) are an effective surgical option for some refractory epilepsy patients. This technique is often considered as palliative, with high risk of sequelae if done in functional areas. We analysed safety and short term seizure outcome of 30 patients operated since January 2003.

Method: 30 patients, 19 male, 11 months to 56 years old at the time of surgery, have a 14 years mean time of epilepsy duration. 11 suffer from cryptogenic focal epilepsy, 3 from CSWS, 9 from tumour or dysplasia in functional areas, 3 from post-traumatic or infectious lesions and 4 from various aetiologies. When possible, cortectomy, lobectomy or lesionectomy were completed with MST to get better seizure control.

Results: Only temporary deficits have been reported in 11 patients. None have a permanent deficit related to MST. Three have been reoperated for intracranial collection. Acute postsurgery seizures occured in 2 patients, concomittant to unexplained antiepileptic drugs plasma levels decreased. All patients have improved at least for behaviour and/or cognition. Eight patients became seizure free with a variable cognitive improvement, but 2 relapsed when AEDs were stopped abruptly. Six remained seizure free for a few months but relapsed with less severe

seizures. Seizures were less severe and/or less numerous in the remaining patients.

Conclusion: MST is a valid and effective option in very difficult to treat patients discarded for classic surgical treatment. MST is a useful complementary treatment when the lesion is near or in a functional zone, to improve seizure control after resection.

016

GAMMA KNIFE CALLOSOTOMY: A SAFE AND EFFICIENT ALTERNATIVE TO OPEN SURGERY

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Purpose: Beside open surgery, a radiosurgical callosal disconnection using the Gamma Knife (GK) for the treatment of generalised epilepsies with drop attacks (DA) is possible. The purpose of this retrospective analysis was to assess long term results of gamma knife callosotomy concerning tolerability and efficacy.

Method: Eight patients (3 female, 5 male, age range from 5 to 69 years) suffering from severe generalised epilepsy associated with disabling drop attacks underwent GK callosotomy between 1993 and 2004. In 6 patients the anterior third of the corpus callosum was radiosurgically disconnected. In 1 patient a second procedure with GK treatment of the middle third of the corpus callosum was added 17 months later. In 2 patients posterior GK callosotomy had followed partial hemispherotomy.

Results: Drop attacks (DA) were completely abolished in 3 patients and 2 patients had a marked DA seizure reduction of 60%. Two out of 4 patients with additional generalised tonic–clonic seizures showed a reduction of 100% and the remaining a 50% and 60% decrease, respectively. Other seizure types responded less well to the radiosurgical treatment. In both patients with posterior GK callosotomy after hemispherotomy partial seizures decreased. Beside transient headache in 2 patients no immediate or long term postradiosurgical side effects were observed.

Conclusion: Radiosurgical callosotomy is an efficient noninvasive alternative to the open procedure as results are comparable. It can be viewed as a safe procedure without severe postradiosurgical side effects.

017

ELECTRICAL STIMULATION OF THE HIPPOCAMPUS IN EPILEPSY PATIENTS

[1]C. Boex, [1]S. Vulliemoz, [1]L. Spinelli, [2]G. Foletti, [2]C. Pollo, and [1]M. Seeck ([1]Hôpitaux Universitaires De Genève, Switzerland, [2]Centre Hospitalier Universitaire Vaudois, Switzerland)

Purpose: Optimal intracranial stimulation parameters in epilepsy patients are still not defined. In the present study, we try to elucidate the efficiency of high or low stimulation frequencies with respect to interictal EEG and seizure frequency.

Method: Two patients were implanted with depth electrodes including the mesial temporal lobe structures bilaterally. Noninvasive (EEG, MRI, PET and SPECT) and later invasive monitoring suggested in patient S1 nonlesional partial epilepsy, in patient S2 nonlesional bitemporal epilepsy with left sided predominance. Stimulation was applied using bipolar biphasic 5 Hz and 130 Hz pulses (450 μs/phase, 1V) on two consecutive days, for 3 hours in S1 and 6 hours in S2. Stimulation sites included right hippocampus in S1 and left hippocampus in S2. Occurrence of seizures and interictal EEG discharges were quantified before, during and after each stimulation period.

Results: The low rate stimulation increased the epileptogenic activity in the mesial temporal structures bilaterally ($p < 0.001$) in both patients, compared to baseline. Two (S1) and three (S2) clinical seizures were noted as well corresponding to the habitual seizure frequency. In contrast, the high rate stimulation significantly decreased the epileptogenic activity in both hippocampi for both patients ($p < 0.005$). During the high rate stimulation and the period thereafter, no seizures were recorded in either patient.

Conclusion: These results suggest that high, but not low rate electrical intracranial stimulation of the hippocampus is efficient in reducing epileptogenic activity in man. The antiepileptogenic effect was observed during and after stimulation.

018

DEEP BRAIN STIMULATION FOR REFRACTORY TEMPORAL LOBE EPILEPSY

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Purpose: Deep brain stimulation (DBS) is under investigation as a treatment for patients with medically refractory epilepsy. The purpose of the present study is to prospectively evaluate the efficacy of long-term DBS in medial temporal lobe (MTL) structures in patients with MTL epilepsy.

Method: Ten consecutive patients with refractory complex partial seizures with and without secondary generalisation (CPS $\pm$ SG) were implanted with bilateral amygdalohippocampal (AH) electrodes and/or subdural strips and/or grids for ictal onset localisation and subsequent stimulation of the ictal onset zone. Side effects and changes in seizure frequency were carefully monitored.

Results: After a mean follow-up of 31 months (range: 12–52 months) 1/10 patient is seizure free (>1 year), 1/10 patient has a >90% reduction in seizure frequency; 5/10 patients have a seizure frequency reduction of $\geq$50%; 2/10 patients have a seizure frequency reduction of 30–49%; 1/10 patient is a nonresponder. None of the patients reported side effects. In 1 patient MRI showed asymptomatic intracranial hemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing.

Conclusion: This open study demonstrates the efficacy of long-term DBS in MTL structures.

Monday July 3, 2006
12:00–13:30
Hall 5c
Platform Session
Paediatric Epileptology I: Status Epilepticus

019

ESTIMATES OF MORTALITY AND MORBIDITY ASSOCIATED WITH CHILDHOOD STATUS EPILEPTICUS ARE DEPENDENT ON STUDY QUALITY

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Purpose: It is widely accepted that convulsive status epilepticus (CSE) in childhood is associated with significant morbidity and mortality, but there is a wide range of estimates of adverse outcome with CSE. Although the variation in estimates may have a biological cause, we investigated whether this variation is also a function of the quality of the studies.

Method: A systematic review methodology search for studies regarding outcome of paediatric CSE was conducted. Each study's methodological quality was evaluated using a scoring system that included scores for study design, type of study, duration of follow-up, aetiology, standardisation of rates, ascertainment adjustment, therapeutic algorithm and definition of outcome parameters. Maximum possible score was 50.

Results: Fifty-nine studies were identified. Median quality score was 25 (range 10–41). Mean score was higher in prospective studies than in retrospective studies (33.5 vs 22, $p < 0.005$). Population-based studies

scored better than hospital-based studies (30.6 vs 24.2, $p = 0.006$). These differences are not attributable to the scoring system itself. Morbidity and mortality estimates each ranged from <1% to >40%. A correlation was found between higher scores (i.e. better study quality) and lower mortality (Rho Spearman $= -0.38$, $p = 0.009$) and morbidity (Rho Spearman $= -0.539$, $p = 0.004$), but not between scores and subsequent epilepsy or CSE recurrence.

Conclusion: Lack of homogeneity and accuracy in methodological designs account for the heterogeneous results observed between studies and impede meaningful comparisons. The best scored studies suggest an overall short-term mortality of 3% and morbidity <15%, values that are likely to be closest to "reality."

020

AETIOLOGY, COURSE AND OUTCOME OF CHILDREN ADMITTED TO PAEDIATRIC INTENSIVE CARE WITH CONVULSIVE STATUS EPILEPTICUS: A FIVE-YEAR EXPERIENCE: 'ZERO MORTALITY AND LOW MORBIDITY'

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Purpose: Convulsive status epilepticus (CSE) is the most common neurological emergency in childhood (1) and is a life-threatening condition with serious risk of neurological sequelae. (2) Mortality and morbidity due to CSE have declined during the last two decades when compared to previous decades. (3) The purpose of this retrospective study was to explore the role of age, sex, previous neurological disorders, aetiology, duration and treatment on the outcome of CSE.

Method: A retrospective study of the aetiology, course and prognosis of children in convulsive status epilepticus (CSE) admitted to a large paediatric intensive care unit (PICU) between January 1999 and April 2004. Status epilepticus was defined as a prolonged (>30 mins) tonic–clonic seizure irrespective of whether the seizure had stopped prior to admission to PICU.

Results: One hundred thirty-seven (74 male) children aged 1 month to 15 years were admitted to PICU with 147 episodes of status epilepticus. Forty-seven children (34%) were admitted following a prolonged febrile seizure. Fifty-three children (39%) had a remote symptomatic cause for the CSE (cerebral palsy in 34 of the 53). Twenty-four children (18%) were admitted for an acute symptomatic cause. Six children had a progressive encephalopathy and no cause was identified in the remaining seven of the 137 children (5%). Forty-nine children (36%) had preexisting epilepsy. The mean duration of CSE was 44 minutes (range, 30 to 120) minutes. Forty nine (36%) children admitted to PICU required treatment to terminate the presenting episode of CSE. Forty-two and 7 of these children were treated with thiopentone anaesthesia and midazolam infusions respectively, successfully terminating the episode of status in all. No child died on PICU as a result of either the CSE or its cause. Of the 70 children considered to be previously neurologically and developmentally normal prior to admission, 64 demonstrated normal neurological or developmental findings on discharge from the PICU. The majority (95%) of the 47 children with febrile CSE demonstrated normal neurodevelopmental findings at a median period of 1.3 years following discharge from PICU.

Conclusion: The most common cause of CSE in children admitted to a large children's hospital PICU was epilepsy. Thiopentone was the most commonly used drug to terminate persisting status on PICU that had proved resistant to first line treatment using a benzodiazepine and phenytoin or phenobarbitone. No child died as a direct result of CSE. Only 1 (0.01%) of the previously neurologically and developmentally normal children demonstrated any abnormality at the time of their latest follow up.

021

SOCIOECONOMIC DEPRIVATION INDEPENDENT OF ETHNICITY INCREASES THE RISK OF CONVULSIVE STATUS EPILEPTICUS IN CHILDHOOD

R. Chin, B. Neville, C. Peckham, H. Bedford, A. Wade, and R. Scott (Institute of Child Health, UCL Medical School, London, UK)

Purpose: The incidence of convulsive status epilepticus (CSE) is higher amongst nonwhite compared to white patients. However, ethnicity effects may be related to socioeconomic factors. The study with the highest reported incidence of CSE worldwide was conducted in a predominantly black, economically deprived population. Thus, we hypothesised that the incidence previously reported in nonwhite patients may in part reflect the effect of socioeconomic deprivation.

Method: Subjects were enrolled as part of a two year prospective population based study. Excluding neonates, children aged < 16 years with CSE were identified using a multitiered notification system. Home post-codes of children were used to determine their Index of Multiple Deprivation 2004 (IMD2004) score of socioeconomic deprivation. Poisson multiple regression analysis was used to investigate the relationships between incidence of CSE, socioeconomic deprivation and ethnicity.

Results: 176 children were enrolled. Ascertainment-adjusted incidence = 19 (95% CI 17–23) per 100,000 children/yr. Nonwhite children were 1.8 times more likely ($p = 0.03$) to have CSE compared to white children. Asian children were 2.1 times more likely ($p < 0.0005$) but black children were as likely (or 1.3, $p = 0.2$) to have CSE compared to white children. For each one point increase in IMD2004 (worsening socioeconomic deprivation) there is a 3% cumulative increased risk of CSE irrespective of ethnicity ($p = 0.003$). There were no differences in IMD2004 scores and aetiology or IMD2004 scores and the interval between CSE onset and arrival of emergency medical services.

Conclusion: The relationship between ethnicity and CSE is complex and is likely to be influenced by socioeconomic and genetic factors.

022

CONVULSIVE STATUS EPILEPTICUS AS INITIAL SEIZURE IN CHILDREN: TYPE OF LATER EPILEPSY

P. Haapala, L. Pekkarinen, A. Kuusela, T. Keränen, and K. Eriksson (Tampere University Hospital and Medical School of Tampere University, Finland)

Purpose: Epilepsy is one of the most common sequelae in patients with convulsive status epilepticus. Whether the seizure prolongation is an independent risk factor for later epilepsy is uncertain and little is known about the type of it. We reviewed data of a set of children treated for prolonged convulsive seizure to determine whether the duration of the initial episode has an effect on the incidence and the type of later epilepsy.

Method: We retrospectively reviewed data of all children (aged 1 month to 16 years) who had been admitted to the Paediatric Emergency Department of Tampere University Hospital from 1993 to 1999, due to an acute convulsive disorder lasting over 5 minutes ($n = 186$). Of those, children with no previous epilepsy were included in the retrospective analysis on the initial seizure episode and clinical follow-up.

Results: There were 159 children included in the analysis and they were divided into two groups based on the initial seizure duration (5–29 min and 30 min or more). The groups did not differ significantly by aetiological or other background factors. 75.5% were neurologically normal prior to the initial seizure episode. The mean age was 3.5 years (range 2 mo–14.7 y), the mean follow-up time 15.9 months. There were 94 children with initial seizure duration over 30 min, of which 26 (27.7%) were diagnosed with epilepsy during follow-up. The risk for later epilepsy associated significantly with the aetiology; the risk was 50–55% in idiopathic or remote symptomatic aetiology groups compared to 13.3% in febrile or other aetiologies ($p < .001$). The type of later epilepsy was significantly more often focal (84.6%) than generalised (15.4%, $p < .001$). In 65 children the duration of initial seizure episode was 5–29 minutes and 14 (21.5%) were diagnosed with epilepsy during follow-up. Almost all (92.9%) of those epilepsies were focal.

Conclusion: Onset of epilepsy after prolonged initial seizure episode occurred in every fourth child. Children with longer (over 30 minutes) initial seizure episode had a 1.3-fold risk for later epilepsy compared to children with a shorter initial seizure. The type of later epilepsy was focal in most patients.

023

STATUS EPILEPTICUS IN CHILDREN WITH PROGRESSIVE MYOCLONUS EPILEPSIES

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Purpose: To evaluate clinical and neurophysiologic characteristics, precipitating factors, response to treatment and outcome of status epilepticus (SE) in children with progressive myoclonus epilepsies (PME).

Method: We analysed 20 episodes of SE in 7 patients (mean age 9 ± 4.6 years) with PME. Molecular biology and/or microscopic analysis were used to confirm aetiology of PME. The follow up duration ranged 1–7 years (4.3 ± 1.6).

Results: Aetiology of PME was estimated: ceroidlipofuscinoses (CLF) (3), Lafora disease (LD) (3) and MERRF (1). The most frequent type of SE was myoclonic (12), secondary generalised tonic–clonic (6) and complex partial SE in 2 episodes. Duration of SE ranged from 30min-7 days (mean duration 850 min). Infection provoked 8 episodes, introduction of lamotrigine aggravated SE in 1 patient with LD and topiramate in 1 patient with CLF. Ten episodes occurred without acute provocation. In control of SE, midazolam was effective in 16, thiopental in 1, phenobarbital in 2 and clonazepam in 1 episode. A patient with MERRF died due to respiratory impairment, and the others returned to the baseline neurological status in a period of 7–20 days after SE.

Conclusion: More than 2/3 episodes of SE in children with PME were long lasting and resistant to appropriate treatment. Most frequent type was myoclonic SE, aggravated by infection and the introduction of some drugs. The most effective drug for control of SE was midazolam administered in continuous intravenous infusion. Duration of recovery and return to the baseline neurological status after an episode of SE was prolonged and correlated to the treatment duration.

024

CHILDREN PRESENTING WITH A FIRST TONIC–CLONIC SEIZURE: THE ROLE OF A "FIRST-FITTER" CLINIC

R. Appleton, K. Williams, J. Daly, and D. O'Hagan (Royal Liverpool Children's Hospital (Alder Hey), UK)

Purpose: A "first-fitter" clinic (FFC) was established to address the concerns of families whose children had attended the Emergency Department (ED) with a first tonic–clonic seizure. The study reports the results of the first 2 years of this FFC held within the ED of a large Children's Hospital.

Method: The study included all children attending the ED after a first tonic–clonic seizure not requiring admission and who were offered an appointment for the FFC. Children were seen by an advanced nurse-practitioner with support from a Consultant in Emergency Medicine after which they were discharged back to their general practitioner or referred to the neurology clinic in the same hospital. The study was retrospective using the child's ED and FFC medical notes.

Results: One hundred twenty-one children (68 boys), aged 2–15 (mean, 9.4 years) attended the ED with a reported first tonic–clonic seizure. One hundred and seventeen of these 121 (97%) attended the FFC clinic, 92 (79%) within 4 weeks of the seizure. After FFC review, diagnoses in the 117 included tonic–clonic seizures (82), reflex anoxic seizures (15), vaso-vagal syncope (13), febrile seizures (3), breath-holding (2) and 'unclear' (2). Forty eight children were referred to the neurology clinic with 90% being assessed within 4 weeks of referral.

Conclusion: Almost one-third of the 117 children had not experienced a tonic–clonic seizure as first diagnosed when they attended the ED. Consequently the FFC could reassure many families but also "fast-track" those children who were considered to have had multiple seizures (epilepsy).

Monday July 3, 2006
12:00–13:30
Hall 3a

Platform Session
Clinical Neurophysiology I

025

SILENT PERIOD MEASUREMENTS IN UNTREATED PATIENTS WITH IDIOPATHIC GENERALISED EPILEPSY

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Purpose: Transcranial magnetic stimulation (TMS) studies reflecting cortical and spinal inhibitory mechanisms. Previous studies of SP in epilepsy have generally provided divergent results. The objective of the present study is to investigate SP in untreated patients with idiopathic generalised epilepsy (IGE) using a novel methodological approach.

Method: Fourteen patients with IGE (9 females, median age 19 yrs, range: 16–22) entered the study. Seven patients suffered from juvenile myoclonic epilepsy (JME), 4 patients from idiopathic epilepsy with generalised tonic–clonic seizures on awakening and the rest from other idiopathic generalised epilepsy syndromes not better defined. All electrophysiological examinations were performed at least 48 hours after the occurrence of an epileptic seizure so as to account for the confounding factor of postictal changes. Results were compared with those of a control group comprising 13 healthy, age-matched subjects. SPs were investigated as recently described [Kimiskidis et al. Exp Brain Res 2005;163:21–31]. First, SPs were elicited using a wide range of stimulus intensities (SIs) (from 5 to 100% maximum SI at 5% increments). At each SI, 4 SPs were obtained and the average value of SP duration was used to construct a stimulus/response (S/R) curve of SI vs SP. The resulting S/R curves were then fitted to a Boltzman function, the best-fit values of which were statistically compared between the patient and the control group.

Results: The SP S/R curve of the patients was significantly different compared to the controls ($p > 0.0001$, F-test and AIC). In particular, the Max value of the patient's curve was 257.5 ± 3.98 ms vs 221.4 ± 2.89 ms in the controls ($p < 0.0001$) and V_{50} was 46.95 ± 0.71 vs 51.03 ± 0.57 ($p < 0.0001$) whereas slope was not significantly different (9.94 ± 0.58 vs 10.09 ± 0.46, $p > 0.05$).

Conclusion: SP, a $GABA_B$ receptor mediated event, is prolonged in IGE. Basic neurophysiology experiments prove that $GABA_B$ IPSPs are more efficiently activated in the presence of $GABA_A$ receptor antagonists. Therefore, it could be hypothesised that a hypofunction of $GABA_A$ receptors in patients with IGE results in increased $GABA_B$ IPSPs reflected in prolonged SPs.

026

PROPOSAL OF AN EEG TIME INDEX VARIATION OF SPIKES (ETIVS) DURING ENDOSCOPIC DISCONNECTION IN INTRACTABLE EPILEPSY ASSOCIATED WITH HYPOTHALAMIC HAMARTOMA (HH)

[1]D. Debatisse, [1]E. Pralong, [1]J. Villlemure, [2]M. Maeder, [3]E. Roulet, [1]O. Delalande, [1]M. Tetreault, and [1]C. Pollo ([1]Neurosurgery-UNN CHUV Lausanne, Switzerland, [2]Neurology Department CHUV Lausanne, Switzerland, [3]Neuropediatric Department CHUV Lausanne, Switzerland)

Purpose: Intractable epilepsy associated with hypothalamic hamartoma (HH) can be controlled by microsurgical resection of the lesion; excision of deep-seated lesions is often associated with morbidity and mortality. Endoscopic disconnection is less invasive and seems to be well suited for this indication. Hypothalamic hamartoma are often associated to a progressive epileptic encephalopathy. Surgery clinical outcome data indicates that destruction or isolation of the hamartoma may stop seizures. We present data of 1 patient with endoscopic disconnection for the treatment of intractable epilepsy. On-line EEG recording was carried out during the surgery. By this surgery technical approach, Epilepsy improved theoretically in the literature in 60% of patients with minimal morbidity. In our knowledge this case report is first one in the literature where the opportunity of EEG neuromonitoring during epilepsy endoscopic surgery is discussed. The authors (a) discuss the interest of

EEG neuromonitoring during endoscopic-assisted surgery in the management of HH-induced seizures; (b) propose an EEG neuromonitoring approach with calculation of an EEG time index variation of spikes (ETIVS) during endoscopic epilepsy surgery (c) give an online "EEG predictive value" (EPV) of post operative outcome.

Method: One patient suffering from intractable epilepsy with a HH lesion. (age 2 years old BD: 07-07-2002). Intractable epilepsy with 10 or 20 ≪Gelastic crisis≫ per day and a strong bad psychomotor deficit (mentally retarded). Endoscopic surgery was proposed in this case by a left approach for the disconnection of the left side of HH, using neuronavigation technique. On-line scalp EEG recording was performed (Fp2-Fp1-C3-C4, T3-T4,O1-O2) during the length of surgery (EEG signals were recorded using a Micromed (Italy) 32 channels system at 512 Hz, low passed filtered at 128 Hz and high passed filtered at 1 Hz. The signal was visualised using a monopolar montage or an averaged reference). An off line analysis was performed using linear and temporal techniques (wavelet and FFT) with EEmagine software from ANT (Germany) to calculate the number of left and right hemisphere epileptic discharges. A time index of variation (duration, amplitude and number) of discharges was calculated and compared between the two hemispheres (using for the analysis FP1 and FP2 electrodes).

Results and Conclusion: We calculated ETIVS spike discharges for both hemispheres. By comparison we observed 1791 spikes on the right Fp2 electrode and 3177 spikes on the Fp1 electrodes during the total recording time (148 min). On the right hemisphere we observed a statistical significance decrease of the number of discharges at time 78 to 127 minutes during the surgery approach. During this period, we observed also a ≪change≫ of the EEG pattern spikes recognition in term of reduction of spike numbers, duration and amplitude but with an increase of small multi spike discharges. At 128 min on the left hemisphere correlated with the surgery location, we observed an increase of spike numbers without modification in duration and amplitude in comparison with the beginning of surgery. Epilepsy surgery in children requires a multidisciplinary approach. This original case report examines the role of scalp EEG monitoring during surgical endoscopic surgery in 1 case with a HH. An illustrative case demonstrates (1) the interest of EEG neuromonitoring during endoscopic approach in intractable epilepsy and (2) can be used as an on-line tool to determine and predict the EEG or epilepsy outcome of the patient; (3) we developed an EEG time index variation of spikes (ETIVS) of epileptic discharges during endoscopic surgery. In conclusion, using EEG neuromonitoring with an ETIVS during endoscopic surgery, we expect that this neurophysiological approach can be a help in the comprehension of mechanisms in epilepsy network in multifocal intractable epilepsy. These first and encouraging results should be confirmed by prospective studies.

027

DIFFERENCES IN EEG INTERICTAL SPIKE PROPAGATION BETWEEN RIGHT AND LEFT TEMPORAL LOBE EPILEPSY

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Purpose: Previous studies revealed structural, metabolic, and neuropsychological differences between right and left temporal epilepsy and suggested that right temporal lobe epilepsy (RTLE) might be a more diffuse or generalised disease than left temporal epilepsy (LTLE). Based on these studies we hypothesised that a more widespread propagation of the epileptiform activity in RTLE patients might underlie these differences.

Method: We analysed spikes of 57 patients with temporal lobe epilepsy (30 left, 27 right), recorded from 29 electrodes. A distributed linear inverse solution (LAURA) was used in combination with statistical parametrical mapping to determine those areas of the brain that showed a significantly different activation in the two patient groups during different phases of the spike-wave complex.

Results: LTLE patients showed significantly stronger ipsilateral temporal activation than RTLE patients, while RTLE patients showed significantly stronger contralateral temporal activation throughout the whole spike-wave complex. Early ipsilateral frontal propagation was seen in both patient groups, but this propagation had a more anterior distribution in the LTLE patients. Later propagation to contralateral frontal areas was more pronounced in RTLE patients.

Conclusion: With the current technique it has been possible to determine statistical differences in the propagation patterns between RTLE and LTLE patients. The stronger contralateral temporal activation and the more extensive frontal propagation in RTLE is in line with the notion of a more diffuse or generalised disease in these cases.

028

INTERICTAL TO ICTAL TRANSITION IN HUMAN TLE: INSIGHTS FROM COMPUTATIONAL MODELLING OF INTRACEREBRAL EEG

[1]F. Wendling, [1]A. Hernandez, [2]F. Bartolomei, and [2]P. Chauvel ([1]Inserm–University of Rennes, France, [2]Inserm–University of Mediterranee, France)

Purpose: In human partial epilepsies, the role of inhibition and the relationship between the inhibition and excitation and epileptogenesis has long been questioned. Pathophysiological mechanisms can be approached by direct recording of brain electrical activity in human epilepsy performed during presurgical evaluation. In this study, we relate electrophysiological patterns typically observed during the transition from interictal to ictal activity in human mesial temporal lobe epilepsy (MTLE) to mechanisms involved in seizure generation through a computational model of EEG activity.

Method: Intracerebral EEG signals recorded from the hippocampus in patients with MTLE during interictal activity, during seizure onset and during ictal activity were used to identify the three main parameters of a model of hippocampus EEG activity (related to excitation, slow dendritic inhibition and fast somatic inhibition). The identification procedure used optimisation algorithms to minimise a spectral distance between real and simulated signals.

Results: Results demonstrated that the model generates very realistic signals for automatically identified parameters. They also showed that the transition from interictal to ictal activity cannot be simply explained by an increase in excitation and a decrease in inhibition but rather by time-varying ensemble interactions between pyramidal cells and local interneurons projecting to either their dendritic or perisomatic region (with slow and fast GABAA kinetics). Particularly, fast onset oscillations (25 Hz) are explained by the model feedback loop between pyramidal cells and interneurons targeting their perisomatic region.

Conclusion: This model-based approach is able to reveal physiological changes that take place inside recorded brain structures during the transition from interictal to seizure activity.

029

ENHANCING THE LOCALISING VALUE OF ICTAL SCALP EEG BY APPLYING THE NEW BSS-CCA METHOD TO REMOVE MUSCLE ARTIFACTS

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Purpose: The influence on the localising value of ictal EEGs on muscle artifact suppression by blind source separation-canonical correlation analysis (BSS-CCA) was investigated.

Method: All patients with refractory partial epilepsy having a reliably defined epileptogenic zone based on multimodal studies were selected. One ictal EEG of all 37 patients was presented to a clinical neurophysiologist (AP) who was blind to all other clinical and localising data. The ictal EEG was rated twice: first after applying a tunable band pass filter, then after eliminating the muscle artifacts using BSS-CCA in combination with a band-pass filter (0.3–35 Hz). Assigned localisations and lateralisations were compared between the two readings and with the other localising data.

Results: In 2 out of 37 ictal EEGs no seizure could be identified. In one case a seizure could only be determined and correctly localised after applying BSS-CCA+filter. Of the remaining 34 EEGs 21 (62%) were lateralised correctly after band-pass filtering, 26 (76%) after applying BSS-CCA+filter. Correct localisation increased from 23 (67%) using

band-pass filters to 29 (85%) using BSS-CCA+filter. Improvements in lateralisation and localisation were both reached for temporal (2 out of 25 cases, resp. 3 out of 25 [0]cases) and extratemporal cases (3 out of 9 cases, resp. 4 out of 9 cases).

Conclusion: The new BSS-CCA algorithm to eliminate muscle artifacts from scalp EEGs enhances the localising value of ictal EEGs from 62% correct lateralisations to 76[0]% and from 67% correct localisations to 85% compared to band-pass filtering.

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030

A NEW SIMULTANEOUSLY OBJECTIVE AND PATIENT-SPECIFIC SPIKE AND WAVE DETECTION ALGORITHM BASED ON TEMPLATE MATCHING

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Purpose: Automatic spike and wave detection is useful to enhance objectivity and reduce human work. Template matching algorithms are computationally simple–hence quick–but it is difficult to find a template that is suitable for all cases. The EEG expert can be asked to score a few spikes and waves to generate a patient-specific template before the automatic detection gives better performance, but is not always suitable because of the time it requires (the amount of data is sometimes huge) and because it reduces the objectivity. We present a new, simultaneously objective and patient-specific, spike and wave detection algorithm. A first spike and wave detection is made with a patient-independent template, showing an average performance. Out of that detection, a patient-specific template is created. Thanks to it, a patient-specific detection is made, showing high performance.

Method: The algorithm was tested against the scoring of three EEG experts over 30 minutes of EEG samples from three different subjects, suffering form the syndrome of continuous spike and wave discharges during slow sleep (CSWSS).

Results: The algorithm showed an average specificity of 81% and an average false positive rate of 11%, compared to the average specificity (90%) and false positive alarm rate (12%) when we compare the three EEG experts.

Conclusion: The algorithm developed shows high performance, is easy to use and is fast. It can be useful to increase the level of objectivity and to decrease the amount of diagnostic work.

Monday July 3, 2006
12:00–13:30
Hall 3D
Platform Session
Basic Science I: Molecules and Networks for Epileptogenesis

031

NEUROGENESIS IN EPILEPTIC BRAIN: AFFERENT SYNAPSES TO NEWBORN CELLS ATTENUATE NETWORK EXCITABILITY

M. Kokaia (Wallenberg Neuroscience Center, Lund University Hospital, Sweden)

Purpose: Neural stem cells in the adult mammalian brain (including humans) continue to produce new functional granule cells in the dentate gyrus subgranular zone and new olfactory bulb neurons in the subventricular zone during an entire life. In the hippocampus, neurogenesis has been proposed to play a role in learning and memory and mood regulation. The new cells develop electrophysiological characteristics and synaptic inputs very similar to those of the rest of the cell population. The purpose of the study was to explore whether tissue environment in an epileptic brain influences properties of afferent synapses formed on newborn granule cells.

Method: Rats were exposed to either a physiological stimulus, i.e., running, or status epilepticus, which gives rise to neuronal death, inflammation, increased network excitability and recurrent spontaneous seizures. Both treatments increase neurogenesis in the dentate gyrus. We labelled newborn cells by GFP-retroviral vector injections right after these treatments to identify the cells and apply whole-cell patch-clamp recordings in live hippocampal slices.

Results: Granule cells formed after running and status epilepticus exhibited similar intrinsic membrane properties. However, new neurons born into the epileptic environment differed with respect to tonic drive and short-term plasticity of both excitatory and inhibitory afferent synapses. The new granule cells formed after status epilepticus exhibited functional connectivity consistent with reduced synaptic network excitability of the dentate gyrus, i.e., decreased excitatory and increased inhibitory input activity.

Conclusion: We demonstrate for the first time a high degree of plasticity in synaptic inputs to the new neurons, which could mitigate pathological activity in the epileptic brain.

032

PERTURBED EXPRESSION OF THE K-Cl COTRANSPORTER KCC2 AND GABAERGIC SIGNALLING IN HUMAN TEMPORAL LOBE EPILEPSY

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Purpose: An interictal-like activity is spontaneously generated in the subiculum of slices obtained from patients with temporal lobe epilepsies and hippocampal sclerosis. This activity is associated with depolarising responses to GABA in a minority of subicular pyramidal cells, probably related to a perturbation of neuronal Cl homeostasis. We therefore studied relations between Cl homeostasis and GABAergic signalling in human epileptic tissue, focusing on the K-Cl transporter KCC2, which is known to be responsible for the generation of hyperpolarising GABA responses in central neurons.

Method: Slices of human temporal lobe tissue with hippocampal sclerosis containing the subiculum were prepared after surgery. Field potentials and unit activity were recorded with extracellular electrodes. Intracellular pipettes contained biocytin so that recorded cells could be anatomically identified. KCC2 expression was studied with in situ hybridisation and immunochemistry.

Results: Morphological characteristics or intrinsic parameters did not differ in the ~20% of pyramidal cells depolarised by GABA. $GABA_A$ response reversal potentials were asymmetrically distributed with a mode near −70 mV and most depolarised values up to −50 mV. Their driving force was positive with respect to resting potential in 20% of pyramidal cells. In situ hybridisation showed that KCC2 mRNA was not detectable in ~30% of subicular pyramidal cells. Combined biocytin labelling and immunohistochemistry for KCC2 showed that 6/6 cells with hyperpolarising responses to GABA were positive, while only 3/7 cells that discharged with epileptiform bursts were immunopositive for KCC2.

Conclusion: A perturbation of KCC2 expression in a minority of subicular pyramidal cells may contribute to human interictal epileptogenesis.

033

ASTROCYTIC-NEURONAL INTERACTIONS DURING EPILEPTOGENESIS IN THE RAT NEOCORTEX

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Purpose: Focal cortical epilepsy is common following different brain insults such as trauma, ischemia and infectious diseases. In many of these insults the blood-brain barrier (BBB) is disrupted. We have recently shown that prolonged cortical BBB opening is associated with high amplitude, slow electroencephalographic activity in humans (Korn et al., 2004) and hypersynchronised epileptiform activity in the rat cortex (Seiffert et al., 2004). However, the mechanisms underlying epileptogenesis after BBB disruption are not known.

Method: We used a rat model to disrupt the BBB by application of the bile salt deoxycholic acid or exposed the rat cortex to serum albumin in vivo.

Results: Here we show that astrocytic activation occurred within the first 24 hours after treatment, while neuronal epileptiform activity was noted from day 4. Extracellular recordings in vitro using ion-sensitive microelectrodes showed that astrocytic activation was associated with reduced K^+ buffering due to a decrease in Ba^{2+} sensitive potassium current, suggesting decreased inward rectifying K^+ current. PCR analyses and immunostainings confirmed the down regulation of KIR4.1 channels. Reduced K^+ buffering lead to potassium accumulation during neuronal activity, subsequently causing NMDA-receptor dependent neuronal hyperexcitability. Serum albumin is rapidly and specifically transported into astrocytes suggesting that it may be a signal for astrocytic activation. Albumin transport into astrocytes was found to be receptor mediated, and could be blocked by antibodies against TGF-beta receptors. Blocking albumin uptake in vivo significantly reduced the likelihood of epileptogenesis.

Conclusion: Our results stress the importance of interactions between the brain's blood vessels, astrocytes and neurons in the pathogenesis of focal neocortical epilepsy.

034

DYNAMIC CHANGES OF PROTEASES AND PROTEASE INHIBITORS REVEALED BY MICROARRAY ANALYSIS IN CA3 AND TEMPORAL LOBE DURING EPILEPTOGENESIS IN THE RAT

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Purpose: In order to find genes that could be potential targets to intervene with epileptogenesis we investigated gene expression in a rat model for temporal lobe epilepsy.

Method: RNA was obtained from three different brain regions (CA3, entorhinal cortex and cerebellum) at three different time points (1 day = acute phase; and 1 week = latent period; 3–4 months = chronic epileptic) after electrically induced status epilepticus (SE); a group that was stimulated but that had not developed epilepsy was also included. Gene expression analysis was performed using the Affymetrics Gene Chip System (230A). We used GENMAPP and gene ontology to identify global biological trends in gene expression data. In this study we focused on the proteolytic process.

Results: Proteolysis occurred mainly in the acute and latent phase. We found noticeable differences in dynamics of the changes of several protease genes such as cathepsins, caspases, matrix metalloproteinases and plasminogen activators. Most genes were acutely upregulated while others were mainly activated during the latent phase. Interestingly several proteolytic genes were still elevated in the chronic epileptic phase. Various protease inhibitors followed a similar time course.

Conclusion: The identification of activated genes involved in proteolysis at critical phases during epileptogenesis could point to potential time specific targets for intervention. The fact that several proteolytic genes were still activated in the chronic epileptic phase makes them interesting candidates to modify and slow down seizure progression.

035

COMMON TRAITS IN ALTERATIONS OF PATTERNS OF GENE EXPRESSION ACROSS DIFFERENT ANIMAL MODELS OF EPILEPTOGENESIS

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Purpose: The main goal of this study was to identify common features in the molecular response to epileptogenic stimuli across different animal models of epileptogenesis. We were searching for highly represented functional gene classes (GO terms) within the data sets, and individual genes that appeared in several data sets, and therefore, could be of particular importance for epileptogenesis.

Method: Fifteen papers describing alterations in the transcription following status epilepticus or traumatic brain injury were selected for analysis. To detect overrepresented GO terms we used GOstat (http://gostat.wehi.edu.au). To find a particular gene with altered expression, all data were re-annotated using a purpose-built relational database and comparisons were performed with SQL queries embedded in a scripting language. The analysis was performed at different time windows following the insult: 30 min to 9 h; 1–4 d; and $\geq$14 days.

Results: Our analysis revealed that epileptogenic insults induce significant changes in gene expression within a subset of predefined GO terms. We also found individual genes for which expression changed across different models of epileptogenesis. Alterations in gene expression appear time-specific and underlie a number of processes that are linked with epileptogenesis, such as cell death and survival, neuronal plasticity, or immune response. Supporting information containing summary of genes with altered expression and results of analysis of GO terms can be viewed at http://www.nencki.gov.pl/labs/epg.htm.

Conclusion: Application of bioinformatic tools to compare the available literature on global analysis of gene expression following epileptogenic insults highlights most prominent phenomena that underlie reorganisation of the epileptogenic circuitry in the brain.

036

INVESTIGATION OF ACUTE HIPPOCAMPAL INJURY FOLLOWING STATUS EPILEPTICUS USING MRI AND PROTEOME ANALYSIS

M. Choy (UCL Institute of Child Health, London, UK)

Purpose: Status epilepticus (SE), in humans, may be associated with hippocampal injury, epileptogenesis and development of temporal lobe epilepsy. The purpose of this MRI and proteomics study is to investigate the mechanisms underlying these relationships using the lithium-pilocarpine model.

Method: Pilocarpine (n = 5) or saline (n = 5) was administered to adult Sprague-Dawley rats. MRI measurements of CBF and T_2 were performed before injections, immediately after, 1 day and 2 days after SE. On day 2, animals were sacrificed for proteome analysis using 2D gels. Statistical analyses were performed using 2-way repeated measures ANOVA.

Results: Significant interactions between treatment and time were observed for both T_2 ($F = 3.86$, $p = 0.05$) and CBF ($F = 7.01$, $p = 0.003$) in the hippocampus. Proteome analysis on day 2 indicated that there was at least a five-fold upregulation of heat shock protein 27 (HSP27) and dihydropyrimidinase related protein-2 (DRP-2) when compared to controls.

Conclusion: We demonstrated that 2 days following SE, both T_2 and CBF increased in the hippocampus with concomitant upregulation of HSP27 and DRP-2. Over-expression of HSP27 has been shown to be neuroprotective following SE (Akbar MT et al. *J Biol Chem* 2003; 278(22):19956–65.) and DRP-2 has been identified as a marker of newborn neurons (Minturn JE et al. *J Comp Neurol* 1995; 355(3):369–79). The parallel changes observed in both MRI and proteomics at 2 days suggest that these proteins may have functional consequences in the hippocampus following SE. Further studies are required to elucidate the contribution of these proteins in epileptogenesis.

Monday July 3, 2006
12:00–13:30
Ballroom 1
Platform Session
Genetics

037
ELECTROCLINICAL FEATURES OF A FAMILY WITH *SCN1A* LOSS-OF-FUNCTION MUTATION ASSOCIATED WITH SIMPLE FEBRILE SEIZURES

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Purpose: To report in detail electroclinical features of a large family in which we recently identified a missense mutation (M145T) of *SCN1A* gene.

Method: We studied a family comprising 35 members spread over 4 generations. Among 14 affected individuals, 13 living members (7 males, mean age 36.6 ± 20.4) underwent a complete electroclinical evaluation. Peripheral blood samples were obtained for DNA extraction from 23 members of the family.

Results: The neurologic and psychiatric status of all 13 affected subjects was normal. All 13 affected family members had febrile seizures (FS). In details, 9 had FS only, 3 had FS and temporal lobe epilepsy (TLE) and 1 had post-traumatic epilepsy. None had febrile seizures beyond the age of six. Only 2 out of 9 patients with FS have had rare complex febrile seizures. In 2 of the 3 patients with FC-TLE the MRI study revealed a mesial temporal sclerosis. All affected members had a M145T within the S1 segment of domain I (DIS1) of the *SCN1A* causing a loss of function.

Conclusion: Our findings illustrate that *SCN1A* mutations can cause simple FS associated with TLE, which differ from the characteristic clinical spectrum of GEFS$^+$. It is questionable if this unusual phenotype might be at least in part related to the fact that M145T is the first missense mutation found in DIS1 of *SCN1A*.

038
MICRODELETIONS OF THE *SCN1A* GENE MAY BE COMMON IN "*SCN1A*-MUTATION-NEGATIVE" SMEI PATIENTS

[1]L. Claes, [1]A. Suls, [1,2]K. Claeys, [1]D. Goossens, [3]R. van Luijk, [3]S. Scheers, [1]L. Deprez, [1]D. Audenaert, [1]T. Van Dyck, [3]S. Beeckmans, [1,2]I. Smouts, [2,4]B. Ceulemans, [4,5]L. Lagae, [5]G. Buyse, [6]N. Barisic, [7]J. Misson, [1]J. Del-Favero, [3]J. Wauters, and [1.2]P. De Jonghe ([1]Flanders Interuniversity Institute For Biotechnology (VIB8), Antwerp, Belgium, [2]University Hospital Antwerp, Antwperp, Belgium, [3]University of Antwerp, Antwerp, Belgium, [4]Epilepsy Center For Children And Youth, Pulderbos, Belgium, [5]University Hospital Gasthuisberg, Leuven, Belgium, [6]University Medical School, Zagreb, Croatia, [7]University of Liege, Liege, Belgium)

Purpose: Severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome is a severe epilepsy syndrome that has an onset in the first year of life and usually starts with febrile generalised or unilateral clonic seizures. Later in life, other types of seizures, retardation of the psychomotor development and other progressive neurological deficits are observed. In 30–70% of SMEI patients, truncating and missense mutations in the neuronal voltage-gated sodium-channel -subunit gene (*SCN1A*) have been identified. About 50% of patients have truncating mutations which predict be loss-of-function alleles. Because mutation detection studies use PCR sequencing or conformation sensitive gel electrophoresis, microdeletions, which are also predicted to be loss-of-function alleles, can easily escape detection.

Method: We selected 11 SMEI patients without a *SCN1A* mutation on sequencing analysis. In addition, none of these patients were heterozygous for any of the single nucleotide polymorphisms (SNPs) in *SCN1A* indicating that they were either homozygous for all SNPs or hemizygous due to a microdeletion of the gene. We subsequently studied these patients with quantitative multiplex PCR for the identification of microdeletions in *SCN1A*.

Results: We observed 3 patients missing one copy of the *SCN1A* gene. All 3 microdeletions were confirmed by fluorescence in situ hybridisation (FISH).

Conclusion: These findings demonstrate that a substantial percentage of "*SCN1A*-mutation-negative" SMEI patients carry a chromosomal microdeletion comprising the *SCN1A* gene and that haploinsufficiency of the *SCN1A* gene is a major cause of SMEI.

039
NOVEL *SCN2A* MUTATION ASSOCIATED WITH BENIGN FAMILIAL NEONATAL INFANTILE SEIZURES IN A BULGARIAN FAMILY

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Purpose: Mutations in voltage–gated sodium channel genes are known to be responsible for inherited idiopathic epilepsy syndromes. Missense mutations in *SCN2A* were identified as a cause for benign familial neonatal-infantile seizures (BFNIS). BFNIS is characterised by afebrile secondarily generalised partial seizures with an age of onset from the first days of life to 7 months. The outcome is usually good with a remission by 12 months. In addition, a *SCN2A* mutation was found in a small Japanese family with phenotypes of febrile and afebrile seizures, where it was difficult to apply a clear syndrome classification.

Method: *SCN2A* was analysed in 24 unrelated patients. These patients were diagnosed as BFNIS, the related syndromes benign familial neonatal convulsions (BFNC) and benign familial infantile convulsions (BFIC), or GEFS+.

Results: One *SCN2A* mutation was detected in a Bulgarian patient with BFNIS. This missense mutation causes a substitution of methionine with valine at position 252 (p.M252V), located within segment S5 of the first transmembrane domain in the protein. Further analysis of the three-generation family revealed cosegregation of this mutation with the disease phenotype. The patients in the family experienced several clusters of generalised tonic and/or clonic seizures within the first year of life. The outcome was good in all patients, none of them had psychomotor retardation or required long-term anticonvulsant treatment.

Conclusion: Here we report one novel *SCN2A* mutation in a family with a classical BFNIS phenotype. The absence of *SCN2A* mutations in patients with other phenotypes confirms the specificity of *SCN2A* mutations for BFNIS.

040
ASSOCIATION BETWEEN THE SYNAPTIC VESICLE PROTEIN SV2A AND MESIAL TEMPORAL LOBE EPILEPSY

A. Heils and C. Elger (Clinic of Epileptology, University Clinic of Bonn, Germany)

Purpose: The novel antiepileptic drug levetiracetam confers its therapeutic effects by a binding interaction with the synaptic vesicle protein SV2a. The gene encoding SV2a therefore defines a novel candidate for genetically determined epilepsies. In this study we tested the hypothesis that genetic variation in SV2a is associated with increased susceptibility to mesial temporal lobe epilepsy (mTLE) in cases with familial risk.

Method: We resequenced the SV2a gene to search for a genetic variation. We tested these in two independent study samples comprising a total of 296 mTLE patients who report a family history of epilepsy with at least 1 affected first and/or second degree relative. Statistical analysis was done by chi-square statistics. A two-tailed type I error rate of 5% was chosen as the significance level.

Results: We identified a novel common polymorphism (IVS6-60G/A) which is significantly associated with mTLE at familial risk. Genotype, and allele frequencies showed an overrepresentation of the A-allele ($p = 0.0001$, $df = 1$, OR = 1.74) and the GA/AA genotypes ($p = .0003$, $df = 1$, OR = 1.78) among patients compared with 515 ethnically matched genomic controls.

Conclusion: Our data strongly suggest a role of SV2a in mTLE. The mechanisms by which the intronic polymorphism leads to this observation are still under investigation. It either confers functional properties or is in linkage disequilibrium with another as yet unidentified sequence variant.

041

NEW SUSCEPTIBILITY LOCUS AT 13Q13.2 FOR EPILEPSY-RELATED PHOTOSENSITIVITY IN A COMBINED EUROPEAN GENOMEWIDE LINKAGE SCAN

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Purpose: Photosensitivity or photoparoxysmal response (PPR) is an heritable EEG trait highly prevalent in idiopathic generalised epilepsies (IGEs). It is characterised by an abnormal cortical response to visual stimuli and can be evoked by standardised intermittent photic stimulation in the EEG laboratory. Given the strong association with IGEs, PPR can be regarded as a potential endophenotype for IGEs. Recently two independent genomewide scans on PPR identified four susceptibility loci in the chromosomal regions 7q32, 16p13 and 6p21, 13q31, varying on the familial background of epilepsy syndromes.

Method: To search for risk factors that are independent of familial epilepsy background we pooled genotype data from all 75 multiplex families and performed a combined nonparametric linkage (NPL) analysis. To account for genetic heterogeneity, family members were classified under a broad (all PPR types I-IV n = 205 affected) and a narrow (only PPR types III and IV; n = 106 affected) trait definition.

Results: We found evidence for a novel, shared locus on 13q13.2 at D13S1493 under broad ($P_{NPL} = 3.64 \times 10^{-4}$) and narrow ($P_{NPL} = 6.81 \times 10^{-5}$) trait definitions, achieving empirical genomewide significance for the narrow model ($P_{gw} = 0.0132$). Accentuated linkage under the narrow trait definition (generalised PPRs) suggests an increase in phenotypic homogeneity, emphasising the close genetic relationship between generalised PPRs (PPR types III and IV) and IGEs.

Conclusion: These findings suggest that the locus on 13q13.2 represent a common genetic component for visually induced and spontaneously occurring generalised spike and wave EEG discharges underlying generalised PPR in IGE patients.

042

FEBRILE SEIZURES AND IDIOPATHIC EPILEPSY: A CLINICAL AND GENETIC STUDY IN A FINNISH FAMILY

[1,2,4]A. Sirén, [3]A. Nuutila, [1]A. Anttonen, [4]S. Abboud, [2]M. Koivikko, [4]M. Pandolfo, and [1]A. Lehesjoki ([1]Neuroscience Center and Folkhalsan Institute of Genetics, University of Helsinki, Helsinki, Finland, [2]Department of Pediatrics, Tampere University Hospital, Tampere, Finland, [3]Department of Pediatrics, Central Hospital of South Oestrobothnia, Seinäjoki, Finland, [4]Department of Neurology, Erasme Hospital, Brussels, Belgium)

Purpose: We describe a three-generation family with febrile seizures (FS), childhood absence epilepsy (CAE) and generalised epilepsy with focal abnormalities in EEG. We report the results of a genome-wide scan.

Method: Detailed clinical description of FS and epilepsy was collected from medical files and by interviewing patients and their parents during a field trip. DNA was extracted from venous blood with standard methods. The genome-wide scan was carried out in the Finnish Genome Center with 382 microsatellite markers using an ABI 3730 capillary sequencer. Two-point lod scores were calculated with the MLINK programme assuming autosomal dominant inheritance with reduced penetrance.

Results: Out of 9 affected individuals 4 had experienced one to four common FS between the ages of 1 and 4.5 years. Three patients had CAE; 1 also had one preceding FS. One boy, on two occasions, had a seizure starting with an absence and evolving to a generalised tonic–clonic seizure. He had an EEG with 3 Hz spike-wave discharges and focal abnormality in the right mid-temporal region. One boy had status epilepticus once and no other seizures. MLINK analysis of the genome-wide data revealed the highest lod score of 1.76 at two markers: D2S305 and D16S423.

Conclusion: Several individuals in the family are affected with FS or epilepsy. Initial analysis of the genome scan data did not reveal a single locus when autosomal dominant inheritance was assumed. Fine mapping combined with linkage analysis using different inheritance patterns is needed to identify a putative major epilepsy susceptibility locus in this family.

Tuesday July 4, 2006
12:00–13:30
Hall 1
Platform Session
Drug Therapy II

043

COMPETING RISKS OF ANTIEPILEPTIC DRUG FAILURE: IMPORTANCE, MEASUREMENT AND ANALYSIS

[1]P. Williamson, [1]C. Tudur Smith, [2]J. Sander, and [1]A. Marson ([1]University of Liverpool, Liverpool, UK [2]University College London, UK)

Purpose: Retention time (time to treatment failure) is a commonly used outcome in antiepileptic drug studies. In this paper we present the issues involved and demonstrate the importance of a full investigation of this outcome.

Method: Fifteen antiepileptic drug monotherapy trials and an add-on therapy clinic cohort are used to illustrate both design and analysis issues. Cumulative incidence analysis is described and applied to a dataset comparing lamotrigine and topiramate. The results are compared to the more common approach using standard survival analysis methods.

Results: A nonsignificant difference in overall retention between lamotrigine and topiramate (logrank test statistic = 2.58, 1 degree of freedom, $p = 0.108$) masked highly significant differences in opposite directions between the drugs with respect to withdrawals due to side effects (Gray's test statistic = 12.26, 1 degree of freedom, $p = 0.0005$) and poor seizure control (Gray's test statistic = 34.58, 1 degree of freedom, $p < 0.0001$).

Conclusion: Retention time can be measured reliably but care is needed to collect sufficient information on reasons for drug withdrawal to allow a competing risks analysis. Important differences between the profiles of antiepileptic drugs may be missed unless appropriate statistical methods are used to fully investigate retention time. Cumulative incidence rather than logrank analysis is likely to be a more powerful approach for comparison of standard and new antiepileptic drugs.

044

MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL INVESTIGATING SAFETY, TOLERABILITY AND PHARMACOKINETICS OF INTRAVENOUS SPM 927 IN SUBJECTS WITH PARTIAL SEIZURES

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[5]Schwarz Biosciences, Inc., RTP, USA, [6]Schwarz Biosciences, GmbH., Monheim, Germany, [7]Schwarz Biosciences, Inc., RTP, USA)

Purpose: SP616 was a double-blind, double-dummy investigation of the pharmacokinetics, safety and tolerability of intravenous (iv) lacosamide (LCM) as a replacement of adjunctive oral LCM in adults with partial-onset seizures.

Method: Subjects (n = 60) currently receiving adjunctive, stable, twice daily (bid) doses (200 to 600 mg/day) of oral LCM were randomised 2:1 to receive iv LCM plus oral placebo (PBO) bid or iv PBO plus oral LCM bid for two consecutive days. Subjects (n = 30) in Cohort A received 60-minute infusions. Cohort B subjects (n = 30) received 30-minute infusions. Serial ECGs and vital signs data were collected. Pharmacokinetic sampling was performed for the morning dose on day 2 for both cohorts at predose and hours 0.5, 1, 1.5, 2, 4, 8, and 12.

Results: Fifty-nine subjects completed the trial. No clear differences in AE reports, ECG intervals, blood pressure, or heart rate were observed for iv versus oral dosing.

60- and 30-minute LCM infusions resulted in similar plasma concentration time curves and pharmacokinetic parameters compared with oral administration after normalisation for body weight and dose. The t_{max} most commonly occurred at the end of LCM infusion (eg, 30 min for Group B) and later for oral LCM dosing (eg, 1.5 to 4 hr for 55% of subjects in Group B).

Conclusion: The safety profile following 60- and 30-minute LCM infusions was comparable to oral LCM. In addition, both LCM infusion rates resulted in similar pharmacokinetics to oral dosing. Funding supported by: Schwarz Biosciences, Inc.

045

INCREASED APPARENT ORAL CLEARANCE OF VALPROIC ACID DURING INTAKE OF COMBINED CONTRACEPTIVE STEROIDS IN WOMEN WITH EPILEPSY

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Purpose: Combined contraceptive steroids (CS) stimulate the glucuronidation of paracetamol, some benzodiazepines, and lamotrigine. As a result of this, the serum levels of lamotrigine are considerably higher at the end of a 7-day CS-free interval than during CS intake (*Epilepsia* 2004;45(suppl 7:330). Valproic acid (VPA) undergoes extensive glucuronide conjugation, and a case report suggested that VPA clearance is also increased by CS (*Epilepsia* 2005;46:970–1). We assessed serum VPA concentration in women with epilepsy in relation to a CS intake cycle.

Method: Nine women aged 18–45 years and stabilised on VPA (500–1500 mg/day) in combination with oral or transdermal CS, without associated antiepileptic drugs, were assessed on two randomised occasions: (i) on the last day of CS intake, and (ii) on day 4 to 7 of the CS-free interval. Serum VPA levels were determined by immunoassay.

Results: Mean total VPA concentrations were 21% higher during the CS-free interval than during CS intake (425 ± 184 vs 350 ± 145 (μmol/L respectively, means $\pm$ SD, $p = 0.002$). Unbound, pharmacologically active, VPA levels increased in parallel by 41%, from 39 ± 25 to 55 ± 37 (μmol/L ($p = 0.005$).

Conclusion: Serum VPA concentrations increase during the interval of interruption of CS intake. This is consistent with a stimulating effect of CS on the enzymes responsible for VPA metabolism, presumably due to induction of glucuronosyltransferases by ethinyloestradiol. The magnitude of interaction varies across patients, and may be clinically significant in some cases.

046

PROPHYLACTIC EFFECT OF FOLIC ACID SUPPLEMENTATION ON SPONTANEOUS ABORTION IN WOMEN WITH EPILEPSY UNDERGOING ANTIEPILEPTIC THERAPY

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Purpose: Antiepileptic drugs (AEDs) like phenytoin (PHT), carbamazepine (CBZ), barbiturates and valproic acid (VPA) interfere with folic acid absorption and metabolism, and consequently can elevate risk for adverse pregnancy outcome. Our objective was to study the prophylactic effect of folic acid supplementation with regard to spontaneous abortion in pregnant women receiving AED therapy and compare benefits of most common dosage and pre- and postconceptional commencement.

Method: Retrospective analysis of data from our epilepsy data bank completed with medical records and patients interviews and in some cases prospective examination of 388 pregnancies in 244 patients of the Department of Neurology of Innsbruck University Hospital from 1971 to 2004.

Results: Pregnancies with folic acid supplementation showed a significantly reduced rate of spontaneous abortions. In women without folic acid supplementation spontaneous abortion occurred in 14.5% compared to 6.3% when folic acid had been taken during pregnancy (odds ratio:2.6, 95% CI:1.2–5.3, $p = 0.007$). Supplementation with 5 mg/d had no advantage over 0.4 mg/d. Preconception commencement of supplementation showed no larger benefit. Folate benefits were higher in pregnancies under AED monotherapy than under polytherapy. With regard to monotherapies, only women in the group taking VPA supplementation had a significant benefit. Other examined monotherapies (CBZ, PHT, PB, LTG, and OXC) showed no significant results.

Conclusion: This study confirms the prophylactic effect of folic acid supplementation on spontaneous abortion. Data did not show clear advantage for dosage of 5 mg/day or preconception commencement, but underlined the particular profit for women under AED monotherapy, especially for those who are taking VPA.

047

DRUG INTERACTION BETWEEN PHENPROCOUMON AND VALPROATE: CLINICALLY RELEVANT INCREASE OF INR IN PATIENTS WITH ISCHEMIC STROKE AND SYMPTOMATIC SEIZURES

B. Tettenborn, A. Felbecker, and B. Weder (Dept. of Neurology, Kantonsspital St. Gallen, Switzerland)

Purpose: Cotreatment with the oral anticoagulant phenprocoumon and valproate is common, especially in patients suffering from cardioembolic stroke and symptomatic seizures. There are no reports of clinically relevant interactions between these drugs.

Method: We reviewed the data of all patients of our neurological department within the last 38 months. Two groups of patients were identified: group 1 was treated with valproate in addition to established phenprocoumon therapy, whereas in group 2 phenprocoumon was started either at the same time or in addition to valproate. For group 1, the latest available International Normalized Ratio (INR) values were achieved, mean values calculated and correlated to the maximum INR values shortly after the initiation of valproate. Patients were excluded if the dosage of the drugs during the relevant time was unknown or compliance was insufficient.

Results: 18 patients received a combined treatment with valproate and phenprocoumon. Three patients met exclusion criteria, the remaining patients were divided into group 1 (11 patients) and group 2 (4 patients). Means of INR values in group 1 before treatment with valproate ranged between 1.6 and 3.2 (SD 0.05–1.22) and raised significantly after initiation of valproate (mean +77%, range from +45 to +138%). In group 2, the intended INR values were achieved with unexpectedly low doses of phenprocoumon.

Conclusion: There is a clinically relevant interaction between valproate and phenprocoumon. Patients on valproate need unusually low doses of phenprocoumon for active anticoagulation. In patients receiving valproate with preexisting phenprocoumon a potentially hazardous rise of INR has to be observed.

048

fMRI REVEALS DECLINED PREFRONTAL CORTEX ACTIVATION IN EPILEPSY PATIENTS ON TOPIRAMATE THERAPY

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Purpose: Topiramate treatment for patients with epilepsy is frequently associated with cognitive side effects, which can be the major reason for drug discontinuation, even when the drug has a favourable effect on seizure frequency. In this study, the functional neuroanatomy of language was visualised in patients with epilepsy on topiramate therapy.

Method: A group of 5 patients with epilepsy on topiramate therapy, and a control group of 10 epilepsy patients, not on topiramate therapy, were examined using neuropsychological testing and functional magnetic resonance imaging of covert word generation, to examine brain activation abnormalities associated with topiramate-induced cognitive impairment.

Results: The control epilepsy patients showed a typical distribution of language-activation involving the left inferior prefrontal cortex (IPC) and the medial prefrontal cortex (MPC), whereas the patients on topiramate therapy showed significantly less activation in these language-mediating cortical regions ($p = 0.01$) together with significantly lower neuropsychological language scores ($p = 0.002$). Furthermore, the IPC and MPC display a higher relat;oive sensitivity to TPM treatment than other brain regions.

Conclusion: These findings suggest that topiramate has a critical effect on the cerebral neural systems that mediate expressive language.

Tuesday July 4, 2006
12:00–13:30
Hall 5A
Platform Session
Adult Epileptology II

049

NEGATIVE MYOCLONUS NOT ATAXIA IS THE MAIN REASON FOR LOCOMOTION DISABILITY IN PATIENTS SUFFERING FROM UNVERRICHT-LUNDBORG DISEASE

H. Vogt, T. Baisch, and I. Mothersill (Swiss Epilepsy Center, Zurich, Switzerland)

Purpose: Unverricht-Lundborg disease or EPM1 is one type of the progressive myoclonus epilepsies. It is generally accepted that locomotion disablement is due to cerebellar ataxia. We observed that in the course of the disease negative myoclonias are one of the most striking symptoms and hypothesised that they were the main reason for locomotor disability.

Method: Negative myoclonias are very difficult to recognise without ictal polygraphic recordings in freely moving patients. We performed ictal polygraphic video-EEG-recordings (16 channel EEG, 8 channel surface EMG) in 14 patients with EPM1 (Unverricht-Lundborg Disease), all proven by mutation of the CSTB Gene. Two or more recordings were performed in 9 EPM1 patients with a mean interval of 12 years.

Results: All 14 patients had documented negative myoclonias in their polygraphic recordings when standing or walking. The duration of the atonia was between 100 and 200 ms. Except 4 patients with EPM1 all where wheelchair bound after a mean disease duration of 19 (10–31) years, mainly due to fear of falls, caused by the frequent negative myoclonias.

Conclusion: We have shown, using simultaneous EEG/EMG recordings in freely moving patients, that the locomotor disability is in fact mainly due to negative myoclonus in voluntary innervated muscles.

050

EPILEPSY AND DRIVING: REPORT OF A EUROPEAN WORKING GROUP

E. Schmedding, G. Wetherall, E. Beghi, J. Burcet Darde, B. Gappmaier, J. Kirker, G. Kraemer, M. Ojala, A. Sundqvist, E. Valdès, H. Vespigniani, and J. Worm-Petersen (Second Working Group on Epilepsy and Driving to the Driving Licence Committee of the European Union)

Purpose: Following an earlier workshop, organised by the ILAE/IBE in 1995/1996, national legislation was adapted to an important degree in several European countries, but remained unchanged in others. This situation led to a renewed call for harmonisation and the installation of the working group on epilepsy and driving by the Driving Licence Committee of the European Union. Later, some members of the ILAE and the IBE were added to the working group. The purpose was to give an overview of the literature and to devise recommendations for European Law in the hope of harmonising regulations all over Europe.

Method: In order to do so, we had to find a criterion for acceptable risk, find the temporal relationship between the period of seizure-freedom and risk decrease in different situations and link this risk to the period of seizure-freedom via a general theory of risk. The risk for the population (attributable risk) is low, theoretically and on calculation. The criterion for acceptable relative risk should mainly be decided on the basis of the risk for the driver. In comparison with other accepted risk variations in the population (e.g. relative risk [RR] for someone older than 75 years of age is 3 or higher) the criterion for individual risk was expressed as a RR of 2 to 3 and used to set the duration of seizure-free periods in different epileptological situations (first seizure, epilepsy, etc). Where data were scant, consensus was applied. Attention was given to the existing regulations in Member States.

Results: The criteria, thus devised are internally consistent. They are conceived as minimum criteria, because the national legislation of the Member States can be more strict, but not more lenient.

Conclusion: New medical criteria for driving and epilepsy were devised for use in the European Union. A short review of the procedure and the resulting criteria will be given and problems addressed.

051

TREATMENT OF STATUS EPILEPTICUS: A RETROSPECTIVE ANALYSIS

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Purpose: Status epilepticus (SE) is a neurological emergency. So far, IV benzodiazepines and phenytoin are recommended as the first-line antiepileptic drugs for SE. IV valproate is widely used, but RCTs comparing PHE and VPA are not available. This study aimed to investigate the overall success rates with various AEDs in a large series of 248 patients.

Method: Retrospective analysis of all patients with SE, admitted to a university medical centre serving as the only neurology and emergency department in that area, between 2001 and 2004. SE was defined as repetitive or ongoing epileptic seizures lasting at least 10 minutes. Coma with severe hypoxic or traumatic brain injury and "status-like EEG patterns" was not included in this series. Clinical variables (type, duration and aetiology of SE) as well as AED treatment were noted. Responsiveness to AED treatment, adverse events and neurological outcome was assessed by chart review.

Results: 248 pts (110w/138m) with SE were analysed (mean age 56yrs, sd23, range 1–94). SE was convulsive in 194 (78%, (69 focal motor, 125 GTC-SE) and nonconvulsive in 54 (22%). Preexisting epilepsy was found in 50% (43% focal, 7% generalised). Aetiology was acute symptomatic in 46%, cryptogenic in 4%. Overall SE was stopped in 92% [95% CI 89–95.6]. Success rates were 56% [95% CI 49.5–61.8] with the 1st drug, 19% [95% CI 13.7–23.4] with the 2nd and 10% [95% CI 6.7–14.3] with the 3rd AED. IV VPA was used in 72 (29%) pts. Success rates with VPA were 69% [95% CI55.4–82.4], with BDZ 63% [95% CI56.2–70], with PHE 51% [95% CI36.8–65.4], with barbiturates 77%

[95% CI64.5–88.7] and with TPM 62% [95% CI29–96]. VPA induced encephalopathy occurred in 2 (3%) pts.

Conclusion: VPA is well tolerated in the management of SE. Success rates are comparable to BDZ and PHE, however, large RCTs are needed to detect differences between the treatment options.

052

LAFORA DISEASE: A GENETIC AND PHENOTYPIC STUDY OF A LARGE CASE SERIES

C. Gomez Abad, P. Gómez-Garre, E. Gutiérrez-Delicado, and J. Serratosa (Fundación Jiménez Díaz, Madrid, Spain)

Purpose: To perform a clinical and genetic study of a large series of Lafora disease patients.

Method: We performed a clinical and mutational analysis of 104 patients, belonging to 82 unrelated families, with a clinical diagnosis of Lafora disease. Statistical analysis was performed using SPSS software for Windows (version 11.5).

Results: A similar male/female ratio was found. Progression from age at onset to complete deterioration of mental status was shorter in males. Brain MR was available in 37 cases: in 34 cases it was normal and in 3 cerebellar atrophy was observed. Photosensitivity was present in 27 out of 36 patients tested. Age at onset ranged from 4 to 22 years and progression of the disease from 5 to 9 years. We identified 72 different mutations in *EPM2A* and *EPM2B*. The R241X in *EPM2A* is the predominant mutation. In patients with *EPM2B* mutations time of progression of the disease is increased, and age at which patients die and onset of gait disturbance occur several years later. Simple partial occipital seizures are more common in *EPM2A* patients.

Conclusion: A slightly milder clinical course associated with *EPM2B* mutations is confirmed. Males present a shorter progression from age at onset to complete deterioration of mental status. Photosensitivity and normal brain MRs are common in Lafora disease.

053

EYELID POSITIONS DURING EPILEPTIC VERSUS PSYCHOGENIC SEIZURES

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Purpose: Aim of this study was to evaluate whether the position of the eyelids (open or closed) helps to differentiate epileptic versus psychogenic seizures.

Method: Forty adults with epileptic seizures (20 with frontal, 20 with temporal epilepsy) and 40 patients with psychogenic seizures were included in the study. We analysed retrospectively by video analysis the position of the eyelids before the clinical beginning of the seizure and during the first 30 seconds after seizure onset. A multivariate variance analysis was performed using the duration of open eyes within the analysis time window after seizure onset as the dependent variable (ranked values). Seizure type (temporal, frontal, psychogenic), gender (male, female) and eyelid position before seizure onset (opened, closed) constituted the independent variables.

Results: A highly significant effect of seizure type was found indicating that eyelids were closed significantly longer ($p < .001$) within the first 30 seconds of psychogenic seizures (20.85s, 69.5% of the time), compared to epileptic seizures of temporal (1.95s, 6.5%) or frontal (9.25s, 30.8%) origin. This difference was more pronounced in male patients with psychogenic seizures yielding a significant interaction between seizure type and gender. In addition, a significant interaction between seizure type and eyelid position before seizure onset indicated that eyes were mostly kept closed after onset of psychogenic seizures whereas eyes were opened early in epileptic seizures.

Conclusion: Our results suggest that keeping the eyes closed or closing them within the first 30 seconds after seizure onset is highly suggestive of a psychogenic nature of a seizure.

054

CAUSES OF LATE SEIZURE RECURRENCE IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY AFTER A LONG PERIOD OF REMISSION

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Purpose: To determine causes of late seizure recurrence in patients with juvenile myoclonic epilepsy (JME) after a long period of remission.

Method: From approximately 2500 patients from our epilepsy clinic, we retrospectively identified 105 patients (female 62, mean age 19.8 ± 7.7 years) with established diagnosis of JME. All patients were treated with antiepileptic drugs (AED) and during a period of at least 1 year, no seizure of any type occurred.

Results: Median period of follow-up was 4 (range 1–17) years. Therapy included valproate in 87.6% of patients (median dose 500 mg, range 250–2750 mg), lamotrigine, benzodiazepines, topiramate or combinations. Seizures of any type recurred in 76 patients (72.4%) after median time of 1 (0.5–17) year. Twenty-five patients (32.9%) presented with myoclonic jerks after 1 (0.58) year, 13 (17.1%) with generalised tonic–clonic (GTC) seizures after 2 (0.5–12) years, and 38 (50%) with the combination of both seizure types. The majority of patients had a single seizure as a recurrence (84.8%), while a series of seizures (13.9%) or prolonged deterioration of seizure control (1.4%) occurred rarely. Cause of seizure recurrence was not obvious in the majority of patients. However, it was associated with sleep deprivation in 46% and AED withdrawal in 15.9% of patients, and less frequently, with alcohol or drug abuse, photic stimulation, or menses. No causative or provoking factors were identified in 31.8% of patients.

Conclusion: Late recurrences of seizures (mainly of GTC type), after a long period of remission are not rare in patients with JME despite best-known therapy. Seizures are probably provoked by sleep deprivation or some other poorly recognised factors.

Tuesday July 4, 2006
12:00–13:30
Hall 5B
Platform Session
Epilepsy Surgery II

055

SURGICAL TREATMENT OF PARIETAL LOBE EPILEPSY

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Purpose: Surgical treatment and outcome of parietal lobe epilepsy (PLE) is poorly understood. The aim of this study was to analyse presurgical characteristics, pathologic basis, surgical procedures and postoperative outcome in a large group of PLE patients.

Method: A prospective database containing all patients undergoing epilepsy surgery at the University of Bonn since 1990 was screened for PLE. Charts, preoperative MRI, surgical reports, and neuropathological findings were reviewed. Seizure outcome was classified according to Engel's score (I–IV).

Results: Forty-one patients with PLE were identified. Twelve patients had a history complicated by trauma, meningitis/encephalitis or preterm birth. Preoperative MRI abnormalities were identified in 98%. Lesionectomy of the dominant ($n = 20$) or nondominant ($n = 21$) parietal lobe and additional MST of the motor cortex ($n = 11$) was performed. Two patients suffered from surgical and 10 from neurological complications, including temporary partial Gerstmann syndrome in most cases ($n = 8$). There was no mortality. Histopathology revealed 17 low grade tumours, 13 cortical dysplasias, 2 cavernous vascular malformations, 7 gliotic scars and 2 others. After a mean follow-up of 43 months, 27 patients (66%) became seizure-free or had rare seizures (Engel I: 56%; Engel II: 10%; Engel III: 29%; Engel IV: 5%). Of the 12 patients with an

unsatisfactory outcome (Engel class III/IV), 9 (75%) had a complicated history.

Conclusion: PLE is rare but can be safely and effectively treated surgically. A temporary partial Gerstmann syndrome occurs postoperatively in a significant proportion of patients. Complicating factors in the history such as trauma or infection portend a poor prognosis for postoperative seizure outcome.

056

EPILEPSY SURGERY IN THE POSTERIOR PART OF THE BRAIN: DIAGNOSTIC PROCEDURES AND SURGICAL OUTCOME

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Purpose: Surgical treatment for epilepsies localised in the posterior cortex is performed with increasing frequency, nonetheless literature data are less numerous than in other cerebral localisations. The purpose of this study is to report our experience with a series of 91 patients operated on in our Centre from May 1996 to October 2004 in the parietooccipito-temporal region.

Method: The studied patients were 53 males and 38 females with: mean age at surgery 24.8 ± 13 years (1–54), mean epilepsy onset 6.9 ± 5.2 years (birth–26), mean epilepsy duration 17.9 ± 11.6 years (1–46). Seizures were several per month in 13 cases (14.3%), per week in 40 (43.9%) per day in 38 (41.8%). Neurological examination was abnormal in 33 patients (36.2%). MRI was negative in 14 cases (15.4%) and positive in 77 (84.6%). Presurgical diagnostic work-up included video-EEG monitoring in 75 patients and stereo-EEG recordings in 69.

Results: Surgery was limited to parietal lobe in 30 cases (32.9%), and occipital lobe in 5 (5.5%), being multilobar in 56 (61.6%). Neuropathology accounted for dysplastic lesions in 43 cases, neoplastic in 28, scars in 8 and ulegyria in 4, resulting cryptogenic in 8 patients. After a mean follow-up of 49.6 ± 25.1 months, 57 patients are in Engel's Class I (62.6%), 15 in class II (16.5%), 5 in class III (5.5%) and 14 in class IV (15.4%).

Conclusion: Our series shows that epilepsy surgery in the posterior brain: is not episodically performed (17.7% of the 514 patients operated on during the same period), often requires invasive recordings (75.8%), frequently is multilobar (61.6%), and allows the achievement of good post-operative results.

057

HETEROTOPIA: NEUROPATHOLOGICAL STUDY OF PATIENTS OPERATED FOR DRUG RESISTANT EPILEPSY

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Purpose: To describe the neuropathological characteristics of different types of heterotopia in patients operated on for drug-resistant epilepsy.

Method: 24 patients out of 583, operated on for intractable epilepsy from June 1996 to December 2005 at the "C. Munari" Epilepsy Surgery Centre, were selected on the basis of MRI and neuropathological diagnosis presenting different types of heterotopia. Specimens were evaluated by routine neuropathological methods and immunocytochemistry.

Results: According to current classification, 4 cases were classified as laminar heterotopia (LH) and 20 as nodular heterotopia (NH). Among the patients with NH, 13 had MRI characteristics of periventricular nodular heterotopia (PNH); in 2 of them PNH was associated with complex cortical malformations. Isolated nodules were observed in 7 patients. Within this group, nodules were associated with other lesions in 6 patients. Architectural dysplasia (type 1A) was present in the overlying cortex in 1 case of LH and 12 cases of PNH. Microscopic organisation was different in PNH and isolated nodules. LH was organised as a ribbon of unlayered grey matter; numerous isolated neurons were present between the cortex and LH. Follow up of at least 12 months was available for all patients and 80% are in class I.

Conclusion: Neuropathological and immunocytochemical data show that the intrinsic organisation of nodules are different in PNH and in isolated nodules. PNH are frequently associated with dysplasia of the overlaying cortex. Good clinical outcome is expected particularly for patients with unilateral PNH and for those with isolated nodules associated with other lesions.

058

PERICOLLATERAL CORTICAL DYSPLASIA: AETIOLOGY FOR REFRACTORY TEMPORAL LOBE EPILEPSY

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Purpose: Cortical dysplasia is an important aetiology of refractory epilepsy, especially in the paediatric population. We describe a distinct type of focal cortical dysplasia which is centered on the collateral fissure and associated to refractory temporal lobe epilepsy.

Method: Five patients with refractory temporal lobe epilepsy were studied. Age ranged from 3 to 25 years (mean = 18 years), age at the beginning of seizures from 2 to 14 years (mean = 8 years) and seizure frequency from 3 to 10/week (mean = 5 seizures/week). All patients had simple (vegetative in 4 and cephalic in one) and complex partial seizures. Interictal EEG showed unilateral temporal lobe spiking in 4 and bilateral discharges in 1 patient. No patient was submitted to video-EEG monitoring. MRI disclosed dysplastic lesions in all patients. These lesions were spread around the collateral fissure, occupying both the parahippocampal and fusiform gyri. In 4 patients, imaging findings suggestive of ipsolateral mesial temporal sclerosis were also noted. In 1 patient, the hippocampus looked normal (visual analysis). All patients were submitted to a cortico-amygdalo-hippocampectomy at the side of the MRI-defined lesion.

Results: All patients were rendered seizure-free after surgery. Pathological examination showed cortical dysplasia and mesial temporal sclerosis in all patients, including the patient with a normal looking hippocampus on MRI.

Conclusion: Pericollateral cortical dysplasia seems to be a very specific aetiology of refractory temporal lobe epilepsy with many features of classical mesial temporal epilepsy. It is usually associated to mesial temporal sclerosis and surgical outcome is probably similar (or better) to that obtained in patients with mesial temporal sclerosis alone.

059

PRESURGICAL DIFFERENTIATION BETWEEN FOCAL CORTICAL DYSPLASIAS TYPE I AND II

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Purpose: Focal cortical dysplasia (FCD) is being recognised as a frequent cause of epilepsy in childhood. It is pathologically noted in about 50% of the children operated on because of drug resistant seizures. According to the current classification, two major pathological subtypes (FCD type I and II) are distinguished. The study was undertaken in order to find clinical, EEG, imaging and surgical outcome differences between the two groups.

Method: We retrospectively analysed a series of 40 children with FCD who had been investigated at the Behandlungszenstrum Vogtareuth, Germany. FCD type I was histologically proven in 24 patients and FCD type II in 16 patients.

Results: Perinatal adverse events as well as different CNS comorbidity were more commonly encountered in FCD I group. Children with FCD type I had lower intelligence quotient scores, worse maladaptive behaviour level scores and more frequent social/emotional behaviour disturbances. Continuous EEG slowing was also more common among FCD I patients. Typical MRI findings in FCD type II were increased cortical thickness, grey-white matter junction blurring, FLAIR and PD grey matter signal changes and T1w and PD white matter signal changes. The MRI pathology more typical for FCD type I was regional reduction of the white matter volume. Surgical outcomes were significantly worse in FCD I group (Engel I outcome had 73% of patients from FCD II group but only 22% from FCD I group).

Conclusion: Clinically important differences, which can be of a key value in the management of patients, were found between patients with different pathological FCD subtypes. Supported by Grant IGA NR/8843–4.

060

DIRECT COSTS IN EPILEPSY SURGERY

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Purpose: Approximately 20% of all epilepsy patients are drug resistant and may benefit from surgical treatment. Direct treatment costs and quality of life (QOL) are measured both retrospectively and prospectively for Finnish patients with epilepsy who are evaluated for surgical treatment.

Method: Group I contains 141 adult TLE-epilepsy patients from KUH operated from 1988–1999 and 118 children, adolescents and adults from HUCH operated from 1991–2002. Patients have been enrolled to prospective group II from April 2004 including all patients referred for surgical evaluation. Until January 2006, over 70 prospective patients have been enrolled. Direct treatment costs from treatments related to epilepsy in primary and special health care (outpatient visits and hospital admissions) are taken into the cost-effectiveness analysis (CE). Count-period covers at least 2 years before and 2 years after surgery. QOL–score is measured three times with 15D and disease specific QOLIE-31 instrument; before, 6 months and 1 year after epilepsy surgery in patient group II, and at once in group I.

Results: Preliminary cost estimation in the retrospective research groups suggests significant decrease in postsurgical costs, especially in outpatient visits, of both children and adults. Results are based to the evaluation of patient data. Final calculations will have HILMO (the Finnish register for treatment announcements) data, which may change results.

Conclusion: Good outcome in epilepsy surgery may predict positive changes in several dimensions, including direct treatment costs and QOL-values. Surgical therapy is a cost-effective treatment even without indirect costs being taken into consideration.

Tuesday July 4, 2006
12:00–13:30
Hall 5c
Platform Session
Paediatric Epileptology II: Paediatric Epilepsy

061

PROGNOSIS FOLLOWING CLINICAL NEONATAL SEIZURES: RESULTS FROM A POPULATION-BASED COHORT 14 YEARS LATER

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Purpose: To prospectively evaluate survival and neurodevelopmental outcome following neonatal seizures (NSz). Most recent population based data are from 1959–1962 and may not be generalisable to current neonatal populations.

Method: We collected prospective data on all neonates (<44 weeks gestation) with clinical NSz (= paroxysmal behaviours with high specificity for "epileptic" seizures) from 1990–1995, targeting all live births in Newfoundland. Uniform video assisted training for standardised seizure recognition preceded the study (*J Pediatr* 1999;134:71). Follow-up data were analysed 10–14 years later.

Results: Data were analysed for 87/90 children (61 term and 26 preterm). At follow-up 30 children (34%) were considered to be functioning normally (including 44% of the term infants and 12% of the preterm group). 21 children (24%) had died (including16% of term infants and 42% of preterm children). Disabilities were apparent in 36 (41%) (of whom 24 (39%) were term infants and 12 (46%) were preterm). Among the 66 survivors, 17/65 (26%) still had epilepsy, 15/66 (23%) had cerebral palsy, 13/65 (20%) were intellectually retarded, and 16/65 (25%) were considered to have learning disabilities. Details of the probable aetiologies of the seizure problems have been identified and will be provided in the full presentation.

Conclusion: Preterm infants with seizures are at higher risk for death and impairment compared to term infants. The 12% normal outcome for preterm is lower than in most studies, possibly reflecting their outborn nature. The lower frequency of normal outcome compared to 47% from 1959–1962 may primarily be due to reduction in hypocalcemic seizures. Cognitive deficits are present in 45% of survivors.

062

IRRITATIVE ZONE IN PAEDIATRIC FOCAL EPILEPSIES ANALYSED BY 3-TESLA EEG-fMRI RECORDINGS AND EEG MULTIPLE SOURCE ANALYSIS

[1]R. Boor, [2]J. Jacobs, [3]S. Wolff, [2]U. Stephani, and [2]M. Siniatchkin ([1]North German Epilepsy Centre for Children and Juveniles, Kiel-Raisdorf, Germany, [2]Department of Pediatric Neurology, University-Children's Hospital Kiel, Germany, [3]Department of Neuroradiology, University Hospital Kiel, Germany)

Purpose: EEG-related fMRI (EEG-fMRI) and EEG multiple source analysis (MSA) are promising functional neuroimaging techniques to analyse the irritative zone in focal epilepsies noninvasively. However, there is scarce functional neuroimaging data studying the irritative network in paediatric focal epilepsies. The present study applies the combined EEG-fMRI and MSA techniques to paediatric focal epilepsies and subdivides the irritative zone noninvasively by discriminating the spike onset zone from propagated source activity.

Method: Six children with focal epilepsies were studied by simultaneous recordings of EEG (Brain Vision@ MR-compatible EEG amplifier, 32 channels, 20 min. recording time) and fMRI (3-T Achieva Philips scanner, TE = 64 ms, TR = 1240 ms, 24 × 24 matrics, 250 scans) during medically induced sleep. After EEG artifact reduction, the event (= spike)-related design was used to analyse the BOLD responses (SPM-2, standard HRF), which were co-registered to T_1-weighted anatomical images. Additionally, interictal EEG spikes were averaged and localised using MSA (BESA 2000), and source locations were displayed in the anatomical 3D-MRI.

Results: In all cases the BOLD responses corresponded to the EEG localisation of the interictal discharges. Using the combination of EEG-fMRI and MSA we were able to discriminate the spike onset zone from propagated source activity.

Conclusion: The irritative zone in children with focal epilepsies can be successfully studied by EEG-fMRI recordings in 3-T scanners. The results of EEG-fMRI and MSA can be combined to distinguish the spike onset zone from propagated activity, using the spatial resolution of the EEG-fMRI technique and the temporal resolution of the MSA.

063

LANGUAGE LATERALISATION IN CHILDREN WITH LEFT HEMISPHERAL EPILEPTOGENIC LESIONS OF PRE- OR POSTNATAL ORIGIN: A fMRI STUDY

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Purpose: The aim of the study was to assess the correlation of language lateralisation with the time of lesion formation, age at onset and duration of epilepsy in children with left hemispheral epileptogenic lesions.

Method: We studied 34 children and adolescents from 7 to18 years of age (mean 13 years) suffering from epilepsy due to left hemispheral lesion of pre- (n = 18) or postnatal (n = 16) origin. All the patients except 3 were right-handed. Hemispheric dominance for language was evaluated by fMRI using a silent word generation paradigm for all patients.

Results: Significant coactivation of the right hemisphere was present in 11 patients (32%); a complete language shift to this hemisphere was detected in the other 4 subjects (11.8%). The average age of these 15 patients was 12.9 years with the mean age at epilepsy onset 5.7 years and epilepsy duration 7.2 years. Only 5 (33.3%) had a prenatal aetiology of epilepsy. However, 3 out of 4 patients with a complete shift were those with a prenatal aetiology. Nineteen children (55.9%), including 3 left-handed individuals, exhibited pronounced left-hemispheric language dominance. They averaged 13.3 years of age; their epilepsy started at the age of 9.2 years and lasted for 4.2 years. Thirteen of them (68%) had a prenatal lesion.

Conclusion: Language dominance shift was significantly more frequent in children with epilepsy manifestation before the age of 6 years and a persistence of seizures of more than 4 years. Surprisingly, prenatal lesions had a lesser tendency to alter localisation of cortical language centres than those of postnatal origin. However, language shift caused by prenatal lesions, when such a shift occurs, tends to be more complete. The study was supported by grant IGA MZ CR NR/7808-3 OK 06.

064

INTRACTABLE EPILEPSY IN CHILDHOOD OWING TO DNET

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Purpose: Dysembryoplastic neuroepithelial tumour (DNET) is recognised as one of the most frequent reasons for medically intractable epilepsy. Patients with DNET present with partial onset refractory seizures following normal development.

Method: Children who underwent surgery for epilepsy from 1994–2005 at Hacettepe University Children's Hospital were analysed and 42 were diagnosed with DNET. We reviewed the charts retrospectively for age at the time of surgery, age at seizure onset, presenting features, location, EEG, MRI, surgical and adjuvant treatment, and seizure outcome.

Results: Male/female ratio was 17/25. Age at the time of evaluation ranged between 5–25 years, age at seizure onset ranged between 7 months–17 years, age at the time of surgery ranged between 4–24 years. 33 patients (78.5%) had complex partial seizures and 9 had simple partial seizures. Follow-up duration was 6 months–6.5 years. In 12 patients interictal EEG before surgery showed no epileptiform discharges. In 27 patients EEG showed lateralising epileptiform discharges with the lesion on MRI. In 3 patients EEG showed localising features. MRI showed a temporal lesion in 31 (73%) patients, and extratemporal in the remaining 11 patients. Three patients had a recurrence of seizures after surgery and underwent a second operation to remove the residual mass. Forty patients had Class IA and 2 had Class IB outcome.

Conclusion: The aim of epilepsy surgery in children with medically intractable partial seizures is to control seizures, and thus improve learning and behaviour. Complete resection of the lesion is necessary for a favourable outcome in patients with developmental tumours including DNET.

065

THE VALUE OF MEASURING GLUCOSE AND BLOOD KETONES WHEN ADJUSTING A CLASSICAL KETOGENIC DIET

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Purpose: Dysembryoplastic neuroepithelial tumour (DNET) is recognised as one of the most frequent reasons for medically intractable epilepsy. Patients with DNET present with partial onset refractory seizures following normal development.

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Conclusion: The aim of epilepsy surgery in children with medically intractable partial seizures is to control seizures, and thus improve learning and behaviour. Complete resection of the lesion is necessary for a favourable outcome in patients with developmental tumours including DNET.

066

SECONDARY (SYMPTOMATIC) GENERALISED EPILEPSY (SGE): A 20-YEAR FOLLOW-UP OF A POPULATION-BASED COHORT

C. Camfield and P. Camfield (IWK Health Centre and Dalhousie University, Dalhousie, Canada)

Purpose: Secondary generalised epilepsies (SGE) are often the most resistant of childhood epilepsies with an unsatisfactory outcome. SGEs may be poorly defined in clinical practice and are relatively uncommon. We carefully defined the 11 syndromes that make up most of this group of epilepsies and describe their response to treatment over long-term follow up.

Method: Children were identified from the Nova Scotia population-based epilepsy study (n = 693). Onset of epilepsy was from 1977–85 and follow-up was in 2003. Secondary generalised epilepsies were defined as having a mixture of >1 generalised seizure type including one of myoclonus, akinetic/atonic, drop attacks, tonic, atypical absence plus an interictal EEG with generalised spike-wave (irregular or slow) and/or multifocal spikes.

Results: SGE represents 11% (75/693) of all childhood epilepsy. Nearly 40% of patients do not fit into one of the currently accepted syndromes (such as Lennox-Gastaut, myoclonic-astatic or West). 63% have seizure onset in the first year of life and only 9% are free of intellectual or physical handicap. 65% (11/17) with Lennox Gastaut had preceding West Syndrome. During a median follow up of 20 years, mortality was 24% and 51% had persistently intractable seizures. Surprisingly one-third had >48 months terminal remission (West 37%, Lennox-Gastaut 0%, myoclonic-astatic 63%, undefined 37%).

Conclusion: Many children with SGE have ill-defined epilepsy syndromes. SGE is characterised by early age of onset, high rates of

handicap, intractability and death; although one third achieve complete seizure control with a long terminal remission.

Tuesday July 4, 2006
12:00–13:30
Hall 3a
Platform Session
Clinical Neurophysiology II

067
EARLY CONTINUOUS VIDEO-EEG MONITORING AND PREDICTION OF NEURODEVELOPMENTAL OUTCOME IN MODERATE NEONATAL HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

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Purpose: Whilst EEG gives excellent prediction of outcome in mild and severe hypoxic-ischaemic encephalopathy, the outcome in infants with moderate EEG abnormalities is unclear, with 20–40% proceeding to neurodisability. We have used early continuous EEG in infants to identify features within the moderate group which could predict outcome.

Method: Infants with evidence of perinatal asphyxia were recruited at birth. Continuous video-EEG monitoring for 24–72 hours was performed from within 6 hours of birth. EEG abnormalities were graded as mild, moderate, severe or inactive. Developmental assessment (Griffiths scales) was performed at 6 and 12 months.

Results: Forty-eight infants had early continuous EEG and completed follow-up. Initial EEG showed abnormalities classified as mild in 23/48, moderate in 17/48, severe in 4/48, and inactive in 4/48. All 23 infants with mildly abnormal EEGs had normal GQ scores at follow up. In the group with severe abnormalities 2 have died and 2 have significant global delay. Of the 4 infants with inactive EEGs 2 have died and 2 have severe spastic quadriplegia. In the infants with moderate EEG abnormalities, 5/17 had abnormal GQ scores or significant motor deficits. A further 3 infants had isolated deficits in Griffiths subgroups. Electrographic seizures occurred in 8/17. Abnormal outcome was seen in 3/8 infants with seizures. In addition to the seizure burden, low amplitude on initial EEG ($<50\ \mu$v), and delayed return of sleep cycling were associated with a poor neurological outcome.

Conclusion: By identifying high risk features, early continuous EEG can be used to predict abnormal outcome in infants with moderate hypoxic-ischaemic encephalopathy.

068
INFLUENCE OF FOCUS LOCALISATION ON PROPAGATION AND CLINICAL MANIFESTATION OF ICTAL ACTIVITY IN PATIENTS WITH FRONTAL AND TEMPORAL LOBE EPILEPSY

A. Schulze-Bonhage, K. Götz-Trabert, C. Hauck, and K. Wagner (Epilepsy Centre, University Hospital Freiburg, Germany)

Purpose: Recently, the implementation of online-seizure detection systems for warning of patients and closed-loop-intervention systems has attained increased interest. Latencies between electrographic seizure onset time, propagation of ictal activity, and occurrence of clinical symptoms are of critical importance for the applicability of detection-based intervention systems. This study evaluates intracranial EEG-recordings for determination of spread of ictal activity and its dependence on focus localisation.

Method: Video-EEG recordings of 215 seizures from 43 patients (mean age 28.8 y, 24 female) with pharmacoresistant focal epilepsy were evaluated. Seizure onset zone was temporomesial in 15, temporalneocortical in 15, and frontal in 13. The first five seizures recorded by intracranial EEG and video were analysed regarding latencies between seizure onset, propagation for a distance of at least 2cm, and clinical seizure onset.

Results: Median latencies between electrographic seizure onset and early propagation were 5s in mesiotemporal epilepsy, 3s in temporolateral epilepsy, and 1s in frontal lobe epilepsy. Median latencies between electrographic seizure onset and onset of clinical symptoms were 18s in mesiotemporal epilepsy, 11s in temporolateral epilepsy, and 4s in frontal lobe epilepsy. Latencies were significantly longer in temporomesial epilepsy as compared to frontal lobe epilepsy ($p < .05$).

Conclusion: There are significant differences with regard to the speed of propagation of ictal activity and onset of seizure semiology depending on focus localisation. This may have implications for the applicability of closed-loop intervention systems based on automated seizure detection algorithms. Mesiotemporal epilepsies may offer best chances for warning and intervention systems based on seizure detection.

069
FRONTAL SEIZURES DURING SLEEP WITH SUBTLE RESPIRATORY CHANGES MAY MIMIC AROUSALS BUT SHOW DISTINCT PATTERNS ON POLYSOMNOGRAPHY

A. Bauerfeind, I. Mothersill, T. Grunwald, and G. Kraemer (Swiss Epilepsy-Center, Zurich, Switzerland)

Purpose: Respiratory parameters during sleep, as monitored by polysomnography, exhibit characteristic changes not only during genuine respiratory events such as apneas, but also following arousals, for which an increase in respiratory rate is characteristic. Aside from any overt clinical signs, frontal seizures may also show an increased respiratory rate for the duration of the discharges. Before assuming that tachypnoea in itself may be considered ictal semiology, this specific polysomnographic pattern must be established and the delineation to arousal made possible.

Method: Respiratory tracings of 16 Patients in whom nocturnal frontal epileptiform discharges were concomitant with tachypnoea were reviewed for spontaneous (nonrespiratory) and induced arousal. Respiratory rate was calculated using either thoracic strain gauge or oro-nasal flow parameters (polysomnography). A minimum of 2 full breathing cycles of a sinusoidal curve was used when calculating frequency changes.

Results: Respiratory changes after arousal were generally in accordance with the observations made by Carley et al., *Sleep* 1996;19(10 Suppl):S189–92, consisting of a moderate increase in respiratory rate for 3 to 5 seconds following the stimulus with a gradual slowing (tapering) to the original respiratory rate after this time. Discharge related increases in respiratory rate, on the other hand, was characterised by an increased and stable frequency for the duration of the discharges, often lasting as long as 8 to 10 seconds.

Conclusion: Tachypnoea during frontal epileptiform discharges in sleep may be regarded as ictal semiology and can be distinguished polysomnographically from an arousal response. Although subtle, these respiratory changes may be the only manifestation of certain nocturnal frontal seizures.

070
ICTAL MANIFESTATIONS OF EMOTIONS: A VIDEO-EEG ANALYSIS

A. Marinas, I. García-Morales, A. Jiménez-Huete, and A. Gil-Nagel (Hospital Ruber Internacional, Madrid, Spain)

Purpose: To analyse manifestations with emotional content during ictal recordings in patients with epilepsy.

Method: From 134 patients with ictal recordings, those with seizures showing manifestations commonly found in association with emotions were selected.

Results: Focal epilepsy was diagnosed in 111/134 (83%) patients, while generalised epilepsies were diagnosed in 23/134 (17%). 34/111 (30%) patients with focal epilepsy had emotional manifestations during their seizures, compared with none of 23 patients with generalised epilepsy ($p = 0.0010$; X_2). Patients with focal epilepsy expressed 41 different emotional manifestations during their seizures. The most common manifestations were: restlessness in 14/41 (34%) and fear in 9/41

(22%). Other manifestations were: laughter, groaning, shouting, crying, anguish, agitation, and kissing. The localisation was temporal in 25/34 (74%), frontal in 4/34 (12%), non localising in 4/34 (12%), and fronto-temporal in one. 19/34 (56%) originated from the right hemisphere, 14/34 (41%) from the left, and one were not lateralised. 25/61 (41%) patients with temporal lobe epilepsy showed emotional manifestations which included fear, anxiety, groaning, agitation, kissing, and shouting; 4/21 patients with frontal lobe epilepsy (19%) showed cry and anguish.

Conclusion: Emotional expressions are common ictal manifestations in partial epilepsy, mostly in temporal and frontal lobe seizures, but are not present in generalised epilepsies. Anxiety and fear are the most common manifestations expressed during seizures, probably in relation to activation of the limbic system.

071

EXCITATORY AND INHIBITORY MECHANISMS OF PHOTOSENSITIVITY

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Purpose: Photosensitivity or photoparoxysmal response (PPR) is a highly heritable electroencephalographic trait characterised by an abnormal EEG reaction to intermittent photic stimulation (IPS), consisting of spikes, spike-waves, and intermittent slow waves. The knowledge concerning the pathophysiology of human photosensitivity is still limited.

Method: Threshold of phosphenes induced by a paired-pulse transcranial magnetic stimulation (TMS, Magstim 200), stimulus-response curves for phosphenes, suppression of visual perception by a single-pulse TMS (40–180 stimulus onset asynchrony, 75% of stimulator output, perception of letter trigrams), visual evoked potentials (2 Hz stimulation rate, 8 c.p.d., N135, habituation paradigm), and duration of the motion aftereffect were studied in healthy subjects with ($N = 17$, age 25.2 ± 12.2 years) and without ($N = 18$, age 26.5 ± 7.3 years) PPR.

Results: Subjects with PPR propagation were characterised by a lower phosphene threshold than subjects without PPR and with occipital spikes ($F(2.32) = 3.73$; $p = 0.035$). Stimulus-response curves of subjects with PPR propagation were steeper than those of other groups (intensity x group $F(9.297) = 4.58$; $p < 0.001$). Amplitudes of VEP were significantly larger in the group with PPR propagation and showed a more pronounced habituation (block of recording x group $F(28.406) = 2.01$; $p = 0.02$). The PPR group demonstrated a shorter motion aftereffect ($F(1.26) = 5.1$; $p = 0.03$) and (5) a more pronounced visual suppression by a single-pulse TMS (interaction SOA x group: $F(14.224) = 2.34$; $p = 0.005$).

Conclusion: This study provides evidence for both increased cortical excitability and intracortical inhibition in the occipital cortex in subjects with PPR propagation. PPR with propagation and with only occipital spikes seem to represent different phenotypic expressions.

072

PHOTOSENSITIVITY IN THE MYOCLONIC EPILEPSIES OF CHILDHOOD

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Purpose: Photosensitivity is seen in a proportion of children with myoclonic epilepsy. This would suggest an idiopathic aetiology, including severe myoclonic epilepsy of infancy (SMEI), and may imply an unsatisfactory outcome. The true range of the group with photosensitivity, however, remains unknown. We aimed to review children with myoclonic epilepsy associated with photosensitivity.

Method: Retrospective study of EEG records of children with a history of myoclonic epilepsy aged less than 10 years at onset, with normal brain imaging and development, presenting for EEG at Great Ormond Street Hospital for Children from 1992–2005. Children with known progressive disorders, structural lesions and abnormal neurodevelopment before the onset of epilepsy were excluded.

Results: The EEG records of 150 patients were studied. Of these, 45 had a single EEG and the remaining 105 had 2–9 recordings. 39 children (26%) had a grade 3–4 photoparoxysmal response. The mean age at onset was 24.7 months; 34 (87.2%) presenting before the age of 5 years. Diagnostic categories were SMEI, myoclonic astatic epilepsy, epilepsy with myoclonic absences and stimulus sensitive epilepsy. Nearly 46% of children were unclassifiable. Of the 5 children with an onset after the age of 5 years, photosensitivity was the most prominent historical feature in 2 children, while another 2 had deterioration of EEG with time.

Conclusion: Photosensitivity was seen in one-quarter of our patients with childhood myoclonic epilepsies. The presence of photosensitivity did not assist the other EEG features in making a clear syndromic diagnosis in almost half the children.

Tuesday July 4, 2006
12:00–13:30
Hall 3D
Platform Session
Basic Science II: Vascular Changes and Inflammation

073

VASCULAR REMODELLING AND ANGIOGENIC PROCESSES IN TEMPORAL LOBE EPILEPSY

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Purpose: We previously described inflammatory processes and proliferation of neural progenitors in the chronic focus of patients with temporal lobe epilepsy (TLE). We noted an increased vascularisation of the focus, compared to non epileptic hippocampi. Here we hypothesized that vascular remodeling is associated with neuroglial reorganisation and we attempted to evidence angiogenic processes in the adult epileptic hippocampus.

Method: We collected hippocampi from 30 patients who underwent surgery for intractable TLE and from 4 non epileptic, autopsied patients (NE). By immunohistochemistry or immunoblotting, we checked: i) microvessel density, ii) markers of immature endothelial cells, iii) angiogenic factors and their receptors. We performed similar studies on epileptic rats (lithium-pilocarpine model) to study the kinetic of neovascularisation.

Results: In TLE, we observed clusters of immature endothelial cells in the neurogenic areas. In CA1 and dentate gyrus, microvessel density was higher in epileptic than in NE patients, particularly in case of hippocampal sclerosis. Angiogenic factors and their receptors were detected in different types of cells. In rats, the degree of vascularisation seems to be related to the intensity of seizures and lesions. A rapid and strong neuronal expression of VEGF was obvious after seizures, whereas its receptor appeared later.

Conclusion: A neovascularisation contributes to epileptic tissue remodeling and likely depends on the severity of epilepsy. The persistence of angiogenic factors in the chronic phase of epilepsy suggests that angiogenesis is recurrently stimulated by spontaneous seizures. The consequences of neovascularisation may concern inflammation, blood brain barrier permeability and haemodynamics.

074

LONG-LASTING INCREASED PERMEABILITY OF THE BLOOD-BRAIN BARRIER DURING PROGRESSION OF EPILEPSY

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Purpose: To get more insight into the role of the blood-brain barrier (BBB) in epileptogenesis, we determined BBB permeability in epileptic rats and humans with epilepsy and studied the possible consequences of a compromised BBB for the subsequent progression of epilepsy.

Method: BBB permeability was investigated at different time points after electrically induced SE using various tracers that bind to albumin. The cellular localisation of albumin was further investigated using immunocytochemistry in rat and human epileptic brain specimens. In addition, we investigated whether BBB opening was related to seizure progression.

Results: In rats, the BBB was most affected 1 day after SE in limbic brain regions and partly restored in the latent period. However, the BBB was still permeable in the chronic epileptic phase. Tracer (albumin) was found in microglia, astrocytes and neurons. Similarly, albumin extravasation in humans was most prominent directly after SE in astrocytes and neurons and to a lesser extent in the hippocampi of temporal lobe epilepsy patients. In chronic epileptic rats, seizure frequency was correlated to BBB permeability. BBB opening by mannitol significantly increased seizure frequency more than 2-fold. Interestingly, mannitol induced the expression of the multidrug transporter P-glycoprotein in control brains.

Conclusion: These results show that albumin still enters the brain in the chronic epileptic phase and colocalises with neuronal and glial cells. The fact that the seizure frequency was correlated to BBB permeability, suggests that BBB leakage may be involved in the progression of epilepsy. Moreover, opening of the BBB induced compensatory mechanisms that could affect drug transport and contribute to pharmacoresistance.

075

MECHANISMS OF GENERATION OF FAST ACTIVITY AT ICTAL ONSET IN THE ENTORHINAL CORTEX OF THE ISOLATED GUINEA PIG BRAIN PREPARATION IN VITRO.

M. De Curtis, V. Gnatkovsky, and L. Uva (Unit of Clinical Epileptology And Experimental Neurophysiology, Istituto Nazionale Neurologico, Milano, Italy)

Purpose: One of the ictal onset patterns commonly observed in the temporal lobe of humans suffering from temporal lobe epilepsy and in experimental models of temporal epilepsy is characterised by recruiting fast activity. Such a pattern has been observed also in extratemporal cortical foci during presurgical stereo-EEG recordings in patients with drug-resistant epilepsy. The mechanisms involved in the generation of fast ictal-onset activity are still largely unknown.

Method: We developed a model of acute ictogenesis determined by transient disinhibition of the in vitro isolated brain of young guinea pigs by means of brief (3 minutes) arterial perfusion of the GABAa receptor antagonist, bicuculline (50 μM). Interictal and ictal discharges were induced with this protocol in the olfactory and limbic cortices that include the hippocampus and the entorhinal cortex (Uva et al. *Epilepsia* 46: 1914, 2005).

Results: Ictal onset in the medial entorhinal cortex was typically characterised by fast activity at 25–35 Hz, followed by ictal burst discharges of increasing amplitude. Bursting activity was always preceded by fast activity. In the present study we performed simultaneous intracellular recordings and extracellular laminar profiles in the medial entorhinal cortex, together with extracellular recordings from the CA1 region during the transition between interictal and ictal discharge in this model. Intracellular recordings in superficial neurons demonstrated that the fast activity was associated with IPSPs of decreasing amplitude, coupled with slow membrane depolarisation. No firing of principal neurons was observed in these conditions. Such activity was followed by cellular burst discharges in coincidence with the bursting ictal phase. Preliminary recordings from putative interneurons demonstrated the presence of sustained firing during ictal onset fast activity. Deep neurons are relatively quiescent during fast onset activity.

Conclusion: The present findings demonstrate that in the entorhinal cortex fast activity at ictal onset in an acute model of ictogenesis is characterised by a prominent interneuronal activation. The study was partially sponsored by Mariani Foundation grant (R-06-50).

076

VASOREACTIVITY TO CO_2 AS MEASURED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING IS ENHANCED IN EPILEPTIC REGIONS IN THE GENETIC ABSENCE EPILEPSY RAT FROM STRASBOURG (GAERS)

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Purpose: To evaluate whether neurovascular coupling is modified in brain regions implicated in absence epilepsy in a genetic rat model using hypercapnia challenges in functional MRI (fMRI).

Method: FMRI was performed at 2.35T in male and female GAERS and their non epileptic controls (NEC) anaesthetised with 1.2% isoflurane. During functional scans, the rate of inhaled CO_2 was varied from 0 to 10% during two periods of 3 min followed by rest periods of the same duration. Functional images were acquired using Echo Planar Imaging (FOV = 35 mm, matrix size = 48∗48, 15 contiguous slices 1.5 mm thick covering the whole brain). fMRI responses to CO_2 were compared between GAERS and NEC after image normalisation, with the atlas of Paxinos and Watson as the reference.

Results: Significant increases of the fMRI response to hypercapnia ($p < 0.05$) were found in GAERS as compared to NEC in the anteroventral thalamus, the primary somatosensory cortex (barrel field), the retrosplenial granular cortex and the most anterior part of the secondary motor cortex. Most of these structures are known from intracerebral EEG to be involved in the generation of spike-and-wave discharges in the GAERS.

Conclusion: FMRI shows enhanced responses to hypercapnia in epileptic regions in a rat model of absence epilepsy. These results suggest that fMRI of vasoreactivity to CO_2 might be of great interest to non-invasively localising epileptic regions in patients.

077

MOLECULAR AND FUNCTIONAL INTERACTIONS BETWEEN TNF-ALPHA AND GLUTAMATE IN THE MOUSE HIPPOCAMPUS: IMPLICATIONS FOR NEURONAL EXCITABILITY AND SEIZURE SUSCEPTIBILITY

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Purpose: TNF-alpha is produced by glia during seizures. Its p55 and p75 receptor (R) subtypes mediate opposite effects on seizures. After intrahippocampal kainate, p55R knock-out (KO) mice show decreased EEG seizures while p75R KO mice show enhanced seizures. p75R mediates the anticonvulsant effects of TNF-alpha in wild-type (WT) mice. We investigated whether TNF-alpha receptor-mediated changes in seizure susceptibility involve functional interactions with glutamatergic system.

Method: We used p55R and p75R KO mice and their C57BL6 WT. Membrane-bound AMPA (GLUR1,2,3), kainate (GLUR6/7) and NMDA (NR1,NR2A/B) receptor subunits were measured in hippocampal homogenates by western blot. Extracellular glutamate was measured in freely-moving mouse hippocampus by microdialysis. TNF-alpha receptors expression was assessed by immunohistochemistry.

Results: In p55R KO mice (less susceptible to seizures), GluR3 (AMPA) and NR1 (NMDA) subunits were decreased in the hippocampus, while all other subunits were unchanged vs WT mice. In p75R KO mice (more susceptible to seizures) GluR2,3 (AMPA), GLUR6/7 (KA) and NR2A/B (NMDA) subunits were increased, while the other subunits did not change. Spontaneous glutamate release was significantly reduced in p55R KO vs WT mice but unchanged in p75R KO; depolarisation-induced glutamate release was unchanged in either KO vs WT mice. In WT mice, p75R was expressed in hippocampal neurons while p55R was below detection limit. Ninety-24 h after seizure onset, both receptors were upregulated in astrocytes.

Conclusion: Functional glioneuronal communications between TNF-alpha and glutamate systems may contribute to changes in seizure susceptibility, thus highlighting a novel mechanism to control neuronal excitability. Supported by Fondazione Mariani Onlus.

078

ROLE OF INTERLEUKIN I AND TNF DURING EPILEPTOGENESIS IN EPILEPTIC MUTANT EL MICE

Y. Murashima, J. Suzuki, and M. Yoshii (Division of Psychobiology Tokyo Instituye of Psychiatry, Tokyo, Japan)

Purpose: Epileptic mutant EL mice show secondarily generalised seizures. Seizure discharges initiate in the parietal cortex and generalise through the hippocampus. We recently provided evidence for an altered equilibrium between pro-apoptotic Bax and anti-apoptotic Bcl-2 in association with a DNA fragmentation without cell loss. The level of neurotrophic factors in the hippocampus showed a significant increase in earlier developmental stages before exhibiting frequent seizures (Murashima et al., *Epilepsia* 2005;48(suppl 5):10–16). It has also been known that limbic seizures may induce pro-inflammatory cytokines to control seizures (Vezzari A et al., *Epilepsia* 2002;43(suppl 5):30-5). In the present study, we examined how interleukins and tumour necrosis factor (TNF) are involved in transition from the interictal to ictal state during development.

Method: EL mice and the control animal, DDY mice of 4, 6, 8, 10, 12, 15, 19, 23 weeks of age were used. Western blotting was employed to assess developmental changes of interleukins and TNF in the hippocampuses of these mice during development.

Results: Western blot analysis demonstrated significant increases in the levels of interleukin and TNF in EL mice compared to the control DDY. In EL, the levels of interleukin were increased predominantly after experienced frequent seizures.

Conclusion: It is concluded that in EL mice, experience of frequent seizures promotes expressions of proinflammatory cytokines, which may facilitate the shift from the interictal to the ictal state. Inflammatory cytokines and neurotrophic factors may work together in the process of epileptogenesis during development.

Tuesday July 4, 2006
12:00–13:30
Ballroom 1
Platform Session
Psychiatric and Social Issues

079

DEPRESSION AND ANXIETY IN WOMEN WITH EPILEPSY

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Purpose: To identify predictors and risk factors for depression and anxiety in women with epilepsy.

Method: Prospective, cross-sectional study using questionnaires. In total, 420 women (aged from 16 to 60 years) with epilepsy and on antiepileptic drug treatment were included. Epilepsy specific data (e.g. seizure frequency, side effects of drugs) and demographic data were assessed. Restrictions and limitations due to epilepsy and quality of life were assessed with the PESOS-Scales; depression and anxiety with the Hospital Anxiety and Depression Scale (HADS). Statistical evaluation: logistic regression analysis.

Results: Depression and especially anxiety were increased compared to the German population (cp. Hinz et al. PPmP 2001; 51: 193–200): anxiety and depression values were in 32% and in 18% of the women, respectively, above the age adjusted 90%-percentile in general population. Depression and anxiety correlated significantly with perceived restrictions due to epilepsy ($r = 0.56$; $r = 0.49$; $p < 0.01$) and with the global quality of life ($r = -0.66$; $r = -0.57$; $p < 0.01$). Multivariate analysis revealed important predictors for depression and anxiety, e.g. tolerability and efficacy of antiepileptic drug therapy, financial situation and education of the women and being registered as handicapped.

Conclusion: Our data indicate that women with epilepsy are at a higher risk for depression and particularly for anxiety. Perceived restrictions due to epilepsy and due to antiepileptic drug therapy as well as the financial situation are significant predictors of anxiety and depression. A comprehensive treatment of women with epilepsy should pay attention to anxiety and depression.

080

SCREENING FOR SYMPTOMS OF ANXIETY AND DEPRESSION IN ADOLESCENTS WITH EPILEPSY AND IN THE GENERAL POPULATION

Z. Martinovic (Institute of Mental Health, Belgrade, Serbia and Montenegro)

Purpose: To assess the symptoms of anxiety and depression among adolescents with epilepsy and in the general population.

Method: A sample of adolescents with epilepsy and a control group of age- and sex-matched healthy adolescents from the general population were screened for symptoms of anxiety and depression with Beck anxiety inventory (BAI) and Beck depression inventory (BDI). All subjects were tested in short 7 to 15 day intervals to determine the retest reliability. In addition, adolescents with epilepsy were tested during a 2 year treatment period. Pearson correlations were used to analyse dependence between variables, and Student's *t*-test was used to compare mean values between test scores.

Results: Each group consisted of 104 subjects, age range 13–19 years (median 17 years), 46% males. Females reported more anxiety symptoms (*t*-test, $p = 0.002$) and depressive symptoms (*t*-test, $p = 0.04$) than males. BAI and BDI scores showed a very high positive correlation (Pearson $r = 0.76$). Adolescents with epilepsy had higher BDI scores (mean $\pm$ SD, 9.48 ± 6.52) than controls (8.21 ± 5.6) ($p < 0.05$), but the difference was not statistically significant except for subgroups of those with increased risk for depression and lack of seizure control ($p < 0.05$). BAI scores of patients with newly diagnosed epilepsy (14.06 ± 9.30) were significantly higher than controls (9.54 ± 4.82) ($p < 0.05$) whereas the subgroups of patients with complete seizure control were no different from controls.

Conclusion: The BDI and BAI showed discriminative power to characterise demographic and epilepsy variables associated with increased anxiety and depressive symptoms in adolescents with epilepsy.

081

INCIDENCE OF EPILEPSY OR SEIZURE DISORDER IN A POPULATION AGED 15 YEARS AND OLDER AFTER TRAUMATIC BRAIN INJURY

E. Pickelsimer (Medical University of South Carolina, Charleston, USA)

Purpose: To estimate the incidence of epilepsy or seizure disorder (ESD) before and after traumatic brain injury (TBI) in a statewide representative sample of 2118 individuals with new TBI.

Method: South Carolina, USA, currently has a follow-up registry that captures a stratified random sample (55%) of individuals aged 15 years and older discharged alive from inpatient hospitalisation after TBI, and collects more in-depth information, including ESD, through chart review and telephone interview. Registry data from the first year post-TBI were used to estimate ESD.

Results: of participants, 5.5% said they had been told by a doctor before their injury that they had ESD. 2.0% had no prior ESD, but said they had had ESD in the four weeks prior to interview or had been told by a doctor they that had developed ESD since the index TBI. Individuals reporting preexisting ESD were more likely to have 'fall' listed as the aetiology of their index TBI than individuals without preexisting ESD (OR = 2.17, 95% CI 1.47, 3.20).

Conclusion: A higher prevalence of ESD was noted before injury (57.8 per 1000 age-adjusted to US 1980 standard population) than is usually reported in the literature for the general population. Increased efforts to control ESD, and to protect individuals with uncontrollable ESD, should result in decreased incidence of TBI in this vulnerable group.

082

DISSOCIATION AND SELF-REPORTED SYMPTOMS OF AROUSAL IN DISSOCIATIVE (NONEPILEPTIC SEIZURES

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Purpose: We have demonstrated that, in addition to scores on the Dissociative Experiences Scale (DES), the numbers of symptoms of autonomic arousal that are experienced during dissociative seizures (DS) help distinguish such patients from those with partial epilepsy. Currently we investigated whether a general tendency to dissociate might be related to particular constellations of autonomic and cognitive symptoms that patients report during their DS, and whether general levels of anxiety and depression contribute further to such relationships.

Method: Thirty-six patients with DS completed the DES, the Hospital Anxiety and Depression Scale and the Attack Symptoms Questionnaire, which subdivides self-reported DS-related symptoms into five categories. Mood and seizure-related symptoms that showed unadjusted significant relationships with DES total scores (and an index of pathological dissociation: DES-T) were regressed onto DES-related scores, with seizure related symptoms in the first block and mood related scores in the second.

Results: Whilst Total DES scores were predicted by all categories of DS symptoms and by anxiety and depression, DES total scores were best predicted by cognitive symptoms occurring during DS ($p < 0.001$, adj $R^2 = 0.32$). All DS symptom-types individually predicted DES-T scores (as did depression scores); the best predictor of DES-T after adjusting for other variables was the number of seizure related cognitive symptoms ($p < 0.001$, adj $R^2 = 0.27$).

Conclusion: Results suggest that autonomic and particularly cognitive symptoms reflecting high arousal levels during DS bear a strong relationship to more general self-reported dissociative tendencies, suggesting that in DS patients, the DES may be measuring arousal-related state dissociative experiences rather than a trait-like vulnerability to dissociation.

083

LEVEL AND CONTENTS OF ICTAL CONSCIOUSNESS IN TEMPORAL LOBE EPILEPSY

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Purpose: To develop a systematic approach for the combined assessment of the level and the contents of consciousness during epileptic seizures of temporal lobe origin, and to identify putative psychopathological correlations.

Method: 33 consecutive patients with temporal lobe epilepsy (TLE) referred to our Epilepsy Unit were evaluated. Accurate descriptions of ictal semiology and subjective experiences were collected by means of clinical interviews with patients and reliable witnesses. All subjects underwent quantitative assessment using the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), and the ICI (Ictal Consciousness Inventory), a new 20-item questionnaire specifically developed to assess (1) the level of general awareness/responsiveness and (2) the "vividness" of ictal experiential phenomena.

Results: We evaluated 41 seizure descriptions and plotted them into a biaxial diagram according to the level vs contents of ictal consciousness (Monaco et al., *Epilepsy Behav* 2005;7:150–160). ICI subscores for level (L) and contents (C) showed a positive correlation ($p < 0.05$). L and C dimensions were not associated with age at onset, duration of disease, seizure frequency, or localisation of EEG focus. Only C subscores correlated significantly with affective psychopathology ($p < 0.01$).

Conclusion: Our quantification of both objective and subjective ictal features in patients with TLE shows that 1) the vast majority (>80%) of seizures involving altered conscious experiences are accompanied by a degree of responsiveness and/or retained awareness of the surroundings; 2) the presence of emotionally vivid experiential phenomena is selectively associated with comorbid affective psychopathology.

084

PRESENTATION OF EPILEPSY IN POLISH NEWSPAPERS

M. Sieminski, J. Kunikowska, and W. Nyka (Medical University of Gdansk, Dept. of Adults' Neurology, Gdansk, Poland)

Purpose: The aim of this study was to examine how epilepsy is presented in Polish newspapers and to assess the relevance and reliability of information on epilepsy found in Polish articles. We also wanted to check how newspapers can influence the prejudices and stigma connected with epilepsy.

Method: We searched the electronic archives of the largest Polish newspapers issued all over the country. We analysed all articles published from 1 January 2002 to 31 December 2005, containing words "epilepsy" or "seizure." We divided articles into the following topical groups: aetiology, clinical symptoms, living with epilepsy, first aid in case of seizure, employment of patients, attitude, antiepileptic drugs, therapy, pregnancy, erroneous articles, noninformative articles.

Results: The largest Polish newspapers published 302,299 articles during the analysed period, out of which 262 contained one of the searched words (0.08%). 59.6% of the articles contained no information about the disease or the patients. The following percentage of articles fit each of the topical groups: aetiology 6.1%; clinical symptoms, 2.3%; living with epilepsy, 10.7%; employment, 2.3%; pregnancy, 0.7%; attitude to epilepsy, 3%; AEDs, 8.4%; therapy, 1.4%; 5.3% of the articles contained errors, in 3% of the articles epilepsy was called a "psychiatric disease." There were no articles about first aid in case of seizure.

Conclusion: Epilepsy is not well presented in Polish newspapers. There is not enough information on epilepsy, especially on first aid for seizures. The errors found in articles may lead to reinforcement of prejudices connected with epilepsy.

Wednesday July 5, 2006
12:00–13:30
Hall 1
Platform Session
Epilepsy Surgery III

085

FRONTAL LOBE RESECTIONS: SEIZURE OUTCOME AND PATHOANATOMICAL DIAGNOSES—DATA FROM THE SWEDISH NATIONAL EPILEPSY SURGERY REGISTER 1990–1999

[1]C. Sundal, [1]K. Malmgren, [2]R. Flink, and [1]B. Rydenhag ([1]Epilepsy Research Group, Insitute of Neuroscience and Physiology, Sahlgrenska Academy, Göteborg, Sweden, [2]Department of Neuroscience, Section for Clinical Neurophysiology, Uppsala, Sweden)

Purpose: Frontal lobe resection (FLR) is the second most common epilepsy resection but constitutes only 10–20% of surgical series. FLR are challenging, since the epilepsy is often devastating while seizure outcome is not as good as for temporal lobectomies. This is a report of the outcome of FLR on a national basis.

Method: The Swedish National Epilepsy Surgery Register, which includes data on all epilepsy surgery procedures in Sweden, was analysed with respect to FLR and pathoanatomical diagnoses 1990–1999.

Results: 448 patients underwent resective surgery 1990–1999 and completed a two-year follow-up. 61 of these underwent FLR. Two years after surgery 44% (n = 27) were seizure-free, and 11% (n = 7) had >75% reduction of seizure frequency. Of 13 patients with lesions (gangliogliomas, astrocytomas or cavernomas) 78% were seizure-free, and one had >75% reduction of seizure frequency. Of 13 patients with cortical malformations 54% (n = 7) were seizure-free, and 2 (15%) had >75% reduction of seizure frequency. Of the 23 patients who had gliosis only,

22% (N = 5) were seizure-free, and 18% (n = 4) had >75% reduction of seizure frequency.

Conclusion: In the Swedish national population-based epilepsy surgery series 1990–1999 14% of the patients underwent FLR. Seizure outcome in patients with lesions equalled that after temporal lesionectomies. Resections of frontal cortical malformations also led to seizure outcomes comparable to those after surgery for malformations elsewhere. Even in patients with gliosis only, 38% obtained significant improvement (seizure-free or >75% reduction of seizure frequency). Patients with frontal lobe epilepsy may have a desolate situation and partial seizure relief can be valuable.

086

PREDICTORS OF OUTCOME AFTER EPILEPSY SURGERY FOR NONLESIONAL TEMPORAL LOBE EPILEPSY

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Purpose: To identify predictors of outcome after epilepsy surgery in patients with nonlesional temporal lobe epilepsy (TLE).

Method: Nonlesional TLE patients with anterior temporal lobe resections were included. (Patients with vascular lesions or tumours were excluded; patients with normal magnetic resonance imaging (MRI) or hippocampal sclerosis on MRI were included). All patients had a standardised presurgical workup including Wada test and quantitative MRI. Outcome 1 year after surgery was classified as good (Engel I and II) or poor (Engel III and IV). Gender, age at onset and duration of epilepsy, history of febrile convulsions, the presence of auras, the frequency of secondary generalisation, right or left sided TLE, the memory ipsilateral to seizure onset on Wada testing, and a series of quantitative MRI parameters including hippocampal asymmetry and volume, amygdala, temporal lobe and hemispheral volume and hippocampal T2 relaxation time were tested for an association with outcome.

Results: 67% had a good outcome. Only a history of febrile convulsions, the presence of auras and hippocampal asymmetry/ipsilateral volume reduction on quantitative MRI were significantly associated with a good seizure outcome. The absence of these parameters did not necessarily exclude a good outcome. About 50% of all patients without febrile convulsions, auras or hippocampal asymmetry still had a good outcome.

Conclusion: Febrile convulsions, auras and hippocampal asymmetry were predictors of outcome after epilepsy surgery in non-lesional TLE. Extrahippocampal structural abnormalities, although frequently present, were not associated with outcome.

087

SELECTIVE AMOBARBITAL TEST IN THE ANTERIOR CHOROIDAL ARTERY: IS IT PREDICTIVE OF POSTOPERATIVE MEMORY?

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Purpose: Surgical resection is a common treatment of pharmacoresistant temporal lobe epilepsy (TLE), with postoperative memory decline as a feared complication. Selective intraarterial amobarbital tests, e.g. with injection in the anterior choroidal artery (IACAT), aim at predicting postoperative memory. However, their predictive value is debated. We compare the results of recognition memory during IACAT with interictal, postictal and postoperative recall memory as well as the amobarbital perfusion pattern.

Method: Sixteen patients with pharmacoresistant TLE underwent IACAT because of concerns of postoperative verbal memory dysfunction. After the amobarbital injection, verbal and visuo-spatial items were presented and their recognition tested. Seven patients had an additional injection of ECD-SPECT tracer in the anterior choroidal artery to identify the anaesthetised territory. Interictal and postictal memory was determined during noninvasive workup; postoperative memory was examined 3–6 months after the intervention.

Results: Of the 7 operated patients, only 1 suffered moderate decrease of verbal memory. This patient had the worst IACAT performance (15%). In all other patients, IACAT performance was not correlated with the postoperative outcome. Also, no significant correlation between preoperative interictal, postictal and postoperative performances was found. IACAT coupled with intra-arterial SPECT revealed major variability of the territory affected by amobarbital.

Conclusion: Only a severe decrease of verbal memory during IACAT, compared to interictal scores, predicted a significant postoperative memory decline. Variation in the anaesthetised areas might explain the lack of correlation between IACAT results and postoperative memory. Postictal memory function did not reliably predict IACAT performance or postoperative memory.

088

LONG-TERM MEMORY PERFORMANCE AFTER SURGICAL TREATMENT OF UNILATERAL TEMPORAL LOBE EPILEPSY (TLE)

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Purpose: To assess long-term memory performance after surgical treatment of TLE.

Method: Altogether 128 adult patients with unilateral TLE were operated on at KUH 1988–2002. Complete neuropsychological evaluation (preoperatively, one year postoperatively, and two or three years postoperatively) was available for 107 patients, with 98 patients eligible for the study. Engel I–II outcome was achieved in 71% of operations. Immediate and delayed verbal memory was evaluated using Wechsler Memory Scale Logical Prose Subtest and Paired Associate Learning. Visual memory was estimated using WMS visual reproduction test and Rey-Osterrieth Complex Figure.

Results: MANOVA for repeated measures showed a significant decrease in the immediate and delayed recall of paired associates among both left and right TLE groups ($p < 0.001$). The delayed recall of paired associates deteriorated especially between one year and long term follow-up ($p < 0.001$). There was no significant change in learning and delayed recall of logical prose. The copying of Rey Figure also decreased among both TLE groups ($p < 0.001$), but there was no significant change in the delayed recall of Rey Figure. Immediate recall in the WMS visual reproduction test improved slightly in both TLE groups ($p < 0.05$) possibly reflecting practice effect, but delayed recall showed no significant change.

Conclusion: Surgical treatment of TLE can have adverse effects on postoperative verbal memory performance irrespective of side of surgery. In this study the delayed recall of paired associates deteriorated especially between one year and long-term follow-up, highlighting the importance of long-term follow-up of operated patients.

089

COGNITIVE OUTCOME IN CHILDREN WITH REFRACTORY EPILEPSY AFTER EARLY SURGICAL TREATMENT

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Purpose: The aim of our study was to investigate cognitive changes after surgery performed before school-age and possibly to study the

cognitive profile in order to evaluate functional reorganisation after early surgical treatment.

Method: Forty five children affected by resistant epilepsy, operated on before 7 years of age and with a postsurgical follow-up (≥1 year) were included. Twenty-five children were affected by cortical malformations, 12 by low grade tumours, 3 by Sturge-Weber syndrome, 4 by porencephalic cysts and one by Rasmussen encephalitis. Presurgical evaluation included clinical examination, seizure semiology, video-EEG monitoring, MRI and neuropsychological assessment. Mean age at surgery was 2.2 years (range 4 months–6 years 9 months). Postsurgical follow-up included neurological examination, seizure outcome, MRI, EEG and neuropsychological assessment. Mean duration of follow-up was 3 years (range 1 year- 8.5 years).

Patients were assessed postoperatively at 6 weeks, 6 months, 1 year and every year.

Results: Nineteen patients underwent a hemispherectomy, 9 a multilobar resection and 17 a focal resection (9 temporal, 4 frontal and 4 parieto/occipital). Thirty-one children were seizure-free (class Ia or Ib of Engel), 8 presented with rare seizures (class II) and 5 presented a 50% seizure reduction. Only 13 children had a normal mental development before surgery. After surgery: in the group with multilobar resection or hemispherectomy 6/19 patients improved, in the group with focal resection 3/17 patients showed an improvement and 4 a further impairment of cognitive functions. Neuropsychological profile revealed an improvement of verbal competences in patients treated with parieto/occipital resection or hemispherectomy, irrespective of the side of surgery.

Conclusion: Early surgical treatment in children with symptomatic resistant epilepsy may sometimes improve cognitive functions. Reorganisation of neuropsychological functions, particularly regarding verbal competences, was observed especially in patients with extensive resections.

090

HEALTH-RELATED QUALITY OF LIFE IN ADULT EPILEPSY SURGERY CANDIDATES: A SWEDISH NATIONAL, PROSPECTIVE, LONGITUDINAL STUDY

[1]E. Sager Magnusson, [1]G. Ekstedt, [2]C. Taft, and [1]K. Malmgren ([1]Epilepsy Research Group, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden, [2]Health Care Research Unit, Institute of Medicine, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden)

Purpose: To prospectively assess and compare the health-related quality of life (HRQL) of adults evaluated for epilepsy surgery: 1) in operated versus nonoperated patients, 2) in operated seizure-free versus seizure-persistent patients, and 3) with population norms.

Method: 141 adult epilepsy surgery candidates (median age = 33; 45% men) completed the SF-36 health survey and a questionnaire including epilepsy-related questions at initial evaluation and two years postoperatively (n = 96) or after having been declined surgery (n = 45). A sex and age-matched reference sample (n = 987) was randomly drawn from the Swedish SF-36 normative database. Data analysis was nonparametric.

Results: 53 (55%) of the operated patients (OP) were seizure-free (SzFree) after 2 years, versus 5 (11%) of the nonoperated patients (NonOP). At baseline, both OP and NonOP had significantly worse scores than referents in all SF-36 domains, except bodily pain for OP. OP scored better than NonOP in only 1/8 domains, versus 5/8 domains at follow-up. Between baseline and follow-up, SzFree improved significantly in 7/8 domains, while neither operated seizure-persistent patients (SzPrst) nor NonOP changed significantly in any domain. At follow-up, SzFree scored better than NonOP in all SF-36 domains and than SzPrst in 5/8 domains. SzFree differed from referents only in social functioning.

Conclusion: Patients rendered seizure-free after epilepsy surgery significantly improved in HRQL to levels largely comparable with those of their counterparts in the population, emphasising benefits of surgery beyond seizure eradication. Conversely, the lack of HRQL decrements in patients with persistent seizures postoperatively suggests that suboptimal surgical outcome may not worsen their health status.

Wednesday July 5, 2006
12:00–13:30
Hall 5A
Platform Session
Adult Epileptology III

091

PROGNOSTIC FACTORS IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY (MTLE): A PRELIMINARY STUDY

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Purpose: To disclose familial, clinical, anamnestic, electrophysiological and neuroradiological factors correlated to prognosis in patients with mesial temporal lobe epilepsy (MTLE).

Method: 170 MTLE patients were studied for family history, clinical findings, neuropsychological and instrumental data (EEG, video-EEG, neuroimaging) and outcome. This population was then divided into lesional (LES: 74 pts, 43.5%) and non-lesional (N-LES: 96 pts, 56.5%) groups.

Results: Among LES pts 38 (51%) were drug-resistant (DR) and 36 (49%) responsive (N-DR). Mesial temporal sclerosis (MTS) was present in 58% of N-DR and in 71% of DR patients. Among 48 pts with MTS 33% had presented with febrile convulsions (FC) during childhood in the N-DR group versus 39% in the DR group. Familial and sporadic cases were equally present in DR and N-DR groups. Among N-LES pts 18% had had FC: 34% were DR and 66% N-DR. CF antecedents were 40% and 6% respectively. Familial cases were 3% in DR group and 41% in N-DR group.

Conclusion: MTLE is a heterogeneous syndrome. Establishing the factors responsible for and associated with drug resistance is important for therapeutic purposes, as prompt diagnosis of drug resistance must lead to an early surgical approach. This preliminary study shows that MTS is not a negative prognostic factor. A positive family history of epilepsy is a favourable prognostic factor in N-LES and LES pts. FC are associated with MTS, but do not constitute a negative factor.

092

PREDICTIVE FACTORS FOR PHARMACORESISTANT EPILEPSY

N. Hitiris, R. Mohanraj, and M. Brodie (Epilepsy Unit, University Division of Cardiovascular And Medical Sciences, Western Infirmary, Glasgow, Scotland, UK)

Purpose: Uncontrolled epilepsy can result in cognitive deterioration, psychosocial dysfunction, and increased morbidity and mortality. Clinical differences between responders and nonresponders to antiepileptic drugs (AED) were analysed for factors that could help predict refractory epilepsy.

Method: Subjects with suspected seizures were referred to the epilepsy clinic of the Western Infirmary, Glasgow, between July 1982 and May 2001. Patients with newly diagnosed epilepsy were divided into 3 groups: responders were patients who went into remission, nonresponders were patients who were pharmacoresistant de novo and relapsers were patients whose intractable seizures returned after at least one year of seizure freedom.

Results: Follow up data were available for 780 (88%) patients from a total of 890 with newly diagnosed epilepsy. We identified 462 (59%) responders, 42 (5%) relapsers and 276 (35%) nonresponders. Median numbers of pretreatment seizures were 4 for responders and 8 for nonresponders (Mann-Whitney test, $p < 0.0001$). Median numbers of seizures reported during the 3 months prior to starting treatment were 2 for responders and 4 for nonresponders (Mann-Whitney test,

$p < 0.0001$). In comparison to responders, nonresponders were more likely to have a family history of epilepsy [OR 2.22 (95% CI 1.42–3.48), $p = 0.001$], traumatic brain injury [OR 3.11 (95% CI 1.92–5.03), $p < 0.001$], psychiatric comorbidity [OR 2.29 (95% CI 1.51–3.48), $p < 0.001$] and febrile convulsions [OR 2.62 (95% CI 1.24–5.52), $p = 0.012$].

Conclusion: The numbers of pretreatment seizures were greater in patients who developed refractory epilepsy than those entering remission. Traumatic brain injury, febrile convulsions, psychiatric co-morbidity and family history were all predictive of uncontrolled epilepsy.

093

DOES THE MECHANISM OF ACTION OF INITIAL ANTIEPILEPTIC DRUG INFLUENCE THE DEVELOPMENT OF PHARMACORESISTANCY IN NEWLY DIAGNOSED EPILEPSY?

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Purpose: We aimed to evaluate whether the mechanism of action of the initial antiepileptic drug (AED) treatment influences the rate of pharmacoresistancy by randomising newly diagnosed patients with adult-onset focal epilepsy to initial treatment with either sodium-channel blocker carbamazepine or GABAergic AED (vigabatrin/tiagabine).

Method: From the population of Kuopio University Hospital District (pop. 250,000) in Finland patients with newly diagnosed focal epilepsy (over 15 years and with normal intelligence (IQ >85) during time period from 1988 to 1999 were enrolled. Patients with progressive neurological disorder, severe psychiatric or other medical condition or substance abuse were excluded.

Results: Altogether 220 patients were randomised and followed for five years. Altogether 111 patients were randomised to treatment with sodium channel blocker and 109 patients to GABAergic AED (56 to vigabatrin and 53 to tiagabine). The baseline demographic variables did not differ between the groups. After 3 years 60 (54%) of the initial sodium-channel-blocker group were seizure free, 40 (36%) had only occasional seizures and 10 (9%) were pharmacoresistant. Altogether 41 (38%) of the patients randomised to GABAergic AEDs were seizure free, 59 (64%) had occasional seizures and 9 (8%) were pharmacoresistant. Preliminary results at 5 years follow-up show a similar pattern.

Conclusion: The rate of pharmacoresistant patients at 3 years of follow-up was equally independent of the mechanism of action of the initial AED.

094

SEXUAL DESIRE, SEXUAL CONFIDENCE AND TESTOSTERONE LEVELS IN MEN WITH EPILEPSY

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Purpose: Sexual dysfunction in men with epilepsy (MWE) is said to be common. AED induced reduction in testosterone levels have been suggested as one mechanism. This ignores the psychosocial impact of epilepsy.

Method: Sixty men with epilepsy aged between 18 and 60 years, taking AED monotherapy were recruited. None took antidepressant medication. A control group of 60 men drawn from patient's spouses, friends and hospital staff were recruited.

Each man completed the Hospital Anxiety and Depression Scale (HADS), the WHOQL-BREF (UK), two validated questionnaires exploring desire for intimacy/ intercourse (SDI) and sexual confidence (SSES). Men also answered 5 questions specifically about sexual dreams, fantasies, and spontaneous arousal. 40 mls of blood was withdrawn between 9am and noon for testosterone, SHBG, albumin, androstenedione, and estradiol.

Results: There was no significant difference between men and controls SDI scores suggesting the MWE did not differ in their desire for sexual intimacy. MWE had significantly lower SSES scores than controls ($p = 0.006$) suggesting they believed themselves less likely to be able to initiate or complete intercourse with a partner. They reported as frequent sexual dreams/fantasies and episodes of arousal when alone as controls. MWE had significantly higher anxiety and depression scores ($p < 0.05$), and there was a significant correlation between depression scores and SSES scores ($p = 0.01$, $r = -0.26$). There was no significant difference in free testosterone, biologically active testosterone (BAT), estradiol, or androstenedione between the groups.

Conclusion: There is no evidence in the literature to suggest that MWE sustain a reduction of BAT to subphysiological levels. More studies exploring the psychosocial impact of epilepsy on sexual function are required.

095

SEX AND GONADOTROPIN HORMONAL LEVELS AMONG TEENAGE GIRLS WITH EPILEPSY

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Purpose: Reproductive-endocrine disorders (RED) are often found among women with epilepsy on AED treatment, especially in women with epilepsy manifested at puberty (EMP) and on AED therapy. We investigated sex and gonadotropin hormonal levels in EMP teenage girls in newly diagnosed patients and in girls under AED therapy.

Method: One hundred and seventeen consecutive girls with epilepsy with age range 12–18 years (mean 16.2 ± 1.6) and EMP were recruited; 64 had cryptogenic focal (CFE) and 53 idiopathic generalised (IGE) epilepsy. In all cases levels of luteinising (LH), follicle stimulating (FSH), prolactin (PRL), progesterone (PG) and free testosterone (FTST) were measured on the days 11–14^{th} with shorter (<24 days) menstrual cycle (MC), on the days 21–22^{th} with normal MC (24–34 days) or oligomenorrhea (34day<MC<3 month), and randomly in girls with amenorrhea (no MC for 3 months). At admittance 50 patients had never taken AEDs, while 67 had taken different AED therapy (mean for 2.6 ± 1.1 years). Statistical analysis used SPSS (12).

Results: Hyperandrogenism (HA) was revealed in 42 cases (35.9%) and hyperprolactinemia (HPRL) in 29 girls (24.8%). Treated and nontreated EMP girls did not significantly differ by the occurrence of HA ($p < 0.7$) and HPRL ($p < 0.9$). Higher than normal LH level was more often found among girls with (38.8%) than without (16%) AED treatment ($p < 0.014$). Among patients with nontreated as well as treated IGE, higher than normal levels of LH and PRL were more often found than in patients with CFE ($p < 0.019$ and $p < 0.022$ respectively).

Conclusion: The teenage period is one of the critical periods for maturation of the reproductive-endocrine system. Some anticonvulsants increase the risk of RED development. So, in EMP girls, hormonal investigation is essential before AED treatment to prevent RED, especially among patients with IGE.

096

STATUS EPILEPTICUS IN PREGNANCY

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Purpose: Traditionally, status epilepticus has been associated with high foetal and maternal mortality. We used the EURAP study of pregnant women on antiepileptic drugs (AEDs) to evaluate the occurrence and outcome of status epilepticus during pregnancy.

Method: EURAP (The International Registry of Antiepileptic Drugs and Pregnancy) is a prospective study aimed at determining the comparative risk of birth defects following intake of AEDs during pregnancy. Originally set up in Europe in 1999, EURAP is now an international project receiving data from 40 countries worldwide. The Registry is based on an electronic database enabling real time checks of case record forms and periodic audits. In addition to collecting data on AED exposure, EURAP records information on occurrence of seizures and status epilepticus each trimester. The present analysis is based on the first 3,358 prospective pregnancies completed by December 2005.

Results: Fifty-five cases (1.6%) of status epilepticus were observed among 3,358 pregnancies. Of these, 16 were convulsive and 39 nonconvulsive. Cases were evenly distributed through the trimesters. Twenty-seven women had localisation-related and 28 generalised epilepsy. No episodes of status epilepticus resulted in maternal death. With regards to foetal outcome 1 stillbirth occurred shortly after an episode of convulsive status epilepticus. One perinatal death, 1 spontaneous abortion and 1 induced abortion were also noted; none occurred close to the period of status epilepticus.

Conclusion: The present study suggests a much more favourable prognosis in terms of maternal and foetal outcome than previous reports of status epilepticus in pregnancies of women on AEDs.

Wednesday July 5, 2006
12:00–13:30
Hall 5B
Platform Session
Paediatric Epileptology IV: Video Session

097
NOVEL SYSTEM FOR AUTOMATED SEIZURE DETECTION IN NEWBORNS

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Purpose: Seizures are a common neurological emergency in the neonatal intensive care unit. Clinical signs of neonatal seizures can be very subtle or entirely subclinical and hence the electroencephalogram (EEG) is the only reliable tool for their detection. However, constant supervision by trained specialists is still needed for adequate seizure detection. An automated seizure detection system would remove the need for constant EEG supervision. The aim of this study was to use a digital signal processing theory to develop a multistage seizure detection system.

Method: The proposed system breaks the seizure detection problem up into three sections: preprocessing, feature extraction and classification. The preprocessing element, based on independent component analysis, incorporates multichannel analysis and reduces the effect of artifacts. Defining features are then extracted from the resulting signals using techniques from a wide range of signal processing techniques, from frequency analysis to modelling. Finally, a classification network makes the final decision based on changes in the characteristic feature set.

Results: Preliminary tests carried out on neonatal EEG data, extracting 10 features, detected 45 out of 46 seizures (97.82%) with a mean delay of only 11.4 seconds between commencement of the seizure and its detection.

Conclusion: The neonatal seizure detection system proposed in this study produces rates and speed of detection surpassing previously documented methods. An implementation of the system will undergo clinical tests after further simulation and development. This system will greatly aid clinical neurophysiologists in detecting seizures rapidly, thus minimising the impact on the infant.

098
IN THE NEONATAL PERIOD, FOCAL MOTOR SEIZURES WITH TYPICAL AUTOMATISMS AND WITH HYPERKINETIC AUTOMATISMS ARE EPILEPTIC EVENTS

M. Mastrangelo (Servizio Di Neurologia Osp Buzzi AO ICP, for the Italian League Against Epilepsy Study Group, On Neonatal Seizures, Italy)

Purpose: Focal motor seizures with typical (temporal lobe) automatisms and with hyperkinetic automatisms are comprised among epileptic seizure types in Axis 2 of the Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology (Engel J Jr, *Epilepsia*, 2001;42:796–803). Regarding the neonatal period, Mizrahi and Watanabe in their Classification and Characterization of neonatal seizures, affirm that the presumed pathophysiology of motor automatisms is nonepileptic (Mizrahi EM, Watanabe K. In Roger J. et al., *Epileptic Syndromes* (3rd ed) John Libbey, 2002;15–31). In order to better understand this dichotomy, we reviewed video EEG recordings of neonatal automatisms to examine the pathophysiology of these ictal events.

Method: We carefully reviewed the video EEG recordings of more than fifty seizuring neonates observed by the Italian League Against Epilepsy Study Group on Neonatal Seizures, considering the clinical ictal semiology with concomitant EEG activity, of oral-buccal-lingual movements, progression movements and complex purposeless movements.

Results: In our sample, some stereotypic oral-buccal-lingual movements, some progression movements such as pedalling or bicycling or rowing, some complex purposeless movements such as sudden arousal with transient increased random activity or with asymmetric tonic posturing, are generally associated to a less or more well defined ictal EEG activity.

Conclusion: In the neonatal period, as in other ages, motor automatisms have to be considered epileptic events. The peculiar and stereotyped characteristics of clinical ictal events are suggestive for epileptic events and in such a condition an ictal EEG concomitant activity is generally recognisable.

099
HEART RATE VARIABILITY IN NEONATES WITH SEIZURES

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Purpose: To document and quantify heart rate variability changes in neonates during seizures and to compare these changes with those in controls.

Method: Time and frequency domain heart rate variability (HRV) measures were compared for 12 records from 10 neonates with seizures and 11 healthy controls. Measures were also compared for seizure and non-seizure periods within each patient. Time domain HRV analysis was performed by examining timing changes in the R–R interval time series as well as changes in the R–R interval spectral entropy (H). The frequency domain HRV was calculated by means of the R–R interval "spectrum of intervals" power spectral density (PSD) method.

Results: A total of 658 EEG documented seizures were recorded in 10 neonates. A significant decrease in the mean R–R interval was observed in 9 records during seizures when compared to non-seizure periods. The mean R–R interval for neonates with seizures was significantly less than for healthy neonates ($\mu_{\text{seizure}} = 0.45$s, $\mu_{\text{control}} = 0.50$s, $p < 0.05$). An increase in R–R interval spectral entropy was observed in seizure babies when compared to controls ($p < 0.05$). A decrease in H was noted in 10 records ($p < 0.05$). This decrease was significant in 7 records. Significant changes in the R–R interval PSD were noted during

seizures with decreases in the LF and HF power in 6 ($p < 0.05$) and 4 records ($p < 0.05$) respectively.

Conclusion: These results show consistent increases in heart rate during clinical and subclinical neonatal seizures. Sudden changes in heart rate in sick newborn babies with no obvious clinical seizure activity may warrant further investigation with electroencephalography (EEG).

100

REFLEX ABSENCE SEIZURES: CLINICAL CASE WITH VIDEO EEG

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Purpose: To present a case of reflex absence seizures in an infant, an extremely rare form of reflex seizures, described only twice before.

Method: Clinical data and video EEG recordings of the patient were revised.

Results: A previously healthy 18-month male infant presented with brief episodes of staring, unresponsiveness and interruption of activity always after stimulation of the face. On the video EEG a normal baseline pattern could be seen. Sudden stimulation of either the right or the left cheek provoked: 1) isolated generalised spikes that did not have clinical significance and 2) absence seizures with a characteristic pattern of diffuse 3 Hz spike and wave complexes, with a duration that ranged one to three seconds. Stimulation of other parts of the face or the body or eating did not induce seizures. VPA was started, resulting in total seizure control and normalisation of the EEG. After two years VPA was tapered and the patient has remained asymptomatic ever since.

Conclusion: To our knowledge, reflex absence seizures have only been reported twice before by De Marco (1990) and Voskuil (2002). Both cases had similar clinical and video EEG characteristics to ours, all having an excellent outcome. We believe that these 3 patients alone represent an extremely rare form of idiopathic generalised epilepsy (IGE) that could be added to those known as "IGE not officially recognised by the ILAE," which are: IGE with absences of early childhood, perioral myoclonia with absences, idiopathic generalised epilepsy with phantom absences, Jeavons syndrome (eyelid myoclonia with absences), and monogenic IGE syndromes.

101

CSWS OR CSWS-LIKE SYNDROME: AN HETEROGENEOUS GROUP COMPRISING CLINICAL AND ELECTROENCEPHALOGRAPHIC FEATURES AND RESPONSE TO TREATMENT

Y. Geerts (Epilepsy Centre S.E.I.N., Zwolle, The Netherlands)

Purpose: To look for different characteristics in clinical presentation as evolution of cognitive impairment, dyspraxia, seizures and electroencephalographic features in children with CSWS or CSWS-like syndrome with or without cerebral lesion, with bilateral but independent foci, with continuous spike waves during sleep or when awake and sleeping.

Method: We retrospectively reviewed all children with CSWS-like syndrome referred to our epilepsy centre from 2000 to 2005. All underwent at least one long term EEG/video registration including a full night of natural sleep and one psychological examination. Many of them also had an orthophonic evaluation.

Results: Twenty-eight children were found with CSWS; 7 had continuous spike waves even during daytime, 4 had cerebral lesions, 3 had two independent epileptic foci with CSWS-features. Most of the children were treated with valproate, ethosuximide and/or lamotrigine. Some also received steroids or levetiracetam. Sometimes carbamazepine could not be discontinued as is recommended in CSWS. The outcome with regard to cognitive impairment, behaviour and dyspraxia was variable but no specific differences were found between the group with or without cerebral lesion, or between the group with only a continuous spike and waves during sleep compared to the group with CSW during sleep and when awake. Even in the children with two independent CSWS-foci there was a different response of the foci to treatment.

Conclusion: Until now no parameter, clinical or electroencephalographic, can be used for drug selection or for prediction of the outcome in children with CSWS. It seems that the outcome in the symptomatic group does not differ from the others.

102

SEIZURES IN IMMUNISED CHILDREN WITH SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

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Purpose: SSPE is a progressive, fatal neurodegenerative disease caused by defective measles virus. Early diagnosis is based on clinical features, high titers of serum and cerebrospinal fluid measles antibodies and EEGs.

Method: A group of 16 children (12 boys, 4 girls) with SSPE aged 4.5 to 16.5 years (mean 11.2) was diagnosed and treated in our Clinic from 1995 to 2005. Measles vaccination was given in 12 children. Disease onset ranged from 4.5 to 15.5 years (mean 8.3 in nonimmunised and 13.2 in vaccinated patients). Epilepsy was analysed with respect to the initial symptoms, clinical course and therapeutic response.

Results: Cognitive dysfunctions followed by myoclonic jerks occurring after 15 days to 3.5 months, were recognised as typical initial symptoms in 5 children. Intractable seizures in 3 patients (focal motor with secondary generalisation in 2 and atypical absences in 1 child) preceded SSPE for 1.5 to 4 years. Five patients presented with focal motor deficits (2), visual loss (2) and psychotic behaviour (1). Focal motor fits (2), generalised tonic–clonic seizures (1) and hemiconvulsive epileptic status (1) occurred early and preceded cognitive decline and periodic myoclonus. Initial segmental myoclonus was seen in 2 additional cases. Unilateral myoclonic seizures persisted during phases II–IIIa in 1 of them. Four non-vaccinated children (including 2 with early visual loss) with fulminant SSPE died 3 and 5 months after the disease onset. Chronic form (mean 4.2 years) was seen in 3 patients (including 2 with seizures preceding SSPE). Intrathecal interferon provoked generalised seizures in 1 patient. There were no therapeutic effects of oral inosiplex, alpha-2b interferon or AEDs on seizure control.

Conclusion: Immunisation seems to be associated with changing the clinical SSPE expression. Later age of onset and atypical course (preexisting intractable epilepsy or seizures dominating in early SSPE stages) could be an increasing problem in differential diagnosis and treatment.

Wednesday July 5, 2006
12:00–13:30
Hall 5c
Platform Session
Paediatric Epileptology III: Paediatric Epilepsy Syndromes

103

PHOTOSENSITIVE BENIGN MYOCLONIC EPILEPSY IN INFANCY

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Purpose: To describe the electroclinical features of subjects who presented with a photosensitive benign myoclonic epilepsy in infancy (PBMEI).

Method: The patients were selected from a group of subjects with epilepsy with seizure onset in infancy or early childhood. Inclusion criteria were the presence of photic-induced myoclonic seizures and a favourable outcome. Cases with less than 18 month follow up were excluded from the analysis.

Results: Eight patients were identified (4 males, 4 females). Personal history was uneventful. All of them had familial antecedents of epilepsy. Psychomotor development was normal in 6 cases, both before and after seizure onset. The remaining patient showed a mild mental retardation and a further patient showed some behavioural disturbances. Neuroradiological investigations, when performed (5 cases), gave normal results. The clinical manifestations were typical and could vary from upward movements of the eyes to myoclonic jerks of the head and shoulders, isolated or briefly repetitive, never causing a fall. Age of onset was between 11 months and 3 years and 2 months. Characteristically, the seizures were always triggered by photic stimulation. Non–photo-induced spontaneous myoclonic attacks were reported in 2 cases during the follow-up. Other types of seizures were present at follow-up in 2 cases. The outcome was favourable, even if, usually, seizure control required high AED plasma levels. Since the clinical symptoms were not recognised early, some patients were treated only many years after the onset of symptoms.

Conclusion: Among BMEI patients, our cases constitute a subgroup in which myoclonic jerks were always triggered by photostimulation, in particular at onset of their epilepsy.

104

TYPICAL ABSENCE EPILEPSY DURING INFANCY: CLINICAL DATA AND OUTCOME

E. Shahar, J. Genizi, Y. Nevo, and R. Kaufman (Child Neurology Unit & Epilepsy Service, Meyer Children Hospital, Rambam Medical Center, Rappaport School of Medicine, Haifa, Israel)

Purpose and Method: Attempt to allocate patients with characteristic findings of childhood or juvenile absence epilepsy presenting before the age of 3 years and delineate the clinical manifestations, EEG findings, therapy and outcome for such infants.

Results: Seven infants presented at age of 11–36 months (mean: 26.4 months) with freezing episodes, one also with myoclonic jerks. These corroborated with generalised epileptiform discharges of 3–4 Hz spike/wave and normal background activity on the EEG, a photosensitive response induced in 3 children. All 7 children were initially treated with valproic acid in order to abort the absences. Six infants were initially controlled but 2 relapsed when therapy was withdrawn after 3 years. These 2 children, with still an epileptiform EEG, required prolonged valproate therapy for 4–6 years that maintains them seizure free, probably transforming into the childhood form of absence epilepsy. These 6 children remain seizure-free within a follow-up period of 1.5–7 years. Cognition was in the low normal range in 3 children, 1 of them with recurrent absences requiring treatment with combined valproic acid and lamotrigine.

Conclusion: The data presented here delineates a rare idiopathic generalised epilepsy presenting with typical absences during infancy prior to age 3 years, very similar to childhood and juvenile absence epilepsy recognised as distinct epileptic syndromes by the ILAE classification. Therefore, early onset typical absences epilepsy before age 3 years may also be added to the current ILAE classification of the epileptic syndromes as a distinct generalised syndrome.

105

AUTOMATISMS IN TYPICAL ABSENCES DO NOT CHANGE THE PROGNOSIS

F. Beccaria, A. Montagnini, P. Avantaggiato, and G. Capovilla (Department of Child Neuropsychiatry, Epilepsy Center, C. Poma Hospital, Mantua, Italy)

Purpose: To evaluate prognostic differences related to the presence of automatisms in typical absence seizures.

Method: We reviewed 96 patients presenting with typical absence seizures. All had prolonged video-EEG polygraphic recordings and a minimum of 6 recorded absence seizures in the same record.

Results: In the whole group, we found a positive familial history for epilepsy in 39% and for febrile convulsions in other 19%. Seizure onset was between 3 years 2 months and 13 years. Absence length varied from 6 to 35 seconds. We found sporadic other types of seizures (mostly generalised) in 15% of cases and all but one patient were seizure free. Sixty-six (69%) presented automatisms during their absences. We found no differences between the two groups regarding familiarity, age at onset, response to treatment, other types of seizures and prognosis. Regarding EEG characteristics, we found no differences for frequency and morphology of the ictal discharge. The only significant difference was longer length of ictal discharge in patients with automatisms. Furthermore, compared to atypical absences and focal seizures, we noted polymorphism of automatisms in typical absences in different episodes in the same patient.

Conclusion: In our patients with typical absences we found no prognostic differences related to the presence or not of automatisms. This must be kept in mind since automatisms are always considered with suspicion by clinicians. Polymorphism of automatisms in the same patient in different episodes is important in differential diagnosis of typical absences versus atypical and focal seizures.

106

PANAYIOTOPOULOS SYNDROME: CLINICAL AND EEG CHARACTERISTICS OF CHILDREN

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Purpose: To review clinical and EEG data of children with Panayiotopoulos syndrome followed by The Neurology Division of Bambino Gesù Children's Hospital.

Method: Children with clinical and EEG features of Panayiotopoulos syndrome consecutively referred for first seizures to our lab between 1992 and 2005, were reviewed. All EEG, MR images and clinical notes were analysed. An interview with parents was performed where clinical data was insufficient.

Results: Ninety-eight children were reviewed. The follow-up was between 1–14 years (mean 4 years). Age at onset was between 3.5 and 5 years. Family history of epilepsy was found in 60% of children. First seizures occurred during sleep in 90% of patients, with all typical symptoms in 45%. It lasted 30 minutes (range 15–90 minutes). In 45% of patients, seizures were stopped by the administration of drugs in the Emergency Room. 5% of patients were referred to the intensive care unit. The first seizure was a single event in 30% of children; it was followed by one seizure or multiple seizures in the subsequent year, respectively, in 15% and 30% of children. Interictal EEG showed occipital spikes in 35% of patients, extraoccipital in 25%.

Conclusion: Panayiotopoulos syndrome is a benign idiopathic epileptic syndrome of infancy, which can present itself with severe onset due to the length of the first seizure. The evolution is benign due to sporadic seizure frequency and to the normal intellectual and motor development of children.

107

CRYPTOGENIC LATE ONSET EPILEPTIC SPASMS: AN OVERLOOKED SYNDROME OF EARLY CHILDHOOD?

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Purpose: Few reports detailing late onset epileptic spasms have been published. In order to determine whether this condition merely represents a late variant of classical West syndrome or exhibits specific features distinct from the latter and related to a later stage of brain maturation, we analysed the whole population with this specific seizure type, excluding symptomatic cases to avoid the effect of brain lesion.

Method: We reviewed the files of the 56 children evaluated for epileptic spasms in clusters having begun at 12 months of age or later, and analysed clinical and video-EEG data of the 22 patients (4–17 yrs, mean 8.5 yrs) without obvious aetiology.

Results: Interictal EEG did not show classic hypsarrhythmia. A temporal or temporofrontal slow wave and/or spike focus could be identified

in all cases. Twelve children showed spasms with a tonic component. Ictal EEG revealed generalised high voltage slow wave followed by diffuse voltage attenuation with superimposed fast activity. All children also exhibited other types of recorded seizures consisting of bursts of spike-waves with temporofrontal predominance, reminiscent of "atypical absences." In contrast with the occurrence of tonic components within a cluster of spasms, no tonic seizure *stricto sensu* was recorded nor reported by the caregivers. In 10 children, treatment (2 vigabatrin, 7 hydrocortisone, 1 ACTH) achieved complete cessation of seizures and disappearance of focal EEG anomalies, but spasms persisted in 12 children.

Conclusion: The cryptogenic group in our series without recognised aetiology and temporal or temporofrontal EEG anomalies seems to represent a type of epileptic encephalopathy intermediary between West and Lennox-Gastaut syndromes, in terms of seizure types and interictal EEG, and could correspond to dysfunction of the maturation process of the temporal lobe, possibly due to an undisclosed lesion.

108

FOCAL CORTICAL DYSPLASIA MAY CAUSE LATE ONSET INFANTILE SPASMS

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Purpose: Our aim was to investigate the features and aetiology of late onset infantile spasms (IS). Previous research has found that epileptic spasms start after the first year of life in 2.5% of patients with infantile spasm syndrome, and frontal lesions are associated with later onset than other localisations (Bednarek et al., *Epilepsia* 1998;39(1):55–60, Koo and Hwang, *Epilepsia* 1996;37(11):1068–71). Symptomatic aetiology was found in half of late-onset IS patients in the study by Bednarek, but no focal cortical dysplasias (FCD) were reported.

Method: A retrospective analysis of all children treated for IS with onset between 1–3 years of life at the epilepsy unit of the Hospital for Children and Adolescents from 1995 through 2005.

Results: Altogether 14 children with onset of spasms between 12–30 months of age were identified. In 4, epileptic spasms were the only seizure type. All patients had spasm clusters. Asymmetric spasms were observed in 2 patients. Either ictal or interictal EEG was lateralising in 6 patients. Four patients had cryptogenic aetiology. Six of 10 patients with symptomatic spasms had cortical dysgenesis (1 lissencephaly, 4 frontal FCD and 1 temporooccipital FCD). Three of the patients with FCD have so far been operated at age 36–53 months. All of them became seizure-free with improved cognitive development after surgery.

Conclusion: FCD, especially frontal, appears to be an important cause for late onset IS. Early surgery may significantly improve seizure outcome and cognitive development in these children.

Wednesday July 5, 2006
12:00–13:30
Hall 3a
Platform Session
Neuroimaging

109

STATISTICAL PARAMETRIC MAPPING AND QUALITATIVE ANALYSIS OF PROVOKED ICTAL SPECT IN TEMPORAL AND EXTRATEMPORAL DRUG-RESISTANT PATIENTS

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Purpose: To compare statistical parametric mapping (SPM) with visual analysis of provoked ictal SPECT in defining the epileptogenic zone of drug-resistant epilepsy patients.

Method: Twenty patients, submitted to epilepsy presurgical evaluation in the Epilepsy Surgery Unit of Catholic University in Rome, were included in the study. They suffered from drug-resistant epilepsy: 14 symptomatic and 6 cryptogenetic (8 extratemporal, 8 temporal, and 4 multifocal). All patients underwent Technetium-99m Ethyl-Cysteinate-Dimer interictal and pentylenetetrazol provoked ictal SPECT scans. After visual interpretation of interictal and provoked ictal studies, SPM analysis was performed on individual provoked ictal SPECT images in comparison with an established normal brain SPECT database. SPM results were compared to those of qualitative analysis.

Results: A good concordance between visual and SPM analysis was found in 19/20 patients with temporal and extratemporal epilepsies. Epileptogenic zone colocalised with the ictal hyperperfusion area in 15 subjects. In 1 case the lateralisation did not correspond, while the other 4 patients were multifocal. Nine subjects were operated with satisfying results (6 Ia, 1 Ib, 1III, and 1 short follow-up).

Conclusion: Even though SPM and visual analysis seemed to be comparably sensitive and accurate in localising ictal SPECT foci in both temporal and extratemporal epilepsies, SPM may overcome the inter-observer variability of visual interpretation and allow a more detailed anatomic localisation. The good concordance between qualitative and SPM analysis of ictal studies would suggest the possibility of avoiding performing the interictal SPECT. Finally, provoked ictal SPECT procedure confirmed its efficacy in determining the ictal hyperperfusion area.

110

MN ENHANCED MRI ASSESSMENT OF HIPPOCAMPAL PLASTICITY AFTER KAINIC ACID INDUCED STATUS EPILEPTICUS

R. Immonen, A. Pitkänen, and O. Gröhn (Department of Neurobiology, A.I.Virtanen Institute For Molecular Sciences, University of Kuopio, Finland)

Purpose: Mn^{2+}-enhanced magnetic resonance imaging (MEMRI) can reveal functional, structural and connectional alterations in high spatial resolution. We hypothesised that MEMRI after systemic Mn injection may provide a robust approach for detection of mossy fibre sprouting in vivo.

Method: $MnCl_2$ (45 mg/kg) was injected i.p. to 10 adult Wistar rats. After 12 hours, 6 of the rats (Mn+SE–group) received kainic acid (KA) injections inducing status epilepticus. T_1 -MRI was performed at 4.7T, 3 and 25 hours after KA injection. Two months later, a follow-up MRI was performed before and 24 hours after systemic Mn injection.

Results: No significant T_1 differences between groups were detected 15h after KA-injection, indicating that activity dependent Mn accumulation during generalised seizures must have been negligible. Two months after KA administration there were clearly visible differences in the Mn-enhanced structures in the hippocampus including thickening of the DG CA3 region, and increased signal intensity in CA1 region. In Mn-SE group the CA3 was $260 \pm 40\%$ thicker than in controls. The signal intensity ratios of CA1 and adjacent corpus callosum in T_1-weighted images were 1.37 ± 0.03 and 1.22 ± 0.03 in Mn-SE and control group, respectively ($p < 0.05$).

Conclusion: After systemic Mn injection MEMRI contrast is rather associated with structural plasticity than brain activation. Alterations in thickness and shape of the DG and CA3 region of the hippocampus can be attributed to mossy fibre sprouting. The increased MEMRI contrast in CA1 of KA injected animals indicates that MEMRI may have potential to reveal the abnormal axonal growth in CA1.

111

CORRELATION OF QUANTITATIVE MRI AND QUANTITATIVE NEUROPATHOLOGICAL ANALYSIS OF WHITE MATTER IN FOCAL EPILEPSY

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Purpose: Current optimal MRI sequences do not reveal either extent or nature of all neuropathologies underlying focal extrahippocampal refractory epilepsies. We wished to determine if new quantitative MRI sequences correlated with underlying pathoanatomical features identified neuropathologically, thus validating their use in MR-negative cases.

Method: Nine patients with known focal epileptogenic lesions (hippocampal and extrahippocampal) were imaged at 1.5T using standard presurgical volumetric and quantifiable research sequences: diffusion tensor, magnetisation transfer, FFT2. Careful perioperative measures, postsurgical imaging and correlation of presurgical imaging with anatomy of the resection specimen allowed coregistration of presurgical experimental imaging and postresection pathological material. Quantitative neuronal counts, GFAP and synaptophysin immunohistochemical data were obtained for comparison with quantitative imaging abnormalities determined by comparison with imaging data from control subjects.

Results: Reliable coregistration of MRI and pathological data was achieved. No correlation was observed between any quantified MR contrast and any quantitative neuropathological measure obtained in the white matter. The newer sequences did not identify a subtle neuropathological abnormality (hamartia) in one case.

Conclusion: We did not find a correlation between quantitative MR data and commonly-used neuropathological measures when quantified, or with qualitative neuropathological analysis. The MR contrasts are amongst the more frequently employed new sequences globally. The findings emphasise the need for both biologically driven newer quantitative MR contrasts, and newer exploratory neuropathological measures.

112

EPILEPTIC FOCUS LOCALISATION AND MULTIMODAL IMAGING IN A PAEDIATRIC POPULATION

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Purpose: In a paediatric population, the number of examinations should be optimised in order to reduce evaluation time and complexity of the presurgical exploration. EEG is still the most fundamental requirement and is performed on all surgical candidates. Could advanced EEG source imaging (ESI) of this always available data lead to a reliable identification of the epileptogenic area?

Method: 31 patients who underwent surgical intervention and had a follow-up of at least 12 months were retrospectively reviewed. All the patients had long-term video-EEG monitoring, high resolution MRI, PET, and if possible an ictal and interictal SPECT. Preoperative EEGs recorded from 19–29 scalp electrodes were reviewed, and interictal epileptiform activity was analysed using a linear source imaging procedure in combination with statistical parametrical mapping.

Results: In 28/31 patients (90%) the ESI correctly localised the epileptogenic region. These numbers compare favourably with the results from other imaging techniques (PET: 83%, ictal SPECT: 71%). In extratemporal epilepsy patients ESI was correct in all cases, and in temporal lobe patients in 10/13 cases. In 2 temporal lobe patients with less accurate ESI results 128 electrodes data could be analysed, and in both cases the 128 electrode ESI was correct.

Conclusion: EEG recordings are fast, noninvasive and are the most widely used technique in presurgical exploration units. Even more, this does not require sedation for acquisition. Consequently, in a multimodal imaging environment, ESI should be taken into account. This is more crucial with paediatric patients for whom noninvasive techniques should be considered as a priority.

113

USING ICA DECOMPOSITION OF EEG SIGNAL IN SIMULTANEOUS EEG-fMRI

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Purpose: Simultaneous EEG-fMRI is becoming a common tool in the study of epilepsy due to its great clinical potential on the localisation of the sources of interictal epileptiform activity. In this study, independent component analysis (ICA) (Makeig S et al., *Proc Natl Acad Sci U.S.A.* 1997;94:10979–84;) of the EEG data is evaluated as a potential blind method to detect interictal activity to then characterise the regressor to be used in the fMRI event related design.

Method: Studies were performed using a 32 channel MRI compatible EEG system (Micromed), and 1.5T MRI scanner (Siemens Symphony). Three patients, out of the 6 selected to be studied using EEG-fMRI, had anomalous activity during the fMRI. Their EEG data was post processed using a Matlab toolbox, EEGLAB (software from SCCN, University of California, San Diego). The fMRI processing was performed using FSL (software from FMRIB, University of Oxford) using event related designs based on: the neurologist's characterisation of spikes (Stephanovic B et al., *Neuroimage* 2005;28:205–215); the component that was found to be more correlated with the interictal activity.

Results: The results from the fMRI studies showed good agreement, and increased significance and size of activated regions (three fold) when using the ICA component design to model neural activity instead of the conventional spike characterisation.

Conclusion: These preliminary results indicate that this methodology could increase the detectability of sources of interictal activity, as well as reduce the time needed to create the event related model.

References: (1) Makeig S., et al, ProcNatlAcadSci. U.S.A. (1997), 94, 10979–84; (2) Stephanovic B. et al., Neuroimage 28 (2005) 205–215.

114

FUNCTIONAL MAGNETIC RESONANCE OF INTERICTAL SPIKES IN CHILDHOOD IDIOPATHIC OCCIPITAL LOBE EPILEPSY

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Purpose: Occipital lobe epilepsy (OLE) presents in childhood with different syndromes, with typical clinical and neurophysiological characteristics. Despite clearly distinct manifestations, the particular area of the occipital lobe where epileptic activity is located for each syndrome it is not known, nor is it known whether spatial segregation of these causes the heterogeneous clinical ictal semiology.

Method: Three children (aged 13, 12, and 12 years) with idiopathic OLE were submitted to simultaneous recording of EEG and functional magnetic resonance imaging (fMRI). An event-related paradigm was used to process the fMRI, taking the time of occurrence of spikes as the events of interest. The activations and deactivations obtained were represented in a high resolution anatomical T_1 image.

A high resolution EEG was obtained outside the scanner and used to optimise source analysis of interictal spikes.

Results: Two patients presented with the syndrome of late onset benign OLE (Gastaut type), and the fMRI activation areas were concordant and localised in the medial posterior parietal lobes. The EEG source analysis revealed discrepant results for one and concordant ones for the other when compared with fMRI data. One patient presented with idiopathic photosensitive OLE, and the fMRI activations involved the lower lateral and inferior occipital areas, as well as the posterior temporal lobes. Source analysis produced dipoles at a different localisation over the parietal-occipital area.

Conclusion: fMRI of interictal spikes in idiopathic OLE of childhood produces distinct maps of activation in different syndromes. EEG source analysis methods are poor predictors of their localisation.

Wednesday July 5, 2006
12:00–13:30
Hall 3D
Platform Session
Basic Science III: Pharmacology and Treatment

115

ANTICONVULSANT ACTION OF A SUBUNIT-SPECIFIC

NMDA RECEPTOR ANTAGONIST IFENPRODIL IN IMMATURE RATS

P. Mareš and A. Mikulecká (Institute of Physiology, Academy of Sciences of The Czech Republic, Czech Republic)

Purpose: To study possible anticonvulsant action of ifenprodil and its side effects on motor performance in immature rats.

Method: Motor seizures were elicited by pentylenetetrazol (100 mg/kg s.c.) in 7-, 12-, 18- and 25-day-old rats. The incidence and latency of minimal clonic and generalised tonic–clonic seizures were evaluated. Motor performance was tested in 12-, 18- and 25-day-old rats using age specific tests; spontaneouos locomotion was measured in open field. Ifenprodil (10, 20 or 40 mg/kg i.p.) was administered 20 min before pentylenetetrazol injection or behavioural testing. Open field was tested once more one hour after ifenprodil administration.

Results: Minimal clonic seizures could be elicited only in 18- and 25-day-old rats. Ifenprodil did not influence their incidence and latency. Specific anticonvulsant action (suppression of the tonic phase of generalised seizures) was found in 7-, 12- and 18-day-old rats. This effect decreased with age and it failed to appear in 25-day-old animals. Latency of generalised seizures was prolonged in 7-day-old but paradoxically shortened in older animals. Locomotor activity was transiently increased by ifenprodil only in 12-day-old rats; it remained uninfluenced in older animals. Motor performace was moderately compromised in the youngest group only. Motor activity was normalised one hour after the administration.

Conclusion: Ifenprodil exhibits specific action against the tonic phase of generalised seizures in the first three postnatal weeks. Unwanted side effects on motor activitites were observed only in 12-day-old rats but not in older animals. Ifenprodil thus differs from other NMDA receptor antagonists. Supported by research projects LC554 and AV0Z5011009.

116

INTRAHIPPOCAMPAL INJECTION OF ENDOTHELIN-1 INDUCES EPILEPTIC SEIZURES AND BRAIN INJURY IN IMMATURE RATS

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Purpose: To find whether focal ischemia, induced by intracerebral injection of endothelin-1 (ET-1) in immature rats results in development of acute seizures and neuronal loss.

Method: ET-1 was injected in doses 10, 20 or 40 pmol into the left dorsal hippocampus of Wistar rats 12 (P12; $n = 34$) and 25 (P25; $n = 30$) days old. After ET-1 infusion, animals were video/EEG monitored for 100 min and monitoring was repeated 22 h later. Parameters of electrographic seizures as well as pattern of their behavioural correlates were evaluated. The pattern of behavioural seizures was used to develop a model-specific scoring system. Cresyl violet and Fluoro Jade B-staining were used to detect brain damage. Extension of the lesion was evaluated semiquantitatively.

Results: After ET-1 injection, seizures occurred in 83–100% animals of all age and dose groups. There were no differences in average seizure duration (18–40s) or seizure frequency (3–7 seizures/100 min) among individual experimental groups. The lowest dose of ET-1 induced more frequent seizures in P12 than in P25 rats. Seizures persisted for 24h except P12 rats with 10 pmol of ET-1. Electrographic seizures were usually accompanied by clonus; the incidence of more severe convulsions (barrel rolling or generalised clonic seizures) increased with dose of ET-1. There were no dose-related differences in severity of hippocampal damage. Damage was, however, more severe in P12 compared to P25 animals.

Conclusion: Our data suggest higher sensitivity of P12 rats to ET-1-induced brain damage, however, no age- or dose-related differences occurred in ictogenic effects of ET-1-induced focal ischemia. Supported by grant 305/06/0713 (GACR).

117

MODULATION OF HIPPOCAMPAL EXTRACELLULAR DOPAMINE CONCENTRATION CONTRIBUTES TO THE ANTICONVULSANT MECHANISM OF ACTION OF NEUROPEPTIDE Y

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Purpose: Neuropeptide Y (NPY) exerts potent anticonvulsant effects in several seizure models, and increases hippocampal dopamine when administered intracerebroventricularly (Drumheller et al., *Neuropeptides* 1994). In the focal pilocarpine model, increased hippocampal dopamine results in seizure suppression via D2-receptor activation (Clinckers et al., *J Neurochem* 2004). Our aim was to investigate the origin of the NPY-induced increase in hippocampal dopamine, and its involvement in NPY's anticonvulsant activity.

Method: Limbic seizures were evoked in freely moving rats by intrahippocampal pilocarpine administration via a microdialysis probe. Prior to pilocarpine administration, NPY was administered intracerebroventricularly (1–10 nmol), intrahippocampally via the microdialysis probe (10–100 μM), or coadministered intrahippocampally with the D2-receptor antagonist remoxipride (4 μM). Changes in hippocampal extracellular dopamine, serotonin, glutamate and GABA concentrations were monitored, and behavioural changes indicative of seizure activity were scored.

Results: Intracerebroventricular (10 nmol) and intrahippocampal (20 μM) NPY administration increased hippocampal dopamine dialysate levels ($188 \pm 16\%$ and $178 \pm 26\%$ respectively, $p < .05$), but had no effect on hippocampal glutamate, GABA or serotonin. Pilocarpine-induced seizures were attenuated in both treatment groups (seizure scores 3.0 ± 1.4 and 3.8 ± 1.9 respectively, $p < .05$ compared to 12.8 ± 3.1 in control group). Hippocampal D2-receptor blockade with remoxipride reversed NPY's anticonvulsant activity (seizure score 9.0 ± 1.2).

Conclusion: NPY-induced increases in hippocampal dopamine are elicited locally in the hippocampus, possibly via activation of NPY receptors on hippocampal dopaminergic terminals. Moreover, the activation of hippocampal D2-receptors caused by increased dopamine is shown to play a central role in NPY's anticonvulsant mechanism.

118

ANTICONVULSANT PROPERTIES OF HYPOTHERMIA IN EXPERIMENTAL STATUS EPILEPTICUS

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Purpose: Status epilepticus refractory to first-line anticonvulsants frequently requires treatment escalation with intravenous anaesthetics. Due to potentially hazardous side effects alternative treatment options are needed. We assessed the anticonvulsant properties of hypothermia in a rat model of electrically induced self-sustaining status epilepticus (SSSE).

Method: Animals with SSSE underwent 3 h of external cooling to 29°C ($n = 7$), intraperitoneal administration of low-dose diazepam (2 mg/kg; $n = 8$), or a combination of both ($n = 9$). Animals that underwent cooling were rewarmed. Severity and number of motor seizures and frequency and amplitude of epileptic discharges were assessed for 5 h and compared with untreated controls ($n = 10$). Clinical features were expressed as motor seizure index (MSI) incorporating time in and severity of motor seizures. Electrophysiological parameters were related to pre-treatment baseline and expressed as fraction of 1.

Results: Diazepam reduced only amplitudes at single time points. Hypothermia had no impact on electrophysiological features, but significantly reduced MSI (0.12 ± 0.31 vs 1.23 ± 1.4 in controls; $p < 0.05$). Combining hypothermia and diazepam, MSI was also significantly reduced (0.08 ± 0.13; $p < 0.05$). Furthermore, there was a significant reduction for amplitudes after 40 min (0.34 ± 0.25 vs. 0.84 ± 0.33 in controls; $p < 0.05$) up to 160 min (0.13 ± 0.13 vs. 0.49 ± 0.29; $p < 0.01$) and for frequency after 20 min (0.58 ± 0.41 vs. 1.00 ± 0.15; $p < 0.01$) up to 180 min (0.47 ± 0.24 vs. 1.02 ± 0.32; $p < 0.01$). After rewarming, frequency reduction was partially reversible.

Conclusion: In this animal model, coadministration of low-dose diazepam and hypothermia exhibits pronounced anticonvulsant properties. Hypothermia, therefore, may become a reasonable endorsement to the pharmacological management of SE in patients.

119

RECOMBINANT ADENO ASSOCIATED VIRAL VECTOR (rAAV) MEDIATES NEUROPEPTIDE Y (NPY) GENE OVER-EXPRESSION IN THE HIPPOCAMPUS OF EPILEPTIC RATS, ARRESTS DISEASE PROGRESSION, AND REDUCES SPONTANEOUS SEIZURES

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Purpose: rAAV mediates long-term human NPY overexpression in normal rat hippocampal neurons, reduces acute seizures and delays kindling. We studied whether intrahippocampal application of rAAV-NPY in epileptic rat hippocampus reduces spontaneous recurrent seizures (SS).

Method: Three months after electrically induced status epilepticus, rats were video-EEG monitored 24h/day for 2 weeks to obtain baseline SS frequency. Then, a rAAV-NPY or rAAV-empty cassette (5.2×10^{12} vg/ml) was intrahippocampally injected bilaterally; 4 weeks later rats were video-EEG monitored for 2 weeks. NPY expression and release were measured by immunohistochemistry and RIA. NPY receptor binding was assessed by autoradiography.

Results: In the rAAV-NPY group (n = 10), progression in SS was observed in 3 rats which showed ~1.5-fold increase in SS frequency and total duration compared to their baseline. Four rats showed a ~2-fold reduction in SS frequency and total duration while 3 rats had similar SS frequency as during baseline recording. In the AAV-Empty group (n = 10), 7 rats showed progression in SS showing ~3-fold increased SS frequency and total duration. None of the rats showed decreased SS frequency and 3 rats had SS frequency similar to baseline. NPY overexpression did not affect hippocampal Y2 while reducing Y1 receptors. In these rats, NPY release was enhanced compared to rats injected with the AAV-Empty.

Conclusion: Overexpression of the human NPY gene in the epileptic rat hippocampus produces a releasable pool of NPY which reduces SS frequency and total duration and arrests disease progression. NPY gene therapy may have a therapeutic potential for inhibiting recurrent seizures at focal onset. Supported by Telethon Onlus Foundation.

120

ANTICONVULSANT EFFECTS OF BOTULINUM NEUROTOXIN E

F. Antonucci, E. Novelli, M. Caleo, and Y. Bozzi (CNR Neuroscience Institute, Pisa, Italy)

Purpose**:** Botulinum neurotoxin E (BoNT/E) blocks neurotransmission by cleaving SNAP25, an essential component of the synaptic vesicle release machinery. We previously showed that BoNT/E injection into the rat hippocampus prevents kainic acid (KA) induced seizures. Here we investigate whether BoNT/E administration after status epilepticus (SE) can block spontaneous seizures in a chronic model of epilepsy in the mouse.

Method: Adult C57Bl/6N male mice received intrahippocampal injections of BoNT/E (25 nM, 0.25 microlitres). The duration of BoNT/E effect was evaluated by in vivo recordings of hippocampal spike activity, performed 1 to 21 days after toxin administration. To assess the anticonvulsant effect of BoNT/E, SE was induced by a single injection of KA (1 nmole) into the mouse hippocampus and seizures were monitored by continuous EEG recordings. Thirty-five days later, following the appearance of spontaneous seizures, BoNT/E was injected into the hippocampus and its effects were evaluated by EEG and histology.

Results: BoNT/E administration into the mouse hippocampus completely abolished hippocampal spike activity, its effect lasting about 10 days. Intrahippocampal injection of KA induced SE which was followed, after a two-week latency period, by spontaneous recurrent seizures accompanied by mossy fibre sprouting and granule cell dispersion. Experiments are ongoing to determine whether BoNT/E administration in chronically epileptic mice can have an anticonvulsant effect.

Conclusion: BoNT/E injection into the mouse hippocampus blocks the spontaneous activity of pyramidal neurons and might be anticonvulsant in a chronic model of epilepsy.

Wednesday July 5, 2006
12:00–13:30
Ballroom 1
Platform Session
Neuropsychology

121

COGNITIVE PERFORMANCE OF SCHOOL-AGED CHILDREN EXPOSED TO ANTIEPILEPTIC DRUGS (AED) IN UTERO

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Purpose: Although major and minor congenital malformations and abnormal growth parameters are known to be increased in children of women with epilepsy, cognitive performance in children of these mothers has not been well characterised. A better understanding of the relative effects of AED exposure and maternal seizures on cognitive functioning would be helpful in managing pregnancies of women with epilepsy.

Method: Mothers with epilepsy (n = 58) were followed prospectively with frequent monitoring of AED doses, plasma levels and seizure occurrence during pregnancy. Their school-age children (n = 96, ages 6–16) underwent detailed neuropsychological testing (NPT). Mothers and fathers of these children also underwent NPT whenever possible. A control group of 93 children of mothers without epilepsy, matched for age and education, also underwent NPT, as did their parents.

Results: Children of mothers with epilepsy have a significantly lower full scale IQ (FSIQ) than controls (exposed = 102; control = 112; $p < .001$). There was no difference between FSIQ of children of mothers who had seizures during the pregnancy than of those who did not (seizures = 102; no seizures = 103; $p = 0.96$). There was no significant difference in FSIQ between children whose mothers had idiopathic generalised epilepsy (IGE) and partial epilepsy (PE) (IGE = 101; PE = 103; $p = 0.56$). Children exposed to polytherapy had lower FSIQ compared to monotherapy, but the difference was not statistically significant (poly = 100; mono = 104; $p = 0.31$). Children exposed to either dilantin or tegretol monotherapy in utero showed no significant difference in FSIQ (dilantin = 105; tegretol = 103; $p = 0.68$).

Conclusion: Cognitive ability was significantly reduced in children of women with epilepsy. Our study suggests that this is due to exposure to AED rather than to maternal seizures during pregnancy. Further analyses will be carried out by trimester and on specific subtests of the NPT battery, also taking into account AED doses and levels.

122

NEUROPSYCHOLOGICAL CHARACTERISTICS OF TEMPORAL LOBE EPILEPSY PATIENTS WITH TYPICAL AND ATYPICAL LANGUAGE LATERALISATION

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Purpose: We studied the effects of language lateralisation and other variables that may affect the crowding phenomenon. We hypothesised limited nonverbal abilities compared to verbal abilities in temporal lobe epilepsy patients with atypical language dominance particularly in subjects with early seizure onset, and atypical language dominance more frequently in patients with a left hemisphere focus.

Method: In a sample of 241 (113 male; 128 female) patients with right or left TLE who are candidates for neurosurgical treatment, neuropsychological assessment and an intracarotid amobarbital procedure were performed. 212 (89%) Patients had a left hemisphere language dominance, 12 (5.0%) patients showed a right hemisphere dominance and 14 (5.9%) patients a bilateral language dominance. Patients were categorised in 4 groups according to age at seizure onset. With a multivariate analysis of variance we analysed the neuropsychological performances by language dominance and epileptic focus, age at onset, handedness, and gender.

Results: Results demonstrated handedness and epileptic focus to be risk factors for atypical language dominance, while no associations between age at seizure onset or gender with language dominance were observed in this sample. Neither language dominance nor language dominance in combination with the lateralisation of the epileptic focus, age at seizure onset, handedness of gender showed evidence for a crowding effect. A significant apposite effect of the crowding phenomenon was demonstrated at a univariate level, as right hemisphere language dominance in patients with early left temporal lobe epilepsy was associated with higher performance on non verbal IQ subtests.

Conclusion: In conclusion, left hemisphere epileptic focus and left handedness are risk factors for atypical language dominance, while age at onset and gender are not. We found no indications for the crowding phenomenon in this population.

123
OCCIPITAL CSWS AND VISUAL AGNOSIA

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Purpose: To describe the long-term follow-up data of neuropsychological functions in a boy originally diagnosed with occipital continuous epileptiform activity during sleep (CSWS) and visual agnosia (i.e., inability to recognise objects without impairment of visual acuity).

Method: The boy was first diagnosed at the age of 8 years old with CSWS by using digital 24-hour video EEG monitoring. Consecutive 24 hour video EEG recordings showed continuous spike and wave activity covering approximately 80% of the non-REM sleep with the maximal topographic distribution bilaterally on the occipitotemporoparietal regions with the spike initiation on the left hemisphere. These were not affected by adequate doses of antiepileptic drugs in mono- or polytherapy. The neuropsychological assessment comprised several tests (e.g., WISC-III, WMS-R, TVPS, Hooper Visual Organization test). Academic achievement was measured using a standardised test of reading, spelling and arithmetic skills.

Results: The original neuropsychological assessment showed that the boy had normal verbal intelligence but major deficits in visual perception. His neuropsychological profile resembled adult-type ventral simultanagnosia. After a 7 year follow up neuropsychological assessment and the complete disappearance of the CSWS pattern in the latest video-EEG recording at the age of 15 years, the deficits in visual perception were still severe (PIQ 40) whereas verbal intelligence was intact (VIQ 96). Visual perception was still characterised by piece-by-piece perception which resembles the adult-type of ventral simultanagnosia. However, more precise neuropsychological assessment revealed improvements in visual perceptual skills especially in object recognition and used compensatory mechanisms, and his academic achievements were relatively good.

Conclusion: This follow-up case study suggests that general intellectual measurement (IQ) is not enough and more precise assessment of neuropsychological functioning and description of academic skills are warranted in patients with CSWS, even after the disappearance of the electrophysiological phenomena.

124
MEMORY CONSOLIDATION AND ACCELERATED FORGETTING IN CHILDREN WITH IDIOPATHIC GENERALISED EPILEPSY

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Purpose: To determine whether children with idiopathic generalised epilepsy (IGE) show accelerated forgetting of verbal and nonverbal information in comparison to healthy controls matched for age and IQ.

Method: Twenty-one children with IGE were compared with 21 healthy controls on measures of verbal and visuospatial memory at delays of 30 minutes, and again at an extended delay of 1 week. Measures included the Stories and Dot Location tests from the Children's Memory Scale and the Wechsler Abbreviated Scale of Intelligence. A minimum-learning criterion controlled for initial learning effects was used.

Results: For the auditory-verbal memory test, group performance was comparable at 30 minutes but children with IGE recalled significantly less than controls after a delay of 1 week. When differences in the number of learning trials to criterion were controlled for, the main effects of group and delay became nonsignificant (although the interaction remained significant). There were no group differences for recognition performance on this test. Group comparisons for the visuospatial task were nonsignificant, although this may have been due to insufficient statistical power. The pattern of performance for this task was similar to that for the auditory-verbal test.

Conclusion: Poor initial learning efficiency led to retrieval difficulties at the longer delay, and was more common in the IGE group. This pattern of deficits may be qualitatively different from those observed in "accelerated forgetting" (Blake et al., *Brain* 2000; 123: 472–483) although may present similarly in clinic. These findings are of interest to theoretical accounts of consolidation and learning in childhood epilepsy.

125
ATTENTION AND WORKING MEMORY IN CHILDREN WITH EPILEPSY: AN EVENT-RELATED POTENTIAL STUDY

I. Myatchin and L. Lagae (University Hospitals KU, Leuven, Belgium)

Purpose: This study investigated attention and working memory in children with epilepsy. We hypothesise that dysfunctions in these 2 neuropsychological functions underlie the frequent learning problems in children with epilepsy.

Method: Cohorts of children with epilepsy (n = 37) and age-matched control children (n = 32) were tested with a visual go-no-go and 1-back working memory task. Behavioural parameters (omission and commission errors, reaction times) and event related potential (ERP) parameters (latencies x amplitude x position) were compared across the groups.

Results: No differences in behavioural parameters across the groups were found in either test. In the go-no-go task no differences were found for P300 amplitude and latency. However, the amplitude of the P500 (at Fz electrode) was significantly lower in the epilepsy group (mean $0.1 \pm 17.8\ \mu$V) than in the control group (mean $13.8 \pm 7.7\ \mu$V). In the 1-back task the amplitude of P300 differed significantly between the epilepsy group (mean $2.4 \pm 5.4\ \mu$V) and the control group (mean $-12.4 \pm 5.6\ \mu$V). Also for the P500, a significant difference in amplitude was found (Cz, mean $13.1 \pm 9.1\ \mu$V in epilepsy and $-9.4 \pm 8.8\ \mu$V in the control group). This latter difference was more prominent in generalised epilepsy. Overall, no differences in peak latencies were found. There was no effect of medication.

Conclusion: Although epilepsy and control patients performed equally in attention and working memory tasks, ERP results clearly showed other patterns of cortical functioning. Especially over the frontal

and central regions, different activation patterns were seen in children with epilepsy.

126

ASSOCIATION BETWEEN GENOTYPE AND NEUROLOGICAL AND COGNITIVE SYMPTOMS IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX (TSC)

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Purpose: To replicate and extend findings of an association between type of mutation (TSC1, TSC2 and no mutation) and cognitive and neurological symptoms in patients with TSC, using sophisticated valid, reliable, and reproducible methods.

Method: Fifty-eight patients (21 TSC1, 30 TSC2 and 7 without mutation) were recruited at the neurology outpatient department. DNA analysis established type of mutation. Computerised tuber segmentation program with 3-D FLAIR MRI provided number and volume of tubers (tuber load). Epilepsy characteristics and EEG recordings were obtained. With a comprehensive neuropsychological battery six cognitive domains were assessed.

Results: All but 6 patients had epilepsy. Age at seizure onset was later in TSC1 (mean = 3.4; SD = 4.9) compared to 0.8, (SD = 1.2; p = .02) and tuber volume was lower (mean = 0.7%; SD = 0.51) compared to 1.7% (SD = 0.98; p = 0.000) than in TSC2. Age at seizure onset was not independently related to tuber volume. Seizure types did not distinguish TSC1 and TSC2. Cognitive test were graded. Grades 1 (severely below average) and 2 (below average) contained predominantly TSC2 patients, whereas grades 3 (average) and 4 (above average) contained predominantly TSC1 patients. Results of patients with no mutation moved, g*rosso modo*, between those of TSC1 and TSC2.

Conclusion: A more favourable neurological outcome in TSC1 compared to TSC2 is supported. With respect to cognition, the study highlights 1) a considerable overlap between the genotypes with 2) a predominance of quite severe impairment in TSC2.

Poster Session

Monday July 3, 2006
13:30–15:00
Poster Session 1
Adult Epileptology

p127
STATUS EPILEPTICUS IN POSTSTROKE EPILEPSY

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Purpose: To analyse the status epilepticus (SE) rate in poststroke epilepsy.

Method: The study population was derived from the Area VII, Alvarez Buylla Hospital, Asturias, Spain, database. Thirty consecutive patients with poststroke SE were identified among a total of 107 patients diagnosed with poststroke epilepsy between 1999 and 2005 (58 males and 49 females) and were enrolled. Patients were evaluated by standard protocol including EEG (when myoclonus or low level consciousness was observed), neuroimaging (head-CT or MRI) and routine blood testing. Patients were grouped (12 males and 18 females) as having early-onset (occurring at initial stroke and within two weeks of the stroke) and late-onset (occurring more than two weeks after the stroke or during follow up) SE. The mean age of males and females was 70 years (range 41–86) and 72 (range 62–93) respectively.

Results: We found 9 early onset status epilepticus (EOSE): 3 males and 6 females. In females the aetiology was: 1 case thrombopenic pupura thrombotic, 3 ischemic cases and 2 haemorrhagic transformation stroke. In males the cause was: 1 spontaneous intracerebral haemorrhage and 2 subarachnoid haemorrhages with old stroke. EEG recording revealed in 4 cases PLEDs and secondarily generalised polyspike/wave in another. Recording could not be obtained for the rest of the patients. Twenty-one patients suffered late onset status epilepticus (LOSE): 9 males and 12 females. In females the causes were: 1 superficial brain siderosis, 3 multi-infarct with leukoaraiosis, 5 stroke, 1 subdural haematoma intracranial acute and 1 haemorrhagic transformation stroke. Between the males we found: 3 stroke cases, 3 patients with multi-infarct and leukoaraiosis, 2 spontaneous intracerebral hemorrhage and neurosarcoidosis in 1 case. EEG recording during SS was obtained in 10 cases: 6 showed PLEDs, 1 BIPLED and finally 3 cases generalised or focal polyspike.

Conclusion: The SE rate in poststroke epilepsy was 28%: 8.4% were EOSE and 19.6% LOSE. The mortality of EOSE was 77.7% y en LOSE was 31.5% but patients suffered cognition disorders.

p128
TREATMENT OF REFRACTORY STATUS EPILEPTICUS IN ICU

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Purpose: Refractory status epilepticus (RSE) is the most severe form of status epilepticus which doesn't respond to first and second line antiepileptic drug therapy and represents a major neurological emergency. We aimed to analyse the aetiology, treatment strategies and outcome of RSE.

Method: A retrospective analysis of all patients treated at Central Intensive Care Unit at University Hospital with a diagnosis of RSE between January 2001 and December 2005. Thirty-two patients (57.6% female; 44.8% male), aged 14–67, mean 39.4 years, admitted in ICU setting and treated with potent anesthetics and mechanically ventilated were analysed in our study.

Results: Preexisting epilepsy was the most common cause of RSE (62.5%); severe head trauma caused RSE in 15.6%, stroke caused RSE in 12.5%, encephalitis in 6.2% and metabolic disorder in 3.1%. 62.5% of patients were treated with propofol; 28.8% with thiopental and 9.6% with propofol and subsequently with thiopental. Median duration of ICU stay was 3.34 days (range 1–12). Twenty-nine patients survived the episode of RSE; 2 patients died and 1 patient is in a persistent vegetative state due to cerebrovascular complications.

Conclusion: There is no consensus for treatment of RSE, but for a successful outcome, anaesthesia coma induction, mechanical ventilation and vital function support is essential.

p129
PROLONGED EPILEPTIC SEIZURES OR STATUS EPILEPTICUS?

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Purpose: Although most epileptic seizures stop spontaneously within a few minutes, some continue and may constitute a life-threatening status epilepticus (SE). This study investigates the probability of SE among patients exhibiting prolonged seizures.

Method: A retrospective study on all patients admitted to the HUCH emergency room with the diagnosis epilepsy (G40) or convulsion (R56) in 2003 ($n = 1205$). Based on medical records, all patients whose convulsion lasted > 5 min were analysed.

Results: One out of 6 cases of all convulsions were prolonged over 5 min, 27% of them having no previous epilepsy diagnosis. 40% of prolonged seizures ceased by 20 min, a further 9% by 30 min, 12% by 60 min, while 39% continued over 60 min. The relative proportion of various aetiologies differed in prolonged seizures (5–30 min), established SE (30–60 min) and refractory SE (>60 min). Preceding alcohol consumption was a common cause in the first two groups (19%, 16%), while such cases were not found in the refractory SE group. The role of previous intracerebral haemorrhage or brain tumour strongly accentuated in convulsions lasting over 60 min. 20% of prolonged seizures (5–30 min) ceased spontaneously, 44% stopped with benzodiazepine, 25% with phenytoin and 11% required anesthesia. Of all cases classifiable as SE based on seizure duration over 30 min, only 65% were diagnosed SE.

Conclusion: SE is grossly underdiagnosed. Prolonged seizures bear a considerable risk of SE, particularly if a previous haemorrhage or brain tumour is the aetiological factor.

p130
ICTAL CARDIAC ASYSTOLE IN A PATIENT WITH FOCAL STATUS EPILEPTICUS

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Purpose: Disturbances of autonomic functions are frequent findings during epileptic seizures, mostly of temporal origin. We report a patient with symptomatic right parietooccipital epilepsy, who experienced an ictal cardiac asystole during a focal status epilepticus (SE).

Method: A case report.

Results: A 66-year-old woman with a right parietal-occipital cerebral tumour (metastases of an adenocarcinoma of the lung) experienced her first focal motor seizure in March 2005. She received no antiepileptic treatment at that time. Routine ECG showed sinus rhythm with first degree AV-blocking. Four months later the patient was referred to our hospital with an episode of dizziness, intermittent jerking of the left arm and leg, at times interrupted by tonic stiffening followed by mild hemiparesis. The symptoms lasted for at least 2 hours. EEG showed continuous rhythmic parietooccipital activity on the right side. Simultaneous coregistered ECG showed a sinus rhythm of 108 bpm, decreasing over 10 seconds and finally an asystole for 13

seconds. EEG showed diffuse slowing. The patient lost consciousness during that time. A focal SE was diagnosed and lorazepam 6 mg IV was administered. Ictal EEG activity ceased subsequently and clinical symptoms resolved completely except for a postictal Todd paralysis. Antiepileptic treatment was started with gabapentin. A cardiac pacemaker was not implanted. The patient remained seizure free for the following 3 months.

Conclusion: Ictal asystole is potentially life threatening and may be related to ictal cardiac autonomic dysfunction. The relationship to sudden unexpected death in epilepsy patients is highly likely but remains unclear.

p131
ICTAL APHASIA AS MANIFESTATION OF PARTIAL STATUS EPILEPTICUS PROVOKED BY BLEEDING CAVERNOMA: DIAGNOSTIC ROLE OF NEUROIMAGING

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Purpose: Cavernomas represent 5–20% of vascular malformations in the central nervous system. Occurrence of epilepsy in patients with cavernoma is 40%–70%. Magnetic resonance imaging (MRI) is the most appropriate method to identify cavernomas; late diagnosis could occur when MRI execution is delayed. Partial status epilepticus could represent the manifestation of an acute bleeding cavernoma. Language disturbance such as ictal aphasia may accompany other signs of seizure involving dominant hemisphere, albeit it is infrequent as the sole symptom of partial status epilepticus.

Method: A 55-year-old right-handed man, affected by partial epilepsy since age 15, was treated with carbamazepine (CBZ) 600 mg/day. MRI was never performed. The patient reduced CBZ in his own way. One week later he was hospitalised because of recurrent episodes of aphasia. Ictal EEG showed a spiky fast activity and sharp waves in the left temporal region, involving homolateral frontal and occipital regions.

Results: Postictal neurological examination was normal but there was an arithmetic calculation deficit. MRI revealed left parietal cavernoma bleeding.

Conclusion: Anatomical lesion involving specific language in the brain area provoked ictal aphasia; postictal impairment in arithmetical calculation is probably related to involvement of left parietal region. We hypothesised that sudden reduction of carbamazepine associated with bleeding cavernoma provoked partial status epilepticus. Albeit the diagnosis of epilepsy in our patient results was not recent, MRI played a key role in the diagnosis of structural abnormalities underlying the epilepsy and is mandatory in patients affected by focal seizures.

p132
DELAY OF TREATMENT RESPONSE IN ADULT STATUS EPILEPTICUS PATIENTS

[1]L. Ritvanen, [1]A. Kataja, [1]O. Häppölä, [2]R. Kälviäinen, and [1]S. Soinila ([1]Helsinki University Central Hospital, Finland, [2]Kuopio University Hospital, Finland)

Purpose: The need to treat prolonged seizures aggressively arises from the observation that seizures lasting over 30 min. may cause cell death and permanent brain damage. Little information is available on factors causing delay of treatment. This study attempts to evaluate the time from seizure onset to burst-suppression as a measure of treatment response and to analyse the factors contributing to the delay.

Method: This is a retrospective study including all patients over 18 years of age, who were diagnosed as status epilepticus (SE) and treated in 2002–2003 in HUCH (population base 1.4 million). The patients were identified from the HUCH electronic patient database chronologically by the ICD10 code G41 and patient data were collected, based on proper permissions, from the medical records.

Results: The total case account is 87. Preliminary analysis of 57 cases shows that 91% of cases are convulsive. Epilepsy had been diagnosed prior to SE in 61% of patients. 72% of the 30 EEG-monitored patients obtained burst-suppression. Mean delay of treatment response (time from onset to burst-suppression) was 34 hours. Mean recovery time (time from onset to return of consciousness) of all patients was 95 hours. Mortality during hospital admission was 11%. Delay in treatment response did not correlate with time of recovery or death.

Conclusion: Our study suggests that delayed treatment response of SE may not predict slow recovery or death. It is yet unknown how delay affects the long-term outcome of SE.

p133
NONCONVULSIVE STATUS EPILEPTICUS (NCSE) PRESENTING WITH PURE ALEXIA (ALEXIA WITHOUT AGRAPHIA)

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Purpose: Pure alexia is a rare disorder usually caused by stroke. It is usually due to a lesion involving the occipitotemporal junction of the dominant hemisphere. We present a case of NCSE with clinical manifestation of pure alexia.

Method: A case of pure alexia associated with NCSE was investigated in detail and the data is presented in the Results section.

Results: A 57-year-old man presented at the emergency department with inability to read and fluctuations in his mental status. He was in diabetic-ketoacidosis with a blood sugar of 678 mg/dl. Following stabilisation of his blood sugar, a neurology consultation was done. The neurological examination revealed that the patient was unable to read any words despite his ability to recognise individual letters. The patient was able to write normally. A brain MRI showed cortical swelling and signal increase in FLAIR sequences over the left temporooccipital junction. During a routine EEG, two electrographic seizures originating from the left temporooccipital regions were recorded. The electrographic seizures were associated with eyes deviated to the right and inability to respond to questions. A diagnosis of NCSE was done and the seizures were aborted following initiation of treatment with antiepileptic medications. In a few hours, the patient started to read most of the words and his alexia was completely resolved 24 hours later. Follow-up EEG did not show any ictal activity.

Conclusion: To our knowledge, this is the first case of pure alexia associated with NCSE. NCSE may manifest in unusual forms and a high index of suspicion is necessary to diagnose and treat those patients.

p134
INTRAVENOUS VALPROATE IN STATUS EPILEPTICUS: A SYSTEMATIC REVIEW OF THE EVIDENCE

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Purpose: Status epilepticus (SE) is a serious epileptic event associated with significant morbidity and mortality. First-line treatment of SE traditionally involves intravenous administration of benzodiazepines, principally lorazepam. However, sometimes, SE is resistant to benzodiazepines and second-line treatments are required. Thereby, the availability since the 1980s of intravenous valproate provides an interesting therapeutic alternative. A large number of reports have suggested that such a treatment may be efficacious. We have performed a systematic literature review to assess the evidence for this.

Method: An electronic literature search was performed using "valproate," "valproic acid" and "status epilepticus" as key-words to identify relevant studies published until 30 September 2005. All identified studies were cross-referenced to identify further reports. The worldwide pharmacovigilance database of Sanofi-Aventis was also interrogated to identify reported adverse events.

Results: No randomised clinical studies were identified. 348 adults or children were included in 6 prospective and 9 retrospective studies. In around $\frac{3}{4}$ of cases, seizure control was achieved during valproate infusion or within 20 minutes. The most commonly reported effective doses were 15 mg/kg in bolus (adults) or 20 mg/kg (children) followed by 1 mg/kg/h infusion. The incidence of adverse events (mainly hypotension, dizziness

and thrombocytopenia) was low (less than 10%) and independent of infusion rate.

Conclusion: Although no randomised double-blind clinical study has been performed, available data from open-label studies have shown intravenous valproate to be effective in resolving SE in patients who have previously failed conventional first-line therapies such as benzodiazepines. No specific safety issues have been identified.

p135

ARE EXPERIENTIAL EPILEPTIC PRODROMES NON-CONVULSIVE STATUS?

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Purpose: 1) To assess the percentage of patients with chronic epilepsy reporting prodromes (experiential symptoms lasting for at least 30 min. before seizures). 2) By acute video-EEG during prodromes to clarify whether prodromes were in fact nonconvulsive status epilepticus.

Method: The study included 985 adult out- and in-patients at a tertiary referral centre, interviewed during a one-year period. The study was approved by the medical ethics committee, and comprised 2 parts: 1) An interview by the treating physician, and subsequently by the authors. 2) Acute video-EEG recording in the case of prodromes.

Results: 23 patents (2.3%) reported prodromes. 16 had focal epilepsy syndromes, and 5 had idiopathic generalised epilepsy (mainly juvenile myoclonic). Two cases could not be classified. In 5, an ictal EEG was obtained, 2 of them showing clear EEG evidence of nonconvulsive status epilepticus (NCSE), and the 3rd had ambiguous findings. In the remainder, ictal EEG could not be performed due to practical problems.

Conclusion: To our knowledge, this study is the first attempt to clarify the role of NCSE in prodromes. This is confirmed in 2 out of 5 cases studied with acute video-EEG, and this mechanism should be borne in mind for patients with experiential epileptic prodromes. Besides this, we found a prevalence of prodromes far below those reported in previous studies (e.g. Hughes et al, Seizure 1993–2:201–203, Rajna et al, Seizure 1997–6:361–368). Notably, prodromes were also quite frequent in idiopathic generalised epilepsies.

p136

THE TRUE PREVALENCE OF EPILEPSY IN ADULTS EXCEEDS 1% IN RURAL NORWAY

E. Brodtkorb and O. Sjaastad (Department of Neurology and Clinical Neurophysiology, Trondheim University Hospital, Trondheim, Norway)

Purpose: Incomplete case finding is a problem in all epidemiological studies in epilepsy. We tried to optimise case-ascertainment by personal interviews.

Method: The study was carried out as part of an epidemiological study of headache in the Vågå community. During a 2-year period, 1838 inhabitants in the age range 18–65 (88.6% of the target population) were interviewed based on a questionnaire. Individuals with learning disability, mental disorders and dementia were excluded (Sjaastad O, et al. The Vågå Study: An outline of the design. Cephalalgia 1999;19 Suppl 25:24–30). One question concerning epilepsy was presented to 1793 consecutive cases: "Have you ever had convulsions, epileptic fits or other epileptic symptoms?" The medical records of those who replied positively were reviewed, and telephone interviews were performed when needed.

Results: 133 individuals confirmed possible epileptic symptoms. Only 40 were diagnosed as ever having had epilepsy. 18 were treated with antiepileptic drugs, of whom 10 had active epilepsy with seizures within the last five years. The prevalence of epilepsy (active + in remission with treatment) was calculated to be 10.0/1000. The prevalence of active epilepsy was 5.6/1000.

Conclusion: By this unique method of case-ascertainment, the prevalence rate of epilepsy was 1%, despite the fact that high risk groups for epilepsy, such as children, old people and individuals with cognitive deficits and communication problems were excluded from the study. Although these findings were derived from a small population sample, they may indicate that the true crude prevalence of epilepsy in Western Europe is higher than previously presumed.

p137

RECURRENT ABSENCE STATUS AND UNILATERAL SUBCLINICAL PAROXYSMAL ACTIVITY: CLINICAL EVOLUTION AND PHARMACOLOGICAL SENSITIVITY

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Purpose: EEG remains the most essential distinguishing tool between focal and generalised nonconvulsive status epilepticus. However, there is evidence of variant or transitional forms with an intermediate EEG state between focal and generalised NCSE.

Method: We report a patient with a history of rare generalised tonic–clonic seizures (GTCS) and recurrent absence status (AS) in whom a highly unusual interictal EEG with a unilateral continuous subclinical paroxysmal activity was once recorded. Such features have never been reported before to our knowledge in patients with idiopathic generalised epilepsy.

Results and Conclusion: Phenobarbital, lamotrigine and topiramate did not control AS, carbamazepine apparently aggravated AS, and ethosuximide did not control GTCS. Total seizure control was only possible with valproate at 1,000 mg/day, which the patient did not tolerate well because of weight gain, and because of this is currently well-controlled on a combination of valproate 1,000 mg/d and topiramate 200 mg/day.

p138

CHANGES OF SERUM LEVELS OF NATURAL NEUROTROPIC AUTOANTIBODIES IN PATIENTS WITH PARTIAL SYMPTOMATIC/CRYPTOGENIC EPILEPSY

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Purpose: To evaluate changes of the serum levels of neurotropic autoantibodies (nAb) against proteins S100b, GFAP, MP65 and NGF in serum of patients with partial symptomatic/cryptogenic epilepsy. NGF and MP65 appear essential to molecular mechanisms of synaptic plasticity, and there are data that S100B, an astrocyte-derived cytokine, is elevated in the temporal lobe of refractory epilepsy.

Method: 50 patients were investigated (age 29.58 ± 11.66 y.o.). As a control 119 clinically healthy age-matched people were used. Levels of nAb: idiotypic (nAbi) and anti idiotypic (nAIAb) against proteins S100b, GFAP, MP65 and NGF were analysed with Enzyme Immunoassay Test-System ELI-N-Test.

Results: Epilepsy patients had lower levels (compared to controls, Mann-Whitney test) of the following neurotropic autoantibodies: nAbi against S100b ($p = 0.037$), MP65 ($p = 0.0001$), NGF ($p = 0.014$), nAIAb against S100b ($p = 0.003$), MP65 ($p = 0.001$), GFAP ($p = 0.007$). Interestingly, a patient with a long duration of epilepsy had a relatively high level of the nAB, still not reaching the level of the control group. Duration of epilepsy positively correlated with the level of nAbi against S100b ($r = 0.3$; $p = 0.03$) and against NGF ($r = 0.29$; $p = 0.037$) (Spearman rank correlation).

Conclusion: The significance of these changes should be further analysed with special attention to the pronounced decrease of nAb level in epilepsy patients. The other important finding is the relative increase of nAb against S100b and NGF that could be related to plasticity changes in patients with a long duration of epilepsy.

p139

CURRENT USE OF SLEEP DEPRIVED EEG: RESULTS OF A FRENCH SURVEY

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Purpose: Activation procedures improve EEG sensitivity. Among them, sleep deprivation is a widely available, although not standardised, technique. We investigated the current use of sleep-deprived (SD) EEG in French adult epilepsy centres trying to identify guidelines for this practice.

Method: A questionnaire was sent to 19 French epilepsy centres. Physicians were asked when and how SD EEG proceeded and the results they expected.

Results: Response rate was over 80%. On average, these centres conducted two SD EEGs a week (range 0.2–7). Indications were mainly syndrome diagnosis and clinical event recording. Sleep deprivation generally exceeded 50% of the sleep time (range 30–100%). Median duration of EEG recording was 3h (range 1–24 h). Occurrence of sleep and video recording were highly recommended by the majority of the centres. A specific contribution to diagnosis was obtained in about 50% of cases, depending on the accuracy of the indication.

Conclusion: This survey shows that the use of SD EEG remains heterogeneous among epilepsy centres in France. This could be improved by promoting guidelines. On the basis of the literature, our proper experience and the present survey, two main procedures can be drawn depending on the recording indication: 1) seeking syndrome classification requires a 50% sleep deprivation delaying sleep onset. Recording should last three hours including sleep and provoked arousal followed by photic stimulation and hyperpnoea; 2) presurgical assessment and identifying the nature of paroxistic events requires a day recording. Sleep deprivation can be more pronounced or even total.

p140

NOVEL TOOLS FOR EPILEPSY CARE AND RESEARCH (EPILCARE): USE OF PROPOSED ILAE DIAGNOSTIC SCHEME WITH SPECIALISED COMPUTER APPLICATION

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Purpose: The purpose of this research is to describe the use of a specialised computer application and clinical database for epilepsy (EpilCare). EpilCare is a tool for supporting the daily registration and storage of clinical events in epilepsy.

Method: The database contains structured terminology of seizure types, syndromes, epilepsy type, aetiology and description of the impairment(s) caused by the epilepsy. We used the new 2001 ILAE proposed diagnostic scheme (Engel J Jr. *Epilepsia* 2001;42:796–803) consisting of 5 axis as the basis of describing individual data in each patient. Medications and other treatments are described in detail.

Results: The EpilCare application is built by MariMedical Ltd who are also responsible for the maintenance of the database. Epilcare has now been tested in the first 30 adult and paediatric patients with drug-resistant epilepsy, with past and present multiple drug treatments and with various seizure types, syndromes and aetiologies in Kuopio University Hospital. We found the ILAE diagnostic approach very practical in daily use.

Conclusion: EpilCare is a novel method for collecting and storing clinically relevant data from patients with epilepsy diagnosed with the proposed ILAE diagnostic scheme. EpilCare allows a fast review of data during the clinical visit or during a phone call. The application improves the flow of information within the hospital information system. The clinical database of EpilCare allows the standardisation of patients' data, and a better organisation of the patient management process.

p141

GENERIC PREPARATIONS OF ANTIEPILEPTIC DRUGS: EXPERIENCES IN GERMANY, AUSTRIA, AND SWITZERLAND

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Purpose: The use of generic drugs may be without problems in some health problems, but chronic diseases with the need of a stable medication may be different. This is especially true for epilepsies, where treatment with antiepileptic drugs (AEDs) is guided with surrogate markers like blood levels and where a single seizure recurrence may have severe consequences. We were interested in the experience of physicians in Germany, Austria and Switzerland with generic preparations of antiepileptic drugs (G-AEDs).

Method: An internet based questionnaire study completed by members of the German, Austrian and Swiss sections of the International League Against Epilepsy, as well as members of the German Society for Neurology. About 2.800 e-mails were sent, together with an accompanying letter signed by the presidents of the three league chapters on 1 December 2005. There was a link to a specially designed website for easy online response.

Results: Until the end of January 2006 we received more than 600 responses. About 80% of the physicians had experience with G-AEDs. About half of them reported problems with their usage, in decreasing percentage additional telephone contacts or visits, hospital admissions, calls for emergency doctors or visits of emergency rooms, disturbances of the physician-patient relationship, sick certificates or injuries. In about half of the physicians these experiences had led to changes in their prescribing behaviour (restrictions for substitution), in addition to increased patient counselling and blood level determinations of AEDs. The current criteria for approval of G-AEDs were considered as inappropriate by about 50% and 90% considered it unacceptable that pharmacists have the possibility of substitution without consultation.

Conclusion: In line with the results of earlier reports our questionnaire study underlines the potential problems with the use of G-AEDs in antiepileptic therapy and justifies recommendations to avoid switching different preparations (from branded preparations to generics as well as between generics or from generics to branded preparations) e.g., in seizure free patients.

p142

FACTORS FAVOURING THE DIAGNOSIS OF STATUS PSEUDOEPILEPTICUS IN THE EMERGENCY SETTING

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Purpose: To assess features helpful in differentiating status pseudoepilepticus (SPE) with generalised convulsions from true refractory generalised status epilepticus (rGCSE) in the emergency setting beyond advanced knowledge in seizure semiology and unlimited availability of EEG.

Method: Patients treated between 1993 and 2002 in the neurological intensive care unit for assumed GCSE were reviewed. The diagnoses of SPE and rGCSE were made retrospectively on the basis of patients' history as well as clinical, electrophysiological, and imaging findings. We looked for differences concerning age, sex, the presence of implanted port systems, the amount of benzodiazepines administered until termination of seizures or occurrence of respiratory failure and expressed as diazepam equivalent, and creatine kinase (CK) levels within 24 h after onset of status epilepticus.

Results: There were 9 episodes of SPE and 10 of rGCSE. Subjects with SPE (27 ± 8 years) were significantly younger than patients with rGCSE (46 ± 20; $p = 0.035$). A port system was present in 4 patients with SPE and in none with rGCSE ($p = 0.033$). The equivalent diazepam dosage to terminate convulsions without respiratory failure was 61 ± 27 mg in patients with SPE and 33 ± 21 mg in rGCSE ($p = 0.026$). Serum CK was 42 ± 23 U/l in SPE and 849 ± 857 U/l in RGCSE ($p = 0.002$).

Conclusion: In the emergency setting, SPE with generalised motor convulsions is as common as rGCSE. Younger age, the presence of a port system, the capability to tolerate high dosages of benzodiazepines

without respiratory failure, and normal CK levels favour the diagnosis of SPE. These factors should alert the clinician as to the correct diagnosis of SPE.

p143
DIAGNOSIS AND AETIOLOGY OF TEMPORAL LOBE EPILEPSY
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Purpose: Among various aetiological factors, determining development of temporal lobe epilepsy (TLE), medial temporal sclerosis (MTS) brain disgenesis and tumours are considered to be the most important. The issue of the aetiological role of perinatal encephalopathia in development of MTS and amigdal-hippocampal epilepsy hasn't been solved up until now. The aim of this research is to estimate the role of different aetiological factors and results of MRI methods in diagnosis of medial and lateral forms of TLE.

Method: There were 117 patients involved in the research. The form of epilepsy was defined on the basis of clinical seizures and changes of EEG.

Results: Unilateral hippocampus sclerosis was found in 14 (21.2%) patients with medial TLE and in 2 (10.8%) patients with lateral TLE. The majority of patients with hippocampus sclerosis had perinatal ischemic damage of CNS. Frequency of febrile seizures in a group of patients with medial TLE was found to be 26.4%. The age of onset of medial TLE is 8–10 years younger that lateral TLE.

Conclusion: As the research showed, the leading role in development of a medial form of TLE in our patients belongs to perinatal encephalopatia. Brain damage and tumour were diagnosed for certain more often in patients suffering from lateral TLE.

p144
EPILEPSY PATIENTS' COMPLIANCE WITH PRESCRIBED MEDICAL TREATMENT
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Purpose: Medically treated patients' noncompliance with the prescribed scheme is an exceptionally important issue, faced relatively often in medical treatment of epilepsy.

Method: Different demographic and clinical data, collected upon questionnaire completion by 146 patients suffering from epilepsy, were sorted and integrated in the present research analyses with the objective to determine the possibility of collected data, and compliance level correlation, registered with the observed patients.

Results: Generally speaking, the examinees took rather regularly the prescribed therapy: with 62% examinees the compliance level was registered as good, with 23% as satisfactory, while with the remaining 15% of the examinees the compliance level was unsatisfactory. The following data have been identified as the possible predictors of the less precise adherence to the prescribed therapeutic regime ($p < .01$): regular consumption of alcohol, medical treatment exceeding the period of 6 or more years, and further, the data on three or more daily doses of the medicine (respectively medicines). The correlation between the greater number of prescribed antiepileptic medicines and lower compliance level ($p = 0.05$) has also been registered. The inclination towards a lower compliance level with patients aged under 30, has also been registered in the research. It is slightly surprising that the same tendency has been noticed with the examinees with a more thoroughly controlled epilepsy condition.

Conclusion: In spite of different experiments aimed to improve the regularity in taking the prescribed therapy, the noncompliance issue still presents a considerable obstacle to the more successful treatment of epilepsy patients.

p145
EPILEPSY DIAGNOSIS AND PREVALENCE OF SEIZURE SUBTYPES IN AN OUTPATIENT SAMPLE
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Purpose: This is a prospective clinical study aimed at the diagnosis of epilepsy and estimation of the prevalence rates of its various subtypes in a sample of outpatients who attended the Neurology and Psychiatry Consultation Clinic in Baghdad Teaching Hospital over a period of 18 months.

Method: One hundred cases (48 males and 52 females) were gathered randomly according to the inclusion criteria of the present study. Diagnosis of epilepsy was based on the clinical history, with or without abnormal EEG findings.

Results: The study revealed that partial epilepsy was relatively more prevalent than generalised epilepsy (54% vs 46%). Partial epilepsy with complex partial seizures was the most common subtype among the study sample with a prevalence of 39%, while that with simple partial seizures reached 13%. Secondary generalisation was high among cases with partial epilepsy (37%), and in addition 37% had multiple seizure types. As for generalised epilepsy, cases with tonic–clonic seizures reached 28%, juvenile myoclonic epilepsy 17%, and absence epilepsy 1%.

Conclusion: The results conform to international data regarding the prevalence of different seizure types, with predominance of complex partial seizures.

p146
THE IMPACT OF LUNAR PHASES ON SEIZURE OCCURRENCE
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Purpose: To ascertain whether lunar phases and particularly the "full moon" period is associated with seizure induction.

Method: All neurological case records of our emergency unit were retrospectively reviewed over a 5 year period (1999–2003) and cases admitted for a single or multiple epileptic seizures were identified and divided into the four quarters of the synodic month according to the moon phases. The crude overall incidence rate (IR) of seizures per quarter, i.e., new moon, 1st quarter, full moon and last quarter was estimated. Patients manifesting seizures of nonepileptic origin such as psychogenic nonepileptic seizures were excluded.

Results: Overall 859 cases manifesting epileptic seizures were identified. 536 patients (62.4%), with mean age 43.8 ± 19.3, were males and 323 (37.6%), with mean age 45.1 ± 20.9 were females. A striking increase in overall seizure occurrence was observed for both genders during the "full moon" days ($n = 294$, 34.2%), whilst at all other cycles of the synodic lunar month the rates of seizure occurrence were significantly lower, ranging between 21.4% for the "new moon" days ($n = 184$) to 22.5% for the "1st quarter" lunar days ($n = 193$). The difference of seizure IRs was strongly significant (chi-square test, $p < 0.0001$) in all comparisons between the "full moon" days and all the other lunar cycles.

Conclusion: A significant clustering of seizures around the "full moon" period was observed, supporting the ancient belief of a periodic increased seizure frequency during "full moon" days.

p147
PARANEOPLASTIC SYNDROME PRESENTED AS PROLONGED FOCAL SEIZURES (EPILEPSIA PARTIALIS CONTINUA)
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Purpose: We describe a man of 59 years old, a smoker (20 cigarettes per day), without any pathologic background, with epilepsia partialis

continua, with a relatively sudden appearance in the last 6 weeks. We purpose to find the cause of these prolonged focal seizures.

Method: We made a history of this case, the physical and neurological examination of the patient with involuntary movements of the right upper limb permanently day and night, awake and during sleep. These involuntary movements were labeled at the beginning as hemiballismus, then after first admission as brachial myoclonia (right) and after second admission the diagnosis was of Kojevnikov encephalitis, prolonged focal seizures, cortical atrophy confirmed by cerebral CT scan and MRI. These prolonged focal seizures were ameliorated by a complex of antiepileptic drugs.

Results: After 5 months, cerebral MRI was repeated which revealed along with the cerebral atrophy, hemispheric periventricular demyelinating lesions, also infiltrative nasopharyngeal mass (left). Three nasopharyngeal biopsies were performed with an interval of 2 months and finally the diagnosis of anaplastic small cell carcinoma was confirmed. Immediately the chest was x-rayed, bronchopulmonary cancer was revealed (confirmed by cervico-pulmonary MRI). Cerebral MRI revealed a secondary cerebral tumour (right temporal lobe).

Conclusion: Paraneoplastic syndrome presented as encephalitis with prolonged focal seizures preceded by 12 months the diagnosis of bronchopulmonary and pharyngeal cancer.

p148
POSTICTAL HEADACHE IN ADULT PATIENTS WITH EPILEPSY

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Purpose: To determine the incidence and type of postictal headache in adult patients with epilepsy and headache, as well as the connections between the specific epileptic seizure and headache type.

Method: 86 out of 259 patients with a confirmed diagnosis of epilepsy had headaches. The type of seizure is classified according to ILAE 1989, and ICHD II 2004 was used in classification of headache types. All patients filled out a detailed questionnaire. Complete neurological examinations, EEG, CT and/or MRI of the brain were performed.

Results: Among 86 (33.20%) patients with seizures and headache, 43 (50%) had postictal headaches. Postictal migraine headaches were observed in 11 (28%) patients out of 40 patients with epilepsy and migraine, and all were women. Generalised seizures were found in 7 (63.6%) patients. Four (36.4%) patients had partial complex seizures. Thirty (76.9%) out of 46 patients with nonmigraine headaches had postictal tension headaches, and only 2 patients had thunderclap primary headaches. Tension headaches occurred postictally in 23 (74.2%) patients after generalised epileptic seizures, and in 7 (22.6%) patients after partial seizures. Thirty-two (74.4%) out of 43 patients with postictal headaches had nonmigraine headaches. Migraine headache was present in 11 (25.6%) patients. Headache postictally linked to seizure was statistically less frequent in patients with epilepsy and migraine than in patients having epilepsy associated with nonmigraine headaches ($p < 0.001$).

Conclusion: Half of the patients with epilepsy and headache had postictal headaches. Tension headaches were significantly more frequent than migraine. Postictal headache more frequently occurred after tonic–clonic seizures.

p149
LATERALISING VALUE OF AUTOMATISM IN MESIAL TEMPORAL LOBE EPILEPSY

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Purpose: To compare the clinical features of automatism between right and left mesial TLE.

Method: We retrospectively reviewed the features of clinical seizures in 28 consecutive patients (16 females and 12 males) with TLE, age range 18–65 years. 17 patients had left TLE (78 seizures) and 11 had right TLE (69 seizures). Automatistic behaviours of manual and pedal, oro-alimentary, vocalisation (mumbling, grunting etc), nose wiping, face wiping, water drinking and retching plus vomiting were assessed and compared between left and right temporal lobe epilepsy focus.

Results: Manual automatism is the most frequent behaviour occurring ipsilateral to the epilepsy focus in 64% in the right and 73% in the left and bilaterally in 29% and 27% respectively. Pedal and oro-alimentary automatism occurred in both sides and there is no significant difference between right and left TLE focus (17.5% and 35% vs 27% and 36% respectively). Vocalisation occurred in 41% of the left compared to 17% of the right TLE focus, which is significantly different between the two sides ($p = 0.05$). Similarly face wiping occurred in 17% on the left and 45% on the right, which is significantly different between the two sides. Water drinking as well as retching plus vomiting occurred only in the right TLE (18%).

Conclusion: Some automatistic behaviours may differentiate between right and left temporal lobe focus, such as vocalisation lateralises to the left TLE and face wiping, water drinking and retching plus vomiting to the right temporal focus.

p150
EPILEPSY AND DRIVING LICENCE IN LITHUANIA

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Purpose: In Lithuania driving is prohibited by law for patients with a current diagnosis or history of epilepsy despite seizure activity. Our aim was to analyse and to compare the view of doctors and patients with epilepsy into the legalisation of driving in appropriate cases.

Method: 260 patients with epilepsy were given a questionnaire regarding epilepsy characteristics, social issues and impact of inability to drive on their quality of life. 156 neurologists completed a questionnaire regarding legal permission to get a driver's license for patients with current or past epilepsy.

Results: 64.2% of patients indicated that driving restrictions have a negative impact on their quality of life. 28.1% of patients, despite official prohibition, hold a driver's license. 73.1% would support legal permission to drive for seizure-free patients. 94.5% of neurologists look with favour to driving of a clearly defined subgroup of epilepsy patients. 87.8% of them would permit the patient to drive if seizure-free without medication. 39.7%, if they are on antiepileptic drug. 19.8% would allow the patient to drive if seizures occur only during night sleep and 14.4% if seizures are focal. 45.2% would permit driving after a 5 year seizure-free period, 43.2% after 2 years. 26.7% would not withhold a driving license after the first seizure. 94.5% would use EEG in the assessment of driving fitness.

Conclusion: Most epilepsy patients and neurologists support legal permission to drive for seizure-free patients. Results of our survey support currently ongoing revision of regulations of driving licensing in Lithuania towards liberalisation according to EU directives.

p151
ICTAL SALIVATION IN TEMPORAL LOBE EPILEPSY

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Purpose: We sought to determine whether hypersalivation helps lateralise seizure onset during complex partial seizures of temporal lobe origin. Several clinical signs, which help lateralise seizure onset, have been reported in temporal lobe epilepsy (TLE). Increased salivation has only occasionally been reported as a manifestation of partial epilepsy.

Method: of 590 consecutive patients admitted for EEG/video monitoring, either as a part of a presurgical evaluation of medically intractable epilepsy or for diagnosis and clarification of their paroxysmal symptoms, we identified 10 patients with ictal hypersalivation as a prominent manifestation of complex partial seizures. We reviewed the clinical features, scalp-sphenoidal EEG/video monitoring, intracarotid amytal (Wada) testing, hippocampal volumetric MRI, and FDG-PET scans of these patients.

Results: of the 10 patients with ictal hypersalivation, 7 patients had nondominant/right TLE, and 3 patients had dominant/left TLE. All patients had hippocampal atrophy on volumetric MRI. Eight of the 10 patients underwent standard temporal lobectomy with amygdalohippocampectomy (6 right, 2 left). All of the operated patients had a seizure free (Engel Class I) outcome, and their increased salivation resolved. Two patients, who did not undergo surgical treatment, continue to have complex partial seizures with increased salivation.

Conclusion: We conclude that increased salivation as a prominent ictal finding in complex partial seizures of temporal lobe origin is more likely to be of nondominant temporal lobe origin. Further studies with larger numbers of patients are needed to replicate this finding.

p152
CEREBRAL NONEPILEPTIC PAROXYSMAL CONVULSIVE MANIFESTATIONS
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Purpose: There are a great number of cerebral paroxysmal convulsive manifestations which are less studied, but they are still frequently present during neurological practice, and ignorance of them may lead to severe diagnosis and treatment errors. Our goal is to emphasise them among patients hospitalised in the Clinic of Neurology of Oradea.

Method: We studied 450 patients interned in our clinic and diagnosed with epilepsy during 2005, using clinical and paraclinical methods. These patients represent 10% of total hospitalisations during 2005.

Results: We found that only 112 patients out of the 450 (25%) were detected with idiopathic epilepsy. The remaining 338 (75%) patients presented nonepileptic paroxysmal convulsive manifestations of proconvulsionary diseases. We made an enumeration of the epilepsy-generating diseases found in our study: strokes (20%), cranial-cerebral traumatisms (10%), syncope (6%), alcoholism (5%), cerebral tumours (5%), infectious diseases (5%), intestinal parasitoses (4%), hypoglycaemia (4%), disorders of the hydro electrolytic metabolism (4%), deficit of B6 vitamin (2%), febrile convulsions (2%), renal failure (1%), hepatic failure (1%), porphyry (1%), sun exposure (1%), convulsive access induced by electrocution (1%), hysterically induced convulsion (1%), degenerative diseases of the central nervous system (1%), disembryoplasiae (1%).

Conclusion: Besides patients with idiopathic epilepsy, there are in our clinic hospitalised patients diagnosed with diseases which have an epilepsy-generating convulsive potential. These conditions must be diagnosed quickly for the patient to benefit from antiepileptic therapy, or by a specific cure, without which the patient may rapidly decease.

p153
A HOSPITAL-BASED STUDY OF CLASSIFICATION OF EPILEPSIES, EPILEPTIC SYNDROMES AND AETIOLOGIES OF 728 EPILEPSY PATIENTS
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Purpose: The purpose of this study is to describe seizure types, types of epilepsy and epileptic syndromes as well as aetiologies.

Method: Seizure types, epilepsy syndromes and aetiologies were classified according to classification of ILAE. A total of 728 patients attending our Epilepsy Center were recruited into this study. All patients were examined by short or/and long-term Video EEG, cranial CT or/and MRI.

Results: (1) Initial onset in 67.17% of all subjects was under 20 years of age, and the ratio of male to female was 1.67:1.22. 3.02% of all subjects had a family history of epilepsy and 76 (10.43%) had a history of fever convulsion. (2) Patients with one seizure type were about 25.14% and with two or more seizure types were about 74.86%. The main seizure types were complex partial seizures (67.44%) and generalised tonic–clonic seizures (69.50%), and a majority of generalised tonic–clonic seizures were secondary (88.14%). (3) Generalised epilepsy was about 90 (12.36%), focal epilepsy was about 621 (85.30%), and the other 17 (2.34%) of all subjects were unclassified as either focal or generalised epilepsy. (4) Analysis of aetiologies showed that idiopathic epilepsy was in 9.89%, cryptogenic in 28.57%, and symptomatic in 61.53%. A majority of patients with idiopathic epilepsy were under the 20 years of age. Meanwhile, the older the initial onset of age, greater was the possibility of symptomatic epilepsy.

Conclusion: According to the classification of ILAE, complex partial and secondary generalised seizures, partial epilepsies and epileptic syndromes, and symptomatic epilepsy were the main types in this hospital-based study.

p154
EPILEPTIC SEIZURES AS A FIRST MANIFESTATION OF MULTIPLE SCLEROSIS
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Purpose: The occurrence of epileptic seizures in multiple sclerosis (MS) is 3–4 times higher than that in the average population. In the case of multiple sclerosis partial epileptic seizures may appear with less typical symptoms with or without secondary generalisation. Sometimes epileptic seizures occur even several years before clinical signs of MS are manifested.

Method: According to McDonald's diagnostic criteria 275 cases of MS have been registered in our database among patients who attended the Neurology Department in Faculty Thomayer's Hospital in Prague from 1 January 2002 to 31 December 2005 (36 months). In this group of patients we analysed the data of 11 patients with history of epileptic seizures. In 4 patients (1.8%), 2 male and 2 female, the onset of epilepsy occurred several years before MS onset. We present the data of these 4 patients.

Results: MRI is an appropriate method for the diagnosis of MS, as well as for the assessment of the relationship between EEG findings and localisation of lesions in the central nervous system. The lesions involved in the pathogenesis of the crises are plaques of demyelination which affect the subcortical and cortical areas. Not only the lesion itself but also the cytotoxic oedema that accompanies an active plaque, seems to be responsible for the development of seizures.

Conclusion: Our data suggest that epileptic seizures are more common in MS than in the general population. Epileptic seizures can be the first symptom of MS, appearing before other signs of the illness. EEG is recomended when paroxysmal epizodes of altered perception or cognitive function are reported by an MS patient.

p155
KNOWLEDGE OF AND ATTITUDE TOWARD EPILEPSY AMONGST RELATIVES OF EPILEPSY PATIENTS AND THE COMMUNITY IN QATAR
H. Al Hail (Hamad General Hospital, Qatar)

Purpose: Improving patients' knowledge about epilepsy has been suggested to be a key factor for the improvement of their quality of life. Similarly, the attitude towards people with epilepsy is influenced by the degree of knowledge in the environment about this clinical disorder.

Method: This study was conducted among relatives of epilepsy patients (REP) as well as in the community at large (CAL) in Qatar. The age group targeted ranged from 10–50 yrs across all nationalities and religions. A semistructured questionnaire was used to evaluate the knowledge and attitude of the interviewee towards epilepsy.

Results: The interview and questionnaire was administered to 28 individuals REP 35.7% and CAL 64.3%. Almost all the REP and CAL had heard about epilepsy; 75% of them associating epilepsy with a central nervous system disturbance. Some REP and CAL still thought that epilepsy was contagious or caused by an evil spirit. Amongst REP and CAL, 53.6% thought that discrimination against people with epilepsy was justified. The knowledge of the interviewees about the clinical characteristics and first aid measures to be taken for a person having a seizure was unsatisfactory. Less than half believed that epilepsy could be cured. 57.1% thought that this disorder should be treated by modern medicine and 28.6% believed in traditional medicines. The majority (64.3%) of

REP and CAL were interested in helping epilepsy patients. One third of people (32.1%) believed that it was safe for an epilepsy patient to drive a car.

Conclusion: In conclusion, there is an urgent need for improving the knowledge of the community especially people surrounding the epilepsy patient. Public and governmental institutions including teachers should create awareness and provide basic information and assistance in health matters, such as epilepsy. The Ministry of Health physicians and the Ministry of Education should ensure through different sources of education that the community has sufficient knowledge of epilepsy.

p156
VALUE OF STANDARDISED MENTAL STATUS TESTING FOR NONCONVULSIVE STATUS EPILEPTICUS
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Purpose: Nonconvulsive Status Epilepticus (NCSE) is a heterogeeous disorder, with serious morbidity and mortality. Some reports have considered mental status impairment an important prognostic finding. The aim of this study is to show that mental status examination is not performed systematically in patients with suspected NCSE, during EEG and in follow-up.

Method: We reviewed clinical and EEG data of 81 consecutive patients (mean age 66.6 years) meeting the accepted criteria for the diagnosis of NCSE. The number and type of tasks for evaluating mental status of patients before and after EEG were collected, as well as whether the patients were retested during follow-up. Mental status improvement after benzodiazepine (BZD) administration was reported. NCSE was classified in focal and generalised form and in relation to degree of mental impairment.

Results: Thirty-nine patients had absence status, 35 patients had complex partial status, and 7 had aphasic status. The main clinical presentation was delirium (60%) or stupor (31%). BZD administration was reported in 61 cases during EEG. In all cases GCS was used, but a standardised mental status examination was performed in 22 cases. In particular, before and after BZD administration, a systematic mental status testing was not perfomed, and only 10 cases had a neuropsychological follow-up.

Conclusion: We found that consistent mental status examination is not performed systematically before and after BZD administration during EEG in patients with suspected NCSE. According to Kirby et al. 2004 we suggest a standardised mental status testing during EEG recording, useful to confirm the severity of cognitive impairment. At follow-up psychological reevaluation, including an Italian version of National Adult Reading Test may be useful to demonstrate neuropsychological sequelae.

p157
CAN SEIZURE SEMIOLOGY DIFFERENTIATE LESIONAL FROM NONLESIONAL TEMPORAL LOBE EPILEPSIES?
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The syndrome of mesial temporal lobe epilepsy with hippocampal sclerosis is now widely recognised. It is often medically resistant but surgically remediable. The clinical, the electroencephalographic, the neuroimaging and the histopathologic features are homogenous with favourable prognosis of epilepsy surgery. On the contrary, neocortical temporal lobe epilepsy and in particular the cryptogenic or the nonlesional temporal lobe epilepsy remains a controversial topic. The incidence of nonlesional temporal lobe epilepsy is unclear. Data on nonlesional temporal lobe epilepsy comes from surgical series as well as genetic data on familial nonlesional temporal lobe epilepsy. The clinical features and seizure semiology of nonlesional temporal lobe epilepsy is non-homogenous in the literature. In this presentation, we review the topic of seizure semiology in nonlesional temporal lobe epilepsy from the available data at the Epilepsy Comprehensive Program at RKH and compare the results to the international literature with video EEG illustrations.

p158
"LATE RESPONSIVENESS": THE VALUE OF CHANGING TREATMENT IN CHRONIC EPILEPSY: AN OBSERVATIONAL STUDY
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Purpose: The response of epilepsy to its early therapy has been long recognised to be important in long-term prognosis (Shorvon SD. The temporal aspects of prognosis of epilepsy. *J Neurol Neurosurg Psychiatry*, 1984;47:1157–1165) and recent studies have confirmed this in various ways (Kwan P et al. Early identification of refractory epilepsy, *N Engl J Med*, 2000;3:314–319). Notwithstanding this, it is common clinical experience that significant numbers of patients with long-standing chronic epilepsy do show good responses to changes in their antiepileptic drug (AED) regimens ("late responsiveness"). We investigated the proportion of patients with chronic epilepsy who do respond well to the addition of a new AED, and factors influencing this.

Method: We studied 200 consecutive patients with chronic epilepsy (defined as epilepsy still active after 4 or more years of therapy) from a single clinic between 2002 and 2004. The response (seizure control/>50% improvement/no improvement) to the addition of a new AED was ascertained over a minimum period of 6 months after the medication change.

Results: There was a good response to the addition of an AED (either add-on or substitution) in a sizeable proportion of patients (depending on the nature of the new drug introduced, severity of epilepsy, aetiology, duration of epilepsy and number of drugs taken) including a minority who gained complete seizure control.

Conclusion: These data are the first of their kind to quantify the response of chronic epilepsy to drug changes ("late-responsiveness") in the setting of everyday clinical practice. These show that drug changes are helpful in many patients who have not responded to initial drug therapy.

p159
JUVENILE MYOCLONIC EPILEPSY AND INHERITANCE
I. Fedotova (Kharkov Medical University, Ukraine)

Purpose: Juvenile myoclonic epilepsy (JME) is an idiopathic generalised epilepsy (IGE) with complex inheritance. Previous studies have suggested maternal inheritance and female excess in IGEs but have not been specific for JME. We investigated evidence for maternal inheritance, female excess and patterns of familial seizure risk in a well-characterised sample of JME families.

Method: We identified 77 families through a JME proband and 40 families through a non-JME IGE proband. JME families were divided into those with and without evidence of linkage to the EJM1 susceptibility locus on chromosome 6. We analysed transmission in 39 multigenerational families, calculated the adjusted sex ratio for JME, and looked for evidence of seizure specific risk in family members.

Results: We found evidence for preferential maternal transmission in both EJM1-linked and unlinked families (2.3:1), evidence even more marked when potential selection factors were excluded. The adjusted female: male risk ratio (RR) was very high in JME (RR = 13.6; 90% confidence intervals (CI): 1.7–88.3). Absence seizures in JME probands increased the overall risk of seizures in first degree relatives (14.9% vs 8.2%, $p = 0.01$), as well as first-degree relatives specific risk of absence seizures (7.1% vs 2.4%, $p = 0.01$), but not myoclonic seizures.

Conclusion: We have confirmed the finding of maternal inheritance in JME, which is not restricted to JME families linked to the EJM1 locus. The striking female excess in JME may relate to anatomical and/or endocrine sexual dimorphism in the brain. Evidence for independent inheritance of absence and myoclonic seizures in JME families reinforces

a model in which combinations of loci confer susceptibility to the component seizure types of IGE.

p160
LIMBIC ENCEPHALITIS AND SEIZURES: A PARANEOPLASTIC PRESENTATION OF OAT CELL LUNG CANCER
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Purpose: A case report of limbic encephalitis (LE) as a rare paraneoplastic disorder that can initially present with partial or generalised seizures, changes in personality, selective early memory loss suggestive of Korsakoff psychosis, confusion or hallucinations.

Method: A 56-year-old man presented with partial and generalised tonic–clonic seizures, drowsiness, agitated behaviour, irrelevant talking, confusion and loss of memory. A month prior to hospital admission, he had multiple generalised tonic–clonic seizures. He was a smoker and nonalcoholic. His father died after lung carcinoma. Physical examination revealed no disturbance. Patient was conscious, incoherent, agitated, talking irrelevant. He could not recognise his family members or remember anything. The patient's mental state progressively deteriorated for 6 weeks. Ten weeks after admission he was seizure free and demented. EEG showed diffuse theta 6/s activity. During and after chemotherapy his neurological status didn't change. Valproate and lamotrigine showed efficacy in seizure control.

Results: Laboratory findings were normal. EEG showed predominant alfa activity along with excessive bitemporal spikes and slow wave discharges. Brain CT scan was normal. CSF revealed 180 cells/cumm, mostly lymphocytes and no malignant cells. Other CSF parameters including protein, glucose, and viral analyses were normal. Oligoclonal bands were positive. Cranial MRI revealed bilateral symmetrical hyperintensities on T2WI with no foci of haemorrhages seen. Thorax CT revealed left hilar nodular change. Pathological examination showed microcellular lung carcinoma.

Conclusion: History, clinical picture, flow of illness and diagnostic results strongly indicated that the patient had LE. The purpose of this presentation will be to present LE as a possible cause in late onset seizures.

p161
EFFICACY OF SEIZURE CONTROL WITH CONVENTIONAL AEDs IN 376 ADULT PATIENTS WITH EPILEPSY IN ARMENIA: EPILEPSY DATABASE IN SITUATION OF NO OTHER TREATMENT OPTIONS
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Purpose: To determine the basic epilepsy effectiveness of seizure treatment in patients in a situation where there is a lack of modern AED and epilepsy surgery.

Method: A retrospective analysis of the patients database set up for selecting those who have been treated with first line AEDs only. Standard examinations included MRI, routine and long-term EEG.

Results: 376 adult patients with distinct aetiology and epilepsy syndrome were identified. General characteristics were: childhood onset–208, juvenile onset–66, late onset–102 patients. Idiopathic syndromes accounted for 145, symptomatic–113, cryptogenic–57, not defined–61 patients. 115 patients suffered from primary generalised types of SZ only; 89 of them had JME and juvenile onset absence epilepsy. In the group of 170 patients with approved focal onset SZ 54 were diagnosed as having TLE, 25–FLE and 91 patients had an undetermined localisation. 51 (14%) patients were SZ free for 1 year, 96 (26%) experienced 1–4 GTCS and 229 (61%) had monthly GTCS. The best control was achieved in patients with PGE on VPA monotherapy and combination of VPA and CBZ and/or PhB and late onset secondary epilepsies on CBZ, PhB monotherapy or combinations with VPA.

Conclusion: The effectiveness of anticonvulsant treatment without latest generation AEDs and non AED treatment options is rather low, even in the case of adequate diagnostic and treatment protocols. Countries with this situation should intensify the implementation of modern treatment approaches. Epilepsy surgery could be the most cost effective and affordable solution in countries like Armenia with sufficient potential but no developed epilepsy care structure.

p162
INSULINOMA AS A CAUSE OF DECOMPENSATION OF PRIMARY GENERALISED EPILEPSY: CASE REPORT AND REVIEW OF LITERATURE
I. Mareckova, Z. Vojtech, T. Prochazka, and M. Kalina (Department of Neurology Na Homolce Hospital)

Purpose: Insulinomas are the commonest hormone-secreting tumours of the gastrointestinal tract. Hypoglycaemia due to them can mimic a number of acute and chronic disorders, including epilepsy. In the literature we found case reports of insulinomas misdiagnosed as intractable adult-onset temporal lobe epilepsy. Reports of confirmed epilepsy worsening due to insulinoma are rare. To our knowledge our patient is the first reported for whom insulinoma caused worsening of myoclonic epilepsy.

Method: A 62 year old man has been treated for epilepsy since 20 years of age. He suffered from myoclonic jerks after awakening. The frequency of myoclonic seizures was approximately twice a month and he had GTCS once a year. He was treated with several AED (VPA, LTG, PHB). The frequency of seizures changed 5 years ago with myoclonic jerks occurring twice a week. He also experienced repeated attacks of derealisation with automatic behaviour.

Results: On video EEG we found normal wakeful background activity and frequent generalised epileptiform discharges (polyspikes) during sleep. The patient had an accumulation of myoclonic jerks in the morning. On MRI a small cavernoma of pons was present. PET brain scan showed glucose hypometabolism in the right thalamus and very slightly in left basal ganglia. Laboratory tests showed hypoglycaemia 2.1 mmol/l. Abdominal MRI and CT scans were normal. Endosonography was done. A small tumour at the head of pancreas was evident (16×12 mm) and a biopsy was performed. Ultrasonography of the epigastrium and fasting test (glycaemia 1,6mmol/l) confirmed the diagnosis. The patient was operated on and the tumour was resected. He has been seizure free for 3 years on AED medication.

Conclusion: In our patient insulinoma and idiopathic generalised epilepsy coexisted. As he was not completely seizure free with AED we can guess that he had been having problems with hypoglycaemia for many years. As he is seizure free after the operation it is highly probable that clinical worsening before the diagnosis was made was due to insulinoma. In conclusion, toxic and metabolic causes of seizures should always be considered in the differential diagnosis because the diagnosis is frequently delayed and they are often curable.

p163
CHRONIC POSTTRAUMATIC HEADACHE IN PATIENTS WITH POSTTRAUMATIC EPILEPSY
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Purpose: The aim of the study was to evaluate the analgetic effect on chronic posttraumatic headache (CPH) in patients who were treated with antiepileptic drugs (AED) for posttraumatic epilepsy (PTE). Furthermore, we assessed the value of electroencephalography (EEG) in detection and monitoring of posttraumatic headache in those patients.

Method: We analysed a group of 102 outpatients with posttraumatic epilepsy (78 males and 14 females, 42 ± 13.8 years). During a period of one year we monitored the AED effect on CPH by the Visual Analogue Scale. We also analysed EEG in those patients.

Results: 57% patients had a generalised form of epilepsy, 13% a partial form, 13% a complex partial form and the rest had a combination of attacks. Monotherapy was introduced to 62 patients (58 were on classical AEDs), and the rest were on add-on therapy (mostly with lamotrigine and topiramate). 36 out of 102 patients with PTE had CPH. Patients on lamotrigine and topiramate had a better analgetic response than those on

classical AEDs. Normal EEG findings were recorded in 1/3 of the group of patients with PTE. Patients with CPH had more expressed pathological changes on EEG (55%) than those without CPH (36%). The latter group had more nonspecific dysthymic changes on EEG.

Conclusion: We observed a good analgetic response to AEDs in patients with PTE and CPH. Better results were recorded in patients on lamotrigine and topiramate. EEG was not a very sensitive tool for monitoring CPH in patients with PTE, although the pathological findings on EEG were more specific in patients with CPH than those without it.

p164
EXCESSIVE DAYTIME SLEEPINESS IN A POPULATION OF PATIENTS WITH EPILEPSY

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Purpose: Excessive daytime sleepiness (EDS) is a frequent complaint among patients with epilepsy, and it is mainly ascribed to the antiepileptic drugs. The role played by epileptologic variables, such as epilepsy type and duration, focus and lesion localisation, circadian pattern, pharmacoresistance, etc., on EDS is still not well defined. The aim of the study is the evaluation of EDS in a well characterised epilepsy population.

Method: The study population comprises 137 consecutive epilepsy patients. EDS has been evaluated by the Epworth Sleepiness Scale, whereas the presence of sleep disturbances has been investigated by a self-administered sleep indicators questionnaire. The effect of epilepsy type, localisation, seizure type, morpheic seizures, pharmacoresistance, brain lesions, age, gender, BMI, on EDS and sleep disturbance indicators, has been analysed by logistic regression methods, including in the final model the variables that were found associated at the univariate analysis (t-Student's and chi-square tests) and other demographic variables.

Results: Sleep disturbance indicators, as revealed by sleep questionnaires, were associated with EDS. EDS was reported in 26.2% of the patients, regardless of age, BMI, epilepsy duration and sex. Among epileptologic variables the univariate analysis revealed an association between EDS, seizures during sleep ($p = 0.027$), pharmacoresistance ($p = 0.057$), and polytherapy ($p = 0.07$). The final logistic regression model, corrected for demographic variables, confirmed the association between EDS and seizures during sleep (OR 2.3, 95% CI 1.01–5.33, $p = 0.047$).

Conclusion: Our study is consistent with the presence of a significant relationship between EDS, seizures during sleep, and sleep disturbances, independently by epilepsy type, focus localisation, and drug treatment.

p165
NEWLY DIAGNOSED EPILEPSY IN STOCKHOLM, SWEDEN: FIRST REPORT FROM THE STOCKHOLM INCIDENCE REGISTRY OF EPILEPSY (SIRE)

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Purpose: To set up a system for prospective identification, registration, and follow-up of patients with newly diagnosed epilepsy in Stockholm, Sweden.

Method: Since September 2001, a pilot system has been in action to identify incident cases of unprovoked seizures and newly diagnosed epilepsy in residents of northern Stockholm, an area with approximately 958,000 inhabitants, median age 37 years. Potential cases are identified through different mechanisms; reports from a network of physicians and other health care professionals in the region; medical record screening in specified units (e.g., the hospital neurooncology section); and review of all requests for EEG-examination. Final classification of potential cases is done six months after the index seizure based on a review of information in relevant medical records. We report the experience from the first year of the Stockholm Incidence Registry of Epilepsy (SIRE).

Results: A total of 315 persons met the criteria for inclusion as potential cases, 151 of whom had a single unprovoked seizure while 164 fulfilled the final criteria for epilepsy. This yielded a crude incidence of 33/100,000 person years. The highest age-specific incidence, 49/100,000 person years was observed in the first year of life (neonatal seizures excluded). An underlying aetiology was identified in 33% of cases while 6% were classified as idiopathic. The estimated incidence was slightly lower than in other studies and the age specific rates indicate an underascertainment among the elderly in particular.

Conclusion: The registration system already works well, but efforts will have to be made in order to improve case finding in the elderly.

p166
DYSFUNCTION OF THE CARDIAC SYMPATHETIC INNERVATION: AN EXPLANATION FOR SUDEP?

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Purpose: Sudden unexplained death in epilepsy (SUDEP) concerns 7–18% of mortality in epilepsy patients. The pathophysiological mechanism is not clearly defined. Ictal and interictal autonomic dysregulations, which may lead to asystole or tachycardia, are also discussed as a reason for SUDEP. We present a possible approach to the pathophysiology of SUDEP.

Method: During 10 years of presurgical video-EEG-monitoring at the epilepsy centre in Erlangen, 663 patients were admitted. 4 patients showed in 8 out of 36 seizures, asystoles with a duration of up to 25 seconds. Cardiological tests (Holter-ECG, echocardiography) and an examination of the sympathetic cardiac innervation (MIBG-SPECT) were performed on these patients.

Results: Whereas the cardiological measurements were without pathological findings, the MIBG-SPECT revealed diminished tracer uptake in the 2 patients with longer asystoles.

Conclusion: The lack of sympathetic cardiac activity shown in our patients may lead to an insufficient counter regulation of the sympathicus, when there is a higher ictal vagotonus and might be a reason for SUDEP.

p167
WHEN COULD WE SUSPECT COELIAC DISEASE IN CRYPTOGENIC EPILEPSY?

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Purpose: Coeliac Disease (CD) may increase the risk of epilepsy although it is still debated that if ignored CD could be related to epileptogenesis. The silent course of CD increases the probability of delayed diagnosis. The study aim was to investigate how and when CD may be suspected in cryptogenic epilepsy (CE).

Method: 48 adults with CE have been recruited on the basis of an uncertain history of food intolerance or event of weight loss in childhood and evidence of drug-resistant epilepsy. All patients underwent haematologic screening for CD, EEG and CT-scan. Jeujunal biopsy has been performed in positive circulating autoantibodies. Patients with CD have been evaluated for at least 1 year after beginning a gluten-free diet (GFD).

Results: For 7 screened patients a diagnosis of CD has been found and confirmed by biopsy. Clinical histories revealed in 6 out of 7 the occurrence of visual seizures, although only in 3 were occipital abnormalities found in the EEG. Cerebral calcifications were observed in 3 of CD patients. Improved outcome of epilepsy under GFD was seen in 1 patient.

Conclusion: Although further studies on larger cohorts are mandatory our study suggests that in refractory CE the presence of visual seizures may be of some relevance in ongoing decisions to investigate CD with or without findings of occipital involvement on EEG and/or CT-scan. This issue could reflect as occipital regions are often involved

by epileptogenesis related to CD. Furthermore we believe that delayed GFD may rarely improve the course of epilepsy.

p168
THE CATAMENIALITY, FOCI LATERALITY, AND AGE AT ONSET OF EPILEPSY AND ENDOCRINE PATHOLOGY IN FEMALES
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Purpose: The purpose of the current study was to find any possible discrepancies in age at onset and duration of epilepsy and endocrine pathology (reproductive dysfunction and thyroid pathology) between catamenial and noncatamenial epilepsy.

Method: 26 women with catamenial and 107 with noncatamenial forms within temporal lobe epilepsy (TLE) were investigated to identify any discrepancies in variables, including the history of epilepsy and concomitant endocrine pathology.

Results: Catamenial epilepsy with right-sided foci was characterised by earlier onset than catamenial with left-sided foci (8.5 ± 5.5 vs 15 ± 3.7 years, $p = 0.029$). Nevertheless, catamenial epilepsy with left-sided foci caused the endocrine pathology in a shorter interval after seizure onset in comparison with right-sided foci catamenial epilepsy (2.2 ± 3.9 vs 9.3 ± 6.6 years, $p = 0.032$). For noncatamenial epilepsy the opposite relationship was revealed: the earlier seizure onset for left-sided foci (13.5 ± 8.8 vs 17.8 ± 7.9 years, $p = 0.044$) and development of endocrine pathology in a shorter period after seizure appearance in right-sided foci in comparison with left-sided foci (1.7 ± 8.8 vs 6.2 ± 8.8 years, $p = 0.048$).

Conclusion: The opposite relationship between catamenial and noncatamenial epilepsy seems to exist in terms of epilepsy and comorbid endocrine pathology, which may be determined by interaction between foci laterality and endocrine functions in female epilepsy. Further research to elucidate the pathogenesis of catamenial and noncatamenial epilepsy is needed.

p169
EPILEPTIFORM ACTIVITY SUPPRESSION IN COURSE OF COGNITIVE TASKS
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Purpose: To report the case of a patient with an awake EEG pattern at rest characterised by a continuous slow-spike wave activity, which is inhibited by tasks requiring mental activation and attention.

Method: A 35-year-old man affected by mental retardation and secondarily generalised epilepsy since his infancy attended our laboratory for a routine EEG check. Neuroradiological and functional exams performed until now had unremarkable results. EEG recordings revealed a diffuse epileptiform activity in the form of subcontinuous bilateral sharp waves and poly-sharp-waves with inconstant prevalence in the left hemisphere. During the recording in our laboratory the awake EEG pattern was characterised by a continuous slow-spike wave activity, with no clinical correlation; the EEG normalised suddenly when the patient was asked to pay attention to an external stimulus. Thus the patient underwent EEG during a series of tasks consisting of mental and aloud reading, speaking, spatial construction, mental and written calculation, listening to music.

Results: During the neuropsychological exercises we observed a prompt suppression of epileptic electrical discharges that tended to reappear soon as the patient lost mental concentration. Thus, with the intent to use a less sedative drug, we are actually trying to substitute the previous carbamazepine treatment by lamotrigine.

Conclusion: In the literature usually much interest is reserved for the facilitatory effect of mental activity on epileptic seizure occurrence, while suppressive effects are underestimated. In our opinion, this possible inhibitory effect deserves more consideration, and could be useful in addressing the pharmacological choice toward drugs with low sedative effect.

p170
PREVALENCE OF EPILEPSY IN CROATIA: A COMMUNITY-BASED SURVEY
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Purpose: This study was conducted to investigate the prevalence of epilepsy in Croatia.

Method: Data collection was performed by using the questionnaires that were submitted to the primary care community physicians in all 21 administrative districts in Croatia. The randomly chosen physicians were informed about the ILAE definition of active epilepsy by word and in writing.

Results: A total of 127 out of 180 (71%) physicians responded by giving requested details about patients whose personal identity remained undiscovered. In this way a sample of 212,069 people (4.8% of the population of Croatia) was studied. We identified 1022 persons having active epilepsy: 54% males and 46% females. The prevalence (No/1000) was calculated for the following age groups: age 0–7: 3.5 (CI 95% 3.2–3.8); age 8–18: 6.4 (CI 95% 6.1–6.7); age 19–45: 5.0 (CI 95% 4.7–5.3); age 46–65: 4.7 (CI 95% 4.4–5.0); age >65: 4.4 (CI 95% 4.1–4.7). Adjustment by age to Croatia's 2004 population was made according to the population estimate from the Croatian Bureau of Statistics: the overall prevalence including all age groups was 4.9/1000 inhabitants.

Conclusion: The prevalence of active epilepsy in Croatia is very similar to the data recently reported in a systematic review covering mainly North-European and Western Mediterranean countries (Forsgren L et al. *European Journal of Neurology* 2005;12:245–253). This suggests that there are no major differences in the crude prevalence rate of epilepsy across Europe.

p171
CLINICAL FEATURES, TREATMENT AND OUTCOME OF STATUS EPILEPTICUS
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Purpose: To evaluate the clinical and electrophysiological features, treatment and outcome of status epilepticus (SE) in adults.

Method: Sixty-three patients, who were admitted to our department with diagnosis of SE, were evaluated between 2003 and 2005. Demographic data, clinical, electrophysiological features, treatment and outcome of SE was investigated for each patient. Two patients were excluded from the study because of pseudostatus.

Results: Sixty-one patients were included in the study. The mean age of patients was 40.9 ± 19.8. Male to female ratio was 1.2:1. Cerebrovascular disease (CVD) was the major risk factor ($n = 21$). Seventeen patients had previously diagnosed epilepsy. The causes of SE in epilepsy patients were inadequate antiepileptic drug treatment, stopping drugs suddenly, changing drug therapy and systemic infection. The other risk factors were central nervous system (CNS) infection, metabolic causes, intracranial tumours, multiple sclerosis, vasculitis, drug intoxification and idiopathic. Eight patients had nonconvulsive SE, whereas remaining 53 had convulsive SE. In 78.7% of patients, seizures were controlled with first and second line drug treatments (diazepam, phenytoin and/or valproate). Thirteen patients had refractory SE (RSE) and needed infusion of midazolam and/or tiopental. There was no mortality in patients without RSE, but mortality rate was 38.5% for patients with RSE. There was no significant relationship between RSE, age, sex and type of status.

Conclusion: SE is a life-threatening condition. There is a high mortality rate in RSE. Epilepsy patients should be under regular follow up. CVD was the most common cause of SE in our study.

p172
LONG-TERM EFFICACY AND TOLERABILITY OF LEVETIRACETAM TREATMENT IN A PATIENT WITH EPILEPSY AFFECTED BY SYSTEMIC LUPUS ERYTHEMATOSUS

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Purpose: A case is reported of a young woman with systemic lupus erythematosus (SLE) and complex partial seizures responsive to treatment with levetiracetam (LEV).

Method: A 28-year-old woman taking prednisone 12.5 mg/day from 1995 for SLE was admitted to hospital after developing mental confusion, 1–2 episodes/week, for the previous 2 months. A 24 hour EEG showed left frontotemporal spike discharges with contralateral spread and a diagnosis of complex partial seizures was made. The patient was discharged on a regimen of prednisone (12.5 mg/day) and oxcarbazepine (OXC 300 mg TID). Five days later, she had another complex partial seizure, and analysis of blood chemistry revealed a clinically significant decrease in total white blood cells. OXC therapy was promptly discontinued and changed to topiramate (TPM final dose 150 mg BID) resulting in seizure remission and normalisation of white blood cell count. Thirty days after starting TPM, the patient developed somnolence, nervousness and angle-closure glaucoma with acute myopia and ocular hyperaemia; TPM was consequently withdrawn and replaced with phenobarbital (PB 100 mg BID), leading to recovery within 2 days. Seven days later, however, the patient showed a decrease in platelet cells that prompted the discontinuation of PB, and LEV treatment was started (final dose 1500 mg/day).

Results: After about 4 years of follow-up on LEV, the patient remains seizure-free with no adverse events reported. No dose adjustments of LEV or corticosteroids have been required during treatment.

Conclusion: This case report suggests that LEV may be useful in treating seizures in epilepsy patients with SLE.

p173

NO EVIDENCE FOR PHARMACOKINETIC INTERACTION OF LEVETIRACETAM WITH OTHER ANTIEPILEPTIC DRUGS IN JAPANESE AND WESTERN ADULTS WITH EPILEPSY

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Purpose: To assess the effects of levetiracetam (LEV) add-on treatment on plasma concentrations of other antiepileptic drugs (AEDs) in both Japanese and Western adults with epilepsy.

Method: Retrospective analysis of plasma concentrations from two placebo-controlled Phase III studies with the same design conducted in Japan and the United States. At baseline and during the treatment period, with either add-on LEV or placebo, multiple AED plasma levels were evaluated by repeated measures covariance analysis, after logarithmic transformation and using 90% confidence intervals (CI) of the geometric mean ratio between both periods in each ethnic group.

Results: Two-thirds of 191 Japanese and 268 Western patients, aged 16–65 years, received LEV (1000–3000 mg/day) as add-on therapy to other AEDs. In the Japanese, geometric mean plasma concentrations (CV = coefficient of variation) varied from baseline to LEV treatment period: carbamazepine (CBZ): 6.7–6.9 μg/mL (CV = 38%); valproate (VPA): 58–56 μg/mL (CV = 43%); phenytoin (PHT): 9.2–8.8 μg/mL (CV = 55%), phenobarbital (PB):18.1–17.8 μg/mL (CV = 36%); clobazam (CLB):135–151 ng/mL (CV = 94%); clonazepam (CZP):19.3–20.7 ng/mL (CV = 57%); and zonisamide (ZNS): 18.3–17.9 μg/mL (CV = 40%). The geometric mean ratio of concentrations (LEV/placebo evaluation vs baseline) was centered on 100% for CBZ, VPA, PHT, ZNS and CI were within the 80–125% range. No relevant ethnicity difference was observed.

Conclusion: LEV did not appear to modify plasma concentrations of CBZ, VPA, PHT and ZNS when used concomitantly with these AEDs in either study population. Thus it does not appear necessary to adjust the dose of any of these AEDs when LEV is either added to, or removed from combination therapy. UCB funded.

p174

CORTICAL REORGANISATION INDUCED BY LONG-TERM EPILEPSY AND THE USE OF LEVETIRACETAM

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Purpose: To investigate cortical reorganisation and the use of levetiracetam (LEV) in a patient with long-term refractory epilepsy.

Method: A case study of a 30-year-old patient illustrating transfer of language function within the right hemisphere. The first seizures (partial seizures and right partial continuous epilepsy appeared at 6 years of age, after normal language development. Serial CT and MRI scans showed progressive atrophy of the left hemisphere and Rasmussen's syndrome was diagnosed. Three years later, the child was hemiplegic, with progressive cognitive deterioration and global aphasia. Surgery was refused by the parents. Follow-up showed stable right sensorimotor deficit. However, cognitive performances showed a slow progressive recovery. Oral expression, comprehension, reading and writing are currently (at age 30 years) substantially normal. Seizures were polymorphous, very frequent daily, and refractory to all antiepileptic drugs (AEDs). In 2003, LEV 2000 mg/day was added to phenobarbital and carbamazepine. To study language function, a BOLD EPI fMRI (1.5 Tesla) was performed using semantic and phonemic fluency tasks.

Results: The patient experienced ~80% seizure reduction after 2 years of LEV add-on therapy. fMRI activated regions were restricted to the right hemisphere, involving frontal (MFG and IFG, area 44) and temporal (STG, area 22) lobes. Language appears supported by a right-sided network homologous with that usually observed on the left.

Conclusion: LEV add-on therapy achieved a high seizure frequency reduction. This case study indicates that cerebral plasticity appears linked to the natural history of disease and that epilepsy may induce a functional reorganisation of cortical areas.

p175

CLINICAL AUDIT OF 676 PATIENTS TREATED WITH LEVETIRACETAM

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Purpose: To assess the efficacy and safety of levetiracetam (LEV) for uncontrolled focal epileptic seizures in 'real-life' patients in the Czech and Slovak Republics.

Method: A clinical audit of patients treated with LEV for partial onset seizures between 2002 and 2004. Primary outcome parameters were retention rate, reduction in frequency of partial seizures per month, change in interictal state (rated 1 [best] to 5 [worst]), number of concomitant antiepileptic drugs (AEDs), change in AED tolerability (rated 1 [best] to 5 [worst]), adverse events (AEs).

Results: 676 patients were included: 657 treated with LEV add-on therapy, since refractory to previous AEDs; 19 with primary LEV monotherapy. Retention rates were 99.4% after 1 month, 92.9% after 4 months. Reasons for discontinuation were poor tolerability (1%), lack of efficacy (3.7%) and unstated (2.4%). Mean frequency of partial seizures/month decreased from 18.7 at baseline to 9.5 after 1 month and 6.5 after 4 months. Responder rate ($\geq$50% seizure frequency reduction) was 56.5% after 1 month and 67.8% after 4 months. Seizure freedom (100% seizure frequency reduction) was achieved by 22.8% patients after 1 month and 25.4% patients after 4 months. The mean interictal state improved significantly from 3.2 at baseline to 2.2 at 4 months ($p < 0.001$). Mean AED tolerability improved significantly from 2.3 at baseline to 1.6 ($p < 0.001$) at 4 months. Few AEs were reported; only 1% (7/676) patients discontinued LEV due to poor tolerability.

Conclusion: LEV, add-on and monotherapy, was effective and very well tolerated in 'real-life' patients with refractory focal epilepsy.

p176

AGE DISTRIBUTION OF PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY IN AN OUTPATIENT CLINIC: ARE ALL MYOCLONIC EPILEPSIES LIFELONG EPILEPSIES?

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Purpose: Juvenile Myoclonic Epilepsy (JME) is an idiopathic generalised epileptic syndrome that has only recently attracted considerable attention. Remarkably, JME is often diagnosed with delay because the physicians involved, including the specialists, are not familiar with a disease whose nature has yet to unfold. JME is believed to be a lifelong epilepsy. However, this view has been debated from time to time.

Method: In a period of 15 years of operation of our Epilepsy Outpatient Clinic, at the 1st University Department of Neurology, a total of 77 patients (5.8% of a total of patients with epilepsy) fulfilled the diagnostic criteria for JME. The mean age of patients was 26.65 years old.

Results: The age distribution of our patients was as follows: 56 were 15–34 years, 4 were 35–54 years and only 2 patients were aged more than 55 years. Antiepileptic treatment had been withdrawn from the remaining 15 patients, aged 32 to 35, who had been treated with low dose valproic acid (VPA) and had remained free of seizures for more than 3 years. 13 patients have been free of seizures without antiepileptic treatment for more than 2 years. However, seizures recurred in one patient after long term sleep deprivation and in one other after excessive alcohol consumption.

Conclusion: Our results suggest that many JME are not lifelong epilepsies. JME may not represent a single disorder. It remains to be clarified which factors, clinical or EEG, are predictors of JME prognosis and which factors, genetic, environmental or life-style, may influence JME's evolution.

p177

LAMOTRIGINE, FEMALE SEX, AND IDIOPATHIC EPILEPSY: RISK FACTORS FOR SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)?

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Purpose: Central or obstructive apnea and cardiac arrhythmia comprise potential pathophysiological mechanisms for SUDEP. Lamotrigine (LTG) was recently shown to possess a potential to inhibit the cardiac rapid delayed rectifier potassium ion current (Ikr) and Ikr. Blocking drugs are generally considered to be associated with an increased risk of cardiac arrhythmia and sudden unexpected death. However, no previous studies have shown any excess of SUDEP in patients treated with LTG.

Method: During the 10-year period 1995–2005 4 consecutive cases of SUDEP in nonhospitalised patients have come to our knowledge at Neurological Department, Stavanger University Hospital, Norway.

Results: All 4 patients were young women (age:16, 24, 25, 37 yrs) with idiopathic epilepsy on LTG monotherapy. Diagnosis after autopsy was consistent with definite SUDEP. Since acidosis may increase the blocking of Ikr the risk for arrhythmias is increased by seizure induced acidosis. In addition, females have an increased risk for drug induced torsade de pointes. Thus, a possible cardiac predisposition to arrhythmia may have worked together with the Ikr blocking effect of lamotrigine to induce a fatal arrhythmia during seizures in our patients.

Conclusion: The combination of female sex, idiopathic epilepsy and the use of LTG may represent risk factors for SUDEP, possibly under the influence of a seizure or a seizure induced acidosis. Further studies are needed to reveal the full clinical importance of these observations.

p178

PROGRESS ON A STUDY OF SPONTANEOUS EEG ACTIVITY IN RECORDS OF EPILEPSY PATIENTS WITH INTERICTAL DISCHARGES AND EPILEPTIFORM DISCHARGES IN HEALTHY SUBJECTS

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Purpose: The aim of our study was to evaluate the prevalence of these phenomena in a population of clinically healthy subjects and to develop a method able to detect differences in EEG activity recorded from these subjects and patients.

Method: The EEG recordings were collected using Neuroscan 4.3 system during screening studies in groups of healthy people, and in epilepsy patients. Ten EEG recordings of healthy people and ten recordings of patients suffering from epilepsy were analysed. In the time domain EEG activity before and after an epileptiform episode was analysed using signal similarity evaluation methods. In the frequency domain the FFT analysis was applied. Coefficients such as: mean frequency, global spectrum power, width of the spectrum and correlation of spectra were utilised.

Results: The prevalence of epileptiform activity in EEG recordings from healthy subjects was around 2%. Spectral analysis coefficients have shown significant changes in spontaneous activity after discharge in patients whereas that was not the case in healthy subjects. The special multi-similarity method able to detect changes of spontaneous EEG activity after an epileptiform episode has been developed.

Conclusion: The results suggest that an epileptiform activity does not significantly change spontaneous EEG activity in healthy subjects as it does in patients. These changes could be detected using a multi-similarity method and using some coefficients of FFT spectrum.

p179

PREDICTIVE FACTORS OF THE POSTINFARCTION SEIZURES

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Purpose: The aim of our study was to assess some predictors of post-stroke epilepsy (PSE).

Method: We observed group 1 of the patients with 110 cases of ischemic stroke without epileptic seizures (40 to 90 years old; males, 52.7%), and group 2 that consisted of 26 cases with PSE (37 to 79 years old; males, 58%). Epileptic seizures developed 6 to 12 months after ischemic stroke (an average of 7.5 ± 0.7 months). Upon admission, the patients were examined using NIH Stroke Scale, Barthel Index, CT scans of the brain, EEG, ECG, general biochemical and haematological parameters.

Results: The mean age of PSE patients was significantly lower than for group 1 (59.8 ± 1.8 vs. 66.9 ± 1.3; $p = 0.003$), whereas heart disorder (atrial fibrillations) tended to be more common in the PSE group (46% vs 19%, $p = 0.07$). There were no sex differences between groups 1 and 2. Neurological deficiency, as assessed by NIH stroke scale, has shown medium-grade clinical severity of stroke, and, like the Barthel Index, did not sufficiently differ between the two groups under study. In the cases of PSE, large brain lesions were more common (59% vs 37% in the group without seizures, $p = 0.02$).

Conclusion: When examining a representative group of patients after ischemic stroke, the following PSE predictors are registered, i.e., age of the patient, presence of atrial fibrillations, large brain lesions.

p180

COMPLETE SLEEP DEPRIVATION IN PATIENTS WITH FIRST SINGLE SEIZURE: AN UNCONTROLLED PILOT STUDY

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Purpose: The main goal of this study was to determine how far complete 24 hrs sleep deprivation (SD) can play a role in the diagnosis of epilepsy as an additional method of confirming suspected epileptic seizures in patients with first single fits.

Method: In present study included 10 patients, all males aged between 21–42 years hospitalised by reason of an unexpected syncope-like attack. An EEG was performed prior to SD, and the next morning a prolonged EEG recording was performed and the latter was compared with the first EEG record.

Results: Six of the 10 patients had no EEG abnormality before exam; subtle EEG abnormalities were found in 4 of the group. In deprived EEG,

ms were determined paroxysmal epileptiform discharges in 5 persons; in the remaining 5 patients EEG, ms did not show changes.

Conclusion: In conclusion, it can be said that complete SD has a useful role as an additional tool for individuals with a suspected epileptic disorder.

p181
EFFECTS OF HYPONATREMIA ON SEIZURES IN PATIENTS WITH EPILEPSY AND POLYDIPSIA
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Purpose: We evaluated aggravation of seizures due to hyponatremia with epilepsy and polydipsia.

Method: We report on 5 patients with epilepsy and polydipsia-hyponatremia (cases 1–5; 1 female and 4 male, aged 24–39 years). Case 1 had an average of 2 complex partial seizures (CPS) per month and the others (cases 2–5) had an average of 2 or 3 CPSs per year under normal conditions. Four of 5 patients had intellectual impairment due to closed head injury (case 1), brain tumour (case 4) or postencephalitic sequelae (cases 2 and 3). Three (cases 2, 4 and 5) of the 5 patients suffered psychotic episodes. Carbamazepine had been given to 4 (cases 1, 2, 4 and 5) of the 5 patients for treatment of seizures. Neuroleptics had been given to all patients for delusions or psychomotor excitement.

Results: The patients experienced marked increases in frequency of their habitual seizures when their serum sodium level decreased to 118–127 mEq/l, a decrease of about 10 mEq/l from the normal level. In all cases, the serum sodium level returned to normal through restriction of water, and the clinical seizures improved, but death resembling sudden unexplained death in epilepsy occurred in case 5.

Conclusion: Hyponatremia caused by polydipsia appears to be a risk factor for aggravation of habitual seizures and even death in patients with epilepsy, even if the hyponatremia is mild and at a subclinical level.

p182
INTERLEUKIN-6 AND INTERLEUKIN-1 RECEPTOR ANTAGONIST LEVELS IN TEMPORAL AND FRONTAL LOBE SEIZURES DURING VIDEO-EEG RECORDINGS
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Purpose: Experimental and clinical studies have shown that prolonged seizures result in increased cytokine production in the central nervous system. However, the effect of seizure type on cytokine production is not well established. The purpose of this study is to examine the concentrations of two key cytokines in patients with temporal and frontal lobe epilepsy undergoing a video-EEG study.

Method: Here we determined the levels of interleukin-6 (IL-6) and interleukin-1 receptor antagonist (IL-1RA) in serum from 16 patients before and after seizure during continuous video-EEG monitoring in Tampere University Hospital. The definition of the seizure focus and classification of epilepsy was based on concordant findings in this investigation, and on MRI examination. Patients were divided into two groups: the temporal epilepsy patient group ($n = 9$), and the frontal epilepsy patient group ($n = 7$).

Results: In all patients with complex partial seizures originating from temporal lobe and in 4 out of 7 originating from frontal lobe there was increased production of IL-1RA with peak levels 6–12 hours after the seizures. Two TLE patients with complex partial seizures had increased concentrations of IL-6 whereas none of the FLE patients with partial seizures only had elevated levels of IL-6. Secondarily generalised seizures were associated with more profound increases in IL-6 concentrations.

Conclusion: The present study demonstrates that single seizures in chronic epilepsy are followed by activation of the cytokine network. The production of IL-1RA and IL-6 are influenced by the origin of the seizures from either temporal or frontal lobes. Since also the laterality of the seizures may affect the cytokine production, larger patient groups with well-characterised seizures need to be studied in order to fully assess the importance of the cytokine responses in chronic epilepsy.

p183
PARTNERS IN EPILEPSY (PIE): EPILEPSY MANAGEMENT WITH INTERNATIONAL ELECTRONIC RECORDS REGISTRY SYSTEM: DATA ANALYSIS UPDATE IN ADULTS
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Purpose: To analyse epilepsy characteristics, outcome, and antiepileptic drug (AED) treatment in a large international adult patient naturalistic data cohort.

Method: Electronic records management in daily clinical practice (demographics, aetiology, syndrome, treatment) in epilepsy centres in Belgium, France, Portugal, Spain, Switzerland and United Kingdom: data analysed from 5262 patients (M/F = 50.5%/49.5%).

Results: Mean age at first attack: 26.7 (range 0–102 years), 4901 had follow-up visits, mean total observation: 776 days (median = 314, range: 1–53 years). Of 2646 with aetiology/risk factors recorded, the most commonly identified were: trauma (11%); family history of epilepsy (8.5%); perinatal history of hypoxia (6%); benign cerebral tumour (5%); and cortical malformations/developmental disorders (5%). Epilepsy was classified in 41% of patients: localisation-related (23%), generalised (9.6%), undetermined (6.8%), and other syndromes (1.6%). 49% were seizure-free at last follow-up visit after $\geq$6 months. Among those still experiencing seizures, 34% had predominantly focal seizures, 21% generalised seizures. Monthly seizure rate averaged 11.2 (0–750) for partial seizures, 15.8 (0–900) for generalised seizures. Of the 4216 adults using AEDs at the last follow-up visit, 58% were on monotherapy: valproate (VPA: 20%), carbamazepine (CBZ: 14%), lamotrigine (LTG: 9.5%), levetiracetam (LEV: 3.0%), topiramate (TPM: 2.9%), phenytoin (PHT: 2.7%). 28% were on two, 14% on three or more AEDs. Most common AED combinations: LTG/VPA (2.8%), CBZ/VPA (2.2%), CBZ/LTG (1.9%) Most common side effects: somnolence, weight gain, tremor, dizziness, headaches.

Conclusion: Registry analysis provided valuable information on epilepsy characteristics, outcome and AED treatment patterns. Epilepsy was classified in only 41% (predominantly localisation-related). About half were seizure-free. The majority were on monotherapy. (PIE is supported by Janssen-Cilag).

p184
SEX AND GONADOTROPHIC HORMONAL LEVEL DISBALANCE IN MALES WITH EPILEPSY
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Purpose: To detect the sex steroid and pituitary trophic hormone levels and clinical symptoms of hormonal disbalance in males with epilepsy.

Method: 22 male patients with idiopathic epilepsy (age 18–68) and 11 controls were examined in the neurological department of Riga 1st. Hospital and Diagnostic Center of Epilepsy in Riga 2004–2005. Special questionnaires were used for collecting anamnestic data. Every patient and the controls underwent EEG investigation and blood hormone level tests: follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2), progesterone (PRG), rostendione (ANDR), total testosterone (T), and dihydroepiandrosterone sulphate (DHEAS).

Results: Hormone imbalance was identified in 15 (68%) males with epilepsy. Low DHEAS blood level in 8 (32%) cases, increased ANDR in 3 (12%) patients, total testosterone decreased in 6 (24%) cases giving evidence of testis dysfunctions. There was an increase of LH and FSH both in 4 (16%) cases. Patients with abnormalities of sex hormones had subjective sexual disorders: erectile dysfunction 6 (24%), decrease of sexual disposition 4 (16%) cases. The frequency of seizures in male patients with epilepsy with sex hormone disbalance was 1 to 6 per month

in comparison with 1 per month or rarer for those of normal hormone levels.

Conclusion: Hormone imbalance was identified in 68% of males with epilepsy. The increased level of gonadotrophic hormones can be estimated as a compensatory stimulating factor for the decreased testis function and as a possible activating factor of seizures.

p185
HIPPOCAMPAL VOLUME DECREASE IN DEMENTED CHRONIC TEMPORAL EPILEPSY PATIENTS
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Purpose: Many observations indicate the relationship between dementia and long duration of temporal lobe epilepsy (TLE), particularly among patients with secondary generalisation. Memory impairment may be a result of structural hippocampal damage, which sensitive measurement is hippocampal volumetry.

Method: We examined 15 patients with drug resistant TLE with secondary generalised partial complex seizures and cognitive disorders established by clinical features and psychological tests: clock drawing and Mini Mental State Examination (MMSE). All patients also had magnetic resonance imaging (MRI) and volumetric assessment of hippocampal volume (HV).

Results: The group consisted of 8 men and 7 women. Mean age was 34.7, and mean duration of epilepsy was 15.9 years. Average frequency of partial complex seizures was 10.9 per month. There were no abnormalities in qualitatively assessed MRI in 9 patients, and abnormal results of MRI in 6 persons. Mean asymmetry of HV (asymmetry between right and left HV) in the group was 10.7% compared at max. 5% was established as a norm in a control study group. Average MMSE was 21.8, and clock drawing has given at least 2 false elements in every patient.

Conclusion: The results of our study support the opinion that seizure induced neuronal loss of hippocampus may cause dementia disorders in patients with drug resistant TLE.

p186
EEG PHENOVENAS IN EPILEPSIA PARTIALIS CONTINUA (CASE OF RUSSIAN TICK-BORNE ENCEPHALITIS)
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Purpose: Epilepsy partialis continua is one of syndromes of Russian tick-born encephalitis.

Method: We investigated 560 EEG of 37 patients suffering from epilepsy partialis continua in the structure of tick-born encephalitis.

Results: The results of our investigation allow the division of EEG into three types.

Type I characterised good modulated alfa-activity without space disorganisation.

Type II characterised a significant rhythmical disorganisation with slow wave prevalence and was divided in two subtypes: the first subtype was characterised by high amplitude and low modulated oscillations with slow wave prevalence; the second was presented by polymorphic activity without rhythmical domination.

Type III EEG presented low amplitude rhythmical and space disorganisation.

Autocorrelation analysis found the low periodical significant in all EEG types.

The functional probes with activation and photostimulation were different in the EEG of the three types. In the EEG of the Type I we could observe significant reply, such as rhythm depression on the opened eye and rhythm appearing on the closed eye. In case of the rhythmical photostimulation we observed a photoactivity reaction. In the Type II EEG photostimulation effects were lost, but reaction on the opened eye was presented. In Type III all EEG reactions were lost. In the disease's development 28 patients had local periodical EEG oscillations in both brain hemispheres. In this case we observed a presentation of pathological local EEG activity in the contralateral hyperkinetic hemisphere. Paroxysms of bilateral-synchronous low oscillations were observed in 439 EEG which included 3 EEG of Type I, 18 of Type II, 103 of Type III. In the first group of cases (18 patients) we observed slow wave paroxysmal activity with amplitude prevalence in the frontal and occipital regions. In the second group (19 patients) we observed paroxysmal activity such as spike-slow wave and sharp-slow wave complexes.

Conclusion: The results have shown that in a case of epilepsy partialis continua we can observe a complex brain disorder on different levels which combine as real epileptiform activity as specific hyperkinetic activity in a case with a subcortical lesion.

p187
GENDER DIFFERENCES IN REPORTING ICTAL FEAR IN EPILEPSY PATIENTS: AN ANALYSIS OF CASE HISTORIES
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Purpose: Male-female differences in emotional expressiveness are the object of research. Many emotions, including fear, are reported more frequently by women than by men. Some studies conducted across different cultures indicate that females verbalise more fear than do males (Brody L.R., *Gender, emotion, and the family*. Cambridge, MA: Harvard University Press, 1999). The purpose of our study is to determine if there are some differences in reporting fear as a symptom of the epileptic seizure in a group of drug-resistant epilepsy patients evaluated for surgery.

Method: All clinical charts (n° 2530) of patients evaluated at the "C.Munari–Epilepsy Surgery Center" of Milan from 1990 to June 2005 were reviewed, looking for patients with subjective ictal fear or frightened expression during seizures.

Results: 266 patients with ictal fear were found, 100 male and 166 female ($p < 0.001$); of those, gender difference is even higher considering patients with ictal fear as a steady element of their seizure semiology (59 male and 121 female, $p < 0.001$), while no gender difference was found considering patients with ictal frightened expression (42 female and 40 male, $p = 0.825$). Interestingly many more male than female (14:3) with ictal fear in childhood showed a disappearance of that symptom in adulthood.

Conclusion: Ictal fear is reported more frequently by females than males, but no gender difference is observed in ictal frightened expression. Males that reported ictal fear in childhood show more often than females a disappearance of this ictal sensation in adulthood.

p188
CORRELATION OF FOCAL SIGNS AND LONG-TERM OUTCOME IN JUVENILE MYOCLONIC EPILEPSY
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Purpose: Juvenile myoclonic epilepsy (JME) is an age related idiopathic generalised syndrome. During recent years different chromosomal mutations were discovered for different clinical subtypes of JME. Data appeared about metabolite abnormalities, neuronal loss and dysfunction in frontal lobes in JME. In clinical practice some cases of JME are characterised by the existence of clinical or EEG focal signs, in particular asymmetrical or focal myoclonic seizures and polyspike-wave (PSW) discharges, mostly presented in the frontal lobes. The aim of our study was to identify the frequency of such focal signs and try to find their correlation with long term prognosis.

Method: Sixty-three patients with JME were evaluated and followed for 10 years. In all cases MRI, repeated and long term EEG was performed.

Results: MRI was normal in all cases. In 44 cases clinical presentation was typical for JME with symmetrical myoclonic seizures and symmetrical, synchronous PSW waves on EEG-group 1. In group 2 (19 cases)

myoclonic seizures were predominantly focal with prevalence on the right side. Focal myoclonic seizures were correlated with bursts of asymmetrical PSW predominantly in frontal regions on EEG. Interictal EEG was also characterised by short bursts of PSW in the left frontal region. There was significant difference in frequency of generalised seizures (GS) in two groups. In group 2 GS were significantly more frequent and disabling than in group 1 ($p < 0.005$). Long term outcome for seizure control, relapse rate and development was worse in group 2 ($p < 0.001$).

Conclusion: Existence of focal clinical and EEG signs in JME correlate with poor long term outcome for seizure control, relapse rate and development.

p189

THE IMPACT OF INCLUDING GREY AND NON-ENGLISH LITERATURE ON COMBINED EFFECT ESTIMATES FROM NON-RANDOMISED ADD-ON ANTIEPILEPTIC STUDIES

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Purpose: Exclusion of non-English and grey literature (i.e., literature not published in peer reviewed journals or limited distribution) studies from systematic reviews may introduce bias and impact on overall treatment effect estimates. We investigated this by using nonrandomised add-on studies of topiramate and levetiracetam in refractory epilepsy.

Method: Electronic searches of MEDLINE (1902–2005), EMBASE (1974–2004), CINAHL (1982–2005), ZETOC (1993–2005), and hand searches of congress proceedings were performed to identify relevant studies. Data was extracted for study attributes, 50% responder and seizure freedom rates. Effect estimates were compared for non-English versus English studies and for studies published in full versus those published in abstract form only. Funnel plots were used to assess publication bias.

Results: Ninety-four nonrandomised studies (42 published in full, 52 abstracts) were identified for add-on topiramate therapy and 80 nonrandomised studies (36 published in full, 44 abstracts) for add-on levetiracetam therapy. Median reported responder and seizure freedom rates were higher in topiramate studies published in full versus those from abstracts (62% vs 55%) and (16% vs 8%) respectively. Combining studies resulted in smaller median responder and seizure freedom rates compared to summary estimates from studies published in full. Including non-English topiramate studies published in full did not impact on overall treatment effect estimates. Similar results were noted for levetiracetam studies.

Conclusion: The exclusion of grey literature from systematic reviews could lead to over inflated summary effect estimates for an intervention. An attempt to retrieve all relevant data is paramount to systematic reviews.

p190

ICTAL SINGING

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Purpose: Vocalisations are frequent ictal manifestations. However, ictal singing is extremely rare (4 cases described) and its mechanism barely studied. We will describe a case helping to define the cerebral lateralisation of this automatism and emphasising the cerebral mechanisms responsible for musical production.

Method: A 41-year-old, illiterate woman, with no musical education, able to sign and embroil with her left hand with refractory seizures since the age of 12 months, consisting of an epigastric aura followed by clonic jerks of the right limbs and simple automatisms.

Results: MRI suggested left mesial sclerosis. Interictal SPECT showing left frontal-temporal hypoperfusion. Video-EEG monitoring revealed bilateral, left predominant, frontotemporal interictal epileptiform activity; ictal chewing and blinking automatisms followed by speech and singing with late right frontal-temporal epileptiform activity. Musical ictal evaluation: key (D major), beat (binary), rhythm (seminim-1.8 Hz), and character (Portuguese folksong malhão). Left selective amygdalohippocampectomy was performed, and microscopic confirmation of mesial sclerosis associated to neuronal dysplasia and amygdaloid nucleus atrophy. Patient is seizure free 8 months after surgery.

Conclusion: In this patient, the dominant hemisphere is probably the right one. Although the diagnostic search failed to precisely identify the ictal onset zone the described seizures favoured a nondominant hemisphere onset. Musical production requires the orchestration of several components (rhythm, pitch, lyrical content). In the ictal singing, several diffuse musical elements are probably brought together and vocalised in such a way to produce a recognisable tune. There is growing evidence that musical functions dynamically recruit several mechanisms/neuronal networks involving regions in both hemispheres.

p191

ELECTROENCEPHALOGRAPHIC AND CLINICAL CHARACTERISTICS OF PHARMACORESISTANT FOCAL EPILEPSIES

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Purpose: To determine the electroencephalographic (EEG) and clinical characteristics of pharmacoresistant focal (partial) epilepsies in a sample of adult patients.

Method: Patients with proven pharmacoresistant epilepsy were compared with a control group of patients with focal epilepsy and complete seizure control. All patients first referred to our department were consecutively included in this study with a follow-up period of three years. EEG and brain neuroimaging were performed in all patients. Seizures, epilepsy and epilepsy syndromes were classified according to the proposals of the International League Against Epilepsy. Patients with pseudopharmacoresistance due to incorrect diagnosis and/or inadequate therapy were excluded.

Results: According to demographic characteristics, a group of 60 patients with pharmacoresistant focal epilepsy (mean age 32.4 years, 48% males) was comparable with a control group also including 60 patients (mean age 29.8, 45% males). When the pharmacoresistant group and the control group were compared, the following characteristics of an unfavourable outcome reached statistical significance: interictal delta activity in EEG ($p < 0.01$), complex focal seizures with a prolonged postictal disorientation phase ($p < 0.01$), mesiotemporal location of epileptogenic lesion ($p < 0.05$), neurological deficits ($p < 0.05$), symptomatic aetiology ($p < 0.05$) and comorbid psychiatric disorders ($p < 0.05$). Temporal interictal rhythmic delta activity showed correct lateralisation of epileptogenic lesion involving mesiotemporal location.

Conclusion: Focal epilepsies contain a cluster of clinical and EEG characteristics which can early be suggestive both of pharmacoresistance and the need for the use of surgical and other nonpharmacological treatment modalities.

p192

SEIZURES FOLLOWING MILD TRAUMATIC BRAIN INJURY AND WHIPLASH: A CASE REPORT

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Purpose: In epidemiological studies, post traumatic epilepsy after mild traumatic brain injury (MTBI) is found to have a low rate of occurrence. In light of the findings in our case, we question the reliability of the diagnosis of epilepsy in these studies. Especially in the context of compensation seeking, an attack disorder occurring after MTBI and/or whiplash (WAD I, II) requires critical investigation and analysis.

Method: Habitual seizures were registered by video-monitoring.

Results: An 18 year old patient was involved in a car accident resulting in mild traumatic brain injury (MTBI) and whiplash trauma (WAD II). Approximately 6 months later the patient presented for the first time paroxysmal alterations of consciousness and sensory motor deficits of the right extremities. Requirements for compensation 8 years post-accident led to the first neurological evaluation including a standard EEG. Posttraumatic epilepsy was diagnosed, and treatment with VPA was indicated. One year later, during the continuing medicolegal process, a video-EEG seizure recording in a specialised epilepsy

centre, and a cerebral MRI, were performed. These investigations led to the diagnosis of a non epileptic attack disorder (NEAD). The psychiatric exploration revealed an adequate psychic conflict.

Conclusion: The early and detailed exploration of seizure semiology, video-EEG monitoring and adequate imaging is essential to diagnose NEAD. The early diagnosis of NEAD is of great value with regard to prognosis and development of the disorder. The management of post traumatic symptoms after head and cervical trauma without structural lesions needs to be optimised, as shown by this case report.

p193

CALLOSOTOMY VERSUS VAGUS NERVE STIMULATION IN DRUG-RESISTANT EPILEPSIES

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Purpose: To compare results obtained by two different "palliative" surgeries, callosotomy and vagus nerve stimulation (VNS) in drug-resistant epilepsy patients.

Method: 56 drug-resistant epilepsy patients were submitted to palliative surgery. From 1985–1998 22 patients underwent callosotomy. Surgical indication was based on high frequency of "tonic-atonic falling seizures" with either an impossibility to perform, or failure, of a previous ablative surgery. From 1995–2005 34 patients suffering partial and secondary generalised seizures underwent vagus nerve stimulation (7 of them were treated less than a year ago). Besides being drug resistant, surgical indication was also based on either an impossibility to perform, or failure of a previous surgery (callosotomy or ablative surgery). "Good" outcome was defined as a reduction of seizures by at least 50%. "Unchanged": reduction of seizures by less than 50%. VNS patients were further evaluated on the basis of epileptic status, clusters and handicapping effects of the seizures.

All patients were assessed 1 and 5 years after surgery, taking into consideration the total number of residual attacks as well as differing types of seizures.

Results: Callosotomy: "good" results were obtained in 15 patients (68.2%), 4 are seizure free; 6 (27.3%) were "unchanged" and 1 worsened. The best results were obtained with generalised seizures, which disappeared in 11 patients (50%), while partial seizures had a worse outcome. Vagus nerve stimulation: "good" outcome were obtained in 5 (18.5%) out of the 27 considered patients, 2 of them are seizure free and no patient worsened. Evaluating surgical outcome considering also cluster, status and handicapping effects of the seizures, "good" results were obtained in 11 patients (40.8%), the remaining 16 (59.2%) were unchanged.

Conclusion: With respect to VNS, callosotomy is shown to be more efficient in reducing the occurrence of tonic-atonic seizures. The differences between VNS and callosotomy are evident in both the reversibility of VNS and the invasiveness of callosotomy. For this reason the two surgeries could be considered, for a single patient, in successive steps: VNS first, while callosotomy could be a second approach if surgical indications are still present. Both types of interventions, when efficient, show unchanging results over time: 1 and 5 years follow up studies.

p194

DIFFERENT CLINICAL MANIFESTATIONS OF HYPERAMMONEMIC ENCEPHALOPATHY

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Purpose: Valproate is an effective anticonvulsant; although it is usually well tolerated, it has been associated with many neurological, hematopoietic, hepatic and digestive system side effects. Among these side effects hyperammonemia without clinical or laboratory evidence of hepatotoxicity is a rare and important clinical consideration. The aim of this presentation is to evaluate the reasons for unexpected symptoms of four epilepsy patients while being treated with valproate.

Method: We evaluated 4 adult patients with localisation-related epilepsy who presented with different acute or subacute neurological symptoms related to valproate induced hyperammonemic encephalopathy (VHE).

Results: Two of the 4 patients were women and 2 were men. The ages of patients ranged from 20–56 (mean: 31.7). Three of 4 patients had an acute onset of confusion, decline in cognitive abilities and ataxia. Among these patients one had a decline in speech, and the other one had increased seizure frequency and new onset tremor. Except these, the last patient had subacute behavioural alteration, an increase in appetite and urinary incontinence. Ammonia levels were elevated in all the patients. After the discontinuation of valproate, complete clinical improvements were observed within 5–10 days.

Conclusion: The pathogenesis of VHE is still unclear, but it has been suggested that hyperammonemia can produce encephalopathy via inhibition of glutamate uptake by astrocytes which may lead to potential neuronal injury and perhaps cerebral edema. In this presentation we suggest that ammonia levels of a patient, who has new neurological symptoms and has been taking valproate, must be checked. The clinicians should be aware that these clinical symptoms may be related to VHE, and the symptoms may resolve dramatically after withdrawal of the drug.

p195

A DETAILED ANALYSIS OF HYPERMOTOR SEIZURES SEMIOLOGY

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Purpose: To describe the detailed semiology and the underlying epileptogenic zone of hypermotor seizures.

Method: We analysed ictal manifestations of 105 hypermotor seizures in 10 consecutive patients who underwent intra-cerebral EEG monitoring and successful surgery.

Results: Two types of hypermotor seizures could be distinguished in this population: Type 1 mainly consisted of marked agitation that either included body rocking, kicking or boxing, without associated dystonic posture or tonic head version. Type 2 seizures mainly consisted of less marked agitation that either included horizontal movements or rotation of trunk and pelvis while lying on a bed, usually associated with dystonic posture or tonic head version. Various auras, vocalisation, grasping and standing up were observed in the two seizure types. Among the 6 patients with type 1 hypermotor seizures, 4 (66%) demonstrated a seizure onset zone that included the orbitofrontal cortex and/or the rostral portion of the anterior cingulate gyrus, whereas the latter brain regions were not involved in the 4 other patients with type 2 hypermotor seizures. In most other patients with either type 1 or type 2 seizures, intracerebral EEG ictal onset was observed in the mesial cortex of the superior frontal gyrus and/or in the dorsal cingulate cortex.

Conclusion: We have identified two types of hypermotor seizures, primarily distinguished on the type and intensity of agitation, and the associated dystonic posture and head version. This distinction might help to determine the underlying EZ, and in particular the involvement of the orbitofrontal cortex and/or the rostral portion of the anterior cingulate gyrus.

p196

HYPERANDROGENISM IN WOMEN WITH EPILEPSY IN THE CHILDBEARING YEARS

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Purpose: Occurrence of hyperandrogenism (HA) and menstrual disorders is higher among women with epilepsy than in the population without epilepsy. One of the probable reasons is the antiepileptic medication used in these patients. We performed open prospective follow-up for symptoms of HA in women in the childbearing years treated with lamotrigine (LTG) as their first monotherapy or after switching to LTG from valproate (VPA), carbamazepine (CBZ) or combination therapy VPA plus CBZ.

Method: Data were collected on 181 women aged 15–50 years. Symptoms like acne, hirsutism (HIR), excessive hair lost (HL), oligomenorrhea (OMR), amenorrhea (AMR), shortened menstrual cycle (SMC) and prolonged menstrual cycle (PMC) were checked-up in patients at two, five and eight months after introducing LTG as afirst-line monotherapy or after switching to LTG from VPA, CBZ or combination therapy VPA +CBZ.

Results: Thirty-eight women started LTG as their first monotherapy; 4 (10.5%) of them had acne, 2 (5.3%) had HL, 1 (2.6%) had OMR, HIR, AMR or PMC, 3 (7.9%) had SMC at the time of introducing the therapy. Eight months later there was no significant change in the frequency of their symptoms. One hundred and seven women switched from VPA to LTG; 31 (28.9%) had acne, 31 (28.9%) had HL, 15 (14%) HIR, 3 (2.8%) AMR, 16 (14.9%) OMR, 13 (12.1%) SMC and 11 (10.3%) had PMC at the beginning of the follow-up. Eight months later 13 (12.1%) had acne (decrease significant $p = 0.001$), 7 (6.5%) had HL ($p = 0.001$), 2 (1.9%) HIR ($p = 0.01$), 6 (5.6%) OMR ($p = 0.01$), 6 (5.6%) SMC ($p = 0.05$), 1 (0.9%) AMR (NS) and 8 (8.4%) had PMC (NS). Sixteen women switched from CBZ to LTG; the frequency of symptoms of HA was not significantly different from the group with LTG first-line monotherapy at the beginning of the follow-up and 8 months later. Twenty women who switched from VPA+CBZ to LTG had a higher incidence of some symptoms of HA than group VPA (acne 10 (50%), AMR 8 (40%), HL 9 (45%), 8 (40%) OMR). Eight months later there was a significant decline in the frequency of acne, HL and OMR in this group.

Conclusion: There was a significantly higher rate of symptoms of HA in the patients treated with VPA alone or combination therapy VPA+CBZ at the beginning of the follow-up compared to the group of patients treated with primary LTG monotherapy. Switching these women to LTG led to a significant decline in the frequency of acne, hirsutism, hair loss, oligomenorrhea and shortened menstrual cycle at 5 and 8 months of follow-up.

p197
THYROID DISEASE AND EPILEPSY: CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS

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Purpose: The main objective of this study is to determine the relation of epilepsy development and prognosis of the patients who have thyroid dysfunction (TD) or disease.

Method: Fourteen patients (10 women, 4 men) with a mean age of 32.64 ± 16.27 (16–70) years were selected. The patients were classified in to 2 groups according to relation of TD to their epilepsy. In group 1 ($n = 6$), TD was diagnosed before epilepsy, in group 2 ($n = 8$); TD was detected after epilepsy diagnosis.

Results: Epileptic disorder was classified as partial epilepsy in 9, and primary generalised epilepsy in 5 of the patients. Six of the patients were on monotherapy, 8 were on polytherapy. All of the patients in group 1, and 4 (50%) patients of group 2 were on treatment because of TD. On the other hand, hypothyroid was detected in 5 (83.3%) of group 1, and in 2 (25%) of group 2 patients ($p = 0.031$). EEG revealed focal abnormalities in 66.6% of the group 1, and subcortical epileptic activity in 50% of group 2. MR imaging showed abnormal findings in 5 (83.3%) of group1 and in 2 (25%) of group 2 patients ($p = 0.025$).

Conclusion: 43% ($n = 6$) of the patients were seizure free and 42.9% ($n = 6$) had partially controlled seizures with regular and continuous antiepileptic therapy. However, 1 patient in each group had no change in seizure frequency in spite of regular therapy for both diseases.

p198
INVOLUNTARY FACIAL TWITCHING INDUCED BY TOPIRAMATE

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Purpose: We present 2 cases treated with topiramate (TPM) who developed a hitherto undescribed side effect consisting of involuntary twitches of facial musculature.

Method: Two cases with partial-onset seizures were investigated in detail. The data is reported in the Results section.

Results: Case 1 is a 28-year-old male with complex-partial seizures (CPS). Since phenytoin was only partially efficacious, it was decided to convert him to TPM as monotherapy. Treatment with TPM was initiated at 25 mg/day with 25 mg weekly increments. The patient tolerated TPM until a daily dose of 150 mg was reached. At that dose, he started to experience twitching of his facial muscles, more prominent in his forehead. The twitches recurred at an average frequency of 5 Hz (documented by EMG) and occurred in clusters several times daily, with each lasting up to 10 seconds. The muscle twitches were not associated with any epileptiform activity on a surface EEG. Case 2 is a 49-year-old woman with new-onset CPS. Treatment with TPM was initiated at 50 mg/day with 25 mg weekly increments. The patient reported no adverse events until a daily dose of 150 mg. At that dose, she experienced facial twitches similar to those described for Case 1 but more prominent around the eyes and mouth. Neurological examinations and routine blood work were normal for both patients. These muscle twitches resolved in both patients upon discontinuing TPM.

Conclusion: TPM may cause twitching of the facial muscles which resolve upon discontinuation of the drug. The mechanisms responsible for this unusual adverse event are not clear.

p199
SOME FEATURES OF EPILEPSY AND EPILEPTIC SEIZURES IN ELDERLY PATIENTS

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Purpose: Epilepsy and single epileptic seizures are third among of the most serious neurological problems in elderly persons. Appreciably it is symptomatic seizures or epilepsy caused by age changes of the brain, and also acute symptomatic attacks, as the remote consequences of trauma, or progressing diseases of CNS. The purpose of this research was to reveal the interrelation between cerebral pathology in persons of elderly and senile age and development of symptomatic seizures and epilepsy for optimisation of antiepileptic treatment.

Method: Material for the research was 10 years supervision which had been carried out in the central clinical hospital of Kharkov. We surveyed 238 patients, with symptomatic seizures or epilepsy de novo from 60 to 79 years old.

Results: Epileptic seizures and epilepsy in the elderly were caused by urgent cerebrovascular diseases in 46%; by metabolic or toxic diseases in 18%, head traumas in 13%, tumours in 9%, infections of CNS in 3%, dementias in about 3%, and some cases was referred as obscure aetiology. The type of seizures in elderly and senile patients depends from aetiology of epilepsy. Generalised seizures prevail in the patients with metabolic and toxic encephalopathy, partial and secondary generalised seizures are characteristic for organic focal lesion of the brain. Most frequently we observed complex partial seizures (on the average 48–52%), secondary generalised seizures (20–27%), simple partial seizures (13–16%).

Conclusion: Acute cerebrovascular diseases were the most common reason of developmental symptomatic epilepsy in the elderly. The treatment of epileptic seizures and "vascular" epilepsy should be individual with application of mainly monotherapies by antiepileptic drugs and parallel treatment of the cerebrovascular pathology.

p200
PROGNOSTIC SIGNIFICANCE OF SYNDROMIC CLASSIFICATION IN NEWLY DIAGNOSED EPILEPSY PATIENTS

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Purpose: To assess the frequency, timing, patterns and prognostic significance of change of the syndromic diagnosis in a cohort of newly diagnosed adults with epilepsy.

Method: 180 newly diagnosed adults from an epilepsy centre were included and followed for 852.4 person years. For each patient, the syndromic diagnosis was made at entry according to simplified categories. Changes of the diagnostic categories were then recorded retrospectively during follow-up. A change of the syndromic diagnosis was made and dated, based on new data on seizure types and/or EEG findings and/or neuroimaging results. Using survival analysis, the cumulative time-dependent probability of change of syndromic category and of 2-year remission was measured. Differences were tested with the log-rank test. A multivariate analysis was performed using Cox's proportional hazard function.

Results: The sample included 104 men and 80 women aged 15 through 84 years. At entry, 61 patients (33.9%) had partial epilepsies, 42 (23.3%) had generalised epilepsies, 19 (10.6%) had undetermined epilepsies, and 58 (32.2%) had isolated seizures. The syndromic diagnosis was changed during follow-up in 54 cases (30%). The cumulative probability of change was 10% at six months, 16%, 19%, and 25% at 12, 24, and 36 months. 83% of changes were in patients with isolated seizures who relapsed (45 cases). A total of 105 patients (58.3%) achieved 2-year remission. The cumulative probability of remission was similar when comparing patients with and without change of the syndromic diagnosis (log-rank 0.11; $p = ns$), after excluding those with isolated seizures at entry, and when adjusting for age, sex, disease duration at entry, and treatment in the multivariate analysis model.

Conclusion: Except for isolated seizures, the syndromic diagnosis at entry changed infrequently (mostly during the first year) in adults and did not affect the chance of long-term remission of epilepsy.

p201

CARBAMAZEPINE AND OXCARBAZEPINE DRUG UTILISATION PATTERNS AND IMPACT ON LIFE IN ADULTS AND CHILDREN WITH PARTIAL SEIZURES: A CROSS-SECTIONAL STUDY

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Purpose: Carbamazepine is a well known antiepileptic drug (AED) indicated for partial seizures and has been widely used during the last decades. Oxcarbazepine has been marketed in Europe since the 1990s. Our aim is to describe drug utilisation patterns of carbamazepine and oxcarbazepine, in routine clinical practice and to study the impact of epilepsy on patients' lives, in adult and child populations.

Method: A cross-sectional survey conducted in specialised clinical settings under the Spanish National Health System. Patients being treated with any of the specified AEDs were asked to participate. Inclusion criteria involved patients suffering partial seizures on maintenance treatment during the previous 4 months. The prescribing patterns for AEDs are established according to titration schedule, dose, and combined AED therapy. Self-reported impact of epilepsy on patients' lives is recorded in adults using the Sheehan Disability Scale and in children using the Cuestionario de Calidad de Vida del Niño con Epilepsia (CAVE).

Results: Fifty patients were included in the study by 63 specialists from around the country. A description of the drug utilisation pattern is documented in the adult and child populations based on the severity and the type of seizure according to ILAE classification of epileptic seizures.

Conclusion: It is relevant to provide data on the utilisation of AEDs in specialised clinical settings from large populations. Information on the impact of epilepsy on patients' lives is also needed, in adults and children, to document the social burden of this chronic condition. This study was funded by Novartis.

p202

A RASMUSSEN ENCEPHALITIS CASE TREATED WITH INTRAVENOUS IMMUNOGLOBULINS

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Purpose: Rasmussen encephalitis is characterised by epilepsia partialis contunia accompanied with focal seizures, progressive neurologic deficiency, hemispheric atrophy and histopathological inflammation.

Method: A case study: A 20-year-old male patient had his first secondary generalised seizure with left side adversion when he was 11 years old and following this seizure focal motor seizures on the left arm and left side of the mouth were observed. At the beginning, the seizures were controlled with antiepileptic therapy, but later epilepsia partialis continua emerged. Neurologic examination was normal except for focal motor seizures. Cranial MRI revealed signal change in the right parietooccipital region and cortical atrophy on the perisylvian fissure. All the other tests did not reveal any other reason for epilepsia partialis continua, so the patient was diagnosed as having Rasmussen encephalitis with cortical hemiatrophy. The patient was treated with intravenous immunoglobulins intermittently in addition to antiepileptic drugs for four years. The patient does not have new neurological deficiency. He still has epilepsia partialis continua intermittently without affecting his daily activities.

Results: Medical or surgical therapy choices for Rasmussen syndrome are still being discussed.

Conclusion: In this paper, we present a patient with Rasmussen encephalitis who was treated with intravenous immunoglobulins effectively and safely.

p203

QUALITY OF LIFE IN ELDERLY PATIENTS WITH CHRONIC EPILEPSY

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Purpose: To investigate the clinical features of elderly patients (>60 years) with chronic epilepsy living in the community and to evaluate patients' quality of life (QOL).

Method: Over a 1 year period data from a consecutive cohort of outpatients were prospectively collected. Patients completed the Health-related QOL 36-item Short Form (SF-36) and the Adverse Events Profile (AEP) questionnaire; comorbility was rated using to the Cumulative Illness Rating Scale (CIRS). Principal cognitive, functional and psychological/behavioural measures were: Folstein Mini-Mental Status Examination (MMSE), cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), Clinical Dementia Rating (CDR), Neuropsychiatric inventory (NPI), Geriatric Depression Scale (GDS), Katz activities of daily living (ADL), and Lawton's Instrumental activities of daily living (IADL). Dementia was diagnosed by means of DSM III-R criteria and according to consensus procedure a more complete neuropsychological examination was used to identify subtle cognitive deficits such as cognitive impairment nondementia (CIND). SF-36, GDS and AEP scores were compared with those of a reference group without chronic conditions with the same sociodemographic characteristics.

Results: Seventy-five patients (mean age 72.6 years, SD 8.1) completed the evaluation. The mean age at seizure onset was 54.8 years (range 2–93 years, SD 24.5), with the majority experiencing seizures after age 60 years (58.7%). Thirty-one (44%) were 1 year seizure free. Forty-seven (63%) were on monotherapy and 28 (37%) on polytherapy. CIRS comorbidity and severity average score was respectively 1.75 (SD 1.28) and 1.40 (SD 0.22). Mean score on MMSE was 21.8 (SD 0.6) and mean score on ADAS-cog was 18.76 (SD 7.1) with 28 patients (37%) that were considered demented and 22 (29%) with CIND. Mean ADL and IADL scores were respectively 4.72 (SD 3.22) and 5.29 (SD 4.24). Depression, anxiety, sleep disturbances and other psychiatric symptoms were detected on NPI in 59 (79%) patients. The z-scores on many SF-36 domains, AEP, and GDS scores were worse than those of the reference group.

Conclusion: In an epilepsy centre of a tertiary referral hospital aged patients with epilepsy frequently present drug-resistant seizures, cognitive impairment, psychiatric symptoms and worse QOL. Long-term studies in the general population are warranted to establish if incorporating health status information into therapeutic decision making may help to attain the ultimate goal of improving patients' health.

p204

RETROSPECTIVE INVESTIGATION OF PREGNANCY AND DELIVERY COURSES FOR WOMEN SUFFERING FROM EPILEPSY DURING THE LAST THREE YEARS

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Purpose: The aim of the investigation was to investigate special features of pregnancy in women suffering from epilepsy, taking as an example, the population of Vitebsk region (Belarus).

Method: We performed a population based case ascertainment of all available sources of medical care from April 2002 until December 2005. Women of fertile age, suffering from epilepsy, were analysed. Only cases with active epilepsy (at least one seizure during the last 5 years, regardless of treatment) were included. All patients were examined by a neurologist or psychiatrist.

Results: There were 4 pregnant women suffering from epilepsy in 2002. Mean age of patients was 23 years (18–29 years). There were 19 patients in 2003 (mean age 25 years, 18–34). In 2004, there were 48 women, mean age 26 years (18–41). In 2005 there were 35 women, mean age 26 years (19–40). All the women were primiparous. Idiopathic generalised epilepsy was the prevailing form. Frequent seizures were in only 2 women (1.8%). Caesarian section was performed in 20% of cases. One woman died from eclampsia at 30–weeks gestation in 2004. Two women had nondeveloping pregnancies at 12 and 18 weeks of gestation. 60% of women were treated with depakin-chrono. 98% of all patients received monotherapy. None of the offspring had abnormalities or malformations.

Conclusion: In connection with the creation of specialised centers, dealing with epilepsy problems and new antiepileptic drugs resulting in more effective treatment for epilepsy, more and more women are eager to have children.

p205

FALSE ALARMS FROM EPILEPSY ALARMS IN THE DANISH EPILEPSY CENTRE, DIANALUND

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Purpose: To assess the occurrence of false alarms from bed alarms and pulse-oxymetres in patients admitted to the Danish Epilepsy Centre, Dianalund.

Method: In 5 short term departments patients were prospectively subjected to close supervision using video camera when they were undergoing significantly increased risk of potentially dangerous epileptic seizures. Patients were included from April 2004 to January 2006. When the patients were in bed, they were constantly supervised by video recording. Each supervised patient carried a pulse-oxymetre, and the bed was equipped with an epilepsy alarm. The video supervision allowed identification of epileptic seizures, and the nursing staff registered alarms from the bed alarms and pulse-oxymetres (desaturation and/or change of pulse), likewise alarms without seizures were registered.

Results: Ninety-five patients (47 female and 48 male), aged 1–63 years (mean 23.8 years) were included. They were under supervision between 1 and 49 days (mean 8.0 days). In total 1471 seizures were observed by video recording. At the same time 273 false alarms by bed alarms (between 0 and 4.3 per day), and 585 false alarms from pulse-oxymeters (between 0 and 4 per day) were registered.

Conclusion: Bed alarms and pulse-oxymeters used in the Danish Epilepsy Centre, Dianalund, have a significant frequency of false alarms. As the sensitivity of these devices is also suboptimal, further development of epilepsy alarms is needed.

p206

FREQUENCY OF SEIZURES AND BRAIN BIOELECTRICAL ACTIVITY DURING STABLE AND UNSTABLE WEATHER CONDITIONS IN SPRING

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Purpose: Patients with epilepsy tend to combine the incidence of seizures with weather conditions especially atmospheric pressure and seasons. The aim of this study is to examine the real influence of atmospheric pressure and temperature changes on seizure frequency and if the incidence of seizures increases during unstable weather conditions is this combined with worsening of EEG findings.

Method: 30 patients (18 men and 12 women) with complex partial seizures and secondary generalised seizures (aged 19–54, mean 32.6) were studied. They have claimed an increase of seizure frequency because of atmospheric pressure changes for at least two years. All patients underwent EEG recordings twice during the spring while there were stable and unstable weather conditions. Each seizure was registered. Data about atmospheric pressure were obtained from The Meteorological Institute. EEG recordings in women were performed during the follicular phase of the menstrual cycle.

Results: During the unstable weather conditions in the spring, seizure frequency increased in 13 (43%) patients while in 16 (53%) it did not change. In 1 patient seizure frequency decreased. Unstable meteorological factors caused worsening of EEG recordings in 17 (57%) patients and in 5 of them changes in EEG so far normal appeared. In other 5 persons EEG changes deteriorated while in 7 epileptiform activity occurred.

Conclusion: The positive relationship between atmospheric changes and seizure frequency was found in less than half of our patients. The greater percentage of the patients with EEG changes during unstable weather conditions compared with those in stable may suggest the influence of meteorological factors on bioelectrical discharges with or without clinical manifestation.

p207

COMPLETE CHANGE OF SEIZURE AND SPIKE LATERALISATION IN TEMPORAL LOBE EPILEPSY AT TWO SEPARATE MONITORING SESSIONS

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Purpose: Video-EEG monitoring is a widely accepted method to determine the epileptogenic focus during presurgical evaluation of pharmacoresistant epilepsy. In the case of temporal epilepsy bilateral epileptogenic foci are frequent. Sometimes, a single video-EEG can miss the existence of a second focus.

Method: The charts of patients recorded in Salpêtrière Hospital between 1991 and 2005 were retrospectively reviewed. Among them, 115 had two independent monitoring sessions and at least one seizure per session. Only 2 cases showed a complete change in epileptic lateralisation at two successive monitoring sessions. We report on these 2 patients, both suffering from bitemporal lobe epilepsy, and who could have been interpreted as unilateral from a first video-EEG monitoring. However, the second video-EEG session revealed the second epileptic focus located in the opposite temporal lobe. Patient 1: a 23-year-old male, first developed temporal lobe seizures when he was 6 years old. A right temporal lobe dermoid cyst was discovered on MRI and a simple puncture of this cyst relieved the patient from seizures for 6 months. Afterwards seizures reappeared. Patient 2: a 45-year-old female, first experienced temporal lobe seizures when she was 37 years old. No noticeable lesion was observed on brain MRI.

Results: Patient 1: during the first monitoring a clear EEG expression of 5 typical seizures and 4 auras was present on the left temporal lobe region associated with an interictal spike focus in the same region. During a second video-EEG 9 typical seizures were expressed on the right temporal lobe region associated with an interictal spike focus of the same location. Patient 2: during the first video-EEG 1 crisis was expressed on the left temporal lobe region. Interictal epileptic abnormalities were bitemporal, right-sided predominant. During a second video-EEG, 5 epileptic attacks were expressed on the left temporal lobe region as were the interictal epileptic abnormalities. During a video-SEEG with

bitemporal electrodes 15 seizures originated from the right hippocampal contacts. Their scalp EEG expression was also right temporal. Interictal spiking of right temporal origin was present during the 24 h period. Left hippocampal interictal epileptic abnormalities occurred during sleep.

Conclusion: A bilateral TLE can occasionally be masked during a routine video-EEG monitoring. Patients without a visible lesion on MRI may benefit from the repetition of video-EEG monitoring sessions and a bilateral intracranial exploration. In patients showing a clear discordance between a lesional site and monitoring results, further monitoring sessions can reveal seizures coming from the lesional site.

p208

PREVALENCE OF EPILEPTIC SEIZURES IN PATIENTS WITH MULTIPLE SCLEROSIS (MS)

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Purpose: The objective of this study was to find the prevalence of "active epilepsy" in patients with MS. Previous studies on prevalence of epilepsy in MS patients report a wide variation of figures from 0.5% to 10.8%. This variation could be due to differences in methodology, small sample sizes, and differences in study populations.

Method: Data on MS patients living in a county in Norway with 218,120 inhabitants (Vestfold, January 1, 2003) in the period 1983–2003 were retrospectively collected. There were 501 patients who fulfilled the Poser criteria for probable or definite MS. 367 patients were still alive on 1 January 2003. "Active epilepsy" was defined as seizures within the last five years.

Results: of the 501 patients, we identified 30 with nonrecurrent seizures ($n = 9$) or epilepsy ($n = 21$). On 1 January 2003, the prevalence of "active epilepsy" was 3.5% ($n = 13$). After excluding 1 patient with a known aetiology other than MS, the prevalence was 3.3% ($n = 12$).

Conclusion: The prevalence of "active epilepsy" at prevalence date in our population of MS patients was 3.3% (3.5%). This is 3.8 times higher than expected in the general population in Norway (0.9%, Svendsen, 2004), and comparable to a previous Norwegian MS study (3.2%, Engelsen, 1997).

p209

INVESTIGATION OF THE LEVEL OF NEUROTROPIC AUTOANTIBODIES IN PATIENTS WITH POSTSTROKE SEIZURES

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Purpose: To evaluate changes of level of autoantibodies of IgG class to neurotropic proteins (n-AAB) in patients with poststroke seizures.

Method: We examined 37 patients (17 female, 20 male; mean age was 64.35 ± 11.61) including 22 patients with partial symptomatic poststroke epilepsy, 15 patients with a single seizure after ischemic stroke. All patients had partial and/or secondarily generalised tonic–clonic seizures. As a control 119 clinically healthy people were used. Evaluation of features of serum immunoreactivity was made by standard variants of IEA.

Results: The levels of nAAB to S100β, GFAP, MP-65, NGF were reliably higher in patients with poststroke seizures compared to control group (e.g. 139.00 ± 21.34 vs 100.60 ± 19.25, $I = 0.0000$ for S100β; 137.91 ± 21.12 vs 103.27 ± 20.11, $I = 0.0000$ for GFAP etc). The positive Spearman rank correlation was revealed between duration of epilepsy and the levels of nAAB to GFAP ($r = 0.405$, $p = 0.032$) and NGF ($r = 0.383$, $p = 0.019$). Also the level of nAAB to GFAP ($r = 0.484$, $p = 0.003$) and MP-65 ($r = 0.364$, $p = 0.034$) significantly correlated with the number of seizures since the onset of disease.

Conclusion: Our investigations showed that the levels of n-AAB to S100b, GFAP, MP-65, NGF were higher in patients with poststroke seizures vs control, especially in patients with a long history of epilepsy and a high number of seizures

p210

INFLUENCE OF NUMBER AND TYPE OF SEIZURES ON QUALITY OF LIFE

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Purpose: A reduction of the number of seizures is a basic parameter of evaluation of antiepileptic treatment. We wanted to find out if the reduction of the number of seizures or if the type of seizure influence the quality of life.

Method: All patients with two and more seizures in the past 8 weeks were examined repeatedly with the QOLIE 31, 1.0 version. Patients were divided into 3 groups according to the type of seizure, also according to the change in the number of seizures in the following 6 month period (no change, 50% reduction and reduction with more than 75%).

Results: We enrolled 86 patients, 41 male, 45 female. 58% of patients only suffered from CPS seizures (mean QOLIE in this group was 69), 23% only GTCS (mean QOLIE 63), and 19% both types (mean QOLIE 62). We did find a difference between these groups ($p = 0.14$). During the following 6 months we found a reduction of the number of seizures more than 75% in 29 patients, more than 50% in 35 patients; 26 patients were in the no change group. We found a significant change in QOLIE in group on1 (more than 75% reduction) in comparison with the others ($p < 0.05$).

Conclusion: The reduction in number of seizures by more than 75% during a 6 month period improved the quality of life in our study. The type of seizures did not influence the quality of life in our group of patients.

p211

FREQUENCY OF CARDIAC SYMPTOMS IN EPILEPSY AND CASE REPORTS

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Purpose: Sudden unexpected death in epilepsy (SUDEP) is an uncommon but feared complication. Several theories have been proposed to explain this phenomenon mostly affecting young patients with refractory epilepsy. Ictal central apnoea (Walker R, Fish DR. Recording respiratory parameters in patients with epilepsy. *Epilepsia* 1997;38 (suppl 11):41–2.) and cardioarrhythmia Rugg Gunn FJ, Simister RJ, Squirell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004;364 (9452):2157–8. are the most believed theories for these deaths.

Method: Frequency of cardiac symptoms using 200 journals of patients with epilepsy are in the process of being analysed. In addition, 7 case reports are under assessment. The symptoms presented by patients in the case reports are suspected SUDEP (2 cases), paroxysmal supraventricular tachycardia (3 cases), asystole with remaining AV block III (1 case) and preictal angina pectoris (1 case).

Results: In the frequency analysis, we discovered that many patients without any known heart symptoms, i.e., not investigated according to the journal, fulfilled several risk factors for SUDEP proposed in the literature. After preliminary evaluation of 100 journals, 4 out of 10 patients have registered cardiac symptoms. Of 49 patients over 60 years, 30 had cardiac symptoms. In this category, most symptoms were thought not to be epilepsy induced. In the cohort between 40–60 years, 4 out of 22 had symptoms, and among patients below 40 years, 5 out of 30 had symptoms. However, it has not yet been assessed to what extent these symptoms can be explained as an epileptic manifestation. This will be discussed.

Conclusion: Our aim is to evaluate whether any cardiac symptoms could be epilepsy related and if so, are they seizure related or not? In our clinical case reports we describe cardiac symptoms of suspected epileptic origin. Another objective is to evaluate to what extent these patients are currently investigated and monitored regarding heart symptoms. In the future we hope this study can contribute to a safer management of patients

with epilepsy and risk factors for SUDEP, particularly in the in-patient setting.

p212

PROPORTION OF PATIENTS WITH HYPOGLYCEMIA MISDIAGNOSED AS EPILEPSY IN PATIENTS WITH CHRONIC EPILEPSY

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Purpose: To determine the proportion of patients with hypoglycaemia erroneously diagnosed as epilepsy in patients with chronic epilepsy.

Method: We retrospectively identified 1567 patients with the diagnosis of chronic epilepsy treated between 1998 and 2005 at the Institute of Neurology, Belgrade, Serbia. We tried to classify their epilepsies in syndromes and to determine their aetiology with all available means. All patients were treated with antiepileptic drugs (AED) and followed for at least 1 year.

Results: During the follow-up, symptoms consistent with hypoglycaemia occurred in 5 patients (0.32%). They presented with periods of disorientation, agitation, sopor, or coma of various durations. Besides, obvious generalised tonic–clonic seizures occurred either at some period of deranged consciousness or independently. Hypoglycaemia (ranging from 0.21 to 1.1 mmol/l) associated with symptoms was repeatedly confirmed in all 5 patients. The diagnosis of insulinoma in 3, ketotic hypoglycaemia due to the glycogen synthetase deficiency in 1 and possible mesidioblastosis in 1 patient was established. We successfully withdrew AED with no reappearance of seizures in the patient with ketotic hypoglycemia and in 3 patients with successfully resected insulinoma. In the patient with mesidioblastosis, pancreatectomy was performed and insulin supplementation was introduced. However, seizures recurred after AED withdrawal, and carbamazepine was continued. In the control group of 26 patients (1.66%) with insulin dependent diabetes mellitus and epilepsy occasional episodes of hypoglycemia were unrelated to the course of epilepsy and AED treatment was sustained.

Conclusion: Hypoglycemia is a rare but important cause of repeated seizures that resemble the course of chronic epilepsy.

p213

COURSE OF ALPHA ATTENUATION TEST AFTER ONE NIGHT SLEEP DEPRIVATION FOR PATIENTS WITH EPILEPSY

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Purpose: To evaluate the vigilance fluctuation of Alpha Attenuation Test (AAT) in patients with epilepsy.

Method: A total of 94 patients, free of medication, were investigated by means of combined neurophysiological techniques: the AAT after one night sleep deprivation and sleep. Before the test, all patients evaluated their sleepiness level by the Visual Analogue Scale. We measured the course of changes of relative and absolute alpha power values six times every two minutes in five second artifact free epochs in the channel O1-A2 before and after eyes closure and calculated the quotient (the AAC, Alpha Attenuation Coefficient).

Results: The epileptic population (34 subjects, 28 male) has similar relative alpha powers before and after eye closure as the control group ($18.27\% \pm 4.8$; $16.76\% \pm 2.5$, Mean $\pm$ SD respectively). Absolute alpha powers during epochs with eyes open showed a gradually increment in both groups as subjects got sleepier, ranging from 26 to 86 picoW. The same variable during eyes closed showed the fluctuation around one line, but significantly higher values among patients with epilepsy. The third variable, AAC, decreased in a significantly steeper decline in patients with epilepsy (from 16 at the first measure to 5.7 at the sixth) in comparison to the control group (7.6 to 5.2).

Conclusion: Patients with epilepsy have a much greater synchronisation of physiological activities, greater values of alpha power and greater fluctuation of the vigilance level than the control group.

p214

SUDDEN UNEXPECTED DEATH IN EPILEPSY: A SEARCH FOR RISK FACTORS

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Purpose: Mortality is higher in people with epilepsy than in the general population. Sudden unexpected death in epilepsy (SUDEP) is a major cause of concern with an estimated incidence of between 1:100 and 1:1000. We reviewed clinical variables in our SUDEP cases with the aim of ascertaining risk factors.

Method: Deaths were identified in the 6000 patients registered with the Epilepsy Unit at the Western Infirmary since 1982. SUDEP was defined as the cause if the death was sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning, with or without evidence of a seizure having occurred and excluding documentation of status epilepticus. For each case, two living controls were randomly matched for year of birth (± 5 years), gender and epilepsy syndrome by computed number generation. Details of death were amassed from family practitioner and hospital records, coroners' reports, death certificates and witnesses.

Results: of 529 deaths, 62 (12%) were SUDEP cases [26 females, 36 males; mean age 36 years (range 18–77 years)]. Mean duration of epilepsy was 18.4 years in cases compared with 11.5 years in controls ($p = 0.000$). Early age of seizure onset was significantly associated with risk of SUDEP ($p = 0.000$). There was a significant association between the risk of SUDEP and having at least one seizure within the last year ($p = 0.007$).

Conclusion: Clinicians counselling patients about SUDEP should particularly target patients taking polytherapy with poorly controlled seizures. A multicentre international approach to the pathophysiology of SUDEP is essential to explore more closely the predictive factors in individual cases.

p215

EPILEPSY WITH BILATERAL HIPPOCAMPAL HYPERINTENSITY AND CELIAC DISEASE: COMORBIDITY OR A REAL ASSOCIATION?

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Purpose: To describe a 20-year-old woman with celiac disease (CD), bitemporal epilepsy with bilateral hippocampal hyperintensity and severe memory impairment.

Method: At age 14 the patient presented 10–15 daily seizures with partial seizures resistant to therapy. Since age 15 she has had gastrointestinal disturbances with a 25 kg weight loss during the last 4 years. At age 19 a severe deficit of fixation memory appeared.

Results: Neurological examination was normal. Repeated neuropsychological evaluations showed severe memory impairment in immediate and delayed recall. Interictal EEG showed frequent epileptiform abnormalities over both temporal regions. Ten seizures with the same clinical symptoms were recorded, starting independently from the two temporal lobes. CT scan of the brain was normal. Brain MRI and functional MRI with diffusion sequences disclosed a signal change on both hippocampal gyri, hyperintense in T_2 weighted sequences. Laboratory screening revealed autoimmune thyroid disease, positivity for antigliadin, antiendomisium and antitransglutaminase antibodies. PCR for HHV6 in the blood and CFS was positive and oligoclonal bands were present in the CFS. Duodenal biopsy confirmed CED.

Conclusion: We hypothesise an aetiopathogenetic relationship different from the usual relationship between CED and epilepsy. In our patient CED might be the epiphenomenon of a more generalised immune impairment with concomitant involvement of mesial structures. Another possibility is comorbidity, i.e., two unrelated diseases in the same patient.

The hippocampal alterations and memory impairment could be the consequence of recurrent prolonged seizures.

p216
USE OF LEVETIRACETAM VERSUS OTHER ANTIEPILEPTIC DRUGS IN THE NEUROSCIENCE INTENSIVE CARE UNIT
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Purpose: NSICU patients require AEDs for seizure management/prophylaxis. Newer AEDs have better side effects and safety profiles than older AEDs. We examined the presence of complications in patients treated in NSICU based on AED use.

Method: We retrospectively reviewed charts of NSICU patients between 1 September 2003 and 30 September 2004 and examined frequencies/percentage distributions for complications, AED prophylaxis before admission, and AEDs administered. We used cross-tabulations/Pearson chi-square tests to determine differences ($p < 0.05$) in complications by AED(s).

Results: of 552 patients treated in NSICU 379 received AEDs. 358 (94.4%) were included in the study. 268 (74.9%) had complications (2% hypotension, 24.9% encephalopathy, 12.3% toxicity, 2% rash, 7.5% agitation, 1.1% ARF, 0.6% liver failure, 2.8% bleeding, 5.9% low platelets, 59.2% other); 27.6% had $\geq$2 complications. 88 (24.6%) received AED prophylaxis before admission: 42 (11.7%) phenytoin,* 11 (3.1%) levetiracetam,* and 39 (10.9%) other (*alone or in combination with other AEDs). No differences in complications were noted before admission. 33.3% of patients receiving levetiracetam monotherapy in NSICU had complications vs 73–81% of other AED(s) including levetiracetam in combination; among patients with complications, 1.9% received levetiracetam monotherapy vs 20–45% multiple AEDs or phenytoin monotherapy ($p = 0.001$). Among specific complications, encephalopathy occurred in 0/15 levetiracetam monotherapy patients vs 7–34% of other patients ($p = 0.009$).

Conclusion: This study describes complications and AED use in NSICU. The retrospective nature of this study does not allow for conclusions whether the complication rates are related to other AEDs vs levetiracetam vs underlying neurological conditions, but patients treated with levetiracetam had overall lower complication rates. Prospective studies are needed to determine differences in complication rates by AED(s).

p217
FREQUENCY OF SEIZURES IN A COHORT OF PATIENTS WITH ALZHEIMER'S DISEASE
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Purpose: To evaluate the frequency of seizures in patients affected by Alzheimer's disease (AD) and possible concomitant reasons for presenting seizures in demented patients.

Method: We retrospectively examined records of AD patients who had visited our memory clinic. For this study we considered patients who had, at least, two neurological controls each year, registered in our record, starting from January 2001. Missing data were collected by phone and inviting patients for an outpatients visit. Of these patients, we recorded sex, age, years of disease, severity, concomitant pathological complaints, concurrent therapy as selective serotonin reuptake inhibitors (SSRI), antipsychotic, acetylcholinesterase inhibitors (AChEI) and N-methyl-D-aspartate (NMDA)-r antagonists drugs (time and dosage) and history of epileptic seizures.

Results: We selected 120 patients with AD (according the NINCDS-ADR-DA criteria). Up to now we found 9 subjects presenting partial or generalised seizures or both (7.5%, mean age 72.1 ± 7.59, M/F = 6/3). Generalised seizures were preponderant (8 patients). Seizures occurred after an average of 3.8 years from dementia onset. Three patients were treated with AChEI, 2 with AChEI and SSRI, 1 with NMDA-r antagonists and antipsychotic drug, 1 with the new antipsychotic drug. The review of the records is still in process.

Conclusion: Literature data related to seizure frequency in AD patients are very different (from 5 to 25%). Seizures usually occur in later stage of the disease. Many factors may contribute to the development of epileptogenesis in AD: neurotransmitters alteration, loss of inhibitory neurons, changes in cellular excitotoxicity and also some medications used in AD. We found early seizure onset in our patients. It might be related to the concurrent therapy as antipsychotic drugs, SSRI and AChEI that lower the seizure threshold. Seizures are a dangerous complication in the progression of AD and their occurrence should be specially considered in the therapy management of these patients. These data need to be confirmed.

p218
EPILEPTIC SEIZURE AS A NEURO-PROTECTIVE PHENOMENON
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Purpose: Epilepsy has come to be regarded as a primary disturbance of the central nervous system function, and medical treatments have been directed at stabilisation of neuronal activity. The objective: epileptic seizures; are they good or bad? Are they useful or harmful? The design: randomised clinical, prospective with retrospective study combined with met analysis study of 25 previously published papers.

Method: Fluorodeoxyglucose studies show that any activity in any particular muscle group results in increased cerebral blood flow in the motor area responsible for the activity. SPECT scans of 127 cases of epilepsy were studied. 104 were temporal lobe, 4 were frontal lobe and 19 were complex seizures. I have classified Ictal SPECT scan studies into two categories: 1) hyperperfusion pattern only, 2) combined patterns of hyperperfusion with hypoperfusion. I assumed that in category (1), hyperperfusion pattern only, may have resulted from reversible vascular spasm with reversible vascular ischaemia.

Results: From the data given above we can evaluate the degree of ischaemia in relation to epilepsy. Retrospective with prospective studies showed that ictal hyperperfusion alone was 18% of the cases; 93% for ictal hyperperfusion combined with interictal hypoperfusion study; 75% for interictal hypoperfusion, (without considering ictal studies). Thus epileptic seizures are associated with hyperperfusion to overcome an aggravated brain ischaemic attack.

Conclusion: This study demonstrated that epileptic seizures are in fact, valuable, important neuroprotective phenomena. Epileptic seizures help restore intracranial blood flow and prevent severe brain ischaemia and infarction; it is good and wise to treat epileptic seizures and not just to stop them.

p219
EPILEPSIA PARTIALIS CONTINUA: A RARE AND EARLY PRESENTATION OF DIABETES MELLITUS: KOSHENIKOV SYNDROME
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Purpose: To recognise the clinical profile, differential diagnosis and management of patients with Koshenikov Syndrome.

Method: We reviewed the clinical findings and laboratory data of our patient who presented with epilepsia partialis continua (EPA) as a first manifestation of diabetes. PUBMED literature was searched using terms "Diabetes" "Epilepsy" "Koshenikov syndrome."

Results: A 59-year-old male with no past history of diabetes presented to our clinic with a 2 week history of jerking of his right arm. The movements occurred approximately 15–20 times per hour and lasted 30–40 seconds. Laboratory tests revealed arterial pH 7.299, glucose 552 mg/dl. His diabetic ketoacidosis was treated with fluids and insulin. No anti seizure medication was started. His movement disorder resolved over 3–4 days.

Conclusion: EPC is a rare and serious epileptic disorder. It involves persistent, clonic movement of one localised muscle group; it is also called Koshenikov syndrome. EPC is aetiologically related to metabolic diseases such as hepatic encephalopathy, non ketotic hyperglycemia, diabetic ketoacidosis and infections such as Ramsussen encephalitis, HIV, CMV and EBV. Seizures can be an initial manifestation of diabetes. In diabetic patients presenting with seizures EPC was noted in 20%. In one study EPC led to diagnosis of diabetes mellitus in 9 out of 21 patients. In patients with diabetes it has been related to hyperglycemia, hyperosmolarity, hyponatremia and elevated Anti GAD-65 antibodies. Treatment of EPC depends on the underlying disorder and the effect of antiepileptics is disappointing. In diabetes, treatment consists of aggressive hydration with fluids and insulin. A surgical approach has been recommended for cases related to cortical dysplasia and brain tumours. Low frequency transcranial magnetic stimulation (rTMS) has been considered a safe and effective treatment in some cases of EPC.

p220

TONIC AUTOMATIC ATTACKS REVISITED: A VIDEO EEG STUDY

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Purpose: "Tonic automatic attacks" were first described by Oller Daurella (1970) in patients with Lennox-Gastaut syndrome (LGS). The aim of this study is to further delineate the electroclinical feature of this unusual seizure type, which is currently not recognised in the ILAE classification of epileptic seizures (1981).

Method: A retrospective analysis of all patients with generalised epilepsies who were examined in our epilepsy monitoring unit from 1999–2005. Four patients demonstrated clinical and EEG patterns corresponding to the description of "tonic automatic attacks."

Results: Four patients [4 w, mean age 28 yrs (range 21–38), mean age at seizure manifestation 11.5 yrs (range 2–28 yrs)] were studied. All patients showed mild cognitive dysfunction. MRI was normal in all patients. A total of 86 seizures could be recorded. The main clinical features were tonic phenomena of the neck and/or both upper limbs followed by arrest, clouded consciousness and oral or gestural automatisms. Ictal EEG demonstrated generalised activity (low voltage fast activity, spikes and polyspike waves) in 3 patients with consecutive slowing in 2 and slow sharp waves in 1. A right temporal alpha-theta activity and consecutive generalised slowing was recorded in 1. Interictal EEGs showed generalised activity in all patients, an independent right temporal focal slowing was recorded in 1. We suggested a kryptogenic generalised epilepsy in all patients.

Conclusion: Tonic automatic attacks should be classified as generalised seizures. They can be observed in several kryptogenic generalised epilepsies, not only in LGS.

p221

EARLY SEIZURES IN ISCHEMIC STROKE: RESULTS OF A MULTICENTRE HOSPITAL-BASED STROKE REGISTRY

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Purpose: To assess incidence and predictive factors of immediate and early seizures after an ischemic cerebrovascular event (CVE).

Method: A total of 2581 patients (mean age 67.8 years) with a recent CVE (including TIA) were enrolled in a prospective multicentre hospital-based stroke registry, with a mean follow-up of 18.5 months. Seizures occurring within the first 14 days after the CVE were classified as early seizures, recurrence of unprovoked seizures as poststroke epilepsy. Immediate seizures (occurring within 24 h after the CVE) were analysed separately. Patients who had seizures before the CVE, were excluded from statistical analysis.

Results: 2% of the patients ($n = 52$) experienced immediate seizures and 2.5% ($n = 64$) experienced early seizures. Multivariate analysis showed leukocytosis (>13G/litre) and a secondary parenchymal haemorrhage to be significantly ($p < 0.05$) associated with both immediate and early seizures after the CVE. Moreover, early seizures were associated with an NIHSS>12. Poststroke epilepsy occurred in 21% ($n = 11$) of the patients with a previous immediate seizure, and in 19% ($n = 12$) of the patients with early seizures.

Conclusion: Secondary parenchymal haemorrhage was associated with the occurrence of immediate- and early seizures after a CVE, and stroke severity (NIHSS>12) with early seizures. A leukocytosis was found in patients with immediate or early seizures which were thought to be secondary to the seizure. Due to the low incidence of epilepsy after immediate and early seizures, antiepileptic treatment does not seem to be justified after a first immediate or early seizure. Acknowledgment: The work was supported by a financial grant of Sanofi Synthelabo and Bristol Meyers Squibb.

p222

SLEEP DEPRIVED WAKE-SLEEP EEG IN NEWLY DIAGNOSED GENERALISED IDIOPATHIC EPILEPSIES

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Purpose: There are reports of delay in correct diagnosis of the syndromes of generalised idiopathic epilepsies (GIE) with consequences on patient morbidity/mortality. There are reports of nondiagnostic EEG findings in the syndromes of GIE. The aim of the study was to present the activation of interictal spike-wave (S-W) discharges and multiple S-W discharges in newly diagnosed GIE in sleep deprived (SD) wake-sleep EEG, but with a normal or nondiagnostic initial routine EEG.

Method: A total of 50 patients, 27 females and 23 males, mean age 18 years, standard deviation 5, with a clinical history consistent with newly diagnosed GIE: juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), grand mal on awakening and generalised tonic–clonic seizures (GTCS), had both routine EEG and sleep deprived single session wake-sleep EEG for the presence of interictal/ictal S-W/multiple S-W discharges. Somatoneurological and imaging findings were normal in all patients.

Results: Initial routine EEG was normal or without specific findings for the syndromes of GIE in all patients. SD produced activation of myoclonic seizures in 1 patient with JME and absences in 1 patient with JAE. SD wake-sleep EEG produced activation of interictal generalised S-W/multiple S-W discharges in all patients, with occasional frontocentral appearance in JME, occasional focal appearance in 1 patient with GTCS on awakening or asymmetric appearance in 11 patients with JME, and GTCS. S-W discharges were recorded in wake and in non-REM sleep EEG and in the transitional wake-sleep intervals. Interictal S-W discharges during non-REM sleep caused sleep fragmentation producing awakenings and shifts towards light non REM sleep stages.

Conclusion: Generalised S-W discharges were the only objective findings in the SD wake-sleep EEG in newly diagnosed patients with a clinical history of GIE, contributing to the epilepsy syndrome diagnosis. Occasional focal and asymmetric appearance of S-W discharges should not be misleading for the correct diagnosis of the GIE. Non REM sleep EEG contributed to the evaluation of the impact of the S-W discharges on the sleep structure.

p223

CONTRALATERAL SPIKES IN MESIAL TEMPORAL LOBE EPILEPSY (mTLE): PREDICTORS OF UNFAVOURABLE SURGICAL OUTCOME?

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Purpose: In this study we wanted to address the question, whether the presence of contralateral spikes can be considered as a negative predictive factor in patients with TLE and unilateral hippocampal sclerosis as it has been claimed recently.

Method: In this retrospective study patients with intractable mesial TLE, who underwent presurgical evaluation including high-resolution MRI and prolonged video-EEG-monitoring prior to selective amygdala hippocampectomy, were included. Interictal spikes were registered by video-EEG-monitoring during a minimum of three days. Patients with less than 25 spikes during this period were excluded. Spikes were divided into predominant ipsilateral spikes (≥60% of all spikes originating from the hemisphere with the hippocampal sclerosis) and predominant contralateral spikes (<40% of all spikes originating from the side with the hippocampal sclerosis). Postsurgical outcome was assessed one to ten years after surgery according to Wieser's classification.

Results: Ninety patients (45 with left sided (l) TLE, 45 with right sided (r) TLE) met the inclusion criteria. Twenty-five patients with lTLE and 33 patients with rTLE presented with good postoperative outcome (class I, Ia, 2); 23 patients with lTLE and predominant ipsilateral spikes had a good postoperative outcome versus 12 patients with bad postoperative outcome (class 3, 4, 5). Twenty-nine patients with rTLE and predominant ipsilateral spikes presented with good and 11 with bad postoperative outcome. When correlating postoperative outcome with contralateral spikes we observed a striking difference between right- and left-sided TLE. In lTLE there was a significant association of predominant contralateral spikes with worse outcome (8 patients with bad versus 2 patients with good outcome; $p = 0.014$); in rTLE 4 patients with contralateral spikes presented with good and 1 with bad postoperative outcome.

Conclusion: In lTLE patients with predominant ipsilateral spikes (≥60% per definition) corresponded with a significant better postoperative outcome than patients with contralateral spikes. These findings were not observed in patients with rTLE.

p224
PURE SLEEP SEIZURES IN THE ELDERLY
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Purpose: To compare the risk of seizures while awaking (SWA) with pure sleep seizures (PSS) in patients with an epilepsy onset under or above 60 years of age.

Method: Fifty-nine patients with PSS followed at a Neurology Department. Group A: 49 patients aged from 18 to 60 at epilepsy onset. They suffered PSS for at least ten years. Group B: 10 patients aged >60 at epilepsy onset. They suffered PSS for at least five years. Clinical, EEG and neuroimaging features for both groups were analysed and compared by nonparametric Fisher test.

Results: Group A: mean age 48.8 (18–82). PSS for 24.9 years (10–67). Epilepsy syndrome: undetermined 42.8%; focal cryptogenic 32.7%; focal symptomatic 22.4%; generalised 2%. At the end of the follow-up 59.2% received monotherapy; 4.1% without any treatment. 34.7% (17) suffered one or more SWA. 88.9% suffered seizures after withdrawal of treatment. Group B: mean age 81.2 (71–88). PSS for 11.3 years (5–25). Epilepsy syndrome: undetermined 50%; focal cryptogenic 40%; focal symptomatic 10%. At the end of the follow-up 90% received monotherapy; 10% without any treatment. Nobody suffered SWA. 80% suffered seizures after withdrawal of treatment. Polytherapy ($p < .05$) and SWA ($p < .02$) were only found in group A. There was no difference in relapsing seizures ($p < .5$).

Conclusion: PSS in patients with age of onset over 60 years have a better prognosis. They achieve good control of their seizures on monotherapy and they have less risk of SWA. Nevertheless they have a similar risk of relapsing than younger patients.

p225
INFLUENCE OF DEPAKINE TO THE CORRECTION OF MENTAL AND PSYCHOEMOTIONAL DISORDERS OF EPILEPSY
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Purpose: Epilepsy is a chronic disease of the brain, characterised by regular unexpected assaults with disorders of movement, sensitive, vegetative, mental and psychic functions, occurring as a result of excessive neuronal discharges. As known, the therapeutic aspects of epilepsy are important and difficult. Among the new anticonvulsants, widespread over recent years, the derivatives of valproic acid have a particular place, for example, one of the better known, depakine. But the effects of depakine to the correction of mental and psychoemotional functions, which are exponents of the quality of patients' lives, are not estimated. Last year more attention was allotted to not only anticonvulsant effects, but their influence on the quality of a patient's life. The purpose of the **i**nvestigation was to study the efficiency of depakine-chrono to the course of epileptic assaults in adults and its influence on mental and psychoemotional functions.

Method: Forty-five epilepsy patients were inspected in the neurological clinic of the Central Railway Hospital from 2003 to 2006. At the time of including patients in the investigation we used diagnostic criteria of epilepsy and epileptic assaults, according to the International Classification of Epilepsies of 1989. The majority of patients have a generalized epilepsy 57.3%; focal 25.5%; patients with different assaults 17.7%. Separate disorders of high cortex functions such as deterioration of memory, attention and mental retardation until treatment were 86.8%. Investigation methods included: neurological, neurovisualisation (CT, MRT) and neurophysiological inspection (EEG, ECHO, REG, USDG and other). The Spielberger physiological test of was used for estimation of emotional exponents, and test MMSE was used for estimation of mental exponents in the dynamic of the treatment. Depakine was appointed as monotherapy in the beginning dose 300–600 mg/day with gradual promotion to middle therapeutical doses (1000–1500 mg/day). Estimation of efficiency began from the 8th day of treatment.

Results: Common quantity of positive effects of treatment was 81.7%. Negative effects of treatment were 19.3%, including the deterioration of patients' general condition (outside effects). Outside effects were expressed by nausea, vomiting, giddiness, shivering, and weight changes. These disorders were lost by reducing the drug dose. According to the investigations, results among patients treated by depakine, at the end of the first month of therapy noted significant improvement of condition with reduction of frequency and gravity of epileptic assaults, but complete control of assaults was attained only in 72%. 30% of the patients had an indication of reduced convulsive activity threshold and increase in slow-wave activity in functional tests. Normalisation of EEG rhythms with the disappearance of paroxysmal activity was noted in 61%. During the use of depakinmental functions improved and their dynamic was 27% on the 4th week of treatment and 40% on the 8th week of treatment. The dynamic of emotional-personal disorders was more resistant and comprised 15% on the 4th week of treatment and 32% on the 8th week.

Conclusion: 1) Including depakine in the therapeutic scheme assists the overcoming of therapeutic resistance by epilepsy patients. 2) According to the results of therapy, depakine is a high efficiency medicine 82.5% for patients with generalised and partial epilepsy. 3) Depakine has not only an anticonvulsive effect, but it has a neurotrophic action, expressed by normalisation of mental functions, and normal rhythmic action, expressed by normalisation of emotional-personal functions. 4) The significant anticonvulsive and normal rhythmic action of depakine permits us to estimate this medicine as expedient, and able to improve the quality of patients' lives with epilepsy.

p226
SEXUAL DYSFUNCTIONS AND EPILEPSY: PILOT STUDY
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Purpose: Sexual dysfunctions (SD) occur in almost 50% of the population. They can be subclassified as organic (predominating in males) and psychogonical (predominating in females). Neurological diseases belong to the most frequent organic SD reasons. In epilepsy patients, SD incidence ranges between 30–60%. The aim of this study was to assess (1) the SD occurrence in epilepsy patients, and the associations between SD occurrence and (2) epilepsy compensation and (3) treatment with the second or/and third generation of antiepileptic drugs (AEDS).

Method: The set consisted of 15 patients (8 males, 7 females, aged 22–54, mean 36.3 years). 12 patients presented with focal, 3 with gen-

eralised seizures. All patients were treated with the second or/and third generation AEDS. Patients completed a shortcut version of the international questionnaire of sexual function: International Index of Erection Function and Female Sexual Function Index. The full international questionnaire was completed in case of the indication of possible SD in the shortcut version.

Results: The following SD occurrence (serious/light/not present) was found: 4/2/2 in males, 1/4/2 in females. Erection dysfunction in males and absence of sexual appetence in females were the most frequent SD. An indirect relationship was present between the degree of epilepsy compensation and SD incidence. No apparent association between SD severity and the use of the 2nd/3rd AEDS was found.

Conclusion: Both the importance of SD assessment in epilepsy patients, and the need for the best epilepsy compensation to reduce SD occurrence was confirmed in this study.

p227

CORPORA AMYLACEA IN REFRACTORY MESIAL TEMPORAL LOBE EPILEPSY: CLINICOPATHOLOGICAL CORRELATIONS

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Purpose: Although corpora amylacea (CoA) is recognised as a marker of mesial temporal sclerosis (MTS), its significance in patients with mesial temporal lobe epilepsy (MTLE) is uncertain. We undertook a study to define the prevalence of CoA in the surgical specimens of patients with MTLE and assess its significance.

Method: We scored, in a semiquantitative scale, the presence of CoA in the CA1sector of the hippocampus and graded as >10/HPF (grade 3), 6–10/HPF (grade 2), <5/HPF (grade 1) and none (grade 0). We compared the demographic, clinical, neuropsychiatric, electrophysiological and outcome data of patients with (CoA+) and without (CoA−).

Results: Out of 387 temporal lobectomy specimens from MTLE patients with ≥1 year postoperative follow-up, CoA was present in 129 (34.5%) specimens. The mean age at surgery of the CoA+ patient group was significantly higher than that of CoA− group (24.5 yrs vs 31.8 yrs, $p < 0.0001$). The mean duration of epilepsy prior to surgery in the CoA+ group was longer (21.7 yrs vs 15.5 yrs, $p < 0.0001$). Other variables like age at seizure onset, febrile seizures, interictal and ictal EEG data and postoperative seizure outcome did not differ between the two groups. Psychiatric symptoms occurred more in the CoA+ group. Fourteen of the 16 (87.5%) patients with major psychiatric comorbidities, showed grade 2–3 deposition ($p = 0.001$).

Conclusion: Our results lend support to the progressive nature of pathology in MTS, and the pathogenetic role of CoA in the psychiatric morbidity of MTLE.

p228

EFFECTS OF FATIGUE ON THE QUALITY OF LIFE OF EPILEPSY PATIENTS

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Purpose: Fatigue and its effects are not adequately researched in epilepsy. In this study the rate of fatigue and its effect on the quality of life (QOL) have been assessed.

Method: Seventy epilepsy patients were evaluated. QOL was assessed with QOLIE-89 and fatigue with fatigue severity scale (FSS). Patients were divided according to whether or not they had fatigue and the QOL values of the two groups were compared. The correlation analyses were done between QOLIE-89 and FSS.

Results: The QOLIE-89 scores in patients with fatigue ($n = 33$) are significantly lower than in patients without fatigue ($n = 37$). In particular, the mental and epilepsy related subscales of QOLIE-89 were significantly lower in the fatigue group ($p < 0.05$). There was a statistically significant correlation between the QOLIE-89 scores and fatigue scores in the whole group ($p < 0.05$). When QOLIE-89 scores decreased, fatigue scores increased.

Conclusion: Our findings suggest that there is very strong relationship between the low QOL scores and fatigue in epilepsy patients. We concluded that fatigue is a very important finding in epilepsy patients. In clinical evaluation and the treatment of epilepsy, understanding the reasons and quality of fatigue is very important for the improvement of QOL in epilepsy patients.

p229

ATTITUDE OF EPILEPTIC PATIENTS TOWARD THE LABEL EPILEPSY (SARAA): STUDY FROM SAUDI ARABIA

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Purpose: Saraa is the synonymous word for epilepsy in Arabic. It means falling violently as if struck. The purpose of this study is to explore the attitude, the acceptance and understanding of the meaning of Saraa (epilepsy) among our epilepsy patients.

Method: Seventy consecutively seen patients in our Adult Epilepsy Clinic were interviewed by the author using a structured questionnaire. All patients were diagnosed as having had epilepsy for more than 2 years. All patients were asked about their understanding and acceptance of the term Saraa (epilepsy), and whether they would prefer an alternative label.

Results: There were 39 males, 31 females with age range 16 to 62, mean age of 30 ± -16.5. Fifty one subjects (72.6%) understood Saraa (epilepsy) as convulsions. Sixty-two patients (88.6%) preferred not to disclose that they suffer from Saraa, while only 5 cases did not mind to reveal their Saraa to other people. Most patients dislike the term Saraa (epilepsy) and preferred other labels such as dizzy spells (27 subjects; 38.6%), convulsions (11 subjects; 15.7%), electro-cerebral disturbance (11 subjects; 15.7%). Interestingly 22 patients believed that supernatural power (Jinn) is one of the causes of epilepsy.

Conclusion: The term Saraa (epilepsy) is misinforming, stigmatising and disliked by most patients. A simple, informative, nonstigmatising and an internationally unified term like electrocerebral disturbance should replace an obsolete label like Saraa (epilepsy). This will help to take epilepsy "Out of the Shadows" and improve the social acceptability of the disorder world-wide as aimed by The Global Campaign against Epilepsy.

p230

NONINVASIVE DETECTION OF APNOEA

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Purpose: Apnoea is not uncommon in generalised tonic–clonic and prolonged complex partial seizures. Sudden unexpected death in epilepsy (SUDEP) occurs in 1/200/year of those with refractory epilepsy. The mechanism of SUDEP is uncertain. The leading contenders are central or obstructive apnoea and cardiac asystole, as a consequence of seizure activity. The prompt detection of apnoea would allow for resuscitation to begin promptly and improve the possibility to avert death.

Method: A new technique for detecting apnoea is presented, for the long-term noninvasive monitoring of respiration. The technique can be used in home and residential care settings, and alert carers to the occurrence of potentially fatal apnoea. The physical implementation of the technique will consist of a miniature sensor device placed on the user's neck with a micropower electronic chip realising a number of filters and sorting algorithms to reject noise artifacts found in the domestic environment. A prototype has been tested, replacing the electronic components for software with identical functionality of the final design. With noise artifacts removed, a reliable detection of apnoea is achievable.

Results: The technique was evaluated in 10 healthy controls who were able to maintain voluntary apnoea for 20–40 seconds. The device reliably detected apnoea in individuals at rest, when moving and with loud ambient noise.

Conclusion: Clinical trials of this device will begin in one year, and will have wide applicability for longterm monitoring of those with

epilepsy, and also for respiratory monitoring of those with respiratory and other neurological diseases, and for monitoring of infants.

p231
MOLECULAR MECHANISMS OF MDR1 EXPRESSION IN HUMAN EPILEPTIC ASTROCYTES
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Purpose: The multidrug transporter MDR1 is overexpressed in response to a variety of signals, including stress or noxious stimuli. The cell cycle and apoptosis controller p53 is also induced by stress and is implicated in MDR1 gene expression. In cancer cells, both up and down regulation of MDR1 in response to p53 have been reported. Epileptic brain astrocytes express low levels of p53 but exaggerated levels of MDR1, suggesting a negative regulatory link.

Method: Astrocytes cultured from resected cortices were analysed for p53 and MDR1 protein levels prior or after transfection with p53 overexpressing vectors. Hypoxia was mimicked by cell exposure to $CoCl_2$.

Results: p53 basal expression did not correlate with MDR1 levels. However, p53 transfection resulted in increased MDR1. $CoCl_2$ (300 μM for 18 and 48 hrs) caused a progressive and rapid increase in MDR1 expression (500% of control at 48 hours).

Conclusion: We confirmed that p53 expression in human epileptic astrocytes is low. Since overexpression of p53 correlated with increased MDR1 levels and hypoxia induced MDR1, it seems that p53 alone cannot be the chief regulator of MDR1 in epileptic glia. We thus propose that increased MDR1 expression may depend on low metabolic activity in epileptic brain as suggested by positive correlation with $CoCl_2$ exposure.
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p232
EFFICACY OF LEVETIRACETAM: A RETROSPECTIVE STUDY
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Purpose: To assess the effectiveness of levetiracetam in a group of adult patients with refractory epilepsy.

Method: Clinical records of patients in treatment with levetiracetam were reviewed. We included 53 patients (29 women, 24 men) and collected data regarding age, age at onset of epilepsy, previous treatment, number of seizures, levetiracetam dosage and outcome.

Results: Mean age of participants was 37.49 years old (SD = 13.13), and mean age at onset of epilepsy was 122 months SD = 110. Thirty patients were on monotherapy, 17 on bitherapy and 6 were under treatment with 3 antiepileptic drugs. The mean period of treatment with levetiracetam was 16.6 months SD = 7.8. Dosages of levetiracetam differed: 5 patients received 1000 mg/day, 31 took 2000 mg/day, 16 started with 2000 mg/day and then increased to 3000 mg/day and one started with 2000 mg/day and increased to 3500 mg/day. Findings showed that 47% of patients (confidence interval 33.7–60.7) were seizure free for at least 7 months SD = 5.2, 32.07% had fewer seizures, 11.3% showed no changes, and 9.4% had stopped taking levetiracetam, mainly due to lack of efficacy.

Conclusion: These results support previous findings regarding the efficacy of levetiracetam as add-on treatment for refractory epilepsy, and the few side effects of the treatment. This study is ongoing in order to obtain a larger sample and to assess long term results of treatment with levetiracetam.

p233
EPILEPSY AND NEUROCYSTICERCOSIS IN QATAR
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Purpose: *Taenia solium* neurocysticercosis (NCC) is increasingly being reported in patients suffering from epilepsy. However, its true prevalence and association with late onset epilepsy is largely unknown in the Middle East particularly in Qatar. Our study will demonstrate that NCC is also a major cause of first seizures in an increasingly young population in Qatar.

Method: This is a retrospective and prospective study, based on hospital populations. Neurocysticercosis was diagnosed on the basis of the following: consistent radiographic findings and a compatible epidemiologic and clinical history (without diagnostic serological findings). All individuals with a suspicion of NCC at the emergency department were admitted for further investigations and treatment. Complementary examinations included an awake EEG, a CT SCAN or MRI of the brain and serum and CSF studies.

Results: Fifty patients were diagnosed as having NCC on the basis of the above criteria. A large majority of patients were male (98%, most of them expatriate from the Asian subcontinent). At first presentation, most of the patients (80%) were older than 20 years. 96% of them presented with seizures. Neurological findings, brain CT and MRI abnormalities, EEG as well as cysticidal therapy and seizure presentations and outcome will be discussed.

Conclusion: This study confirms that NCC is a major cause of epilepsy in a hospital based (increasingly young) population in Qatar. NCC is a relatively new disease in this country, imported recently from areas where NCC is endemic in a growing Indian subcontinent work force. However, the prognosis of NCC related seizures is good.

p234
INCIDENCE OF EPILEPTIC SEIZURES ASSOCIATED WITH ISCHEMIC STROKE
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Purpose: Patients who suffer ischemic strokes might develop subsequent epileptic seizures or symptomatic vascular epilepsy. Our aim was to determine the frequency and predisposing factors for occurrence of epileptic seizures in patients with cerebral ischemic stroke.

Method: We studied patients with acute or previously supported ischemic stroke admitted during a 5-year period to the Neurology Department of Emergency Hospital, with stroke or epileptic seizures related to stroke. All patients were given a clinical examination, laboratory tests, EEG and cerebral CT.

Results: In our study 76 patients (mean incidence 6.37%) developed epileptic postischemic seizures, 39 male and 37 female. Twenty-four patients (37.6%) had early seizures (during first week) and 52 (68.4%) late seizures (after one month or more). Ischemia involved the cerebral cortex in 58 patients (76.3%). EEG changes with slow rhythms and pathological waves were found in 48 patients (63.2%).

Conclusion: Mean incidence of epileptic poststroke seizures in our study is 6.37%. There is no significant gender prevalence in the studied cohort. Late seizures (after one month or more) developed more often than early seizures. Cortical involvement is associated with a higher risk of seizures and epilepsy. EEG changes are predictors of seizures.

p235
LEVETIRACETAM MONOTHERAPY IN PATIENTS WITH SYMPTOMATIC FOCAL EPILEPSY AND ALCOHOLIC CHRONIC EXOTOXICOSIS
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Purpose: To evaluate levetiracetam efficacy in 3 patients with symptomatic focal epilepsy and a history of alcohol abuse.

Method: Three patients with a 10-year history of alcohol abuse, with posttrauma (2) and postsurgery (1) focal epilepsy have been evaluated to verify levetiracetam efficacy in reducing seizures along with its effect on liver functions. Patients characteristics: 1) B.L. (female) aged 64, with posttrauma epilepsy since 2000 and hepatopathy evolving to cirrhosis (transaminases were up to 3 folds over normal). Seizures

occurred monthly. 2) T.M. (male) aged 41, with posttrauma epilepsy since 1995 and hepatic steatosis (transaminases were up to 6 folds over normal). Seizure frequency: 3–4 episodes/year. 3) B.G. (male) aged 58, with epilepsy since 1988 following surgery for right frontal basal AVM and with hepatopathy evolving to cirrhosis (transaminases were up to 4 folds over normal). Seizures occurred monthly. Patients were all alcohol abusers. At our initial evaluation, patients were on phenobarbital (100 mg/die). Due to unsatisfactory therapeutic effects and to minimize the effect of AED treatment on livers compromised by alcohol abuse, phenobarbital was replaced with levetiracetam (mean dosage 1666 mg/die).

Results: Patient 1 and 2 have respectively been seizure free for 4 and 12 months. Patient 3 had only 1 seizure during the last 6 months. Levetiracetam had no impact on liver functions as values of transaminases significantly decreased in 2 cases and were normalised in 1 case.

Conclusion: Our limited experience suggests that levetiracetam may be considered as a valid treatment for epilepsy patients with a history of alcohol abuse.

p236
SEMIOLOGY OF GRAND MAL SEIZURES

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Purpose: Grand mal (GM) seizures (SZs) are classified as generalised tonic clonic SZs according to the current ILAE classification. (Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.) However, the sequence of GM SZs is not stereotyped and only a few studies investigated the varied semiology. Therefore, we aimed to describe the semiology in detail.

Method: We retrospectively evaluated all video-EEG recordings of patients (pts) admitted to the Epilepsiemonitoringeinheit of the Universitätsklinik für Neurologie Innsbruck, Austria, over a period of 3.5 years with primary generalised tonic–clonic SZs (GM).

Results: In 19 pts (9 M/10 W), median age 31 yrs, range 13 to 63), 36 GM were registered. Five pts had idiopathic generalised epilepsy (IGE), 7 symptomatic or cryptogenetic generalised epilepsy (SGE) and 7 had primary generalised seizures without a clear syndromatic diagnosis ("unclassified" group). According to the sequence of the tonic and clonic phases, four GM seizure types were defined: I tonic–clonic ($n = 15$), II clonic–tonic–clonic ($n = 10$), III at least two tonic and clonic phases ($n = 7$), IV mixed tonic-(myo)clonic phase ($n = 4$). Pts with IGE mainly showed SZ type II ($p < .005$), while pts with SGE exhibited all SZ types and pts in the "unclassified group" mostly had type I GM ($p < .005$). Pts with IGE showed focal/lateralising signs in 3/7 SZs, pts with SGE in 12/15 SZs and pts with unclassified epileptic SZs in 13/14 SZs.

Conclusion: The semiology of GM is not homogeneous; four different GM types are described. The term "generalised tonic–clonic seizures" is misleading and does not apply to all GM.

p237
EFFECT OF ANTIEPILEPTIC DRUG MONOTHERAPY ON SEXUAL FUNCTION IN MEN SUFFERING FROM EPILEPSY

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Purpose: We compared the incidence of sexual dysfunction and blood hormonal profile in males suffering from various types of epilepsy and taking various antiepileptic drugs (AEDs) in monotherapy.

Method: We analysed prospectively sexual functions and hormone blood levels in 42 male patients (age ranged 24–45 years, with average of 34.6 ± 4.2 years) with both focal and generalised epilepsy treated by monotherapy AEDs. Seventeen patients received carbamazepine (CBZ), 16 patients one of the newer antiepileptic drugs (NAEDs) [8 patients lamotrigine, 4 patients levetiracetam and 4 patients topiramate] and 9 patients received valproates (VPA). We used the Czech version of the structured questionnaire called "International Inventory of Erectile Function" (IIEF) to assess patient's sexual functions. The subscales of this questionnaire evaluate separately the erectile function (IIEF I), orgasmic function (IIEF II), sexual desire (IIEF III), satisfaction of sexual intercourse (IIEF IV) and overall satisfaction with sex life (IIEF V). In all patients the following blood tests were performed: quantitative assessment of blood levels of prolactin (PRL), total testosterone (total-T), free androgen index (FAI), sexual hormone binding globulin (SHBG), estradiol (E2), dihydroepiandrosterone–sulfate (DHEAS), progesterone (PRG), follicle stimulating hormone (FSH) and luteinising hormone (LH). All these quantitative laboratory data were correlated with the type of the treatment and results of IIEF. Chi-quadrate and Wilcoxon tests were used for statistical analysis. $p < .05$ was considered to be statistically significant.

Results: Although the proportion of age, duration of epilepsy, type of epilepsy and seizure frequency were comparable in all "treatment groups," we found the higher incidence of all types of sexual dysfunction (IIEF I–III) and lower score of overall satisfaction with sex life (IIEF V) in patients treated with CBZ in comparison to patients treated by NAEDs ($p < .01$). Similarly we found the higher incidence of erectile dysfunction (IIEF I), disorder of sexual desire (IIEF III) and lower score of overall satisfaction with sex life (IIEF V) in patients treated with VPA in comparison to patients treated by NAEDs ($p < .05$). In patients treated by CBZ we noticed the significant increase of SHBG and decrease of DHEAS and FAI in comparison to patients treated by NAEDs and VPA ($p < .01$). We did not find any difference in hormonal profile between patients treated by VPA and NAEDs.

Conclusion: Our study showed that males with epilepsy treated by monotherapy of NAEDs (lamotrigine, levetiracetam, topiramate) have greater sexual functions and are more satisfied with their sex life than those treated by CBZ or VPA.

p238
TREATMENT CHALLENGES IN PATIENTS WITH EPILEPSY ASSOCIATED WITH ARTERIOVENOUS MALFORMATION

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Purpose: Epilepsy is an important manifestation of cerebral arteriovenous malformations (AVMs). Epileptogenic and ruptured AVMs surgery is supposed to allow a good control of epilepsy. The failure to eliminate a seizure disorder after AVMs surgical treatment is presented in our cases.

Method: We report 5 cases of epilepsy associated with cerebral vascular malformations. All patients were admitted to the Clinic of Neurology for partial motor seizures with secondary generalisation or primary generalised epilepsy. EEG, CT and MRI were performed. The patients were submitted to surgery for vascular malformation and they received anticonvulsant therapy.

Results: In 2 cases the examination showed mild pyramidal signs. Laboratory examinations were within normal limits. EEG was abnormal in 2 cases with generalised synchronous discharges of spikes. Computed tomography (CT) of the brain revealed a hyperdense lesion with contrast enhancement and corticosubcortical topography in 2 cases. IRM angiography revealed vascular malformation in the other 3 cases. The patients where put on anticonvulsant treatment and all cases were submitted to surgery. The patients continued anticonvulsant therapy after surgery and remained seizure free for a few months, when new seizures occurred.

Conclusion: These cases prove that surgical treatment in the AVMs is not always efficient to prevent new seizures. The localisation and architectural characteristics of the AVM might contribute to the risk of post surgical seizures.

p239
SUDDEN UNEXPECTED DEATH IN EPILEPSY: PILOT STUDY IN THE WEST OF IRELAND

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Purpose: To review initial data from the National Study on Sudden Unexpected Death in Epilepsy (SUDEP).

Method: Cases were ascertained by contacting general practitioners and neurologists, to report epilepsy-related deaths from October 2000 to September 2005. For all cases identified, we reviewed medical records and postmortem reports, where available, to determine circumstances of death, and to classify as definite, probable, possible and non-SUDEP deaths, and to identify any potential risk factors.

Results: Eleven cases of epilepsy-related death were identified in the pilot area (population 380,297). Four were definite SUDEP, 1 probable SUDEP, 1 possible SUDEP, 1 non-SUDEP death, and 5 cases had insufficient data to classify at present. Details of ten additional cases are pending. In the 5 cases of definite or probable SUDEP (2 male, 3 female) average age at death was 30.2 years (range 6–45 years). All had a history of generalised convulsions. One had daily seizures, 2 had more than one seizure per week, 1 had more than one seizure per month, and 1 patient had been seizure free for more than two years. Three patients were on polytherapy. Only 2 of 5 patients had attended a neurologist.

Conclusion: In this retrospective case series, which represents a subanalysis of an ongoing population-based incidence study, 5 of 11 epilepsy-related deaths were due to definite or probable SUDEP. Of note, 60% had never seen a neurologist, but the sample size was small and further population-based data will be required to confirm these results.

p240

PROGNOSIS OF EPILEPSY DUE TO NEUROCYSTICERCOSIS: A LONG TERM FOLLOW-UP

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Purpose: Evaluate the prognosis of symptomatic epilepsy due to cerebral calcifications secondary to neurocysticercosis (NCC).

Method: An observational and transversal study of 83 patients with secondary epilepsy due to calcifications caused by NCC, who have been followed up as outpatients at a multidisciplinary centre for epilepsy care in southern Brazil from 1991 to 2002. The diagnoses were based on clinical history, EEG findings, epidemiological settings and neuroimage (CT scan and MRI) to register the calcifying process. NCC were classified according to *Del Bruto* as definitive, probable and possible, but only the first two were included in this study. Epileptic seizures, epileptic syndromes, active and in remission epilepsies were classified according to that proposed by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE). Kaplan-Meyer test was applied to the data.

Results: Of the 83 patients included in the reported study, 53 (63.9%) were women. The mean age of the whole group was 30 ± 10.4 years [10–57] at admission. They were followed during an average 7.4 ± 2.5 years. CT scans showed a lesion in all patients, 51 (61.4%) presented multiple lesions while 32 (38.6%) showed 1. The frequency and severity of seizures decreased as the study came to an end. Actually, epilepsy went into complete remission in 30.2% of patients, 12% were in withdrawal of antiepileptic drug therapy, and 57.8% still presented seizures. Although an important decrease of seizure frequency and severity were seen in most of those patients suffering from active epilepsy, the Kaplan-Meyer test showed half of the sample went into remission after 8.3 years of starting seizures.

Conclusion: NCC is a major cause of epilepsy in Latin American countries. There is an ancient proverb among neurologists: "epilepsy due to NCC is easy to treat but difficult to cure." However it should be reviewed, because in our sample, epilepsy related to NCC was a benign condition. It seems that the natural history of this symptomatic epilepsy is going into remission of seizures as the time goes by.

p241

LONG-TERM OUTCOME OF SURGERY IN PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY

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Purpose: Our retrospective study was aimed at evaluating the five-year outcome in surgically treated patients with refractory temporal lobe epilepsy (TLE).

Method: We had a group of 39 patients (24 males and 15 females aged 15 to 55 years) with refractory TLE who underwent surgery in our centre from 1996 to 2000. The patients were assessed according to Engel classification annually for 5 years. All the patients underwent MRI evaluation before the surgery. Hippocampal sclerosis was found in 20 of them. Amygdalo-hippocampectomy was performed in 12 patients; anterior medial temporal resection was performed in 10 patients and tailored lesionectomy in 17 patients.

Results: According to the Engel classification we obtained the following results:

After 1 year: I = 77%, II + III = 23%, IV + V = 0%; after 2 years: I = 82%, II + III = 15.5%, IV + V = 2.5%; after 3 years: I = 77%, II + III = 20.5%, IV + V = 2.5%; after 4 years: I = 74%, II + III = 23.5%, IV + V = 2.5%; after 5 years: I = 62.5%, II + III = 35%, IV + V = 2.5%. 24 patients achieved the "Ia" classification one year after the surgery. Sixteen (66.5%) remained in the "Ia" category for the five years.

Conclusion: These excellent outcomes of epilepsy surgery measured by Engel classification in patients with TLE remained relatively stable over the first three years after surgery. A slight decrease in the number of patients classified "I" and an increase in the number of patients classified "II" + "III" in the fourth and fifth years after surgery is associated with a reduction of antiepileptic drugs in about 50% of them. In spite of the said decrease, surgery of refractory TLE is an effective procedure in these patients.

p242

EPILEPSY OF THE TEMPORAL LOBE: CASE REPORT

E. Obdrzalkova and P. Kanovsky (Departement of Neurology, University Hospital Olomouc, Czech Republic)

Purpose: Temporal epilepsy is a frequent diagnosis. Nevertheless, it can cause diagnostic problems because it can imitate other neurological disorders.

Method: A 34-year-old female had a history of two generalised tonic–clonic epileptic seizures in 2000. Treatment with topiramate was started and afterwards she was without epileptic manifestation. In 2003 the medication was changed to lamotrigine (LMT). After an interval of several months a low back pain occurred with widespread pain irritation of the right leg, followed by spontaneous semiflexion of the hip and the knee, with pronation of the foot. Since 2003 the frequency of these symptoms has increased, finally occurring every night. Nonsteroid antiflogistic and analgesic-anodyne drugs were added to the therapy, but no effect was observed. She was admitted to our department in November 2005. A physical examination, x-ray and MRI of the lumbal spine, ultrasound examination of the pelvis and electromyography were normal. Serology for viruses and IgM Borrelia antibodies were negative as well as cerebrospinal fluid analysis. Because of persisting symptoms and unknown aetiology electroencephalography was performed, in which a focus of specific activity at the left frontocentral area was found. An analogous pathological finding with spike-waves episodes occurred also in the EEG after sleep deprivation and during the clinic seizure on video-EEG. The dose of LMT was increased, and clonazepam was gradually discontinued.

Results: The symptoms resolved completely after four weeks of boosted antiepileptic therapy.

Conclusion: Temporal epilepsy with partial simplex seizures can rarely imitate vertebral problems. This can lead to mistaken diagnosis and long-term unsuccessful treatment.

p243
PSYCHOLOGICAL EVALUATION OF QUALITY OF LIFE IN SEIZURE-FREE EPILEPSY PATIENTS
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Purpose: Epilepsy and its treatment have a great chronic impact on the life of those affected. Epilepsy patients are mostly young and the diagnosis sometimes has a stigmatising nature. Quality of life (QoL) is an important tool for understanding the distress of epilepsy patients, even when seizures are well controlled. The purpose of this study is to investigate the psychological, social and physical aspects of health related quality of life in patients suffering from epilepsy, who have been seizure-free for the past year, and to identify patients who are at risk of developing an adjustment disorder. Moreover, we correlated QoL and INTERMED, identifying patients at risk of poor QoL and high complexity of care.

Method: Fifty patients, seizure-free for the past year, aged 18 to 60, without cognitive deficits and 50 age matched controls were enrolled. The patients were invited to a clinical interview about multidimensional domains of QoL. We used the INTERMED interview to assess biopsychosocial factors of risk. At the end of the interview, QoL was assessed and quantified using a self-completion questionnaire, the Quality of Life in Epilepsy–31 (QOLIE-31), a sensitive measure of the impact of the condition on daily life. CES-D and Zung Anxiety Scale were completed by patients to determine the contributions of depression and anxiety on quality of life.

Results: There was a good correlation between QoL test scores and seizure control.

Conclusion: In conclusion psychopathological assessment is crucial in evaluating drug epilepsy therapy benefits, in addition to standard neurological evaluation and seizure control.

p244
COHERENCE FLUCTUATIONS OF BACKGROUND EEG ACTIVITY HIGHER IN GENERALISED EPILEPSY THAN IN TENSION HEADACHE
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Purpose: In the present study, the difference between coherence fluctuations in the group of 20 patients with generalised epilepsy and the group of 20 tension headache patients is studied. Higher coherence fluctuations may reflect pathophysiological processes involved in human epilepsy.

Method: EEG coherence analysis has been used to estimate the dynamics of background EEG activity in a group of 20 patients with primary or secondary generalized epilepsy and 20 patients with tension headache. Low artifact, 31 sec. segment of EEG background activity was manually selected for each patient. Rectified difference between 1 second segments were estimated for all pairs of 19 scalp electrodes in the range 1–32 Hz. Wilcoxon-Mann-Whitney test was used for comparison of coherence fluctuations between both groups.

Results: Significantly higher fluctuations in the range 3–15 Hz and 19–32 Hz were found in the epilepsy group. The mean coherence difference between both groups was 0.016. The most prominent differences were found for frequencies 7–8 Hz and 24 Hz.

Conclusion: These results can be interpreted as a functional decoupling of distant brain sites followed by an abnormally high recoupling in epilepsy patients, as also observed in other studies (F. Wendling et al. 2003). They may reflect the concept of "disruption" that is complementary to that of "activation," both giving insights into our understanding of pathophysiological processes involved in human epilepsy.

p245
GENDER DIFFERENCES IN THE ASSESSMENT OF LEVEL OF NEUROTIZATION AND QUALITY OF LIFE INDICES IN PATIENTS WITH TEMPORAL LOBE EPILEPSY
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Purpose: To study the differences in the level of neurotisation and quality of life indices in male and female patients with temporal lobe epilepsy.

Method: One hundred patients with temporal lobe epilepsy (47 males and 53 females aged from 15 to 50 years) were studied. To assess the level of neurotisation of the patients, the J. Aleksandrowicz Neurotic Disorders Inventory was used. QL was assessed using the core module of the WHOQOL-100 questionnaire. QL was assessed dynamically: at admission and at discharge, after the completion of a restorative therapy course. Drugs in the carbamazepine and lamotrigine group were the most often used in the pharmacotherapy of patients.

Results: The severity of neurotisation in the females was higher than that in the males on the majority of the scales. Differences were found on the affective strain scale and on the scales of depressive, neurasthenic, hypochondriac, and somato-vegetative disorders. Statistically significant differences were found on the hysteric disorders scale ($p < .05$). The females assessed their QL lower than the males, except for the social relationships and spirituality domains. The mean physical domain index in the females was significantly lower than in the males ($p < .05$). The overall QL increased in the course of restorative therapy from 84.92 to 89.95 scores in the males and from 83.96 to 84.6 scores in the females.

Conclusion: Females with temporal lobe epilepsy, in comparison with male patients, have a higher level of neurotisation and lower subjective QL indices.

p246
SECONDARY EPILEPSY AFTER ISCHEMIC ICTUS IN A CONTEXT OF FAMILIAL ANGIOPATHY
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Purpose: The authors studied 7 cases of facomatosis, which were investigated clinically and paraclinically through MRI and Angio MRI. The clinical picture in all cases suggested neurocutaneous melanosis: 1) giant pigmented naevi with a marked tendency to originate from the posterior midline–cervical region predominantly; 2) smaller, multiple pigmented naevi on the thoracal region and limbs; 3) blue naevi with left radicular D6–D8 topography. In all cases patients presented repetitive TIA or pseudo-TIA (haemometakinesia phenomenon), in time lacunar infarcts in carotidian and vertebro-basilar territory. Two cases presented cicatricial epilepsy after middle cerebral artery; in 3 cases infarcts have pseudotumoural evolution, 1 in the left carotid artery, and 2 in the right carotid artery territory, with focal seizures and secondary generalisation.

Method: The biopsy of the pigmented naevi in 3 cases suggested the junctional naevocellular naevus. The paraclinical investigations were normal: CSF, VEP, AEP, Doppler and echocardiography. MRI revealed infarcts of different ages. Immunological investigations excluded parasites vasculitis, brain microabcess, and other vascular diseases.

Results: We concluded that the ischemic infarcts with secondary epilepsy were determined by a familial genetic angiopathy.

Conclusion: Both the melanin forming cells and the cells from the muscular tissue of the cervical arteries have a common embryological origin in the neural crest. The authors suggested the pathogenic role of the cells with origin in the neural crest in programming infarcts.

p247
LEVETIRACETAM THERAPY IN PATIENTS WITH BRAIN TUMOURS AND EPILEPSY
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Purpose: Epilepsy is common in patients with brain tumours; tumour-related seizures are often difficult to control, with treatment complicated

by frequent interactions between antiepileptic drugs (AEDs) and antineoplastic agents. Levetiracetam (LEV) is a new AED with a unique mode of action and no clinically relevant pharmacokinetic drug interactions. This open study investigated the safety and efficacy of LEV in patients with brain tumours and epilepsy.

Method: Patients with supratentorial gliomas were included. LEV 1500–3000 mg/day was added to existing AED treatment for persisting seizures. Patients visited the Outpatient Centre every 1–3 months and were followed for 5–47 months (mean 22.1, median 17 months).

Results: 19 patients (6 females; age 28–70, mean 48 years) with brain tumours (7 glioblastoma multiforme, 2 anaplastic astrocytoma, 9 low grade astrocytoma, 1 meningioma) were enrolled. Seizure types were simple partial in 4 patients, complex partial in 4, complex partial with secondary generalisation in 7, and generalised tonic–clonic in 4. Eight (42%) patients became seizure-free (seizure-free period 5–33, mean 14.9, median 10.0 months); 5 (26%) patients showed $\geq$50% seizure frequency reduction. Seizure frequency was unchanged in 5 patients and increased (<50%) in 1. No LEV-related adverse effects were observed, and no significant changes in blood chemistry reported. LEV plasma concentrations monitored in 13 patients ranged from 11.9–93.7 μg/ml.

Conclusion: These preliminary data indicate that add-on treatment with LEV in patients with brain tumours is safe and efficacious. Controlled studies on larger populations are warranted to confirm these observations.

p248

THIRTEEN YEAR INTERIM RESULTS FROM AN INTERNATIONAL OBSERVATIONAL STUDY OF PREGNANCY OUTCOMES FOLLOWING EXPOSURE TO LAMOTRIGINE

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Purpose: To characterise the overall risk of major congenital malformations (MCM) associated with exposure to lamotrigine.

Method: Physicians report exposure to lamotrigine during pregnancy and subsequent outcomes on a voluntary basis. Prospective reporting (prior to any knowledge regarding the possible outcome of the pregnancy) early in pregnancy is encouraged. Major congenital malformations (MCMs) are classified according to CDC criteria and are reviewed by an external scientific advisory committee paediatrician. The percentage of MCMs is calculated using only prospective first trimester lamotrigine monotherapy and polytherapy exposures. Conclusions are developed and endorsed by the scientific advisory committee.

Results: As of September 2005, 20 MCMs were observed among 707 first trimester monotherapy exposures giving a risk of 2.8% (95% CI 1.8%–4.4%). The observed risk among 118 lamotrigine and valproate polytherapy exposures was 11.8% (95% CI 6.8%–19.3%) and was 2.7% (95% CI 1.2%–5.8%) among 256 exposures to lamotrigine polytherapy without valproate. The mean and median monotherapy doses for subjects with MCMs respectively were 250.7 and 200 mg/day; the mean and median doses for those without defects were 281.1 and 200 mg/day. No consistent pattern of malformation types was observed.

Conclusion: The current data do not indicate any substantial increase in the overall risk of major defects associated with prenatal lamotrigine exposure, though the sample size is insufficient to allow definitive conclusions concerning specific defect types. The higher frequency of major malformations following lamotrigine-valproate polytherapy exposure was consistent with publications on valproate monotherapy. Continued registration of exposed pregnancies will enhance the statistical power of the study.

p249

WHO AMONG PATIENTS WITH ISCHEMIC STROKE IS PRONE TO SEIZURES?

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Purpose: Only a small percentage of patients with ischemic stroke (IS) develop seizures. The aim of our study was to evaluate the risk factors for seizures in a population of patients with IS.

Method: We retrospectively reviewed the records of all patients with IS who had seizures and were hospitalised in two major medical centres in Israel during 1993–2000. We identified 78 patients. Their data was compared with 55 randomly chosen IS patients without seizures who were admitted to the same hospitals during that period and included: medical history, medications, neurological examination, laboratory tests, ECG, echocardiography and brain CT.

Results: Forty three (32%) patients had a seizure the first day of stroke (immediate), 6 (5%) after 24 hours and within 14 days following stroke (early), and 29 (22%) later than two weeks. Risk factors for atherosclerosis were not more prevalent in any group of patients with IS and seizures compared to controls. Pharmacologically treated diabetes was significantly less prevalent in patients with immediate (5%) ($p = 0.002$) and late (7%) ($p = 0.018$) seizures compared to controls (29%). Cardio-embolic stroke was observed at a significantly higher frequency in patients with late seizures (55%), when compared with both controls (24%) ($p = 0.004$) and patients with immediate seizures (21%) ($p = 0.003$).

Conclusion: Patients with cardioembolic stroke may be more prone to late, but not to immediate. seizures. Atherosclerotic risk factors were not increased in patients with IS who had seizures compared to IS patients without seizures.

p250

PSYCHOGENIC NONEPILEPTIC SEIZURES IN PATIENTS WITH LEARNING DISABILITY

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Purpose: A cohort of patients with psychogenic nonepileptic seizures (PNES) and learning disability was studied in order to determine the characteristics of this PNES population and the semiology of the PNES themselves.

Method: A retrospective observational study of 27 consecutive patients admitted to a short term residential centre for evaluation of patients with epilepsy who had a diagnosis of mild or moderate learning disability and PNES.

Results: For 21 patients diagnosis was based on video EEG recording of attacks. For the remainder, diagnosis was based on ambulatory EEG and video recording of direct observation of attacks. Eighteen patients (67%) had a dual diagnosis of PNES and epilepsy. Mean age at onset of PNES was 28 (9–48) years. Fifteen (56%) were female. Five patients (19%) had a history of abuse (sexual = 2, physical = 2, both = 1). PNES semiology consisted of falls (6), unresponsiveness with limb movement (10), tantrum-like spells (5), or blanks (6). In the 18 patients who had epilepsy, PNES semiology did not resemble that of epileptic seizures.

Conclusion: If generalisable, our results suggest that patients who have LD and PNES more often have epilepsy, have a more even gender ratio, and less often have a history of sexual or physical abuse than a general population of patients with PNES. Our data also suggests possible differences in PNES semiology.

p251

MEN WITH EPILEPSY: THE LOST TRIBE?

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Purpose: Epidemiological studies show a higher incidence of epilepsy in men compared with women. Yet there is a clear publication bias in favour or women, and a relative lack of information specifically for men. Against this backdrop Epilepsy Action (British Epilepsy Society) carried out an extensive study of men's experience of living with epilepsy, their

views on services and their opinions about how access for men could be improved.

Method: 1200 questionnaires were distributed to a random sample of men who had contacted Epilepsy Action helpline in the previous year; 373 were returned and analysed.

Results: 27% were seizure free at time of study, 48% had "occasional" seizures, 93% took AEDs, 39% were in employment, 46% lived with a partner and 33% said epilepsy had affected their relationship with their partner, and 27% their sex life. The most commonly cited adverse impact on lifestyle was driving at 69%. 74% considered themselves, "knowledgeable" or "very knowledgeable" about their epilepsy, 43% said they would turn first to their GP for advice, 16%, their consultant, 11.8% a specialist nurse. When asked what they would do if they had a specific question about epilepsy 85% said they would find out for themselves. When asked to give their 3 preferred options for accessing information 57% said their GP, 45% consultant, 34% the internet and 33% a telephone helpline. Specialist nurses were ranked 5 in their order of preference after books and leaflets.

Conclusion: Men may differ from women in how they access information about their condition. Further studies are needed to gain a greater insight into the needs of men with epilepsy.

p252

A COMPARISON OF SELF-REPORTED QUALITY OF LIFE BETWEEN PATIENTS WITH EPILEPSY AND NEUROCARDIOGENIC SYNCOPE

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Purpose: Generalised tonic-clonic seizures and complex partial seizures have very different pathophysiological mechanisms to syncope, but share a final common pathway of loss of consciousness with social disruption. Quality of life has been studied in epilepsy and to a lesser extent syncope; there have been no studies comparing these two populations.

Method: Fifty-two consecutive patients between the ages of 16 and 60 referred for tilt table testing were recruited. Patients had at least 2 episodes of syncope in the preceding year. Ninety-two consecutive patients attending an epilepsy clinic (71 localisation related and 21 IGE) were recruited. Twenty-eight had been seizure free for at least one year at time of study. A control group of 100 people consisting of spouses/partners of patients and hospital employees were recruited. All completed HADS and WHO-QOL-Bref.

Results: There were no significant differences between the syncope and seizure groups in depression and anxiety subscales of the HADS. Both syncope and seizure groups were significantly more depressed and anxious than controls ($p < 0.01$). There were no significant differences between the seizure and syncope groups in overall quality of life and in the 4 domains of the WHO-QOL-Bref. In 3 of the 4 domains of WHO-QOL-Bref the epilepsy and syncope groups, however, reported significantly poorer quality of life than controls ($p < 0.001$).

Conclusion: This is to our knowledge the only study comparing quality of life in syncope and epilepsy. If our results are replicated it implies repeated loss of consciousness has as great an impact on quality of life as epilepsy's many comorbidities.

p253

DESIGN AND DEVELOPMENT OF A WEB-BASED DATABASE SYSTEM FOR THE MANAGEMENT AND ANALYSIS OF EPILEPSY PATIENTS' DATA: EPILEPSY DATABASE EPILDA

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Purpose: To present a database system (EPILDA), designed and developed for the efficient management, processing and analysis of epidemiological, clinical and other patient related data concerning epilepsy in Greece. Furthermore, given the high diversity of cases and the variety of available treatment approaches, the system aims at assisting objective therapy evaluation.

Method: The EPILDA system is based on web technologies enabling accessibility from remote medical centres and hospitals. The study and processing of epilepsy data is accomplished via a user friendly interface on either desktop PCs or portable devices such as laptops or PDAs. Since medical data protection is of paramount importance, the implementation of strict security measures at the data storage and transmission level as well as at the application level is the cornerstone of the EPILDA system.

Results: The EPILDA system maintains data related to the general characteristics of a patient, the patient's visits, the drug treatment, the characteristics of epilepsy, medical imaging data, surgical treatment data, EEG and video-EEG recordings. The basic system functionalities comprise data entry, search and review as well as the generation of reports based on specific criteria.

Conclusion: The proposed system can (a) assist the user toward the efficient management of a large volume of available epilepsy-related data (b) contribute to the automation of statistical analysis towards the extraction of major epidemiological conclusions, as well as towards therapy planning, monitoring, and evaluation.

p254

DIABETES MELLITUS AND EPILEPTIC SEIZURES

H. Bozdemir, K. Aslan, and Y. Sarýca (Neurology, Istanbul, Turkey)

Purpose: Disturbance of glucose regulation in patients with diabetes may result in an epileptic disorder.

Method: Twenty-six patients (12 women, 14 men) with a mean age of 54 years were selected for this study.

Results: For 7 patients mean epilepsy duration was 12 years and mean diabetes mellitus (DM) was 4.5 years (Group A). For 19 patients the mean DM duration was 11 years and epileptic disorder was detected on an average of 4 years after DM diagnosis (Group B). Epileptic disorder was primary generalised in 3, and partially generalised in 23 patients. For Group B stroke ($n = 7$), DM ($n = 11$), MTS ($n = 1$) were risk factors for epilepsy. The aetiologic factors of group A were, tumour, head trauma, idiopathic (3) and criptogenic (1). EEG revealed active subkortical epileptic abnormalities in 2, lateralized abnormal activity in 14. MRI revealed cortical infarct in 1 of the group A, and in 4 of the group B patients. In 15 of the patients in group B antiepileptic treatment (AET) was proposed. For the remaning patients, for 2 convulsions began during a hypoglicemic coma, and in 2 during a nonketotic hyperglycemic coma (NKHC) state. For these patients convulsions were under control after blood glucose regulation. AET was proposed to the patients who were hospitalised because of NKHC and right hemiparesia.

Conclusion: Cerebral ischemia or infarct can be detected without hypo or hyperglycemic coma, and these cerebral changes can be risk factors for an epileptic disorder.

p255

UNVERRICHT-LUNDBORG DISEASE: A CONDITION WITH SELF-LIMITED PROGRESSION

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Purpose: To assess the long-term evolution of Unverricht-Lundborg disease (ULD), especially concerning myoclonus, seizures and EEG characteristics.

Method: We retrospectively evaluated 20 patients (6 F, 14 M, mean age 37.9 years, range 26–53) with ULD who had been closely followed since the onset of the disease (mean age: 12.3 years, range 6–17) for an average of 25.6 years (range 13–41). ULD was confirmed by genetic tests in all. We used simplified myoclonus and seizure rating scales.

Results: The geographic origin of the patients was Northern African in 9, French in 2, Italian in 6, mixed European in 3. Three patients were severely handicapped, 6 led fully autonomous lives and 11 required various degrees of social support. Myoclonus progressed only during the first 5 years of disease. Major seizures occurred in 19. Three patients had a single seizure and 8 became seizure-free, while 6 retained rare seizures and 2 frequent attacks. Overall, seizures became much less frequent after 10 years of evolution. EEG changes abated during follow-up: background activity remained stable or improved, spontaneous discharges disappeared, and photoparoxysmal responses were abolished in all patients but 2.

Conclusion: This study shows that ULD progresses only over a limited period and stabilises thereafter. This self-limited progression may be the consequence of age related apoptosis of selected neuronal populations.

Monday July 3, 2006
13:30–15:00
Poster Session 1
Alternative Therapies

p256
ROLANDIC EPILEPSY: COMPARISON OF ALLERGEN-FREE DIET AND CONVENTIONAL TREATMENTS

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Purpose: Rolandic epilepsy is the best known form of idiopathic partial epilepsy and unquestionably the one with the best prognosis. When such treatment does prove necessary, sodium valproate (VPA) or carbamazapine (CBZ) are nearly always used. In view of previous experiences showing the efficacy of an elimination diet for cow milk in cases of partial idiopathic epilepsy, a study was carried out on children with rolandic epilepsy to compare the results of treatment with VPA or CBZ and an elimination diet for proteins of cow milk.

Method: All the patients were subjected to a diagnostic procedure to ascertain allergy to this foodstuff. The diagnosis was confirmed by means of an elimination/ provocation test with the foodstuff in question. The subjects were divided into 3 random groups: group A (17 cases) treated with VPA, group B (17) treated with CBZ, and group C (20) treated with an allergen-free diet.

Results: The children of group A displayed complete remission in 14 cases out of 17 (82.3%). In group B only 6 cases out of 17 (30%) displayed complete remission. The allergen-free made it possible to obtain complete clinical remission in all the children of group C as well as the normalisation of EEG.

Conclusion: The study suggests that while CBZ and VPA are effective drugs with comparatively few undesired effects, an allergen-free diet makes it possible to obtain complete clinical and electroencephalographic remission with no side effects as well as a behavioural improvement in cases where there is valid evidence of hypersensitivity.

p257
PRESENTING THE DEFINITIVE DIAGNOSIS OF PSYCHOGENIC NONEPILEPTIC SEIZURES MAY HAVE THERAPEUTIC EFFECTS

N. Vojvodic, A. Ristic, D. Sokic, S. Jankovic, and A. Sindjelic (Institute of Neurology, Clinical Centre of Serbia)

Purpose: The aim of this retrospective study was to evaluate the therapeutic effects of informing patients with psychogenic nonepileptic seizures (PNES) about the accurate diagnosis, coexisting psychological problems and possible provocative factors.

Method: During the five year period we treated 73 patients (17 men and 56 women, aged 16–57 years) with PNES. Definitive diagnosis of PNES was established in all patients according to clinical and inpatient video EEG findings. During video EEG monitoring all patients had their seizures without ictal EEG abnormalities. After family members or eyewitnesses confirmed that the recorded seizures were habitual events, 45 patients were informed about the accurate diagnosis and coexisting psychiatric disorders and possible precipitating factors were explained. Twenty-eight patients didn't get such convincing information about the nature of their condition. Those two categories of patients were followed at six months; in order to compare the frequency of seizures prior to and after the definitive diagnosis of PNES was established.

Results: Six months after the diagnosis of PNES was established we found a statistically better outcome in the first category of patients: 18 vs 7 (39.5% vs 25%, $p < 0.05$) had seizure cessation, 18 vs 11 (39.5% vs 40%) had a reduction in seizure frequency by at least 50% and 9 vs 10 (21% vs 35%, $p < 0.05$) continued with undiminished seizure frequency.

Conclusion: The treatment of PNES should start with clear and convincing communication of the accurate diagnosis to patients and their families, which may have therapeutic effects on seizure frequency.

p258
MEDICINAL PLANTS AND EPILEPSY: AN ANIMAL MODEL

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Purpose: Medicinal herbs have a broad spectrum of application in folk medicine, but rarely anyone regards their unwanted effects, especially for chronic diseases. In our experiment we investigated the potential effects of Ginkgo biloba and Panax ginseng on epilepsy in rabbits with kindling epileptogenic focus in the hippocampus. We investigated the number of epileptic seizures and their duration in rabbits before and after applications of different extracts.

Method: Electroencephalographic method of registering bioelectric activity of different brain structures (EEG) was used. Gingko biloba was administered orally at a dose of 2 mm per BW, Panax ginseng was administered orally at a dose of 1 mm per BW (the doses of the substances were defined after experience from our former investigations). EEG was registered immediately before and after administration of the substances in a period not shorter than two hours.

Results: The results obtained clearly reveal that the application of Gingko biloba and Panax ginseng increased the number as well as the duration of epileptogenic seizures in most of the experimental animals.

Conclusion: The question is still open regarding which active components of the analysed medicinal plants influence experimental epilepsies. The answer requires further neurophysiological investigation.

p259
INCREASE IN BRAIN SEROTONIN IMPROVES CLINICAL OUTCOME IN EPILEPSY PATIENTS

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Purpose: The hypothesis that an increase of brain serotonin could have an anticonvulsant effect turned up in the early 1990s; moreover fluoxetine (an SSRI) has shown an antiepileptic effect. Serotonin is synthesised in the brain from tryptophan (Trp), an essential amino acid, so a decrease brain influx of Trp is expected to affect brain serotonin synthesis. In previous work we found a decreased plasma level of Trp and a significant 30% reduction of Trp brain uptake rate in epilepsy patients compared to controls. Trp competes across blood brain barrier with the other large neutral amino acids (LNAAs), and the same competition is in gastrointestinal mucosal. Furthermore, Trp is the limiting amino acid

in most sources of protein and most proteins, thus causing a decrease in plasma Trp-LNAAs ratio and therefore not suitable for supplementation of Trp. Alpha-lactalbumin (ALAC) is a whey protein, naturally occurring in human milk, with the highest Trp-LNAAs ratio of all quantitatively relevant, food-derived proteins. It was shown that ALAC can increase the plasma Trp-LNAAs ratio of up to 48% compared to casein. The use of the food supplement Serplus (Giofarma S.r.l) as an add-on drug, containing ALAC, in drug resistant epilepsy patients was then tested.

Method: Fifteen epilepsy patients, 6 male and 9 female; 9 drug resistant patients, the others with from 2 to 5 seizures a month, but showing a drug intolerance, in therapy with: 2 pts: PB, CBZ, VPA, 4 pts: PB, CBZ, 1 pt: PB, VPA, 1 pt: PB, VPA, LTG, 1 pt: PB, CBZ, LTG, 2 pts: PB, 3 pts: CBZ, 1 pt: VPA since, at least from 2001. Average age: 48, ranging from 28 to 67. Ten patients were affected by partial complex seizures, 2 patients myoclonic, 1 patient partial complex with atonic, 1 patient atonic and 1 patient tonic–clonic. The add-on Serplus therapy was of 1.5 g/die in 3 daily administrations. After 2 months an auto evaluation test was performed (0 = no benefit, 10 = full benefit). Furthermore an evaluation of clinical outcome (seizure frequency) was performed.

Results: Before Serplus treatment 6 pts showed from 4 to 10 seizures a month, 5 from 21 to 30, 2 from 31 to 100, 2 over 100, after Surplus 9 pts showed from 0 to 5 seizures a month, 4 from 21 to 30, 2 from 31 to 100. The average percent in decrease of the number of seizures was 60% in patients. No patient has shown worsening of seizure frequency or relevant side effects. Auto evaluation test was: 0, 2, 2, 3, 4, 5, 5, 5, 6, 7, 7, 9, 10, 10, 10; with an average of 5.6. In 13 patients the seizures were milder than before Serplus, in 5 pts we also noted an antidepressant effect. Eleven pts showed a percent decrease of seizure frequency from 50% to 100%, 5 pts from 80% to 100%.

Conclusion: Our data is completely in agreement with Jobe's theory (2005) on the role of serotonin in depression and epilepsy. Serplus, being able to increase Trp/LNAAs ratio in plasma, could be able to increase Trp brain uptake rate and therefore brain serotonin. Then Serplus is able to correct the reduction in Trp brain uptake rate found by our previous work with epilepsy patients. We outline that our results were obtained with a low Serplus dosage, being Alac in human milk at about 2 g/l, the dosage could be increased without side effects.

Monday July 3, 2006
13:30–15:00
Poster Session 1
Basic Science

p260
REELIN METHYLATION ASSOCIATES WITH GRANULE CELL DISPERSION IN EPILEPSY PATIENTS WITH HIPPOCAMPAL SCLEROSIS

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Purpose: Hippocampal sclerosis (HS) is the most common lesion in chronic, intractable temporal lobe epilepsies (TLE) and is characterised by segmental loss of pyramidal neurons in sector CA1, CA3 and CA4. Another histological hallmark includes granule cell dispersion (GCD), an architectural dysplasia of the dentate gyrus (DG) encountered in approximately 50% of HS patients. The reelin molecule is synthesised and released by Cajal-Retzius cells of the molecular layer, plays a key role in cortical development and previous studies have shown that reelin transcript levels are down-regulated in surgical specimens with GCD. Mutational analysis of reelin and components of the signalling cascade virtually exclude a genetic pathomechanism. Our present study focussed on epigenetic regulation of reelin expression by promotor methylation.

Method: Hippocampal sectors CA1 and DG were microdissected from human specimens. Genomic DNA was isolated, Bisulphite modified and used for nested PCR amplification of the reelin promoter, subsequent cloning and sequencing. Surgical specimens were retrieved from 12 TLE patients with AHS, 8 of which displayed severe GCD. Autopsy samples from 3 patients without neurological histories served as controls.

Results: Our analysis revealed increased methylation levels of the reelin promotor in all TLE-patients with GCD. In addition, striking differences were observed for the methylation pattern between CA1 and DG sectors of same patients.

Conclusion: These findings point to epigenetic regulation of the human reelin promoter in TLE-patients with GCD as a potential pathomechanism. In addition, our data would be compatible with an intimate relationship between neuronal hyperactivity ("epileptogenesis") and functional gene regulation.

p261
LEVETIRACETAM ADMINISTERED AFTER PROLONGED STATUS EPILEPTICUS IN AN EXPERIMENTAL MODEL OF STATUS EPILEPTICUS DOES NOT PROTECT AGAINST MITOCHONDRIAL DYSFUNCTION

H. Cock, and J. Gibbs (St Georges, University of London, UK)

Purpose: Status epilepticus (SE) is associated with reduced activities of essential mitochondrial enzymes, linked to neuronal damage (Cock et al. *Epilepsy Res* 2002;48:157–168). We previously showed, using the perforant pathway stimulation model, that levetiracetam (LEV) administration during established SE prevents mitochondrial dysfunction (Gibbs et al., *J Neurol* 2005;252(S2):16). This study addresses whether this protective effect is simply consequential of the reduced seizure severity associated with LEV treatment.

Method: Stimulating and recording electrodes were implanted into the perforant pathway and dentate granule cell layer, respectively, of anaesthetised rats. 6 days later, rats underwent 2h, 20 Hz stimulation followed by 3h of self-sustaining SE, terminated with diazepam. LEV (1000 mg/kg) or saline was subsequently administered i.p. and then bi-daily. 44h post-SE, the hippocampi were extracted and prepared for spectrophotometric assays to measure mitochondrial enzyme activity in saline/LEV treated SE rats compared to sham-operated rats.

Results: There were no significant differences in EEG spike frequency or behavioural seizure severity between treatment groups. In confirmation of earlier studies, activities of alpha-ketoglutarate dehydrogenase, aconitase, citrate synthase (and to some extent complex I) fell significantly in the hippocampi of saline treated SE rats. In contrast to results following LEV administered during SE, LEV administration after prolonged SE did not reverse this attenuation.

Conclusion: Administration of LEV post-SE did not protect against mitochondrial dysfunction. This may be because LEV has no independent neuroprotective biochemical effects; our previous results reflected subtle reductions in seizure severity. Alternatively the level of mitochondrial damage induced by 5 h uninterrupted seizures may be irreversible.

p262
ACUTE MODULATION OF UNIT FIRING BY DEEP BRAIN STIMULATION IN THE HUMAN HIPPOCAMPUS

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Purpose: About 30% of epilepsy patients do not respond adequately to specific (combinations of) antiepileptic drugs. Besides resective surgery, they can try deep brain stimulation (DBS) as a new therapy. Here high frequency stimulation is applied to a selected brain region in an attempt to reduce excitability and/or increase seizure threshold. Basic mechanisms are not understood and optimal protocols are under development.

Method: We investigated the response of units to DBS in patients that underwent surgery for focus localisation. During anaesthesia, microelectrode tracks were made in the left/right hippocampus. Units were characterised and their response to stimulation with a macroelectrode in the same structure was evaluated in 7 patients, who were selected for not having structural abnormalities on 3T MRI and who were all potential candidates for resective surgery and/or DBS.

Results: A total of 87 single units were recorded from 46 sites. 45 were recorded from the site that was classified as the ictal onset zone, as evidenced by the results of a comprehensive dEEG analysis. The remaining 42 units were recorded in the hippocampus contralateral to the temporal lobe generating the habitual seizures. The mean firing rate of neurons was higher (8.6 ± 0.7 Hz; $p < 0.005$), in the ictal onset zone than in the contralateral side (6.3 ± 0.7 Hz). Stimulation activated 21 out of 46 units tested. Sixteen were inhibited for 200 ms, while 5 showed a sharply timed activation during the inhibition.

Conclusion: A surprisingly large fraction of the spontaneously active units responded to stimulation; the majority with a long period of inhibition. The cellular mechanisms and the correlation with DBS outcome need to be established.

p263

DENTATE GYRUS NEUROGENESIS IN HUMAN TEMPORAL LOBE EPILEPSY

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Purpose: Adult neurogenesis is the process by which new neurons are created in the mature central nervous system. This phenomenon has been shown to occur in the dentate gyrus (DG) of the hippocampal formation in a wide variety of species, including humans. Experimental works have suggested that seizure discharges stimulate dentate gyrus neurogenesis, while chronic temporal lobe epilepsy appears associated with a declined production of new neurons.

Method: We studied the dentate gyrus neurogenesis in 2 patients submitted to anterior-mesial temporal resection for pharmacoresistant temporal lobe epilepsy. Presurgical duration of epilepsy was 18 and 30 years, age at surgery was 37 and 41 years, 1 was right-sided; the other one was left-sided. Histopathological examination showed architectural dysplasia of temporal pole and amygdala in 1 case and Ammon Horn sclerosis in the other.

Results: Our study demonstrates the presence of neural stem cells in the dentate gyrus of 2 adult patients with temporal lobe epilepsy. These neural stem cells were cultured in vitro and neurospheres were obtained. In the absence of any specific proliferative stimulus, these neurospheres differentiated in all the three mature cell types: neuron, astrocyte and oligodendrocyte.

Conclusion: Our results show that neurogenesis can persist in humans with chronic epilepsy and in patients with hippocampal sclerosis. Further studies are necessary to better define the stimulating factors for each cellular lineage, and to investigate the role that a persistent postnatal neurogenesis may have in the development of an epileptic network and cortical dysplasia.

p264

INCREASE ON CALCINEURIN ACTIVITY AFTER IN VIVO ACTIN DEPOLYMERIZATION BY LATRUNCULIN A MICRO PERFUSION IN THE RAT HIPPOCAMPUS

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Purpose: The role of calcineurin in epileptic seizures is still controversial. Calcineurin activity increases after kindling and pilocarpine administration, and an important link has been established between calcium influx leading to calcineurin activation and the intrinsic excitability of pyramidal neurons. The aim of this study is to improve the knowledge about the possible role of calcineurin in latrunculin A-induced epileptic seizures.

Method: Latrunculin A (4 μg/ml) was dissolved in ringer fluid and perfused into the rat hippocampus during 8 hours for three consecutive days using a CMA/120 microdialysis system for freely moving animals and CMA/12 microdialysis probes, with continuous EEG and videotape recording. Calcineurin activity was measured in hippocampal homogenates using the Promega ProFluor^{TM} Ser/Thr phosphatase assay kit in three groups of rats: controls, after 3-days acute latrunculin A administration, and when spontaneous seizures started to be observed.

Results: During latrunculin A microperfusion, at least one seizure was recorded from 70% of the animals. 40 days after treatment, 80% of the rats studied had shown a variable number (4.3 ± 1.7) of spontaneous seizures. When compared to controls, a significant increase ($p < 0.0001$ by one-way ANOVA) in calcineurin activity was found in the hippocampus of latrunculin A-treated rats showing chronic spontaneous seizures. However, no significant differences were found just after the 3-days latrunculin A treatment.

Conclusion: This study provides additional evidence of the involvement of dephosphorylation mechanisms in epileptogenesis. Our results show that calcineurin activity is chronically increased in rats showing spontaneous seizures after hippocampal latrunculin A microperfusion, and support previous data suggesting that calcineurin inhibition may be a possible strategy in the search for new anticonvulsant drugs. (Supported by grant XUGA PGIDIT03PXIB20803PR from the Consellería de Educación e Ordenación Universitaria, Xunta de Galicia, Galicia, Spain.)

p265

STIMULATION OF THE ANTERODORSAL THALAMUS IN GENETIC ABSENCE EPILEPSY RATS FROM STRASBOURG (GAERS)

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Purpose: Deep brain stimulation (DBS) is a widely used treatment option for refractory patients with various neurological disorders. Genetic Absence Epilepsy Rats from Strasbourg (GAERS) constitute a well established genetic animal model for absence epilepsy. The aim of the study was to investigate the effect of acute (3 s) and subacute (15 min) electrical stimulation of the anterodorsal thalamus in GAERS.

Method: 12 GAERS (4–5 months) were implanted with bipolar electrodes in the anterodorsal thalamus. During the acute experiment, the rats ($n = 8$) received unilateral high (130 Hz) (HFS) and middle frequency (60 Hz) (MFS) stimulations when spike-and-wave discharges (SWDs) appeared on the electroencephalogram (EEG). In the subacute experiment, the animals were continuously stimulated for 15 min. The number, duration and cumulative duration of the SWDs were compared before, during and after the stimulation period. Electrode positions were verified postmortem by histological analysis.

Results: Acute HFS reduced the duration of SWDs ($p < 0.01$). Acute MFS had a similar effect, that failed to reach statistical significance ($p = 0.07$). Subacute HFS and MFS did not influence the number or the duration of SWDs.

Conclusion: In GAERS, acute HFS but not MFS of the anterodorsal thalamus resulted in an antiepileptic effect, noticeable as a significant reduction in SWD duration. Subacute HFS and MFS did not result in a similar effect. These data confirm the involvement of the anterodorsal thalamus in the control of generalised seizures and suggest that this region could be a target for focal stimulation to treat intractable seizures in humans.

p266

PHARMACOLOGICAL PROFILE OF $GABA_A$ RECEPTOR SUBTYPES IS ALTERED BY STATUS EPILEPTICUS IN THE DEVELOPING RAT BRAIN

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Purpose: GABA is the main inhibitory neurotransmitter in the adult brain, whereas it acts as a trophic excitatory transmitter in the developing brain. Enhanced excitation, i.e., seizures, alters $GABA_A$ receptor structure, function, and pharmacology in adult rats, but whether this occurs in

the developing brain is not known. We have studied the binding properties of $GABA_A$/benzodiazepine receptors using [^{3}H]flunitrazepam and zolpidem, a ligand selective for $\alpha1\beta2\gamma2$ receptor subtype, in immature rats after status epilepticus (SE).

Method: Receptor ligand autoradiography was used to study the displacement of the $GABA_A$ receptor agonist [^{3}H]flunitrazepam by zolpidem, in 9 day old rats acutely (6 h) and subacutely (7 days), after kainic acid (KA)-induced SE. The regional changes in the binding properties were further corroborated at the cellular level by using specific $GABA_A$ receptor subunit antibodies and fluorescent secondary antibodies.

Results: The binding results revealed that SE significantly decreased the affinity of zolpidem in displacing the [^{3}H]flunitrazepam ligand in certain brain regions. The displacement was decreased 6 h after KA treatment in the dentate gyrus of the hippocampus, in the frontal and parietal cortex, and thalamus, whereas a reduction was found one week after KA treatment in the hippocampal CA3 and CA1 cell layers.

Conclusion: Our results show that SE region-specifically alters the pharmacological properties of $GABA_A$ receptors in the immature rat brain during the sensitive postnatal period. Based on our results we suggest that seizures could disturb the normal, strictly developmentally-regulated maturation of $GABA_A$ receptors, and alter the balance between excitation and inhibition.

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p267

ASSESSMENT OF THE EFFECT OF CHRONIC LEVETIRACETAM TREATMENT ON EPILEPTIFORM ACTIVITY AND PAIRED PULSE INTERACTIONS IN THE DENTATE GYRUS OF FREELY MOVING RATS DURING ALTERNATE DAY RAPID KINDLING

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Purpose: In kindling, testing for antiepileptogenic properties usually involves administering drugs prior to stimulation, hampering a clear-cut distinction between antiepileptic and antiepileptogenic effects. This study investigates the effect of chronic postkindling levetiracetam (LEV) administration on paired pulse interactions (PPi) and establishment of the fully kindled state in alternate day rapid kindling (ADRK).

Method: Using intraoperative EEG, rats (n = 20) were implanted with a hexapolar stimulation/recording electrode-complex in the hippocampus. PPi were sampled prior to each ADRK session (12 stimulations/day on 4 alternating days). The rats were then implanted with an osmotic minipump containing either LEV (500 mg/ml) or saline (0.9% NaCl). After one week of treatment, PPi were analysed and the kindled state was reassessed using the Racine seizure score and the electroencephalographic afterdischarge duration (ADD).

Results: Following chronic LEV treatment, a significant decrease of seizure severity was noticeable only during the first of 12 retest stimulations: seizure score was reduced from 4.2 ± 0.8 to 2.1 ± 0.8 compared to controls, while ADD showed a decline from 93.0 s $\pm$ 42.5 s to 40.2 s $\pm$ 27.1 s ($p < 0.05$). Analyses of the PPi revealed a shift towards increased inhibition over larger intervals in both groups.

Conclusion: Chronic LEV administration had a prolonged effect on the kindled state but could not prevent seizures. For the first time in ADRK, a detailed characterisation of in vivo PPi in the epileptogenic focus is presented; PPi in ADRK proved to be comparable to standard kindling and provided a refined, complementary tool for assessing local excitability.

p268

AMYGDALA KINDLING IN RAT PUPS WITH GENETIC ABSENCE EPILEPSY

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Purpose: A recent kindling study in rats with genetic absence epilepsy showed that Genetic Absence Epilepsy Rats from Strasbourg (GAERS) failed to progress beyond stage 2 after the application of 25 electrical stimulations. Spike-and-wave discharges start to appear on postnatal day (PN) 40. In order to evaluate age-related changes on the kindling progress in GAERS pups, we examined the amygdala kindling rate and afterdischarge characteristics of PN30 and PN60 GAERS.

Method: Electrodes for stimulation and recording were stereotaxically implanted into the basolateral amygdala and cortex of male Wistar (n = 6 each group) and GAERS (n = 6 each group). After a recovery period, animals were stimulated every 90 min at 400 μA. Animals received kindling stimulation until they reached five stage 5 or the maximum number of stimulations (45). The seizures were scored by using Racine's 5-stage scale.

Results: All the nonepileptic control rats and five out of six (83.3%) PN30 GAERS achieved stage 5, whereas 1 (16.7%) PN30 GAERS stayed at stage 2 after 45 stimulations. Four out of 6 (66.6%) PN60 GAERS reached stage 5, 2 of 6 (33.4%) PN60 GAERS stayed at stage-2 and no motor seizures was observed after the application of 45 stimulations. Additionally, the amygdala kindling rate of 5 PN30 and 4 PN60 GAERS was significantly slower when compared to nonepileptic control rats.

Conclusion: The results of our study demonstrate that resistance to the secondary generalisation of limbic seizures during amygdala kindling in GAERS is age-related.

p269

PARTIAL RECOVERY OF CYTOCHROME C OXIDASE ACTIVITY IN THE HIPPOCAMPUS AFTER STATUS EPILEPTICUS IN THE RAT IS BOTH AGE AND STRUCTURE DEPENDENT

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Purpose: Dysfunction of the respiratory chain enzymes was described in various pathologies including temporal epilepsy. In the present study we addressed the question of whether change of activity of the mitochondrial respiratory chain Complex IV–cytochrome c oxidase (COx) during status epilepticus (SE)-induced epileptogenesis is age and structure dependent.

Method: SE was induced by LiCl/pilocarpine in P12, P25 and P90 rats as described before (Otahal et al., *Epilepsia*, 2005; 46:S5:89–93). In order to assess COx activity, rats were decapitated one week (latency period) or three months (chronic period) after the SE. Coronal sections (1-of-5 series) throughout the entire brain were used for COx histochemistry. Adjacent sections were used for Nissl staining to identify anatomic boundaries. COx activity of the hippocampus was then evaluated by corrected optical density measurement of CA1, CA3, dentate gyrus (DG) and hilus separately. To evaluate Cox recovery ratio of values from 3M/1W after SE was calculated.

Results: COx-activity was lower in all age-and-interval groups in all hippocampal regions compared to controls (on average $-7.29\% \pm 1.96$). Recovery ratio increased significantly ($p < 0.05$) in all regions except the hilus. The difference was most pronounced in P12 and decreased with age. In controls, COx activity showed significant decrease with ageing in both P25 and adult rats.

Conclusion: Our data suggests that after SE, age and structure both show dependent partial recovery of the respiratory metabolism. Supported by grant 1QS501210509 (Academy of Sciences of the Czech Republic). Experiments were approved by the Animal Care and Use Committee.

p270

EFFECTS OF ß-HYDROXYBUTYRATE ON NEUROGENESIS AFTER PILOCARPINE-INDUCED SEIZURES IN MICE

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Purpose: Epileptic seizures have been shown to stimulate the proliferation rate of granule cell progenitors in the brain. Recently, we reported that ketogenic diet (KD) enhanced neurogenesis after seizures in mice [Kim DW et al., *Epilepsia* 2004;46(Suppl 6):373]. KD remains a therapy in search of explanation although it is an established treatment for patients with intractable seizures. It was originally devised to mimic the biochemical changes seen upon fasting, specifically the formation of ketone bodies: β-hydroxybutyrate (BHB), acetoacetate, and to a lesser extent, acetone. In this study, we investigated the effects of BHB on neurogenesis after pilocarpine-induced seizures in mice.

Method: Eight male ICR mice were divided into two groups. Experimental mice ($n = 4$) were injected intraperitoneally with BHB (20 mmol/kg), while control mice ($n = 4$) with normal saline. Fifteen minutes later, seizures were chemically induced by intraperitoneal injection of pilocarpine (300 mg/kg) in both groups. Then, bromodeoxyuridine (BrdU, 50 mg/kg) was subsequently administered once a day for 6 consecutive days, staring at 24 hours after pilocarpine treatment. Mice were sacrificed 7 days after pilocarpine administration. BrdU-positive cells in the hippocampus were counted in every seventh section in a series of 30 μm coronal sections.

Results: In the experimental group treated with BHB, BrdU-labeled cells increased significantly compared to the control group (377.57 ± 150.40 vs. 230.55 ± 59.50, $p < 0.0002$).

Conclusion In this study, quantitative analysis of BrdU labelling revealed a significant increase in the proliferation rate of neuronal progenitor cells after pilocarpine-induced seizures in BHB-treated mice. Our results suggest that BHB enhances neurogenesis after seizures.

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p271

UNEXPECTED SHORT-LASTING EFFECTS OF VIGABATRIN ON ABSENCE SEIZURES IN WAG/RIJ RATS

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Purpose: The duration of the effects of a single dose of vigabatrin on spontaneous spike-wave-discharges (SWDs) in the EEG of WAG/Rij rats was studied. The WAG/Rij rat is recognised as an animal model for generalised absence epilepsy in humans. Both $GABA_A$ and $GABA_B$ receptor agonists have pro-absence effects in these animals. Vigabatrin inhibits GABA transaminase irreversibly. Consequently, the endogenous GABA concentration is enhanced for days, even after a single dose.

Method: Male WAG/Rij rats received a single dose of vigabatrin (500 mg/kg, isotonic intraperitoneal) or an equal volume of saline (12.5 ml/kg) ($n = 8$ each group). EEG was recorded until 48 hours post injection (p.i.) in freely moving animals.

Results: The mean incidence of SWDs in the controls was 16/h. Vigabatrin increased the incidence by a steep S-shaped time-effect curve with a maximum of 150/h (SEM 30/h) at 3.1 hours (SEM 0.4h) p.i. About the 7^{th} hour the SWD incidence abruptly returned to baseline level. Nevertheless, other effects of vigabatrin treatment were observed for well over 24 hours p.i.: the morphology of the SWDs was changed from the 1st hour p.i. until the end of the observation period.

Conclusion: Tolerance to the changed incidence of the SWDs was observed within 7 hours but the EEG remained altered long after this period. The question is whether a (neuro)-pharmacokinetic origin together with differences in dose response curves for the various effects are enough to explain this unexpected, short lasting effect of vigabatrin or whether pharmacodynamic-neuroplastic changes are involved as well.

p272

EVALUATION OF TWO SEIZURE PREDICTION METHODS BASED ON LONG-TERM INTRACRANIAL EEG RECORDINGS

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Purpose: Concerning the predictability of epileptic seizures, recent work has shown that methods from nonlinear dynamics can be used to analyse neurophysiological recordings for detection of preseizure changes. When utilising these methods for seizure prediction it is crucial to assess their prediction performance on long-term EEG data, including tests for statistical significance.

Method: A bivariate phase synchronisation index and the univariate "Dynamic Similarity Index" were adapted for seizure prediction (Mormann et al., *Physica D* 2000;144:358–369 and Le Van Quyen et al., *NeuroReport* 1999;10:2149–2155). Based on the seizure prediction characteristic (Winterhalder et al., *Epilepsy Behav* 2003;4:318–325) and a long-term intracranial EEG database with continuous recordings of 15 patients for up to 14 days (mean 7.5) including 330 seizures we performed an analysis with prediction windows up to 4 hours. All results have been validated by a statistical test procedure (Schelter et al., *Chaos* 2006;16:013108).

Results: When using the phase synchronisation index for seizure prediction, significant prediction performance could be observed for 11 patients with a mean sensitivity of 52.1% ranging from 38.1% to 66.7%, for a maximum false prediction rate of 0.15 false predictions per hour. Sensitivity increased selecting specific EEG frequency bands for several patients by 10% to 20%. Results for the dynamical similarity index were significant for 11 patients with a mean sensitivity of 51.7%.

Conclusion: The investigated univariate and bivariate analysis techniques have shown similar performance in predicting epileptic seizures. Both methods have achieved statistical significant prediction performance on long-term EEG data with considerable interpatient variability.

p273

BRAIN CORTEX INVOLVEMENT IN CHRONIC EPILEPTISATION IN PILOCARPINE TREATED RATS

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Purpose: Pilocarpine (Pi) -induced epilepsy is a model of limbic recurrent seizures and status epilepticus (SE). The goal of the present work was electrophysiological registration of the Pi-induced SE free of recurrent seizures period with the aim of evaluation of structures responsible for epileptic activity (EpA) initiation.

Method: Wistar rats were implanted with electrodes into the brain cortex left frontal, temporal and occipital lobes, substantia nigra (SN), ventral hippocampus (VH), amygdala (A) and nucleus caudatus (NC). 7–10 day animals were free of trials. 30 min after scopolamine hydrobromide (1.0 mg/kg, s.c.) pretreatment, a generalised convulsive SE was induced in rats by Pi hydrochloride (300 mg/kg, i.p.) injection. EEG was recorded 210 min after SE induction. Recordings were made using discrete frequency of 2 kHz with the help of National Instruments DAQ (PCI-6071E) and specially designed software. Signals were filtered and sampled at 0.5 to 40 Hz. Repetitive data files recorded from each animal during experiments were used for the Pi-induced EpA analysis in the time-frequency domain.

Results: Electrical activity progressive enhancement was registered 20–25 min after Pi injection that was mostly evident in VH, frontal and temporal lobes. It was synchronised in frontal and occipital lobes, NC and VH in all rats 25–30 min after Pi administration. Convulsions started at 36 ± 3 min after Pi injection also had EEG correlates in the form of epileptic spike amplitude increasing in the frontal lobes, NC and VH. Highly amplitude spikes (0.8–1.0 mV, frequency 12–17 Hz) appeared firstly in VH in 12 rats of 16. 3 rats showed EEG signs of seizure initiation in the temporal lobe (0.5–0.6 mV, frequency 2-3 Hz)

and Pi-induced convulsions appeared firstly in SN in 1 rat that was characterised by spike amplitude of 0.35-0.45 mkV and their frequency of 2-3 Hz.

Conclusion: Brain cortex (mainly frontal and temporal lobes) has direct participation in chronic Pi-induced EpA initiation and its following spread over the whole brain. These data might also further our understanding of chronic epileptogenesis pathophysiological mechanisms contributing to certain brain cortex lobes importance in Pi-induced SE initiation and cessation.

p274

GENE ARRAY ANALYSIS OF DNA-DAMAGE SIGNALING PATHWAYS AFTER PROLONGED SEIZURES: DIFFERENTIAL RESPONSE IN YOUNG ADULT VERSUS AGED RATS

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Purpose: Status epilepticus (SE) results in neuronal cell death and DNA damage. Little is known about the regulation of DNA-damage response pathways following seizures. Here we examined the regulation of these pathways after SE as a function of age.

Method: SE was induced in young adult and aged rats by systemic administration of kainate at doses ensuring comparable seizure manifestations between the age groups. SE was terminated after 30 min with diazepam, and the rats were sacrificed for tissue collection at 4 or 8 hr. DNA-damage Signaling Pathways Gene Array (SuperArray) containing 96 genes was used to examine changes in gene expression in the rhinal cortex. A two-fold change in expression was used as the cutoff criteria for analysis.

Results: Approximately 25 genes showed greater expression levels in control young adult rats as compared with aged rats. In young adult rats, at 8 hr following SE, 4 genes were upregulated and 8 genes were downregulated as compared to corresponding control animals. In aged rats under the same conditions, only 1 gene was upregulated as compared to age-matched controls following seizures, while 15 genes were downregulated.

Conclusion: Our results indicate that DNA-damage response pathways are activated following prolonged seizures and that the level of activation of specific pathways is age-dependent. Aged rats displayed overall lower levels of expression of the DNA-damage/repair pathways and a diminished response of these pathways to SE. These results suggest that impairment of this response may contribute to age-dependent vulnerability to seizure-evoked injury. Supported by NIH grants F31NS461991, MH02040, NS041231, and AG019165.

p275

NEOVASCULARISATION OF THE EPILEPTIC FOCUS IN RAT LIMBIC EPILEPSY: CONSEQUENCES ON BLOOD–BRAIN BARRIER FUNCTION

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Purpose: In human temporal lobe epilepsy (TLE), an increase of vascularisation was noted in the focus, compared to nonepileptic tissue. We hypothesised that this pathological vascularisation is associated with changes in microvessel density and with the secretion of angiogenic factors and the expression of their receptors. To understand the mechanisms and the kinetic of this pathologic vascularisation, we used a rodent model of TLE (lithium-pilocarpine).

Method: Rats that underwent status epilepticus (SE) were sacrificed at different time points (as from 1 hour until 2 months after SE). Brains and/or hippocampi were collected and treated for histology, immunohistochemistry or immunoblotting. We checked: i) the density of microvessels, ii) the expression of angiogenic factors and their receptors, iii) the disruption of the blood brain barrier (BBB).

Results: As from 2 weeks after SE, the density of hippocampal microvessels was significantly increased compared to those of age-matched control animals. A strong neuronal expression of the angiogenic factor VEGF was observed rapidly after seizures, whereas its receptor Flk-1 was expressed by endothelial cell from one week after the SE. Both VEGF and Flk-1 were still expressed at later time points. Moreover, at all stages studied, a BBB disruption was evidenced by IgG leakage around capillaries.

Conclusion: Severe seizures induce in adult rats a vascular remodelling of the epileptic focus, due to the release of angiogenic factors. This neo-vascularisation is associated with an increase of BBB permeability and with inflammatory reactions that may contribute to the secondary epileptogenesis.

p276

$GABA_A$ RECEPTORS IN THE HUMAN NEOCORTEX: DIFFERENTIAL DISTRIBUTION AND SUBTYPE-SPECIFIC ALTERATIONS IN TEMPORAL LOBE EPILEPSY

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Purpose: Imaging studies have revealed both increases and decreases in flumazenil binding in the neocortex of patients with refractory temporal lobe epilepsy (TLE). We investigated whether these changes reflect differences in the expression of specific $GABA_A$ receptor subtypes.

Method: Neocortical tissue was obtained at surgery from patients with TLE resulting from hippocampal sclerosis (HS) or other causes (non-HS), and was compared with postmortem control samples. The distribution of the $GABA_A$ receptor subunits alpha1, alpha2, alpha3, beta2.3 and gamma2 was visualised immunohistochemically.

Results: In control grey matter tissue, labelling for the three alpha subunits was layer-specific whereas expression patterns of beta2.3 and gamma2 subunits largely followed those of the alpha1 subunit. In control white matter tissue, which contains large numbers of neurons in the human, the alpha1 subunit was expressed in numerous pyramidal cells and interneurons, the alpha3 subunit only in pyramidal cells, and the alpha2 subunit in virtually no neurons. In the two patient groups, subunit-specific changes were observed in grey and white matter. In a subset of patients, it was exclusively the expression of the alpha3 subunit that was decreased, and this only in the superficial layers. Striking alterations in soma size and dendritic morphology of neurons positive for the alpha1 subunit were seen in white matter.

Conclusion: These results show a stereotypic layer and cell type-specific expression of $GABA_A$ receptor subtypes in the human neocortex. The marked changes detected in white matter neurons and their $GABA_A$ receptors may contribute to the disease mechanisms underlying epilepsy.

p277

FUNCTIONAL ANALYSIS OF A NOVEL *KCNQ2* GENE VARIANT FOUND IN A LARGE PEDIGREE WITH BENIGN FAMILIAL NEONATAL CONVULSIONS (BFNC)

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Purpose: Benign familial neonatal convulsion (BFNC) is a rare epilepsy disorder with autosomal dominant inheritance. Mutations in the potassium channel genes *KCNQ2* and *KCNQ3* are highly associated with BFNC. *KCNQ2* and *KCNQ3* subunits form tetrameric voltage-gated channels via assembly of their conserved A-domain, located in the carboxy-terminus of the proteins, resulting in a classical M-current. Previously, we reported a splice-site mutation in the *KCNQ2* gene in a BFNC family with 13 affected members (de Haan GJ et al., *Epilepsia* in press). This mutation (c.IVS14-6C>A) creates a new, preferentially used, splice site, that results in a premature stop codon and a predicted protein truncation (p.R588X). This study reports the biophysical properties of this mutant.

Method: Wild-type (WT) and mutant channel cDNAs were co-expressed in HEK293 cells. Transfection with KCNQ2/KCNQ3 cDNAs in a 1:1 ratio mimicked expression in healthy subjects. Transfection with KCNQ2/3 WT and c.IVS14-6C>A cDNAs in a 0.5:1:0.5 ratio mimicked expression in patients heterozygous for the mutation. The resulting potassium currents were measured using whole-cell patch-clamp techniques.

Results: Cells expressing WT heteromeric KCNQ2/KCNQ3 channels revealed a large noninactivating, slowly deactivating M-type potassium current (current density 781 $\pm$ 170 pA/pF, n = 7). Cells expressing mutant channels showed a significant reduction in M-current (224 $\pm$ 53 pA/pF, n = 7). Furthermore, the voltage dependence of mutant channel activation was shifted in the depolarising direction by 6 mV.

Conclusion: The decreased current density and depolarising shift in activation caused by the mutant channels may result in hyperexcitability, which is likely to cause epilepsy in neonates.

p278

MITOCHONDRIAL COMPLEX I INHIBITION IN CEREBRAL CORTEX OF IMMATURE RATS FOLLOWING HOMOCYSTEIC ACID-INDUCED SEIZURES

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Purpose: Mitochondrial dysfunction (in terms of the deficiency of complex activities) has been demonstrated in brains of adult rats following status epilepticus (SE). We asked whether it may also occur in the brain of immature rats following SE.

Method: Seizures (having a character of SE) were induced by bilateral icv infusion of DL-homocysteic acid (DL-HCA, 600 nmol/side) in 12-day-old male Wistar rats with implanted cannulae. Control animals received a corresponding volume of the vehicle. The activities of citrate synthase (CS) and respiratory chain complex activities were determined in isolated mitochondria by spectrophotometric assays.

Results: A marked decrease (~64%) of complex I (evident when expressed either as the specific activity or as a ratio to CS) was already observed during the acute phase of seizures (60–90 min after DL-HCA infusion) and it still persisted at ~20 h of survival following seizures. The activities of complex II and IV remained in the control range at both time intervals. Decrease of complex I activity was substantially attenuated when animals were treated with substances providing an anticonvulsant effect and also with selected free radical scavengers.

Conclusion: These findings suggest that mitochondrial dysfunction may also occur in the immature brain following seizures. Supported by Grant Agency of the Czech Republic, Grant No.309/05/2015.

p279

INFLUENCE OF RECURRENT EARLY FEBRILE SEIZURES ON THE DEVELOPMENT OF ABSENCE EPILEPSY IN ADULT RATS

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Purpose: The aim of the present experiment was to evaluate the effect of early recurrent experimental febrile seizures on the development of absence epilepsy in adult rats.

Method: Pups of two litters (n = 6 each) of WAG/Rij rats were used. The experimental febrile seizures were conducted in a mild regime by light (lamp 200 W) from a distance, providing a temperature a 38°C inside a box. The modified scale developed by Mares was used to evaluate the seizures. The mean temperature of pups was measured before and after seizures with a lubricated probe from the rectum. The control group of pups was placed in the same box at room temperature. For experimental febrile seizures pups were heated on the 3th, 5th, 7th, 9th and 11th postnatal days. EEG was recorded after 6 months for 1 hour. EEG electrodes were chronically implanted into the frontal cortex. The mean duration and number of SWDs were calculated.

Results: A significantly larger mean duration of SWDs ($F1.8 = 15.77$; $p < 0.01$) was found for the treatment group compared to the control rats, while there was no significant interaction effect between treatment and litter, nor a litter effect. Analysis of number of SWDs showed no significant effects.

Conclusion: It is known that children with long-lasting febrile convulsions are at risk for temporal lobe epilepsy. According to our results we can suggest that febrile convulsions of WAG/Rij pups in early postnatal ontogenesis does not affect the excitability of the corticothalamic system later in life, however, it does affect a stopping mechanism, responsible for the ending of an ongoing seizure.

p280

CONVULSIVE SEIZURES, NONCONVULSIVE SEIZURES, AND NEURODEGENERATION: LESSONS FROM A RODENT PENTYLENETETRAZOLE KINDLING MODEL

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Purpose: Pentylenetetrazole (PTZ) kindling, the regular application of subthreshold doses of PTZ, provokes a behaviour in rodents very similar to chronic secondary generalised seizures. As a rule, there is a portion of PTZ-resistant animals which do not demonstrate convulsive behaviour and are removed from the experiment. The purpose of the study was to perform a comparative investigation of PTZ-prone (PTZPR) and PTZ-resistant rats (PTZRR) from a population of Wistar rats.

Method: Oxidative stress, neurodegeneration in hippocampus was studied, and EEG pattern was monitored.

Results: Intraperitoneal injection of PTZ at a subconvulsive dose resulted in the separation of two distinct groups, PTZPR demonstrating the development of clonic seizures, while PTZRR displayed preconvulsive stages. In hippocampi of both groups, a similar decrease of glutathione level was revealed indicative of oxidative stress accompanied by a similar degree of hippocampal neurodegeneration (8–13%). PTZ challenge of kindled animals induced similar short generalised discharges (2–3 sec, 5–8 Hz) in neocortex and hippocampus (amplitude 800-900 μV in PTZPR vs. 400–500 μV in PTZRR). Further changes of EEG pattern in PTZPR corresponded to the development of convulsions, while short discharges in EEG of PTZRR (7–8 Hz) corresponded to freezing episodes. Other differences in EEG characteristics of PTZPR and PTZRR were revealed (latency, number of discharges, frequency power peak).

Conclusion: Generalised nonconvulsive epileptic activity found in PTZRR may be intimately involved in gross structural changes in the brain, including neurodegeneration. Our data confirm supposed injurious effects of absence epilepsy on neuronal cells. Supported by RHSF and RAS Grant Fundamental Medicine.

p281

THE NOVEL SV2A LIGANDS BRIVARACETAM AND SELETRACETAM MANIFEST DIFFERENT EFFECTS AGAINST THE EPILEPTIFORM MARKERS OF FIELD POTENTIALS IN A "HIGH K+–LOW CA2+" RAT HIPPOCAMPAL SLICE MODEL

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Purpose: Brivaracetam (ucb 34714; BRV) and seletracetam (ucb 44212; SEL) bind to the synaptic vesicle protein 2A (SV2A) with affinity 10-fold higher than levetiracetam (Keppra), and display superior but distinct profiles in animal models of epilepsy. Here we compare the effects of SEL vs BRV on field potentials recorded in rat hippocampal slices in vitro, under perfusion with a "high K^+ – low Ca^{2+} fluid" (HKLCF).

Method: Perfusing rat hippocampal slices with HKLCF induces spontaneous field bursts in CA3 area of slices silent when in normal physiological solution. Also, HKLCF increases population spike (PS) amplitude and leads fimbrial stimuli, which evoke a single PS under normal perfusion, to elicit repetitive PSs. The effects of either BRV, or SEL 1–10 μM, added to the perfusion 20 min before shifting to HKLCF, were

quantified via the rate of spontaneous bursts, the amplitude of PS and the number of repetitive PSs evoked by constant stimuli.

Results: Either BRV, or SEL inhibited these epileptiform markers to various extents, most consistently at 3.2 μM. BRV (3.2 μM) significantly reduced (by $\cong$40%) the rate of spontaneous bursting, while SEL (1– 10 μM) had no effect on this parameter. BRV (3.2 μM) inhibited less the HKLCF-induced increase in PS amplitude (ΔPS), but it reduced by >33% the number of evoked PSs. In contrast, SEL (3.2 μM) strongly inhibited ΔPS, while reducing by only <25% the number of evoked PSs. BRV, but not SEL, tended to shift the peak of power spectra of spontaneous bursts towards lower frequencies.

Conclusion: The difference in antiepileptic effects in vitro of BRV and SEL suggest distinct abilities of these two high affinity SV2A ligands to inhibit epileptiform synchronisation and neuronal hyperexcitability.

p282

DEVELOPMENTAL AND STATUS EPILEPTICUS-INDUCED CHANGES IN THE EXPRESSION OF MICROTUBULE-ASSOCIATED PROTEIN 2 (MAP-2) IN THE DEVELOPING RAT HIPPOCAMPUS

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Purpose: The cytoskeletal MAP-2 proteins are involved in the development, maintenance and plasticity of neuronal processes. They promote microtubule assembly, and by promoting interaction with neurofilaments and actin, MAP-2 may contribute to plastic changes in the cytoskeletal structure in response to external stimuli. The purpose of this study was to analyse developmental changes in the expression and localisation of MAP-2 isoforms, and their reactivity in status epilepticus (SE) in the postnatal (P) rat hippocampus.

Method: MAP-2a-d expression in the hippocampi of P1 to P21 rats, and their temporal expression patterns (0.5 h to 7 d) after kainic acid (KA)-induced SE in P9 rats were studied with Western blotting. Immunocytochemistry was used to localise MAP-2a and b in the hippocampi of P1 to P21 rats, and the effect of SE on their localisation in P9 rats.

Results: The expression of MAP-2a and b significantly ($p < 0.0001$) increased, whereas those of MAP-2c and d significantly decreased ($p < 0.0001$) in the rat hippocampus through P1 to P21. KA-induced SE significantly ($p < 0.0001$), rapidly, but transiently increasing the expression of MAP-2a and b. MAP-2a/b immunostaining was temporally and spatially heterogeneous in neuronal compartments and the staining intensity increased through P1 to P21 particularly in dendritic regions.

Conclusion: Our results show that MAP-2 isoform expression is strictly developmentally regulated, and that MAP-2a/b distribution is heterogeneous in different neuronal compartments in the hippocampus. The SE-induced reactivity of MAP-2 could contribute to structural integrity of intracellular cytoskeleton and enhance neuronal viability during cell stress. Acknowledgements: Sigrid Juselius Foundation, the Special State Grant for Clinical Research to I.E.H, and Lea and Arvo Ylppö Foundation.

p283

LONG-LASTING ANTICONVULSIVE EFFECT OF LEVETIRACETAM ON AUDIOGENIC SEIZURES IN RATS

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Purpose: The duration of the anticonvulsive effect of a single dose of levetiracetam on audiogenic seizures in rats was tested.

Method: Rats of the Krushinski-Molodkina strain ($n = 24$) in which sound stimulation induces seizures consisting of running and clonic–tonic convulsions received a single intraperitoneal injection of a low (3 or 6 mg/kg), a high (50 mg/kg) dose of levetiracetam or saline ($n = 6$ in each group). Audiogenic seizures were induced one hour, one, two and three weeks after drug injection. At the three-week time point, those rats previously injected with the 3 mg/kg dose were again treated with 6 mg/kg. Incidence and latency of running and tonic components of audiogenic seizures were recorded.

Results: The single injections of the low doses (3 or 6 mg/kg) did not significantly change the seizure pattern as compared to the saline group. The 50 mg/kg dose blocked tonic convulsions in 4 of 6 rats and completely suppressed audiogenic seizures in the others. The effect of the high dose was long lasting: a significant increase in the seizure latency was observed for at least three subsequent weeks postreatment ($p < 0.05$). Moreover, the double injection of the low dose, with the three-week interval, showed a significant anticonvulsive effect blocking tonic convulsions in 4 of the 6 rats and completely suppressing audiogenic seizures in 1 rat.

Conclusion: A single injection of levetiracetam induces a long-lasting anticonvulsive effect on audiogenic seizures. Treatment, with even low doses of levetiracetam, increases susceptibility of rats to subsequent drug injections for at least three weeks postreatment.

p284

CHARACTERISATION OF THE INTRAHIPPOCAMPAL KAINIC ACID STATUS EPILEPTICUS MODEL USING LONG-TERM VIDEO-EEG MONITORING

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Purpose: The intrahippocampal kainic acid (KA) status epilepticus (SE) model has been extensively described histopathologically and during short term EEG monitoring. However, no studies have characterised this model using long term video-EEG monitoring to determine other seizure parameters such as mean frequency, duration and severity.

Method: Female Sprague-Dawley rats ($n = 17$, 200–250 g) were stereotactically implanted with a guide cannula in the right hippocampus and depth recording electrodes in both hippocampi. One week after implantation KA (0.4 μg/0.2 μl) was injected in awake rats. Video-EEG monitoring was performed during SE and 72 hours/week for 16 weeks. A second recording of one week was performed 9 months after SE in 4 rats.

Results: Injection of KA resulted in the occurrence of SE in all rats. One rat died during the first week after KA administration. 87% (14/16) of the rats had spontaneous seizures during the first monitoring period. In the remaining 2 rats, seizures were detected during the second monitoring. On average, 1.41 ± 2.05/24 h convulsive seizures (mean duration 71 ± 22 sec) and 0.55 ± 1.08/24 h periods with interictal discharges (mean duration 43 ± 22 sec) were detected on EEG during the first monitoring period. During the second recording period on average 1.88 ± 2.90/24 h convulsive seizures (mean duration 75 ± 39sec) and 1.17 ± 1.70/24h periods with interictal discharges (mean duration 41 ± 19sec) were detected on EEG.

Conclusion: The intrahippocampal KA SE model is a reliable model to induce spontaneous epileptic seizures in rats. Mortality is very low, a reasonable number of seizures occur and by 9 months after KA administration epileptic discharges are found in all rats.

p285

DEVELOPMENT OF SPATIOTEMPORAL DYNAMICAL TRANSITIONS DURING EPILEPTOGENESIS

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Purpose: We have used a spontaneously seizing animal model of limbic epilepsy to investigate the occurrence of spatiotemporal transitions involving dynamical convergence among different regions in an epileptogenic brain. We hypothesise that the frequency of these transitions

increases progressively from the time of initial insult to the subsequent manifestation of epilepsy.

Method: Young adult male Sprague-Dawley rats (N = 4) were used in the study. The model was developed using chronic hippocampal stimulation (CHS). The animals were connected to an automated system that monitored the T-index calculated from short-term maximum Lyapunov exponents estimated from multiple brain regions. A transition was defined as a drop in T-index from a preset upper threshold ($U_T = 10$) to a lower threshold ($L_T = 2.662$). The time leading to the first seizure was divided into blocks of 12 hours and the frequency of transitions in each block was calculated. The null hypothesis is rejected if the regression slope is found to be significantly positive ($p < 0.05$).

Results: Two out of the 4 animals developed spontaneous seizures after CHS. The first showed a progressive increase in frequency of spatiotemporal transitions leading up to the first seizure (recording time before seizure ~232.9 hrs, slope = 0.09, p = 0.0005), the second animal showed an abrupt increase in incidence immediately preceding the seizure (recording time before seizure ~142.5 hrs, slope = 0.07, p = 0.0228). No dynamical transitions were observed in the 2 animals that did not develop spontaneous seizures.

Conclusion: These results suggest that spatiotemporal transitions involving convergence of dynamical values among brain regions may be a marker for epileptogenesis.

p286

DAILY POSTNATAL MATURATION OF RAT CORTICAL NEURON SIZES, ORIENTATIONS, AND THEIR GLUTAMATE RECEPTORS AFTER PRENATAL RADIATION: IMMEDIATE CORTICAL DYSPLASIA BUT DELAYED ONSET OF CORTICAL EPILEPSY

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Purpose: Cortical dysplasia (CD) is a frequent pathology in infants with intractable epilepsy. Cellular characteristics of the paediatric dysplastic cortex have altered subunit proteins of the *N*-methyl-d-aspartate receptor. This study determined if and when the dysplastic cortex of postnatal rat pups also showed altered NMDA subunit expressions compared to age-matched controls.

Method: Dams were radiated with 145 Rads at embryonic day 17; all offspring were studied at 24 hour intervals, ages 0 through 6. Cresyl violet stains were used to measure neuron sizes and orientations. Immunocytochemical (ICC) stains for receptor subunits NR1 and NR2 were compared to the CV cytology, and the NR1 and NR2 protein levels were measured by Western blots. Statistical comparisons between control and radiated age matched pups were made within and between treatment groups.

Results: Cresyl violet stains showed radiated pups sacrificed at birth had cortical dysplasias and their siblings, examined subsequently, showed neuron sizes and disorientations that increased linearly daily. Daily increases were significant for neuronal lengths ($p > 0.002$) and neuronal diameters ($p > 0.01$). NR1 and NR2 protein expressions increased daily, but the groups were not significantly different.

Conclusion: We conclude that neurons surviving prenatal radiation have all the molecular mechanisms for protein synthesis in the cytoplasm (cell sizes), in the specialised receptors (NMDA subunits) and in neuritic extensions that appear as early as day two. Hence, the process of epilepsy likely occurs weeks later when all the axo-dendritic connections are fully mature. (Support: NS 41375)

p287

ROLE OF OXIDATIVE STRESS IN PENTOXIFYLLINE-INDUCED PROTECTION AGAINST STATUS EPILEPTICUS IN IMMATURE RATS

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Purpose: Status epilepticus (SE) is a common neurological disorder associated with significant neurodegenerative changes. Role of oxidative stress (OS) in neuronal structure and function has been suggested in SE patient. Recently, pentoxifylline (PTX), a potent immunomodulating agent and free radical scavenger has been shown to protect pups against experimentally induced SE. The present study was designed to determine the role of oxidative stress in PTX-induced protection against SE in immature rats.

Method: SE was induced in immature rats by administering a single dose of lithium chloride (Li) (3mEq/kg, i.p.) on post natal day 19 (PD19) followed (24 h later) by pilocarpine (Pc) (20 mg/kg, s.c.) on PD20. The animals in test group received PTX (0, 20, 40 and 60 mg/kg, i.p.) 30 minutes before pilocarpine administration. The animals were sacrificed at 1 and 24 h after the dose of Pc, their hippocampus and striatum were removed for the determination of OS marker thiobarbituric acid-reactive substances (TBARS) and glutathione (GSH).

Results: Ninety percent of the pups developed a SE seizure within 5 minutes of Pc injection which lasted for around 30 minutes. A significant increase in TBARS and decrease in GSH was observed in the striatum and hippocampus region both at 1 and 24 h after SE induction clearly suggesting the role of OS. PTX dose-dependently attenuated the seizure and OS in SE.

Conclusion: PTX significantly protected the pups against Li-Pc induced SE and the OS. The protective effect of PTX may be attributed to its antioxidative activity.

p288

ANTIEPILEPTOGENIC EFFECT OF ANTERIOR THALAMIC HIGH FREQUENCY ELECTRICAL STIMULATION (ES) ON PENTYLENETETRAZOL (PTZ) KINDLING IN RATS

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Purpose: Previous reports indicate that focal ES of discrete brain structures inhibited seizure activity. The aim of this study was to analyse the effect of single and multiple ES of anterior thalamic (AN) on the PTZ-induced kindling in rats.

Method: Adult male Wistar rats were implanted with bipolar stimulating electrodes in the AN bilaterally. After recovery kindling was induced by PTZ (30 mg/kg) i.p. administration daily for 4 weeks. Stimulation parameters of AN were: 100 Hz, 300-800 μA, 0.1 ms pulse duration for 30 sec. Two protocols were used: 1) single ES of the AN at the early stage of development kindling and fully kindled animals, 2) multiple ES-effects after 7 daily ES of the AN in kindled animals.

Results: Bilateral ES of the AN completely suppressed EEG epileptiform activity in the early stage of PTZ-kindling and partially in fully kindled rats. Acute ES of the AN did not appear to have any effect on behaviour seizures. Multiple ES of the AN decreased by two-thirds the number of rats with constantly generalised clonic-tonic convulsions produced by PTZ-kindling. This ES resulted in increasing intensity of seizure severity in kindled rats with seizures of stages 2-3.

Conclusion: We conclude that high-frequency ES of the AN can be anticonvulsant, but the effects appear to depend on the intensity and type of seizures.

p289

INFLUENCE OF DIPHOSPHONATE GERMANIUM WITH NICOTINAMIDE (MIGU-5) ON THE ANTICONVULSIVE ACTIVITY OF CONVENTIONAL ANTIEPILEPTIC DRUGS IN MICE

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Purpose: We previously reported antiepileptic effects of MIGU-5 on different forms of seizure activity. Since polytherapy is required for about 30% of epilepsy patients, the aim of this study was to characterise the effect of MIGU-5 on the protective activity of the conventional antiepileptic drugs.

Method: Electroconvulsions were produced with corneal electrodes and alternating current (50 Hz, 0.2 s stimulation duration) delivered by a Grass S48 stimulator. The full tonic extension of hindlimbs was used as an endpoint. The protective effect of MIGU-5 was evaluated in the threshold test, while that of phenobarbital, carbamazepine, phenytoin and valproate in the maximal electroshock test induced by current intensity of 30 mA.

Results: MIGU-5 (100 mg/kg, 30 min before the test) significantly elevated the threshold for MES from 11.8 to 16.5 mA, being ineffective up to 25 mg/kg. In the subprotective dose of 25 mg/kg MIGU-5 significantly decreased the ED50 value of phenobarbital from 22.7 to 16.4 mg/kg, phenytoin (from 7.8 to 5.2 mg/kg), carbamazepine (from 9.5 to 6.1 mg/kg), valproate (from 286 to 190 mg/kg).

Conclusion: The results suggest that MIGU-5 possesses the potential of an antiepileptic drug and can be used as an adjuvant antiepileptic drug.

p290

INFLUENCE OF SUPEROXIDE DISMUTASE ON CONVULSIONS EVOKED BY PENTYLENETETRAZOL

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Purpose: In the pathogenesis of epilepsy, as well as in experimental convulsions, oxidative stress has an important role.

Method: We thus investigated whether superoxide dismutase (SOD), a part of the antioxidative defense system, can modulate pentylenetetrazol-evoked convulsions in adult mail Wistar rats (n = 7). For intracerebroventricular application of SOD, in pentobarbital anesthesia we inserted polyethylene cannula in the left lateral ventricle. Seven days after recovery from surgery, rats received SOD (0.06 mg). It was applied 25 minutes before pentylenetetrazol (PTZ, 80 mg/kg of body weight, intraperitoneally). In the first four minutes after PTZ application, we recorded the appearance and latent period of forelimb dystonia (FLD), generalised clonic (GCC) and clonic–tonic convulsions (CTC).

Results: All convulsive patterns were evoked by PTZ. Pretreatment with SOD significantly influenced GCC and CTC, although in a different way. The latent period of GCC was shortened ($p = 0.03$), but the incidence was not changed. Opposite to GCC, CTC, defined as hind limb extension, did not appear in any rat, but in all of them we recorded front leg extension, with a shortened latent period than for hind limbs extension in PTZ-treated rats ($p = 0.02$).

Conclusion: In the applied experimental model, SOD action depended on the convulsive pattern. It deteriorated in the latent period for GCC, prevented CTC, but it evoked tonic extension of front limbs, a pattern that was not evoked by PTZ.

p291

ROLE OF SEX STEROID HORMONES IN THE REGULATION OF ABSENCE SEIZURES

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Purpose: A few recent studies have demonstrated that membrane effects of progestins are important in the regulation of typical absence seizures in humans and in rats. In an animal genetic model of absence epilepsy, acute injections of progesterone exacerbate the number of spontaneous spike-wave discharges (SWDs) in both male and female WAG/Rij rats (van Luijtelaar et al., *Epilpesy Res* 2001;46:225–239). However, in contrast to this, we found that chronic elevation of progesterone during pregnancy is accompanied by a decrease of SWDs during this period (Tolmacheva et al., *Physiol and Behav* 2004;81:623–627). In the present study we tested whether castration and ovariectomy, which eliminate the resource of gonadal steroids, would alter basal level of spike-wave activity.

Method: The present study was performed in castrated and sham-operated males and in ovariectomised and sham operated females of WAG/Rij rats equipped with permanent EEG electrodes. Castration, ovariectomy and sham operations were performed 2 weeks after implantation of electrodes. EEG recordings (4 hours) were made before and at 4th, 6th, 8th, 10th, 20th, 23th, and 35th day after the operation.

Results: The ANOVA showed a time effect in the dynamic of both the number and duration of SWDs for all groups of rats, but no difference between groups: either between castrated and sham operated male rats or between ovariectomised and sham-operated female rats.

Conclusion: The present results suggest that a decrease in plasma level of sex steroid hormones has no effect on the occurrence and duration of absence seizures in WAG/Rij rats in basal conditions.

p292

EPILEPTOGENESIS AFTER CORTICAL PHOTOTHROMBOTIC LESIONS IN RATS

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Purpose: To investigate the development of epilepsy after experimental photothrombotic stroke.

Method: Male Spraque-Dawley rats (n = 78) were included in the study. Lesions to the somatosensory cortex or the motor cortex were induced with intravenous injection of Rose Bengal dye and photoactivation. Sham-operation included only injection of the dye. Control rats had only electrode implantation. Epileptic seizures were monitored with video-electroencephalography 2, 4, 6, 8, and 10 months poststroke (24 h/d, 7–14 d). At the end memory was assessed with the Morris water-maze, and brains were processed to detect mossy fibre sprouting in the hippocampus.

Results: Epilepsy developed in 19% of the rats with lesions in the somatosensory cortex. Electrographic seizures were accompanied by bilateral forelimb clonus or rearing and falling. Mean daily seizure frequency was 0.22 ± 0.17 and seizure duration 104 ± 65 sec. Seizures were not detected after lesioning the motor cortex. Memory impairment was detected in rats with lesion in the somatosensory cortex ($p < .05$). Histological analysis revealed that the epileptic rats had increased mossy fibre sprouting in the hippocampus ($p < .01$).

Conclusion: Lesion to the somatosensory cortex results in epilepsy in a subpopulation of rats. The model provides a tool to investigate pathophysiological changes leading to poststroke epilepsy.

p293

NEUROPROTECTIVE EFFECT OF ZONISAMIDE ON HYPOXIC ISCHEMIC BRAIN INJURY IN NEONATAL RATS

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Purpose: The objective of this study was to determine the ability of a novel sodium channel blocking compound, zonisamide, to reduce neuronal damage by preventing the ischemia-associated accumulation of extracellular glutamate in postnatal day 7 Sprague-Dawley rats.

Method: The right common carotid artery of the rat was coagulated and then the rat was exposed to 8% oxygen for 2 hrs. Zonisamide (20, 50, 100, 200 mg/kg, every 12 hrs for 5 days) administered by intraperitoneal injection in pre- and posttreatment regimens, and controls received vehicle. Severity of injury was assessed 5 days later by visual evaluation of ipsilateral hemispheric infarction, and by measurement of bilateral hemispheric cross sectional areas.

Results: Zonisamide pretreatment resulted in a decreased incidence of liquefactive cerebral infarction ($p < 0.05$). Quantitation of hemispheric areas in rats receiving zonisamide and control littermates confirmed the results of initial inspection ($p < 0.01$).

Conclusion: Pretreatment with zonisamide decreases the incidence and severity of ischemic brain damage in this animal model of perinatal cerebral hypoxia ischemia. These data indicate that zonisamide plays a role in the evolution of hypoxic ischemic injury to the developing brain, and that zonisamide pretreatment may offer an effective means to decrease the incidence and severity of perinatal hypoxic ischemic brain injury.

p294

INFLUENCE OF 1.4-BENZODIAZEPINE DERIVATIVES ON SPONTANEOUS NEURONAL BURSTS OF HIPPOCAMPAL CA1 PYRAMIDAL CELLS

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Purpose: Synaptic networks are important for epileptiform activity (EpA) genesis, spreading and cessation. Hypersynchronisation of neuronal activity takes place without participation of action potential-dependent chemical synaptic transmission (low-Ca^{2+}/low-Mg^{2+}mediums). Using in vitro extracellular recording in area CA1 we characterised the antiepileptic properties of 1.4-benzodiazepine derivatives diazepam, gidazepam and cinazepam.

Method: Male Wistar rats were used for the experiments and slice preparations. After decapitation the rats' transverse slices were incubated at 32°C using aCSF. Other solutions lacking $Ca^{2+}$and Mg^{2+} ions were used. Populational responses were recorded by placing a tungsten microelectrode in the stratum pyramidale of the hippocampal CA1 field. The population spikes (PS) were bandpass filtered at 300 Hz before being digitised (PCI-6071E, National Instruments, USA) at 5 kHz sampling rate. Quantitative parameters of electrical activity (spikes amplitude, numbers, threshold of excitation etc) were analysed with a programme entirely written in LabVIEW.

Results: Perfusing of the slices with low-Ca^{2+}/low-Mg^{2+}aCSF induced self-excitation of pyramidal neurons (8–15/min, 3,5–5 mV) at 14–17 min of observation. Coinfusion with diazepam completely prevented and with gidazepam delayed the appearance of low-Ca^{2+}/low-Mg^{2+}EpA. Cinazepam administration statistically failed in spikes generation but decreased their frequency and amplitude.

Conclusion: Thus, in the model of spontaneous paroxysmal bursting activity induced by decreasing $Ca^{2+}$and Mg^{2+}contents we showed the importance of GABA mediated processes in epileptiform process in the CA1 region of rat hippocampal slices. A different profile of effects of 1.4-benzodiazepine derivatives was revealed. This model in vitro might be of great value for the potential antiepileptic substances efficacy investigation.

p295

COMPARISON OF ANTICONVULSANT EFFECT OF TWO DIFFERENT NONCOMPETITIVE NMDA RECEPTOR ANTAGONISTS IN IMMATURE RATS

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Purpose: To compare the anticonvulsant action of noncompetitive NMDA-receptor antagonists, memantine and ifenprodil.

Method: Cortical stimulation and registration electrodes were implanted to 12-, 18- and 25-day-old Wistar rats. Memantine (10 and 20 mg/kg) and ifenprodil (20 and 40 mg/kg) were administered i.p. Control siblings received saline. All individual groups were formed by 8 rats. Stimulation started 20 min after administration. Electrical stimulation of sensorimotor cortex was repeated with increasing current intensity (0.2–15 mA). EEG was recorded before and during stimulation, during the AD and 2 min afterwards. Behaviour of animals was marked into the recording. ADs duration and threshold current intensities for four different phenomena were evaluated.

Results: Memantine: Threshold intensity necessary for elicitation of movements accompanying stimulation was increased by the higher dose in 18- but decreased in 25-day-old rats. Threshold for spike-and-wave type of ADs was increased by the higher dose in 12- and 18-day-old rats whereas threshold for transition into the limbic type of ADs was increased only in 25-day-old rats. Both doses used led to shortening of ADs in all three age groups. Ifenprodil: Threshold intensities for movements and spike-and-wave ADs were not significantly changed. In contrast, ifenprodil decreased thresholds for transition into the limbic type of ADs in 18- and 25-day-old animals. Duration of ADs was not changed in 12-day-old rats but it was increased in both 18- and 25-day-old rats.

Conclusion: Memantine exhibited anticonvulsant action whereas ifenprodil mostly potentiated cortical epileptic afterdischarges in immature rats. Supported by research projects 305/06/1188 and AV0Z5011009.

p296

COMBINATION OF DELTA SLEEP-INDUCING PEPTIDE AND VALPROATE IN METAPHIT MODEL OF AUDIOGENIC SEIZURES IN RATS

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Purpose: Effects of delta sleep-inducing peptide (DSIP), a natural nona-peptide and valproate, a conventional antiepileptic drug on metaphit (1-[1-(3-isothiocyanatophenyl)-cyclohexyl]-piperidine)-induced audiogenic seizures as a model of generalised, reflex audiogenic epilepsy were studied.

Method: For that purpose, valproate in the dose of 50 or 75 mg/kg and DSIP (1.0 mg/kg) were i.p. injected either alone or in combination with DSIP (1 mg/kg,i.p.) to adult Wistar rat males with fully developed metaphit seizures after 8th audiogenic testing. The animals were stimulated using an electric bell (100 $\pm$ 3 dB and 5–8 kHz, for 60 s) 60 min after metaphit injection and afterwards at hourly intervals during the experiment. For power spectra and EEG recordings, three gold-plated screws were implanted into the scull.

Results: In metaphit-treated animals EEGs appeared as polyspikes, spike-wave complexes and sleep-like patterns, while the power spectra were increased comparing to the corresponding controls. Neither valproate nor DSIP given alone expressed significant effects on behavioural characteristics of metaphit-induced seizures. However, when given in combination, valproate and DSIP significantly decreased the incidence and intensity of seizures and prolonged the latency period for 6 h after administration. None of the applied dose combinations eliminated the EEG signs of metaphit-provoked epileptiform activity.

Conclusion: The results of the present study suggest that the combinations of valproate and DSIP could be considered as beneficial polytherapy in metaphit model of epilepsy.

p297

PROPHYLACTIC TREATMENT WITH VALPROATE AFTER STATUS EPILEPTICUS IN RATS PREVENTS HIPPOCAMPAL DAMAGE AND IMPROVES BEHAVIOUR BUT HAS NO EFFECT ON THE DEVELOPMENT OF EPILEPSY

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Purpose: The development of temporal lobe epilepsy (TLE) is often associated with an initial insult such as status epilepticus (SE). TLE is frequently accompanied by cognitive and behavioural alterations. An intriguing aim in the treatment of TLE is to prevent epileptogenesis after the initial insult or at least to modify this process in such a way that the developing epilepsy is easier to treat and without cognitive decline. One strategy to interfere with epileptogenesis is the prevention of the occurring neurodegeneration. We investigated the effect of prophylactic valproate (VPA) treatment on the development of spontaneous recurrent seizures (SRS), hippocampal sclerosis and cognitive and behavioural alterations in a TLE-model.

Method: Self-sustained SE was electrically induced in rats and was interrupted after 4 hours by diazepam. VPA (400 mg/kg i.p.) was administered immediately thereafter and was continued 3 times daily (200 mg/kg) for 4 weeks. Rats treated with saline after SE served as controls. Four weeks after drug treatment SRS were monitored by continuous video/EEG-recording for 1 week. Subsequently, the rats were tested in a battery of behavioural tests. Neurodegeneration was evaluated in the hippocampus in horizontal thionin stained sections.

Results: Prophylactic treatment with VPA prevented neurodegeneration in the hippocampus. Still, all rats developed SRS after the treatment was terminated but VPA-treated rats showed marked improvement in several behavioural paradigms compared to the vehicle-treated epileptic rats.

Conclusion: VPA seems to be a valuable tool to reduce neurodegeneration and behavioural alterations in a rat model for TLE but it does not prevent the development of epilepsy.

p298

IS ETHOSUXIMIDE INEFFECTIVE IN KINDLING PROCESS?

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Purpose: Ethosuximide (ETS), a first choice antiabsence drug, has no consistent efficacy for any convulsive type of epilepsy. In this study, we aimed to evaluate the effect of ethosuximide on epileptogenesis in a kindling model.

Method: In the experiments Wistar animals were instrumented stereotaxically with bilateral stimulation and recording electrodes into the basolateral amygdala and recording electrodes on the cortex. After one week recovery period, animals were injected intraperitoneally with physiological saline (control group, n = 7), ETS 50 mg/kg (n = 2) or ETS 100 mg/kg (n = 4) an hour before each electrical stimulation. Animals were electrically stimulated twice daily at their afterdischarge thresholds. The seizure severity was evaluated using Racine's 5-stage scale. Animals were considered as fully-kindled when they experienced five stage 5 seizures.

Results: All animals in the control group were fully kindled and the mean number of stimulations for the development of the first stage 5 seizure was 13 ± 0.6. Wistar rats treated with ETS (50 mg/kg) showed a similar rate and pattern of kindling with control group. ETS delayed the development of forelimb clonus in 100 mg/kg treated group. Two out of 4 Wistar rats in this group remained at stage 3 or 4 although 30 stimulations were applied. The mean number of stimulations for the development of the first stage 5 seizure in the remaining 2 animals was 25 ± 2.1.

Conclusion: Although ETS is considered as ineffective on convulsive seizures it may delay the development of convulsive seizures in a kindling model.

p299

NEUROPATHOLOGICAL CLASSIFICATION OF AMMON'S HORN SCLEROSIS

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Purpose: Histopathological investigation of hippocampal specimens obtained from patients with temporal lobe epilepsies shows different degrees of neuronal loss within hippocampal subfields and dentate gyrus. We employed cluster analysis to identify distinct pathological groups.

Method: We obtained 178 surgically resected hippocampal specimens. Neuronal cell counts per mm^2 were performed within hippocampal subfields CA1-CA4 and dentate gyrus using immunohistochemistry. These data provided a basis for cluster analysis. All clusters were correlated with clinical data.

Results: Cluster analysis revealed five pathological subgroups (clusters). A first cluster revealed neuronal densities within normal range (n = 34, 19%). Three clusters showed severe cell loss within hippocampal sector CA1 and different degrees of neuronal loss within the other anatomical subfields. We could separate CA1-sclerosis (n = 10, 6%) with moderate neuronal loss from classic hippocampal sclerosis (n = 33, 18%) with marked, and severe hippocampal sclerosis (n = 94, 53%) with extensive neuronal loss in all other segments. End folium sclerosis was defined by moderate loss within CA2-CA4 and dentate gyrus and neuronal cell densities nearly normal in CA1. Correlation with clinical parameters showed significant differences between age at fist event and distinct clusters: in classic and severe hippocampal sclerosis the first event occurred within the first three years of life, in CA1-sclerosis within six years and in end folium sclerosis and normal appearing hippocampus within 13 or 16 years, respectively ($p = 0.001$).

Conclusion: Cluster analysis identified five distinct grades of hippocampal pathology. CA1-sclerosis occurred as a new entity. Manifestation of the first event, respectively the developmental state at which the first event compromised brain maturation influences patterns of hippocampal pathology.

p300

ASTROCYTES MIGHT PLAY A ROLE IN EPILEPTOGENESIS

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Purpose: The pilocarpine model is used to study complex partial seizures with secondary generalisation. The astrogliosis is a prominent feature of epileptic foci, and may play a causal role in the development of seizures and the persistence of this epileptic disorder. Previous studies demonstrated that the rodent Proechimys guyannensis (PG) exhibits resistance to experimental models of epilepsy. The Wistar rats present long-lasting status epilepticus (SE), and spontaneous seizures and PG shows short-lasting SE, which did not evolve to the chronic phase. Thus, reactive astrogliosis was compared in PG and Wistar rats, submitted to the pilocarpine model of epilepsy.

Method: The brains of both species of rodents were removed 3 h after pilocarpine-induced SE. Immunohistochemistry (n = 3) and Western Blotting (n = 6) were performed to study the expression of glia fibrillary acid protein, (GFAP) in the hippocampal formation from both species of rodents. Both protocols were used in saline-treated animals and with 3h after SE onset.

Results: Show i) The saline-treated PG showed, by both experimental protocols, increased expression of GFAP, when compared with saline-treated Wistar rats ($^{*}p = 0.0123$); ii) When compared with their proper control, both species showed increased expression of hippocampal GFAP, after SE (PG $^{**}p = 0.00019$; Wistar $^{***}p = 4.29 \times 10^{-9}$). When both SE-groups were compared no difference was found.

Conclusion: Both species showed astrogliosis after SE onset but, as the expression of GFAP is already major in saline-treated PG animals, its increase is minor compared with those observed in Wistar rats, suggesting a possible function of gliosis in the epileptogenic process.

p301

HIPPOCAMPAL EXPRESSION OF KININ B2 RECEPTOR IN FEMALE RATS SUBMITTED TO THE PILOCARPINE MODEL OF EPILEPSY

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Purpose: Kinins, a class of polypeptides represented by bradykinin, kallidin, and their metabolites, acting via B1 and B2 receptors, have been related to inflammation, cytokines action, glutamate release and prostaglandin production. Several studies indicate that in the central nervous system and peripheral tissues, estrogen regulates the expression of the B2 receptor and reduces cytokine production and inflammatory responses. Accordingly, the present work aimed to investigate the expression of kinin B2 receptors in normal and neutered female rats, submitted to the pilocarpine model of epilepsy.

Method: The brains of Wistar adult females of rats in both groups were removed 6h, 12h, 5 days and 60 days after pilocarpine-induced status epilepticus and immunohistochemistry (n = 4) was performed to study the expression and distribution of kinin B2 receptor in the hippocampal formation.

Results: The results showed decreased immunoreactivity against B2 receptor in non-neutered rats during the acute and silent periods of this epilepsy model. In contrast, the immunoreactivity against B2 receptor

in neutered rats was increased during the acute and silent periods when compared with control neutered rats.

Conclusion: This study provides evidence that the expression of kinin B2 receptor in the hippocampus is modified in female rats during epileptogenesis and that the expression of this receptor is modulated by steroid hormones. Supported by FAPESP, CNPq, CAPES.

p302

TRANSGENIC MICE CARRYING APPSWE/PS1(DE9) MUTATIONS EXHIBIT EPILEPTIC SEIZURES

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Purpose: Alzheimer's disease (AD) increases the risk of epilepsy 9-fold (Hesdorffer et al., *Neurology* 1996;46(3):727-30) and is one of the most common underlying factors for epilepsy in the elderly. Occurrence of seizures is especially high in rare familial cases of AD with mutation in presenilins (Velez-Pardo et al., *Epilepsia* 2004;45(7):751-6). Until now there is no animal model for AD-related epilepsy.

Method: In the study we used 12 week old male mice, 21 APPswe/PS1(dE9) (Jankowsky et al., *Hum Mol Genet* 2004;13(2):159–70), and 9 nontransgenic littermates. A week before the recording all mice were implanted with chronic cortical electrodes. Mice were video-EEG monitored (Lähteinen et al., *Eur J Neurosci* 2002;15(4):721–34) for 2 weeks (24 h/day) to detect spontaneous seizures.

Results: Electrographic seizures were detected in 24% (5) of transgenic animals (duration 0.22 $\pm$ 0.02 SEM) and none of the controls. Interictal spiking activity was found in 43% (9) of transgenic mice but in no control mice. Epileptiform discharges were present in 48% (10) of transgenic and in 11% (1) nontransgenic mice.

Conclusion: APPswe/PS1(dE9) mice provide a promising model to study molecular mechanisms underlying AD-related epileptogenesis.

p303

GENERATION OF EPILEPTOID ACTIVITY IN THE ÑÀ1 HIPPOCAMPAL AREA UNDER THE ACTION OF EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

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Purpose: This work was aimed at the study of formation of field excitatory postsynaptic potentials (fEPSPs) and population spikes (PS) in the CA1 area of rat hippocampus with respect to glutamatergic synapses.

Method: Experimental series were performed on 400 μm-thick hippocampal slices from 4-week old rats. PS and fEPSPs in the CA1 area evoked by the first and second paired pulses (50 ms interval, 30–50 μA, 200 μs/phase) were recorded in series on 58 hippocampal slices from 18 young rats. Slices were perfused with $10^{-4}-10^{-10}$ M of ibotenic acid or $10^{-3}-10^{-10}$ M of kynurenic acid.

Results: Ibotenic acid in the concentration of $10^{-4}-10^{-10}$ M resulted in a simultaneous decrease of fEPSPs and PS amplitudes. Ibotenic acid in the toxic concentration of $10^{-4}-10^{-5}$ M completely inhibited responses after 90 sec of application. At concentration of $10^{-6}-10^{-10}$ M a progressive decrease of fEPSPs and PS amplitudes was achieved down to a level 30-50% to initial, where the amplitudes finally stabilised. Kynurenic acid in the $10^{-3}-10^{-10}$ M concentration resulted in the decrease of fEPSPs and PS amplitudes. At concentration of 10^{-3} M the toxic effect of full blockade of responses was observed. After application of 10^{-4}–10^{-7} M ibotenic or kynurenic acids (agonist and antagonist excitatory amino acid receptors) in the CA1 hippocampal area the convulsive activity not typical for this hippocampal area was found out.

Conclusion: Thus, this model of epileptoid activity in the CA1 area is supposed to be used for screening of new anticonvulsive drugs.

p304

LAMOTRIGINE (LTG) ENHANCES ENDOGENOUS ANTIEPILEPTIC PROCESSES IN THE SINGLE NEURON (BUCCAL GANGLIA, HELIX POMATIA)

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Purpose: Mechanisms of LTG in the nervous system are still poorly understood.

Method: Effects of LTG were studied in the buccal ganglia of *Helix pomatia* used as a model nervous system. Under in vitro conditions the buccal ganglia are structurally and functionally intact. Ganglia contain identified giant neurons. The snail nervous system corresponds in all epileptogenic aspects to a mammalian nervous system. Epileptiform activity (paroxysmal depolarisation shifts, PDS) was induced with bath application of pentylenetetrazol (1 mM to 40 mM). LTG (5 μM to 200 μM) was added to the solutions.

Results: Endogenous antiepileptic processes terminate "neuronal seizures" and block status epilepticus. Endogenous antiepileptic processes depend on $[Mg^{2+}]_o$ which could not be replaced by Sr^{2+}. LTG enhanced endogenous antiepileptic processes; its effects cannot be washed out. Pretreatment with LTG weakened subsequent epileptiform activity. LTG-effects survive LTG application for hours.

Conclusion: Slow commencement as well as lack of wash out of LTG-effects is not in agreement with direct effects of LTG by receptor binding. LTG appears to accelerate and enhance endogenous antiepileptic processes in the single neuron. Cell's natural defence was strengthened by Mg^{2+} and LTG.

p305

EFFECT OF ACUTE AND CHRONIC LIGHT/DARK CYCLE ALTERATION ON SEIZURE THRESHOLD IN MICE: MODULATION BY MELATONIN

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Purpose: Changes in seasonal and circadian rhythms have been shown to alter the anticonvulsant properties of various drugs. In this study, we investigated the effect of light/dark (LD) cycle alteration on pentylenetetrazol (PTZ)-induced clonic seizure threshold in male mice.

Method: In acute experiments, LD cycle of 2 groups (n = 6–7 for each group) of mice were changed from 12/12 to 8/16 or 16/8 LD cycles and seizure threshold was determined at zeitgeber time (ZT) = 4 of the next day. In chronic experiments, 3 distinct sets of mice were maintained on 12/12, 8/16 and 16/8 LD cycles for 2 weeks prior to testing.

Results: In acute experiment, mice maintained on a longer photoperiod showed a significant decrease (seizure threshold as mean $\pm$ SEM: 25.63 $\pm$ 0.88) in seizure threshold, while keeping animals under longer photoperiod (32.72 $\pm$ 0.89) did not produce a significant proconvulsant effect compared to animals under 12/12 LD cycle (32.41 $\pm$ 0.68). This proconvulsant effect was reversed by single i.p. administration of melatonin (10 mg/kg) at ZT = 10 on the first day. Chronic LD cycle alterations (both 8/16 and 16/8) decreased the seizure threshold significantly in comparison to animals under 12/12 LD cycle (26.69 $\pm$ 1.63, 26.57 $\pm$ 0.80, 34.52 $\pm$ 0.73 respectively). Chronic i.p. administration of melatonin (10 mg/kg) at ZT = 10 in these photoperiod groups reversed the effect of LD cycle alteration on seizure threshold.

Conclusion: These results suggest that both acute and chronic alteration of LD cycle may influence seizure susceptibility and this effect could be modulated by administration of exogenous melatonin.

p306

COMPARATIVE ANALYSIS OF TWO ANTIEPILEPTIC DRUGS IN DIFFERENT ANIMAL MODELS

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Purpose: Epilepsy is a widespread chronic brain disorder with different backgrounds. Introducing a new specific antiepileptic drug can improve life conditions of several patients. In a recent series of experiments we tested the efficacy of the sodium channel blocker lamotrigine

and the non-competitive NMDA receptor antagonist memantine in different epilepsy models.

Method: In in vitro cortical brain slice experiments the effect of lamotrigine or memantine on evoked field responses was tested. Slices were prepared from young, male Wistar rats and sensitised with different convulsants (4-aminopyridine, bicuculline-methiodide, Mg2±free solution). The efficacy of memantine was also investigated in immature rats (12, 18 and 25 days old) both with in vitro and in vivo methods. In slices the change of evoked field responses while, in freely moving rats with implanted electrodes the cortical epileptic discharges in the sensorymotor area were analysed.

Results: In the presence of the three convulsants a late component of evoked responses developed which was significantly reduced by lamotrigine. Memantine hardly affected the pattern of evoked responses either in the in vivo or in vitro models, however it suppressed cortical epileptic afterdischarges in all three age groups of rat pups studied.

Conclusion: Our data indicate that lamotrigine effectively blocks the overexcitation of different underlying mechanisms. Memantine has a weak inhibitory effect on overexcitation, however, strongly suppresses seizure activity.

p307

MATRIX METALLOPROTEINASE-9 INDUCES INTEGRIN-ASSOCIATED HIPPOCAMPAL CELL DEATH IN MICE WITH PILOCARPINE-INDUCED SEIZURE

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Purpose: Recent evidence has demonstrated that matrix metalloproteinase-9 (MMP-9) is activated and involved in neuronal cell death in response to excitotoxic stresses such as ischemia or seizure. However, the exact role of the MMP-9 in the seizure-related cell death remains to be elucidated. In this study, we investigated the role of MMP-9 in seizure-related hippocampal cell death, hypothesising that the activation of MMP-9 after seizure would induce cell death by interrupting integrin signaling.

Method: Seizures in C57BL/6 mice were induced by intraperitoneal pilocarpine injection. Hippocampal cell death was evaluated using cresyl violet staining and TdT-mediated UTP-biotin nick end labelling (TUNEL). The expression and activity of MMP-9 after a seizure were evaluated by zymography, Western blot analysis, and immunohistochemistry. Caspase-3 activity and integrin expression were also investigated. MMP-9 specific hydroxamic inhibitor was administered intracerebroventrically 3 hours after a seizure.

Results: The activity and expression of MMP-9 increased after a pilocarpine-induced seizure. TUNEL-positive cells and neuronal death were evident in the hippocampus 24 hours after a seizure. Caspase-3 activity was also increased, but the integrin level was markedly reduced after a seizure. MMP-9 specific inhibitor attenuated MMP-9 activity and hippocampal cell death. DNA fragmentation and caspase-3 activity were reduced also. Furthermore, the reduction of integrin expression after a seizure was alleviated by treatment of MMP-9 inhibitor.

Conclusion: Our results suggest MMP-9 may be associated with mice hippocampal cell death after pilocarpine-induced seizures, in part, through inhibition of integrin signalling.

p308

OXYGEN GLUCOSE DEPRIVATION (OGD) INDUCED TOLERANCE UP-REGULATES THE NOVEL NEUROPROTECTIVE PROTEIN, 697-27, IN RAT CORTICAL CULTURES

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Purpose: Ischemic preconditioning is a powerful phenomenon in which a sublethal stimulus provides protection against subsequent lethal stress; however, the exact mechanism of ischemic preconditioning in the brain is not known. Understanding the molecular mechanisms behind preconditioning could provide valuable information for drug design to prevent or repair tissue from cerebral ischemia or epileptic seizures.

Method: In this study we examined more precisely one of the novel cytoprotective genes that was found from OGD preconditioned rat cortical neurons using a functional screening strategy.

Results: The transcript of, 697-27, is $\sim$ 2.7 kb in length. Its protein encoding region results in a 303 aa protein, 34 kD in size. The C-terminal part of 697-27 possesses an ATPase domain belonging to the AAA+ protein family. 697-27 also has a longer transcript from its N-terminus resulting in a 40 kD protein. The full-length form of 697-27 protein has a putative transmembrane domain in the most N-terminal part. Northern blot reveals that 697-27 mRNA is expressed in a variety of organs studied including several brain regions. Our polyclonal C-terminal peptide antibody detects 697-27 protein from all the organs studied. OGD preconditioning up-regulates 697-27 protein as early as 1 hour after treatment and protein levels return back to the basal level at 72 hours. Transient transfection 697-27 protects rat cortical neurons against subsequent lethal OGD.

Conclusion: These findings suggest that 697-27 protein might play a crucial protective role in OGD preconditioning.

p309

PERSISTENT SUSCEPTIBILITY TO SEIZURES AFTER TRAUMATIC BRAIN INJURY

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Purpose: To examine long-term seizure susceptibility in rats with traumatic brain injury (TBI) with or without epilepsy.

Method: TBI was induced by lateral fluid-percussion injury to 30 rats (10 shams). Twelve months postinjury, rats with TBI were divided into nonepileptic and epileptic subgroups based on occurrence of spontaneous seizures in video-EEG monitoring. Seizure susceptibility was tested by injecting pentylenetetrazol (PTZ, 30 mg/kg, i.p.) and monitoring behavioural/electrographic responses for 1 h. Latency to the first epileptiform change in EEG, latency to the first behavioural/electrographic seizure, duration, and behavioural seizure severity were measured.

Results: PTZ produced seizures in 100% of rats with TBI with epilepsy, in 82% of rats with TBI without epilepsy, and in 73% of shams. Latency to the first change in EEG was the shortest in nonepileptic animals (1.9 ± 0.8 min) compared to epileptic rats (2.6 ± 2.6 min) and shams (3.5 ± 4.6 min), ($p > 0.05$). Latency to the first electrographic seizure differed between the epileptic rats, nonepileptic rats and shams (1.9 ± 0.8 vs 3.3 ± 1.8 vs 7.2 ± 6.0 minutes, respectively, $p < 0.05$). Post hoc analysis indicated a difference between the shams and both TBI groups ($p < 0.05$). In both TBI groups, latency to the first behavioural symptom was 30% of that in shams ($p < 0.01$, no difference between the TBI groups). Behavioural seizure score was the lowest in the TBI nonepileptic rats (3.3 ± 0.8) compared to epileptic rats (4.8 ± 0.4) or shams (5.0) ($p < 0.01$). Seizure duration did not differ between the groups.

Conclusion: Our data show that TBI results in chronic neuronal excitability also in rats without overt behavioural and electrographic spontaneous seizures.

p310

NEWLY ONSET CLUSTER SEIZURES CAUSED BY ORAL CONTRACEPTIVES: RELATED CEREBRAL VENOUS THROMBOSIS

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Purpose: Newly onset focal seizures with a history of pill taking are an important diagnostic clue for venous thrombosis.

Method: We evaluated two females with new onset cluster seizures and pills use.

Results: Case one is a 42-year-old female. First seizure attack presentation was right upper limb twitching evolving to 4 limbs twitching with impairment of consciousness. These episodes occurred three times.

Neurological signs revealed right upper limb weakness. The brain CT showed hyperintensity of superior sagittal sinus (SSS). She took pills for 3 years. Further brain MRI with MRV showed high density at the precentral gyrus of the left frontal lobe with poor visualisation of SSS. The homeostatic investigation revealed normal levels of protein C, protein S, antithrombin III and Leiden V. The seizure and the focal weakness improved after treatment. Case two is a 45-year-old woman. She experienced headache for three days followed by focal seizure of the left arm and leg. Focal seizure later evolved to generalised seizures two times. She took oral contraceptives for one month. Neurological examination showed left hemiparesis. Brain MRI revealed right side occipitoparietal high density. MRV showed disappearance of SSS. The weakness of limbs and consciousness were more downhill during heparinization. Three direct focal streptokinase injections were administered into the sinus for the thrombosis.

Conclusion: During the gestational age in women with newly onset seizures, oral contraceptive history is very important for the early diagnosis and prognosis for cluster seizures and cerebral venous thrombosis.

p311

PARALDEHYDE ADMINISTRATION DURING NONCONVULSIVE STATUS EPILEPTICUS IN YOUNG RATS MODIFIES ITS LATE CONSEQUENCES

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Purpose: To study delayed consequences of paraldehyde intervention during nonconvulsive status epilepticus (NCS) induced in immature rats.

Method: NCS was elicited by pilocarpine (40 mg/kg i.p.) in 25 day old rats pretreated with LiCl (3 meq/kg, i.p.). Paraldehyde (0.3 ml/kg i.p.) was administered after two hours of continuous NCS. Control groups received saline instead of paraldehyde or only saline instead of all drugs. Cortical stimulation and registration electrodes were implanted 2 months after NCS. After one week recovery cortical epileptic afterdischarges (ADs) were elicited by a 15-second series of low-frequency pulses. Intensity was increased stepwise from 0.2 to 15 mA, interval between stimulation series was 10 minutes. Threshold intensities for movements during stimulation, spike-and-wave ADs, clonic seizures, and transition to limbic (mixed) ADs and recurrent ADs as well as durations of spike-and-wave (SW) and mixed ADs were measured.

Results: Threshold for movements bound to stimulation was identical in the three groups. Higher stimulation intensities had to be applied to elicit SW ADs in paraldehyde-treated NCS rats than in saline control group. A significantly higher threshold for clonic seizures was found in NCS rats with paraldehyde in comparison with NCS rats without paraldehyde and saline controls. No differences were observed in thresholds for mixed and recurrent ADs. Duration of both SW and mixed ADs did not differ among the three groups.

Conclusion: Paraldehyde administration during NCS in 25 day old rats resulted in an increase of thresholds for SW ADs and accompanying clonic seizures in adulthood, i.e., the excitability of system generating this type of ADs was changed.

p312

MICROINFUSION OF γ-VINYL-GABA BUT NOT MUSCIMOL INTO THE ANTERIOR SUBSTANTIA NIGRA PARS RETICULATA EXERTS ROBUST ANTICONVULSANT EFFECTS IN MALE KINDLED RATS

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Purpose: The substantia nigra pars reticulata (SNr) is critically involved in seizure propagation in various models. Intranigral potentiation of GABA-mediated transmission has been shown to inhibit seizure spread in such models. While unconsidered in former studies, more recent observations emphasise that the effects on seizures are site-specific within the SNr and seem to depend on age, gender, strain, and seizure-model.

Method: In order to reevaluate former studies, we investigated the effects of bilateral microinfusions of γ-vinyl-GABA (GVG, vigabatrin, 10 μg) and muscimol (60 or 120 ng), respectively, in the anterior or posterior SNr of amygdala-kindled rats of different strain and gender. 24 hours (GVG) or 30 minutes (muscimol) after microinfusion, seizure parameters were determined in each rat.

Results: Compared to vehicle controls, GVG microinfused to the anterior SNr significantly increased the threshold for the induction of afterdischarges in the amygdala in male Spraque-Dawley rats. The seizure severity tended to be reduced in response to local GVG. Although not significantly different from controls, in 3 out of 6 animals a dramatic increase in the threshold for generalised seizures could be observed. However, muscimol failed to exert pronounced anticonvulsant effects independent of strain and gender.

Conclusion: The data extend previous findings that in kindled rats the anterior SNr is not a site at which muscimol causes robust anticonvulsant effects. However, using GVG, anticonvulsant effects could be observed, suggesting that increasing GABA-mediated neurotransmission in given pathways seems to be more important than increasing the overall $GABA_A$-receptor activity, at least in the kindling model of epilepsy.

p313

SUBTHRESHOLD CHANGES OF VOLTAGE-DEPENDENT ACTIVATION OF THE KV7.2 CHANNEL IN NEONATAL EPILEPSY

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Purpose: A benign familial neonatal convulsion (BFNC) is an autosomal dominant epileptic disorder resulting from mutations in *KCNQ2* and *KCNQ3*, encoding the potassium channels $K_V7.2$ and $K_V7.3$.

Method: We screened both genes in two unrelated BFNC families and performed functional studies using expression in *Xenopus* oocytes and two-microelectrode voltage clamping.

Results: We identified novel *KCNQ2* mutations in both families. In Family 1, the mutation c.740C>A was identified in the 5 affected family members. This mutation will generate a truncated protein (S247X) that lacks the channel's pore region and C-terminus. The mutation c.365C>T, predicting the amino acid substitution S122L in the S2 segment of $K_V7.2$, was observed in the 3 affected members of Family 2 and was not detected in 800 control chromosomes. Comparison of the biophysical properties of the mutant S122L channel with wild-type (WT) $K_V7.2$ revealed a significant positive shift in the voltage dependence of activation with an increased slope and a slowing of the activation time course. The shift was most pronounced in the subthreshold range of an action potential predicting a current reduction of 75% at –50 mV, which is likely to be the physiologically relevant voltage range for this noninactivating potassium channel to regulate neuronal firing.

Conclusion: These results establish an important role of the $K_V7.2$ S2 segment in voltage-dependent channel gating and suggest that subtle mutation-induced gating alterations restricted to the physiologically relevant subthreshold range can cause neonatal epilepsy.

p314

DEVELOPMENT OF HIPPOCAMPAL SCLEROSIS IN RATS EXPOSED TO IN UTERO IRRADIATION AND POSTNATAL HYPERTHERMIA

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Purpose: Hippocampal sclerosis (HS) is characterised by gliosis, neuronal loss and synaptic reorganisation in the hippocampus where pathophysiology remains obscure with several hypothesis. Clinical studies implied a relationship between HS and febrile seizures (FS) in early childhood. Experimental studies showed hyperthermia (HT) induced seizures are more easily elicited and have higher mortality accompanied by neuronal loss in rats with cortical dysplasia. The aim of this study is to investigate the role of HT induced FS in genesis of HS, applied during the maturation period of rats with irradiation (IR) induced cortical dysplasia.

Method: Three groups of rats were designed. 1) HT group; had FS induced by HT in postnatal 10th day. 2) IR group; were exposed to 225 cGy IR on the 17th gestational day. 3) HT-IR group; were exposed to both in utero IR then postnatal HT. Control group were sham operated. Three and 6 months after the experimental procedure, the animals were perfused with paraformaldehyde and glutaraldehyde. Forty μm cryostat sections were obtained from the hippocampus and then stained with cresyl violet and examined with the light microscope.

Results: No damage was seen in the HT group. The hippocampus was atrophic with neuronal loss (in CA1, CA3 and CA4 regions) and ectopic neurons in IR group. More severe damage in all regions with more atrophy was demonstrated in the HT-IR group. The control group had normal hippocampus.

Conclusion: This study supported the double hit hypothesis in development of HS as in utero IR and HT applied consequently caused more degeneration in the hippocampus than IR and HT alone.

p315

EFFECT OF LACOSAMIDE ON STRUCTURAL AND FUNCTIONAL RECOVERY AFTER TRAUMATIC BRAIN INJURY IN RATS

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Purpose: Traumatic brain injury (TBI) can result in early and late epileptic seizures that are treated with antiepileptic drugs (AEDs). Because treatment with AEDs occurs in parallel with the cerebral recovery process, it is important to show that AEDs do not compromise postinjury functional outcome. We evaluated the effects of a novel AED, lacosamide (LCM), on structural and functional recovery following TBI.

Method: Lateral fluid-percussion brain injury (FPBI) was induced in adult rats that were randomised to vehicle (FPBI-vehicle, $n = 12$) or lacosamide (FPBI-LCM, $n = 12$) treatments. Treatment was started 30 min postinjury (30 mg/kg, i.p.) and continued at 8 h intervals for 3 d. Sham-vehicle ($n = 8$) and sham-LCM ($n = 7$) served as nontraumatised controls. Motor function was evaluated using composite neuroscore and beam walking tests 1 d before FPBI and on days 2, 7, and 15 postinjury. Spatial learning was tested using Morris water-maze 12 d after FPBI. Hippocampal and cortical damage were assessed from magnetic resonance images (MRI) and histologic sections.

Results: At 2 d post-injury, lesion severity in MRI did not differ between FPBI-vehicle and FPBI-LCM groups. Also, no difference was found in the severity of cortical or hippocampal neuronal or axonal damage 15 d postinjury ($p > .05$). There were no differences in neuroscore or beam walking performance between FPBI-vehicle and FPBI-LCM groups (all time points, $p > .05$). Also, spatial learning did not differ between groups ($p > .05$).

Conclusion: Lacosamide treatment started 30 min postinjury at a dose of 3×30 mg/kg/d for 3 d did not compromise the structural or functional outcome after TBI.

p316

EPILEPTIFORM ACTIVITY IN THE HIPPOCAMPUS CAN BE EVOKED BY DISTURBANCE OF THE GABAergic INTRASEPTAL INTERRELATIONS

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Purpose: The medial septum region (MSR) is the major subcortical input to the hippocampus and theta oscillation generator, but its role in temporal lobe epilepsy is not clear. Investigations in this direction may provide a better understanding of seizure genesis mechanisms.

Method: Activity of inhibitory interneurons and EEG were recorded extracellularly in the CA3 field of the hippocampus in control and after intraseptal microinjection of bicuculline, the $GABA_A$ receptor antagonist (1 nM/1 μl). Neuronal activity was processed using the software for calculation of mean frequency, autocorrelation and spectral functions. EEG was converted by fast Fourier transform.

Results: Bicuculline delivery into MS led to sharp increasing of background activity of hippocampal interneurons (50.02 ± 19.1 versus 21.6 ± 7.6 imp/s in control, $p < .01$). Theta oscillations became more regular, mean frequency of theta bursts increased on 1 ± 0.3 Hz ($p < .05$). Delta component of neuronal activity also increased. Strong augmentation of both theta and delta bands and 13–15 Hz oscillations was observed in simultaneously recorded hippocampal EEG. Repeated daily bicuculline injections brought to periodical appearance of the expressed epileptiform activity, which was accompanied by anxiety of animal. Intraseptal infusion of $GABA_A$ receptor agonist muscimol (10–20 nM/1 μl) usually weakened an expression of epileptiform discharges. However, in the animals with steady pathological activity, injection of the muscimol could exert the opposite influence, increasing the expression of epileptical discharges and anxiety.

Conclusion: Thus, it has been revealed that $GABA_A$ receptors blockade in the MSR increases the oscillatory activity in the hippocampus and forms epileptic focus in it.

p317

SYNAPTIC LOCALISATION OF ADENOSINE A1 RECEPTORS IN THE RAT DENTATE GYRUS

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Purpose: Status epilepticus (SE) is a serious clinical condition, occurring when normal termination of a seizure is impaired. Adenosine, acting via A_1 receptors (A_1Rs) to inhibit neurotransmitter release or hyperpolarise neurons, has been shown to have anticonvulsant properties in several models of epilepsy and may be important in regulating the transition from self-terminating seizures to SE. In order to understand the underlying mechanisms, we investigated the expression of A_1Rs in the dentate gyrus (DG), the gateway to the seizure susceptible hippocampus.

Method: 50 μm horizontal slices containing the hippocampus and entorhinal cortex were prepared from paraformaldehyde fixed adult (6–8 weeks old) Wistar rat brains. Using immunohistochemistry and confocal microscopy we examined the cellular localisation of A_1Rs in the dentate gyrus and assessed colocalisation with the synaptic marker proteins synaptophysin and PSD-95.

Results: We have shown A_1Rs to be expressed abundantly in dentate granule cells and some hilar neurons. The expression pattern was punctate both at the cell body and in the molecular layer, suggesting dendritic as well as somatic expression. Some puncta of A_1R expression were shown to colocalise with those of presynaptic synaptophysin expression, whereas they did not colocalise with puncta of postsynaptic PSD-95 expression.

Conclusion: Our results indicate that adenosine released during seizures may exert an inhibitory influence in the DG by acting presynaptically to modulate glutamate release, thereby behaving as an endogenous anticonvulsant. Further studies aim to identify the nature of synapses expressing A_1Rs.

p318

3-NITROTYROSINE IS INCREASED IN RAT BRAIN 44 HOURS AFTER STATUS EPILEPTICUS

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Purpose: Many of the short- and long-term consequences of epilepsy may be due to excitotoxicity, of which protein nitrosylation is a central feature. Levels of 3-nitrotyrosine (3NT) are raised in other neurological diseases, and known to have key functional consequences. We set out to establish whether 3NT was also raised in the hippocampus following electrically induced status epilepticus (SE).

Method: Using the perforant path model of epilepsy, self-sustaining SE was induced for 3 hours, and terminated with diazepam. After 44 hours, the rats were decapitated under anaesthesia, the hippocampal subregions dissected on ice, and snap frozen. Sham controls underwent identical procedures, with the exception of electrical stimulation. 3NT was quantified using high performance liquid chromatography with electrochemical detection.

Results: Overall Hippocampal mean 3NT levels (expressed as a ratio to L-tyrosine) were higher in status animals ($5.26 \times 10^{-5} \pm 1.57 \times 10^{-5}$ SEM) compared with controls ($3.18 \times 10^{-5} \pm 0.68 \times 10^{-5}$ SEM). Subregional analysis demonstrated this difference was most marked in the dentate gyrus/hilar (DG/H) region (SE $7.97 \times 10^{-5} \pm 3.18 \times 10^{-5}$, sham $2.22 \times 10^{-5} \pm 0.63 \times 10^{-5}$), with no differences in the SE vs sham Ca1 or Ca3 regions.

Conclusion: This is the first study of 3NT in a model which avoids the use of potentially confounding chemoconvulsants, which confirms that as in other degenerative brain diseases, 3NT is significantly increased in rat brain following SE. That the change was most marked in the DG/H section is intriguing given the relative protection of the DG area following SE. Further studies are required to understand the functional localisation and consequences of this protein nitrosylation following SE.

p319

REVISED PHARMACOKINETIC PROFILE FOR A WIDELY USED NEUROTOXIN, METHYLAZOXYMETHANOL ACETATE: HOW SHORT IS A SHORT HALF LIFE?

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Purpose: Methylazoxymethanol (MAM) is widely employed to study as model of cortical dysplasia. MAM is believed to selectively affect neuroblasts and, owing to an extremely short half life (12 hrs) to have specific actions on developing neocortex. These properties are derived by indirect experimental evidence but were never truly studied. We now report pharmacokinetic results obtained after MAM exposure.

Method: Pregnant rats received 2 injections of MAM on day E15 at doses of 15 mg/Kg at 12 hour intervals. Maternal blood, foetal brain and liver MAM levels were measured by HPLC at 30' and12, 24, 36, 48 hours after exposure.

Results: MAM's half life in maternal blood and in foetal brain was around 32 hrs, or three times longer than previously assumed. The maximum concentration of MAM (75 uM) was well below the toxic concentrations used to ablate neuroblasts in vitro (>500 uM) but was significantly higher than the dosage capable of inhibiting angiogenesis in vitro and in vivo (<100 uM).

Conclusion: Our results demonstrate that MAM may exert persistent and perhaps non-neuronal effects in the foetal brain by virtue of its long lasting serum and brain levels. These findings warrant a reinterpretation of the commonly accepted pharmacokinetic and mechanistic details of its action. Supported by HL51614, NS43284, NS38195, and NS49514.

p320

EVALUATION OF NUMBER OF AXONS IN THE FORNIX IN MESIAL TEMPORAL LOBE EPILEPTIC AUTOPSIES USING ELECTRON MICROSCOPY

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Purpose: The aim of this study was to assess the number of fornical fibres in 4 mesial temporal lobe sclerosis (MTS) and 4 normal human autopsies.

Method: To evaluate the average number of fibres forming the fornix, cross sectional area, fibre density and the ratio of myelinated and unmyelinated fibres, light, electron microscopy and computer programs were used.

Results: Morphometric results showed that the number of fibres forming the left and right fornix in the nonepileptic autopsies was higher than autopsies with MTS. The average number of fibres forming the right fornix was higher than the left in both nonepileptic and MTS autopsies. A striking reduction in the average number of unmyelinated fibres was observed in MTS autopsies compared to nonepileptics. Electron microscopic evaluations showed degeneration of the myelinated fibres in MTS autopsies. The right and the left fornix of MTS autopsies showed reduction in the cross-sectional area, the reduction on the right was more striking. An increase in the average density of myelinated fibres for both right and left fornix in the MTS autopsies and a decrease in the average density of unmyelinated fibres were observed.

Conclusion: The neuronal loss observed in the dentate gyrus and the CA3 sector of the hippocampus in the present study, may result in Wallerian or transneuronal degeneration causing a decrease in the number of fornical fibres in the MTS autopsies. Further, the reduction of unmyelinated fibres in the MTS autopsies may play a role in the assessment of the MTS and other limbic system abnormalities.

p321

DIFFERENT EXPRESSION OF P-GLYCOPROTEIN IN PHENOBARBITAL AND LEVETIRACETAM TREATED MADIN-DARBY CANINE KIDNEY (MDCK) CELLS

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Purpose: Levetiracetam (LEV) is a new antiepileptic drug (AED) effective in reducing partial seizures. LEV has a unique mode of action that is, currently, incompletely characterised. This study investigated LEV's effects on the expression of P-glycoprotein (Pgp), a transmembrane protein of 170 kDa, MDR1 (or hABCB1) gene product, and used the AED phenobarbital (PB) as a control.

Method: Madin-Darby canine kidney (MDCK) cells were treated with LEV and PB at 30 and 300 μM for 72 hours. Drug-containing medium was replaced every 24 hours. Expression of Pgp was determined by Western blot analysis using a primary mouse monoclonal Pgp antibody. To verify the effects of the study drugs on cell viability, a tetrazolium salt assay (MTT) was performed.

Results: PB interfered with cell viability in a weakly significant manner (85% at 30 and 76% at 300 μM compared to the control MDCK cells ($p = 0.001$), and induced dose-dependent overexpression of Pgp (+50% at 30 and +53% at 300 μM). LEV had no effects on cell viability (93% at 30 and 92% at 300 μM) compared to the controls, and produced Pgp expression (alkaline DNA unwinding (ADU) $= 0.53 \pm 0.02$ and 0.53 ± 0.03 at 30 and 300 μM, respectively) almost similar (ADU $= 0.50 \pm 0.03$) to the controls.

Conclusion: LEV may be particularly useful in patients who are unresponsive to other AEDs. Further investigations are in progress using other cellular systems.

p322

PRECLINICAL PROFILE OF THE NOVEL ANTICONVULSANT LACOSAMIDE

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Purpose: Lacosamide, previously called harkoseride or SPM 927, belongs to a series of functionalised amino acids which have been

synthesised as a new class of anticonvulsant agents. A series of experiments was designed to describe its anticonvulsant profile and potential mode of action.

Method: Lacosamide was evaluated in standard rodent models for epilepsy as part of the antiepileptic drug development program by the NIH (White HS et al.. *Adv. Neurol* 1998;76:29-39.). In addition, lacosamide's effects on targets described for other antiepileptic drugs were assessed in radioligand binding and electrophysiological experiments. Finally, potential neuroprotective effects of lacosamide were measured in organotypic hippocampal slice cultures following exposure to oxygen glucose deprivation or glutamate.

Results: Lacosamide showed anticonvulsant activity in various rodent models for partial and generalised seizures in the dose range 1–20 mg/kg. In contrast, lacosamide was largely inactive against seizures induced by various chemoconvulsant agents such as picrotoxin or bicuculline. Radioligand binding experiments did not show binding to GABAergic or glutamatergic targets. Moreover, no modulation of calcium (N-, L-, P- and T-type) and potassium currents (A-type, delayed rectifier, KCNQ2/3) were observed. In addition, lacosamide did not affect fast inactivation of sodium channels–a mechanism shown by a variety of antiepileptic drugs. Finally, lacosamide displayed neuroprotective properties in hippocampal slice cultures.

Conclusion: In summary, the overall anticonvulsant profile of lacosamide in animal models for epilepsy appears to be broad and its mode of action unlike that of other AEDs but currently unknown.

Monday July 3, 2006
13:30–15:00
Poster Session 1
Genetics

p323
MILD PHENOTYPE IN TUBEROUS SCLEROSIS PATIENTS WITH CODON 905 MISSENSE MUTATIONS IN THE *TSC2* GENE

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Purpose: Tuberous sclerosis complex is an autosomal dominant disorder characterised by hamartomatous growth in various organs, and caused by mutations in the *TSC1* (9q34) or *TSC2* (16p13) genes. Overall, *TSC2* mutations have been associated with a more severe disease phenotype than *TSC1* mutations. We report the clinical and molecular features in16 families with *TSC2* mutations and mild phenotypes.

Method: We carried out a detailed study of the TSC phenotype and genotype in a large French-Canadian kindred (Family A). In addition, clinical and molecular data on 15 families with mutations at the same codon were collected. Functional studies were performed on three different missense mutations and related to the phenotypes.

Results: A 2714G > A (R905Q) missense mutation in exon 23 of *TSC2* was identified in 25 individuals in Family A. The TSC phenotype in this family was unusually mild, characterised mainly by depigmented skin lesions and by seizures that remitted spontaneously or that were easily controlled with antiepileptic drugs. Diagnostic criteria were met in only a minority of family members, delaying diagnosis. All other families with the R905Q mutation were found to have a similar mild phenotype. Patients with a 2713C > T (R905W) mutation or a 2713C > G (R905G) mutation had a more severe phenotype. In 3 different assays, the R905W and R905G substitutions had a more severe effect on tuberin function than the R905Q substitution.

Conclusion: We identified 16 families with codon 905 missense changes in *TSC2*. In the R905Q families, the TSC phenotype was unusually mild, consistent with the functional studies. Our findings support the observation that familial TSC is less severe than sporadic TSC, even when it is due to a *TSC2* mutation. Genotype-phenotype correlations indicate that mild TSC phenotypes may be associated with specific *TSC2* mutations.

p324
CHOREA-ACANTHOCYTOSIS (ChAc) IN FRENCH CANADIANS: FOUNDER EFFECT, SEIZURE CHARACTERISATION AND GENOTYPE-PHENOTYPE CORRELATIONS

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Purpose: To characterise the clinical and molecular findings in French Canadian (FC) families with chorea-acanthocytosis, and to determine genotype-phenotype correlations.

Method: We ascertained 12 affected individuals in four families. Detailed medical and family histories were obtained. EEG, video-telemetry, brain MRI with volumetric studies of the amygdala and hippocampus, as well as neuropsychological testing were performed. Blood smears were examined for acanthocytes, and CK levels were determined. Field trips in two families yielded over 175 blood samples for mutation analysis.

Results: All families originated from Quebec. There was parental consanguinity in 4 of 6 affected sibships, and probably in a fifth. Epilepsy was a prominent feature, although family members had very diverse clinical manifestations, including tics, chorea, psychosis and dementia. Seizures preceded the onset of movement disorders by up to 15 years. Most seizures were suggestive of mesial temporal onset. EEGs showed temporal or bitemporal epileptic discharges and seizure onsets. There was no evidence for hippocampal atrophy. Seven affected individuals were homozygous for a deletion including exons 70–73 of *VPS13A* and exons 6–7 of *GNA14* (EX70-EX73del). These patients shared a common haplotype in the same region. Two affected sisters were homozygous for a splice mutation 4242 + 1G > T, whereas their 2 male cousins were heterozygous for EX70-EX73del and 4242 + 1 G>T. Of 9 patients with the deletion, including 2 heterozygotes, 7 had epilepsy (77%). The 2 sisters with the splice mutation did not develop seizures.

Conclusion: The identification of a common 9q21 haplotype associated with EX70-EX73del in 4 apparently unrelated FC ChAc families implies a founder effect. Routine testing for EX70-EX73del in suspected ChAc cases may be worthwhile in this population. Genotype-phenotype correlation suggests that the deletion mutation is strongly associated with epilepsy.

p325
FUNCTIONAL POLYMORPHISM IN THE *SCN1A* GENE AND TREATMENT OF REFRACTORY EPILEPSY

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Purpose: Recently, a polymorphism in the voltage gated sodium channel gene *SCN1A* has been identified that presumably affects the alternative splicing of the gene. This SNP (rs3812718, A -> G) has been reported to be associated with dosages of prescribed antiepileptic drugs acting on this channel (carbamazepine and phenytoin) (Tate et al., 2005). The purpose of this study was to investigate the association of this SNP with treatment refractory focal epilepsy and with the dosages of prescribed carbamazepine.

Method: We genotyped 334 patients and 364 matched controls for the *SCN1A* gene rs3812718-SNP. Patients suffered from mesial temporal lobe epilepsy or cryptogenic focal epilepsies; 88% of them were considered treatment refractory. Genetic stratification between controls and patients was largely excluded by genotyping 11 unrelated control polymorphisms.

Results: We detected a significant overrepresentation of A alleles (59.1% vs 51.2%) and AA genotypes (33.8% vs 27.2%) amongst patients in comparison to controls (allelic and genotypic tests, uncorrected $p = 0.003$). However, there was no significant difference in the average carbamazepine dose between the three genotype groups (AA, AG, and GG, ANOVA: $p = 0.26$).

Conclusion: The significant association between the rs3812718-SNP with largely treatment refractory epilepsy supports the notion that genetic variations in the *SCN1A* gene may underlie an individual's susceptibility to epilepsy and/or may influence the severity of the condition.

p326

CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES OF ITALIAN NEURONAL CEROID LIPOFUSCINOSIS PATIENTS WITH *CLN8* MUTATIONS

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Purpose: Neuronal ceroid lipofuscinoses (NCLs) are neurodegenerative disorders characterised by epilepsy, visual failure, psychomotor deterioration and accumulation of autofluorescent lipopigment. Six NCLs genes have been identified so far. *CLN8* mutations result in Northern Epilepsy and Turkish variant late infantile NCL (v-LINCL). We describe the clinical and neurophysiological findings of 3 Italian patients carrying *CNL8* mutations.

Method: Three patients from southern Italy underwent neurological examinations, EEG, MRI and skin biopsy. Genetic analysis showed *CLN8* mutations in all cases.

Results: Psychomotor regression was the first manifestation. Unsteady gait and epilepsy appeared within the first years of life, with myoclonic, tonic–clonic and atypical absence seizures. EEGs showed focal and/or generalised abnormalities and progressive signal deterioration. In all cases, cortical blindness and progressive attenuation of the electroretinogram were observed. MRIs showed progressive cerebral and cerebellar atrophy, thinning of corpus callosum and deep white matter hyperintensity. In all cases hyperintensity of the posterior limb of internal capsules was also evident. Skin biopsy revealed storage in the cytoplasm of fibroblasts. Epilepsy was drug-resistant with valproate and clonazepam giving some benefit.

Conclusion: The clinical picture of our patients closely resembles the phenotype of the Turkish patients whereas it clearly differs from Northern Epilepsy showing a more prolonged course and lacking myoclonus and visual loss. The identification of different *CLN8* mutations in a subset of Italian v-LINCL patients would suggest that the present phenotype is that commonly associated to *CLN8* mutations. The definition of the clinical spectrum of this condition will help its recognition with implications for the diagnosis and genetic counselling.

p327

MAPPING OF CHROMOSOMAL BREAKPOINTS ASSOCIATED WITH CORPUS CALLOSUM AGENESIS AND EPILEPSY: A BYPASS FOR ISOLATION OF CANDIDATE DISEASE GENES

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Purpose: Agenesis of corpus callosum (ACC) is a congenital anomaly that can manifest as partial agenesis, hypoplasia across the entire structure, or complete agenesis. To date ACC has been found to occur in over 50 different human congenital syndromes, but the nonsyndromic forms are more common. In the majority of the nonsyndromic forms the underlying gene defects are unknown. Here we present a case of an 11-year-old girl with a de novo balanced translocation t(2;11) (p25.1; p15.1) and mental retardation, epilepsy and partial agenesis of corpus callosum.

Method: Cytogenetic analysis was conducted on G-banded metaphases of cultured peripheral lymphocytes. Translocation breakpoints were mapped by fluorescence in situ hybridisation (FISH) using bacterial artificial chromosomes (BACs) from the regions of interest. DNA samples were prepared according to standard protocols.

Results: By G-banding of chromosomes from peripheral lymphocytes, a balanced translocation t(2; 11)(p25.1; p15.1) de novo was identified. The breakpoint on chromosome 2p25 is mapped within a 200 kb region and the 11p15 breakpoint disrupts an evolutionary conserved gene empty region.

Conclusion: The present case reports a balanced translocation in a patient with epilepsy and partial corpus callosum agenesis. This study may add new genes and regulatory mechanisms to the current list of candidate loci involved in epilepsy and corpus callosum agenesis.

p328

READING EPILEPSY AND PARTIAL DUPLICATION OF CHROMOSOME 18: A NEW SYNDROME?

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Purpose: A 20-year-old man was admitted to the neurology unit after a focal seizure, involving facial and perioral area, started during a reading activity, executed with a loud voice. This type of seizure was the third in his life, with the same characteristics and mode of starting. Therefore, the diagnosis of reading epilepsy was performed on clinical bases. The neurological examination was normal, a neuropsychological test showed mild attentional and behavioural problems, an electroencephalogram (EEG) performed during a prolonged lecture showed no pathological findings, but a mild facial dysmorphia, with large low-positioned ears and hypertelorism, was evident: in his family both his 31-year-old brother and his 30-year-old sister showed the same facial features and mild cognitive deficits but they did not report an epilepsy history. Nevertheless, they showed EEG focal bitemporal sharp potentials.

Method: The patient and his family we given a prolonged EEG according to 10–20 International System, neuropsychological tests, and a cell culture (cultural test) for karyotype examination (GIEMSA standard; GAG; GTG) with standard and molecular cytogenetic analysis were performed.

Results: The karyotype study revealed a duplication 18q segregated from the mother to her 3 sons. Standard and molecular cytogenetic analysis revealed the presence of two cell lines in the mother and her karyotype has been interpreted as: mos46,XX,dup(18)(q21.3q22.2)[90]/46,XX[10]. Instead, the karyotype

of the 3 sons was homogeneous: 46,XY,dup(18)(q21.3q22.2) mat for the 2 males and 46,XX,dup(18)(q21.3q22.2)mat for the female.

Conclusion: For the first time, a chromosomal defect has been identified in a patient with reading epilepsy. This could be only a casual association, but the presence of focal EEG alterations in other members of the family appears very intriguing. The hypothesis of a new syndromic complex could be put forward: partial duplication of chromosome 18q, cortical hyperexcitability (in our patient expressed as reading epilepsy), mild cognitive deficits and mild dysmorphic features.

p329
TUBEROUS SCLEROSIS COMPLEX: ATYPICAL FAMILY PRESENTATION

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Purpose: Tuberous sclerosis complex (TSC) is a genetic disease with a wide clinical spectrum even within the same family. We describe a three-generation Italian family with multiple cortical dysplasias in 5 members, suggestive of a TSC phenotype restricted to the brain.

Method: The proband II:1, both parents I:1-I:2, the sister II:2, the son III:1 and the two sister's children III:2 and III:3 were investigated for signs and symptoms in the major organs involved in TSC by imaging (brain, kidneys, thorax), neurophysiological recordings, heart-skin-fundus oculi evaluation, and mutation analysis of *TSC1* and *TSC2* genes.

Results: Originally, the proband came to our attention after 8 years of epilepsy seizures; MRI showed multiple cortical tubers without any other sign of TSC. Later on, due to onset of neurological symptoms in the son, the sister and the first sister's son, the full TSC evaluation was extended to 7 family members. No signs were found in skin, heart, kidneys and fundus oculi of any subjects. Clinically, II:2 and III:1 had partial epilepsy seizures. I:2, II:2, III:1 and III:2 showed cortical tubers on MRI. The thorax CT scan showed a diffuse pulmonary fibrosis in II:2. The genetic test revealed a variant never described before in *TSC2* (c.1922G > T; p.461 Ser > Ile) in all 5 subjects with pathological MRI and in the youngest (35-months-old) III:3 with normal MRI.

Conclusion: If the pathogenicity of the *TSC2* variant will be confirmed by functional tests, these data suggest that aminoacid changes might account for organ- or tissue-specific phenotypes not fulfilling the current TSC diagnostic criteria.

p330
TEMPORAL LOBE EPILEPSY AND SOMATOSENSORY AURAS

V. Fedotov (Kharkov Medical University, Ukraine)

Purpose: To determine the prevalence, manifestations, lateralising value, and surgical prognostic value of somatosensory auras (SSAs) in patients with refractory temporal lobe epilepsy (TLE).

Method: Thirty-two consecutive patients undergoing temporal lobectomy for refractory complex-partial seizures were screened for SSAs. The characteristics of the somatosensory phenomena, occurrence of other aura types, seizure semiology, findings of EEG and imaging studies, temporal lobe neuropathology, and postoperative seizure outcome were determined in each patient with SSAs.

Results: Nineteen (17.1%) of 111 patients with refractory temporal lobe seizures reported distinct SSAs as part of their habitual seizures. The most common manifestation of SSAs was tingling (16 of 19), but sensory loss (2 of 19) and pain (1 of 19) also were reported. Eight patients had unilateral somatosensory symptoms, and 5 patients had bilateral somatosensory symptoms. Seizure origin was in the contralateral temporal lobe in 6 of 8 patients with unilateral SSAs, including all patients with unilateral SSAs affecting a limb. Partial temporal lobe resection produced complete seizure remission in all patients 2 years after surgery and in 5 patients 3 years after surgery.

Conclusion: SSAs occur more frequently than previously appreciated in patients with refractory temporal lobe seizures and usually manifest as either unilateral or bilateral tingling. In patients with temporal lobe seizures, unilateral SSAs involving a limb suggest a seizure origin in the contralateral temporal lobe. The surgical outcome of TLE patients with SSAs is favourable. Thus the presence of SSAs should not serve as a deterrent to temporal lobe resection in patients with clearly defined TLE.

p331
POLYMORPHIC VARIATION IN GENES ENCODING METABOLISING ENZYMES FOR CARBAMAZEPINE: ALLELE AND GENOTYPE FREQUENCIES IN A WEST OF SCOTLAND EPILEPSY POPULATION

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Purpose: The pharmacokinetics of carbamazepine (CBZ) exhibit significant interindividual variability. CBZ undergoes extensive biotransformation by the drug metabolising enzymes (DMEs), CYP3A4, CYP3A5, CYP1A2 and microsomal epoxide hydrolase (EPHX1). Genes encoding these enzymes show polymorphic variation. To understand the relative contribution of polymorphisms to variability in CBZ pharmacokinetics, we first investigated common genetic variants of DMEs involved in CBZ metabolism.

Method: Four hundred epilepsy patients from across the West of Scotland (201 male; median age 40 years, range 18–84 years) were included in this analysis. DNA was extracted from venous blood and common genetic variants in *CYP3A4*, *CYP3A5*, *CYP1A2*, and *EPHX1* identified by either conventional polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) or direct sequencing.

Results: All genotype frequencies were consistent with Hardy-Weinberg equilibrium ($p > 0.10$). The variant allele and genotype frequencies were similar to published data for Caucasian populations, with minor allele frequencies ranging from 3.5% *CYP3A4*1B*) to 31.1% (*EPHX1 337C*). Association between variant markers was demonstrated for *CYP3A4*1B* and *CYP3A5*3* alleles ($p < 0.001$), but not between the common 337T>C and 416A>G polymorphisms in *EPHX1* ($p = 0.087$).

Conclusion: This study indicates that the West of Scotland epilepsy population has a relatively stable genotype frequency distribution and one that is consistent with other Caucasian populations. The implications of the apparent coexpression of CYP3A4*1B and CYP3A5*3 alleles are not immediately clear but this phenomenon does not appear to extend to common genetic variants in the *EPHX1* gene. These results are being used in an ongoing investigation of CBZ pharmacogenetics.

p332
EPILEPTIC SEIZURES AS MAIN SYMPTOM IN A MALE PATIENT WITH A HETEROPLASMIC 7.4 KB mtDNA DELETION

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Purpose: Although epileptic seizures are frequently reported in patients with mtDNA point mutations, they usually do not dominate the phenotype of syndromes due to mtDNA deletions. We present a male with an mtDNA deletion and epileptic seizures as prominent phenotypical feature.

Method: Case report

Results: Male, born 1950 with partial seizures and sometimes myoclonic jerks since 1960, seizure freedom since 2000 under antiepileptic polytherapy with oxcarbazepine, primidone and clobazam, normal MRI, mild left frontotemporal neuropsychological signs. Repeatedly observed slight increases of creatine kinase without clinical signs of myopathy led to an EMG which showed only mild neurogenic changes. An ophthalmological examination including VEP and perimetry because of increasing visual disturbances since 2001 disclosed optic nerve atrophy without ocular movement disorders. After exclusion of an autoimmune disease an extended analysis of mtDNA in blood cells demonstrated a homoplasmic polymorphism (T9582C) which was also found in his two asymptomatic brothers. Finally in mtDNA of a muscle biopsy which otherwise showed only mild neurogenic changes, no ragged red fibres and normal oxphos activity a heteroplasmic 7.4 kb deletion going beyond the Kearns-Sayr deletion was found.

Conclusion: mtDNA deletions can be associated with epileptic seizures as a leading symptom. Thus, patients with epilepsy and an aetiology remaining unknown after a routine diagnostic programme should be closely checked for mitochondrial signs and, if positive, molecular genetic tests, if necessary in different tissues, should be performed.

p333
UNCOMMON RELATIONS OF DISTINCT GENETIC DISORDERS WITH EPILEPSY
T. Mayer (Saxonian Epilepsy Center, Radeberg, Germany)

Purpose: In some chromosomal disorders (e.g., trisomy 21, Angelman syndrome) epilepsy is quite frequent (1). We investigated 3 patients with different genetic syndromes, in which epilepsy is uncommon.

Method: Three case reports describe the correlation of epilepsy in aberrations of chromosome 22 (n = 2) and in Klinefelter syndrome.

Results: T.A. 9.4-year-old, suffered from Catch syndrome (22q11 deletion) with ventricle septum defect, persistent Ductus Botalli, stenosis of the larynx and hyperbilirubinaemia. After 2 febrile convulsions in early childhood 2 afebrile generalised tonic–clonic seizures happened at the age of 9. Her MR scan showed heterotopias in both hemispheres, the EEG-recording focal slowing right temporal. S.O., 10.7-year-old, had first atonic seizures at the age of 7 months with good response to valproic acid. Due to developmental delay intensive diagnostic investigations showed a trisomy 22. Aetiology of the epilepsy may be seen in small white matter lesions in the frontal cortex (MRT). EEG-recording presented focal slowing in the right hemisphere. At the age of 7.1 years seizures reappeared as hemi-grand mal on the right side, with a frequency of 2–3 seizures a month. Since the age of 9.9 she is now seizure-free with valproic acid and levetiracetam. J.L., now 2.5 years old, suffered from Klinefelter syndrome (49, XXXXY, male) with typical clinical signs: Dandy Walker syndrome, hydrocephalus internus, anomalia of the genitals, facial dysmorphia and strong developmental delay. Epilepsy started at the age of 1.3 with clonic seizures of the left face, spreading to the left side of the body without the patient losing consciousness. Some of these seizures lasted 30 minutes and had to be stopped with diazepam. All seizures happened during sleep. Carbamazepine remained without any effect (160 mg/d). The EEG during the first contact in our outpatient clinic showed typical rolandic sharp waves right central and central. With sulthiame (75 mg/d) he has now been seizure-free for 6 months.

Conclusion: Epilepsy may occur in abnormalities of chromosome 22 (2, 3). Furthermore, it is known that the first time rolandic epilepsy was diagnosed was in Klinefelter syndrome, which may be accidental, but it may be helpful to find out the gene of rolandic epilepsy.

p334
BENIGN FAMILIAL NEONATAL CONVULSIONS: CLINICAL AND GENETIC ANALYSIS IN SEVEN DUTCH FAMILIES
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Purpose: To study the yield and spectrum of mutation analysis of the *KCNQ2* gene (20q13.3) in Dutch benign familial neonatal convulsions (BFNC), and the phenotypic expression regarding late onset epilepsy and mental retardation.

Method: Clinical data were obtained from 7 families. Sequence analysis of the *KCNQ2* gene was performed in all, including linkage analysis in 1 family.

Results: Four different mutations were detected; 1 nonsense mutation (c.1756C>T, p.Gln586Stop), 1 missense mutation (c.1076C > A, p.Thr359Lys) and 2 frameshifts (c.1229delC, p.Pro410fs; c.1601delC, p.Pro534fs). The smallest family had only 2 affected members and a de novo mutation was demonstrated in the affected parent. In the family with the 1229delC-mutation, epilepsy after the neonatal period was reported, but was not cosegregating with the mutation. In a fifth large family, linkage analysis was compatible with the 20q13.3-locus. *KCNQ2* analysis did not reveal a mutation, but gave some indication for a large deletion. Two out of 10 subjects with BFNC in this family had subsequent epilepsy and 1 of them mental retardation. Several other family members also had mental retardation and epilepsy, but clinical and DNA data on BFNC-status were not available.

Conclusion: Five different mutations in the *KCNQ2* gene were detected in 7 families with BFNC (71%). Mutation analysis should include testing for large deletions. Small families or sporadic patients may also benefit since they may represent new or recent mutations. The diagnostic results helped to avoid other expensive and stressing diagnostic procedures in affected newborn relatives, but cannot reliably predict the occurrence of late onset epilepsy.

p335
SEGMENTAL ANEUPLOIDIES IN PATIENTS WITH EPILEPSY OF UNKNOWN ETIOLOGY DETECTED BY ARRAY-CGH
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Purpose: Epilepsy and epileptic EEG abnormalities are common symptoms and signs of specific chromosomal abnormalities. The objective of this study was to determine the value of array-CGH in patients with epileptic disorders and to evaluate the use of a clinical checklist in preselecting patients.

Method: In a cohort of 675 pediatric patients that underwent an EEG-examination at the University Medical Centre Utrecht, 35 patients were selected for analysis by array-CGH. Inclusion criteria were refractory epilepsy of unknown etiology, mental retardation and at least one of the items described in the 5-item checklist developed by de Vries et al. (*J Med Genet* 2001;38;145–150). Array-CGH was applied to the first 16 patients with scores ranging from 1–5 items.

Results: Four out of 16 (25%) patients analyzed by array-CGH showed segmental aneuploidies, including duplications involving chromosomes 9 and 16, and combinations of deletions and duplications involving chromosomes 3 and 4. Two of those aberrations were found in patients with a normal karyotype. All four patients had a score 4 on the clinical checklist, whereas no abnormalities were found in patients scoring 3.

Conclusion: We demonstrate the added value of array-CGH by detection of submicroscopic segmental aneuploidies in patients with epilepsy of unknown etiology. This study shows that a clinical checklist is useful in preselecting candidate patients with epilepsy for analysis by array-CGH. Early recognition of chromosomal abnormalities might prevent patients from undergoing unnecessary diagnostic investigations and is important for genetic counseling. Array-CGH may also contribute to more refined mapping of genes involved in epilepsy.

p336
PHARMACOGENETICS OF ABCB1 AND BRAIN KINETICS OF 99m-Tc-MIBI IN EPILEPSY PATIENTS
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Purpose: ABCB1 expression is associated to antiepileptic treatment sensitivity, and two single nucleotide polymorphisms (SNPs) in exon 26 (C3435T) and exon 21 (G2677T) predict for ABCB1 gene expression. Moreover, ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI), an ABCB1 substrate, can be used to investigate the transporter activity in vivo by means of brain scintigraphy. Therefore, the present study was aimed at evaluating epilepsy patients' response to treatment, their ABCB1 genotype and the pattern of brain ^{99m}Tc-methoxyisobutylisonitrile kinetics.

Method: Genomic DNA from 50 consecutive patients with partial seizures was analysed for C3435T and G2677T SNPs by polymerase chain reaction-restriction fragment length polymorphism assay. Within

this population, 16 patients, divided into 2 groups with high (n = 6) and low (n = 10) seizure frequency respectively (cut >4 seizures/month), underwent a brain scintigraphy with ^{99m}Tc-MIBIoff.

Results: Among 37 subjects responsive to antiepileptic treatment, 10% had a TT/TT genotype (exons 21 and 26, respectively), 45% were GT/CT, but nobody was GG/CC. On the contrary, 61% of 13 pharmacoresistant patients was GG/CC, but none of them was TT/TT. Early ^{99m}Tc-MIBI uptake was significantly lower ($p < 0.05$) in the high seizure frequency group than in the low frequency group, especially when GT/CT heterozygous patients were considered ($p < 0.01$).

Conclusion: Pharmacogenetic analysis allows detection of a correlation between clinical response to antiepileptics and patients' genotype. A reduced early uptake of ^{99m}Tc-MIBI was detected in epilepsy patients with clinically unfavourable prognostic factors.

p337

PIPECOLIC ACID CONCENTRATIONS AND MOLECULAR ANALYSIS OF THE ANTIQUITIN (*ALDH7 A1*) GENE IN PATIENTS WITH PYRIDOXINE-DEPENDENT EPILEPSY

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Purpose: Following the description of elevated pipecolic acid (PA) as a diagnostic marker of pyridoxine dependent epilepsy (Plecko B. et al.. *Annals of Neurology* 2000;48:121–125, *Neuropediatrics* 2005;36: 200–205), the molecular background has been identified by mutations of the antiquitin (*ALDH7 A1*) gene on chromosome 5q31 (Ph. Mills et al., *Nature Medicine* in press). We report on biochemical and molecular findings of 14 patients with probable or definite pyridoxine-dependent epilepsy.

Method: Following parental consent, 1 ml of plasma and 5 ml of EDTA blood were collected while on pyridoxine-HCl. PA was determined by GCMS. Mutation analysis of the *ALDH7 A1* gene was performed by direct sequencing of all 18 exons and flanking introns. Detected mutations were confirmed by restriction fragment polymorphism analysis.

Results: We were able to detect homozygous or compound heterozygous mutations in 8 patients, while in 3 patients only one mutation and in 3 patients no mutation of the *ALDH7 A1* gene have yet been identified. We found elevated PA (3.4–16.8 μmol/l, normal <2.46) in all patients with mutations on both alleles and in 2 patients with one mutation identified. PA in plasma was normal in 3 patients with no mutation identified and in 1 heterozygote, while her affected sibling did not carry the mutation.

Conclusion: With respect to limited data, PA in plasma seems to be a reliable marker of pyridoxine-dependent epilepsy caused by mutations of the *ALDH7 A1* gene. Molecular analysis of the *ALDH7 A1* gene enables prenatal diagnosis in forthcoming pregnancies.

p338

FUNCTIONAL ASSOCIATION OF THE $GABA_A$ RECEPTOR BETA3 SUBUNIT GENE PROMOTER WITH CHILDHOOD ABSENCE EPILEPSY

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Purpose: Childhood absence epilepsy (CAE) is considered to be a genetic disease, but the genes responsible have not yet been identified. In a previous study of our group, association between the $GABA_A$ receptor beta3 subunit gene (*GABRB3*) and 48 CAE cases was found (Feucht M et al., *Biol Psychiatry* 1999;46:997–1002). Subsequently, we identified several SNPs (single nucleotide polymorphisms) in the *GABRB3* gene sequence. In the present work, we performed an associated study with haplotypes of the *GABRB3* gene and we examined the transcriptional activity of the promoter haplotypes using a luciferase reporter assay.

Method: Haplotypes were determined by cloning and sequencing of the respective DNA fragments and tag-SNPs were genotyped in 45 CAE core families. Further, exon1a promoter haplotypes were cloned in front of the reporter gene luciferase. These constructs were transfected into human NT-2 cells and luciferase activity was measured.

Results: Four haplotypes were defined and a subsequent association study showed significant association ($p = 0.007075$) between the *GABRB3* gene and CAE. We further verified that the promoter haplotype2 associated with CAE has a significantly lower activity in an in vitro luciferase expression assay compared with those haplotypes overrepresented in controls. In silico analyses of the GABRB3 exon1a region suggested that haplotype2 differs in putative transcription factor binding sites. Currently, electromobility shift assays are performed to confirm these results, which will be presented.

Conclusion: These data suggest a role for the exon1a promoter haplotype2 in the pathogenesis of CAE. Supported by the Jubiläumsfonds of the Austrian National Bank.

p339

MUTATIONS IN THE *EFHC1* GENE ARE FREQUENT IN FAMILIAL IDIOPATHIC EPILEPSIES

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Purpose: Previously on chromosome 6p12-p11, a region associated with juvenile myoclonic epilepsy (JME), a gene called *EFHC1* (EF-hand domain C-terminal containing 1) was described. This gene encodes a protein which is supposed to induce apoptosis. Mutation analysis identified five missense mutations in this gene in families with JME. In experimental studies these newly described mutations were shown to lower significantly the apoptotic activity of *EFHC1* and therefore might lead to increased density of neurons and hyperexcitable circuits. To confirm this finding in our patient sample we screened 96 patients with idiopathic generalised epilepsy (IGE) and temporal lobe epilepsy (TLE).

Method: We screened the entire open reading frame of the *EFHC1* gene consisting of 11 exons by direct sequencing 61 patients with IGE, 28 with a positive family history for seizures, and 35 with TLE with a positive family history for seizures (FH-TLE). Possible pathogenic variations were tested in a further sample of 300 patients with sporadic TLE and 368 control individuals.

Results: We identified three heterozygous mutations, all resulting in amino acid substitutions (I174V, C759Y, A394S). None of those could be detected in controls and have been described previously. Interestingly the I174V mutation was found in 2 patients, 1 with juvenile absence epilepsy (JAE) and the other with TLE. Haplotype analysis suggested that this is not due to a common founder, but is generated by recurrent mutational events. The other described mutations were both found in patients with IGE.

Conclusion: We describe three new heterozygous mutations in a newly described gene called *EFHC1* in patients with different epilepsy syndromes. These data suggest an important contribution of the *EFHC1* gene to the genetic background of epilepsy syndromes.

p340

MUTATION ANALYSIS OF *SCN1A* AND *SCN2A* IN FINNISH PATIENTS WITH INFANTILE ONSET INTRACTABLE EPILEPSY

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Purpose: Mutations in *SCN1A* are associated with many epilepsy syndromes such as severe myoclonic epilepsy of infancy (SMEI) and generalised epilepsy with febrile seizures plus (GEFS+). Mutations in *SCN2A* have been described in benign familial neonatal-infantile seizures and GEFS+ but to date only one *SCN2A* mutation has been associated with intractable epilepsy. We evaluated the contribution of *SCN1A* and *SCN2A* mutations to infantile onset intractable epilepsy in Finnish patients.

Method: *SCN1A* and *SCN2A* were screened for mutations in 33 patients, 21 of which had a clinical suspicion of SMEI. We amplified all exons and exon-intron boundaries of *SCN1A* and *SCN2A* from genomic DNA and sequenced the PCR products with an ABI 3730 DNA analyser. Sequences were analysed using the Sequencher4.5 program.

Results: We found 6 different de novo mutations in *SCN1A*: 1 nonsense, 2 splice site, 1 frameshift-causing and 2 missense mutations that change highly conserved amino acids. One of the mutations was previously described. The clinical presentation in 3 of the mutation positive patients is SMEI. Two patients have borderline SMEI and 1 has a milder phenotype with normal cognitive development. We also found 1 previously undescribed de novo missense mutation of a conserved amino acid in *SCN2A* in a patient with infantile onset epilepsy and episodic ataxia. None of the mutations were observed in 192 control chromosomes.

Conclusion: Our findings are compatible with previous findings showing that de novo *SCN1A* mutations are a major cause of SMEI. *SCN2A* mutations are found only in a small subset of infantile onset intractable epilepsy.

p341

SUGGESTION OF LINKAGE TO CHROMOSOME 3p24.3 IN A SPANISH FAMILY WITH AUTOSOMAL RECESSIVE FAMILIAL TEMPORAL LOBE EPILEPSY

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Purpose: To characterise the genetic and clinical features of a four generation consanguineous Spanish family with familial temporal lobe epilepsy.

Method: We identified an extended family including 3 affected individuals presenting temporal lobe epilepsy. Personal interviews and DNA samples were obtained from 5 individuals. A whole-genome-screen using microsatellite markers and haplotype and linkage analysis were performed. The coding sequence of the candidate gene *KCNH8* (H8 subunit of the channel of potassium) was sequenced.

Results: The affected individuals presented temporal lobe seizures characterised by feelings of being out of their body, déjà vú, and decreased levels of consciousness. Age of seizure onset ranged from 16 to 25 years. The EEGs showed temporal discharges and the brain MR was normal. The mode of inheritance was consistent with an autosomal recessive pattern. We excluded linkage to the autosomal dominant partial epilepsy with auditory features (ADPEAF) 10q24 locus. A suggestion of linkage to chromosome 3p24.3 with a maximum lod score of 2.08 (theta = 0) was found. This locus has been recently associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The *KCNH8* gene is localised within the candidate gene region but no mutations were found.

Conclusion: We describe a family that may represent an autosomal recessive form of familial temporal lobe epilepsy. A suggestion of linkage to chromosome 3p24.3 was found.

p342

MUTATION ANALYSIS OF THE SCN1A GENE IN 92 PATIENTS WITH SEVERE MYOCLONIC EPILEPSY OF INFANCY

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Purpose: De novo mutations in the *SCN1A* gene, encoding the alpha1-subunit of the neuronal voltage-gated sodium channel Nav1.1, are the most frequent genetic cause of severe myoclonic epilepsy of infancy (SMEI) known so far. In order to establish genotype-phenotype correlations and investigate the pathological mechanisms responsible for SMEI, we analysed a large group of patients including 86 isolated SMEI probands, 5 SMEI sib pairs and 1 SMEI patient in a large family with generalised epilepsy with febrile seizures plus (GEFS+).

Method: The *SCN1A* gene was screened by DHPLC and abnormal profiles were systematically sequenced.

Results: We identified 39 *SCN1A* mutations, 31 of which are novel. Most of the *SCN1A* mutations responsible for SMEI were de novo events, but in 10% of cases, they were inherited from an asymptomatic or mildly affected parent. In 2 unrelated families, we showed evidence that somatic and germline mosaicism in the transmitting asymptomatic parents resulted in recurrent transmission of the disease.

Conclusion: This first report of parental mosaicisms in the *SCN1A* gene has major consequences for genetic counselling for parents with a SMEI child.

p343

DOES THE G-PROTEIN BETA-3 SUBUNIT C825T POLYMORPHISM HAVE AN IMPACT ON TEMPORAL LOBE EPILEPSY (TLE)?

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Purpose: Experimental studies suggest a role of G protein-coupled receptors in epileptogenesis. A genetic variation in the G protein subunit Gβ3 denoted the C825T polymorphism has been reported to be associated with several diseases including hypertension, diabetes type II and obesity, as well as major depressive disorders. The present study is the first to examine whether this polymorphism is associated with TLE.

Method: The study included 227 TLE-patients, 186 controls and 106 family members of TLE patients. DNA was extracted from blood samples, and typing of the polymorphism performed. Case record forms were analysed for all the homozygote TLE patients and homozygote controls as well as for 28 matched TLE patients without the mutation (16 females, 12 males).

Results: Typing showed that 14 of the cases (6%; 8 females, 6 males), 13 of the controls (7%; 6 females, 7 males) and 8 of the family members (7.5%) were homozygote for the polymorphism. 100 of the cases (44%), 70 of the controls (38%) and 43 (41%) of the family members were heterozygote, while 113 of the cases (50%), 103 of the controls (55%) and 55 of the family members (52%) were normal. The homozygote TLE patients had higher BMI, weight and waist circumference than TLE patients without the mutation, but did not show higher frequency of hypertension and diabetes.

Conclusion: There was no increased frequency of TLE in the homozygote group compared to healthy controls or family members without epilepsy. The homozygote patients, however, had increased obesity in consistence with earlier studies.

p344

MIGRAINE HEADACHE OR PHOTOSENSITIVE EPILEPSY?

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Purpose: To find out whether complaints of migraine in a photosensitive family are the expression of an inherited liability to photosensitivity or comorbid migraine attacks.

Method: After clinical histories, video-EEG recordings with extra visual stimulation were carried out on a mother at age 45, and her daughters of 21 and 16 years. Intermittent photic stimulation (IPS) was performed in accordance with the European protocol with determination of photosensitivity ranges. Likewise, thresholds of pattern sensitivity were determined with black-and-white striped patterns.

Results: Mother had a history of photosensitive epilepsy since the age of 15 with generalised photoparoxysmal EEG responses (PPRs). The video-EEG with VPA 500 mg showed sharp-waves over the left temporal occipital region. Her photosensitivity range was 8 to 60 Hz. Daughter A had a history of complex partial seizures since the age of 13 with also generalised PPRs. Her video-EEG with 700 mg VPA showed 40 sec after pattern stimulation sharp-waves in both occipital regions lasting for 18 seconds. During that episode she complained of headache. Daughter B suffered since one year from episodes of vertigo, loss of vision followed by headache. Her EEG showed sharp-waves over the right temporal occipital region and generalised PPRs between 12 and 25 Hz. During IPS she complained of her headache.

Conclusion: In this family the headaches were shown to be epileptogenic and photosensitive during video-EEG recordings. Even when no clear photosensitive seizures are reported, headache can be an ictal sign and part of the phenotype of photosensitivity.

p345

ASSOCIATION BETWEEN GEFS+3 LOCUS AND GEFS+ SYNDROME IN TWO AFFECTED TUNISIAN FAMILIES

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Purpose: The aim of this report is to search for a correlation between clinical phenotype and genotype in affected Tunisians families with generalised epilepsy with febrile seizure plus (GEFS+).

Method: A total of 69 members belonging to two large Tunisian families with a phenotype compatible with GEFS+ were studied. Seizures and syndromes of probands and affected relatives were classified according to the international classifications. Genetic analysis has been performed using microsatellite markers spanning all FS and GEFS+ loci.

Results: Nineteen patients with a history of seizures were collected. The phenotype comprised febrile and afebrile seizures. Afebrile seizures were generalised tonic–clonic. There was no patient with childhood absence epilepsy or juvenile absence. A genetic study was performed for 14 patients and 55 collateral members of the two families. Statistical analysis demonstrates an association with the GEFS+3 (GABRG2) loci with a significant p value.

Conclusion: The position and/or severity of the mutation in *GABRG2* may determine different phenotypes. Our families were probably linked to a different mutation in the *GABRG2*.

p346

EXPANDING THE AGE SPECTRUM OF INFANTILE CONVULSIONS (BFIC) BEYOND THE FIRST YEAR OF LIFE

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Purpose: Benign familial infantile convulsions (BFIC) belong to the idiopathic epilepsies with an autosomal dominant mode of inheritance. BFIC is characterised by partial and generalised tonic–clonic seizures appearing between months 3 and 12 of life. The disease has a benign course with a good response to antiepileptic drugs and normal psychomotor development. The main locus for BFIC is on chr 16p12-q12, while infantile seizures can be associated with paroxysmal dyskinesias in some families. Another locus for pure BFIC was identified on chr 19q. Here we describe a three generation BFIC family with 8 affected members with a slightly different clinical picture.

Method: We collected a BFIC family of German origin with 8 affected members and performed a standard two-point linkage analysis.

Results: Mainly generalised tonic–clonic seizures, and in rare cases complex partial or atonic seizures were observed. They occurred in typical clusters and responded well to anticonvulsive treatment with sulthiam or other AEDs. Uncommonly for BFIC, the onset of the seizures was between months 14 and 16 of life. We performed a linkage analysis and found a positive linkage to the known BFIC locus on chr 16p12-q12.

Conclusion: Our results expand the clinical spectrum of this syndrome and suggest that either a potentially similar but different gene at the same locus or alternatively other modifier genes or the genetic background are responsible for the late onset within this family.

p347

GABBR1 POLYMORPHISMS IN PORTUGUESE MESIAL TEMPORAL LOBE EPILEPSY PATIENTS

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Purpose: Mesial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis (HS) is of unknown aetiology, although there is emerging evidence for a genetic component. A variant, G1465A, in the *GABBR1* gene, which encodes the gamma-aminobutyric acid type B receptor 1, has been suggested as a risk factor for TLE (Gambardella et al., 2003), but was not confirmed in subsequent replication studies (Cavalleri et al, 2005). Prolonged febrile seizures (FS) are associated with hippocampal cell death and may predispose some individuals to develop MTLE-HS. Here we analysed two *GABBR1* variants 1465G > A and 1974T > C in a sample of MTLE-HS patients of Portuguese origin. We further evaluated a possible relationship between these variants and the occurrence of FS.

Method: Seventy-two unrelated MTLE-HS patients, of which 36 had FS, and 141 unaffected controls were studied. Genomic DNA was obtained from peripheral blood and genotyping of the two SNPs was performed using PCR-RFLP methodology.

Results: We found the 1465G > A variant in 1 epileptic patient that was not detected in any of the control subjects. The allele frequency of 1974T>C did not differ significantly between the control group and patients, with or without FS.

Conclusion: The present results do not provide evidence that the GABBR1 polymorphisms 1465G > A and 1974T > C confer a substantial susceptibility to MTLE-HS, preceded or not by FS. Our studies do not support the previous described relationship between such variants and TLE. Work supported by a TECNIFAR 2005 Grant for Epilepsy Research.

p348

VANISHING WHITE MATTER (VWM) DISEASE AS A CAUSE OF PROGRESSIVE MYOCLONUS EPILEPSY

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Purpose: The progressive myoclonus epilepsies (PMEs) are a group of symptomatic generalised epilepsies with a progressive course and poor outcome. Advances in molecular genetics have begun to elucidate the causes of PME, including Lafora disease, Unverricht Lundborg disease, neuronal ceroid lipofuscinosis, dentatorubral-pallidoluysian atrophy

(DRPLA) and myoclonic epilepsy with ragged red fibres (MERRF). We report eIF2B related leucoencephalopathy with VWM as another cause of PME.

Method: Detailed medical and family histories were obtained on the proband and his relatives. EEG, MRI and MRS of the brain, EMG, MRS of the muscle, skin-muscle-nerve biopsy, brain biopsy, bone marrow biopsy, CSF studies, metabolic work-up and molecular genetic studies for MERFF, DRPLA, spinocerebellar ataxia types 1 and 3, and VWM leucodystrophy were performed on the proband.

Results: The proband, a 38 year-old man, developed learning problems at age 9, after head trauma with loss of consciousness. At age 22, he began to have myoclonic jerks as well as generalised tonic–clonic seizures. At age 38, he had a cerebellar syndrome with severe dysarthria and ataxia, as well as a bilateral pyramidal syndrome. He was wheelchair bound since age 31. The myoclonus that had been very disabling had almost disappeared. Infrequent brief generalised seizures persisted. EEGs showed diffuse slow waves and epileptic activity from both temporal regions. MRI showed marked selective loss of white matter volume with extreme thinning of the corpus callosum. Brain biopsy revealed loss of white matter. The proband was homozygous for the R113H mutation in the *eIF2B5* gene.

Conclusion: Mutations in any of the 5 genes encoding subunits of the translation initiation factor eIF2B can cause vanishing white matter leucodystrophy (VWM)/childhood ataxia with central nervous system hypomyelination (CACH). Mutations in these genes should be included in the differential diagnosis of progressive myoclonus epilepsy.

Monday July 3, 2006
13:30–15:00
Poster Session 1
Psychiatry

p349

PERSONALITY OF PATIENTS WITH SYMPTOMATIC EPILEPSY AS A FUNCTION OF LESION LOCALISATION AND SEIZURE CONTROL: A ONE-YEAR PRE- TO POSTOPERATIVE FOLLOW-UP STUDY OF 151 PATIENTS

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Purpose: Since Kraepelin (1923) the question of a relationship between epilepsy and personality is a recurring issue in epileptology. This study evaluated this issue in patients with focal symptomatic epilepsy before and after epilepsy surgery.

Method: 151 patients were evaluated before and one year after epilepsy surgery. Dependent measures were 4 scales (organic psycho-syndrome, intro-extraversion, neuroticism, addiction) and 21 subscales of a personality inventory for epilepsy patients, which was standardised with 300 healthy subjects. Independent measures were focus localisation, pathology, AED, onset & duration of epilepsy, demographic variables, and seizure outcome.

Results: Introversion was the major problem in the epilepsy group (38%), followed by 28% with elevated/lowered neuroticism scores, 16% with hints of an organic psycho-syndrome, and 10% with elevated addiction scores. Gender predicted neuroticism, mesial temporal lobe epilepsy introversion. Follow-up analysis indicated an effect of surgery on neuroticism and an interaction effect of seizure control by surgery on organic psycho-syndrome scores. Subscale analysis revealed a differential effect of seizure control on personality change dependent on the side of surgery. Right TLE patients reported decrease of anxiety, vegetative symptoms, somatisation, and external control, left TLE patients reported emotional stabilisation and improved impetus.

Conclusion: Introversion appears as a frequent trait particularly in patients with temporal lobe epilepsy. Neuroticism or a psycho-organic syndrome are less common and appear more state dependent. Postoperative changes dependent on seizure outcome indicate hemisphere specific release effects after temporal lobe surgery.

p350

PREVALENCE AND SEVERITY OF NEUROPSYCHIATRIC DISORDERS IN EPILEPSY – RESULTS OF THE GERMAN DAS-PROJECT, A NATIONWIDE EPIDEMIOLOGICAL EVALUATION FOCUSING ON DEPRESSION, ANXIETY, AND SLEEP DISORDERS

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Purpose: Neuropsychiatric disorders (depression, anxiety and sleep disturbances) are common in patients with epilepsy, although often underdiagnosed. We report on the results of the German DAS-Project, a Nationwide Epidemiological Evaluation Focusing on Depression, Anxiety and Sleep Disorders.

Method: Profile survey of patients suffering from partial or generalised epilepsy (PE/GE) using standardised questionnaires focussing on depression, anxiety and sleep disorders to evaluate their prevalence in German epilepsy patients.

Results: Six hundred sixty-four patients (49.5% female) participated (P/GE: 52.7/47.3%). Overall, 16.8% suffered from depression, 22.0% from anxiety and 12.1% reported sleep disturbances. Seizure free patients were significantly less impaired (12.0% vs 22.6%; 15.1/29.7%; 9.2/15.2%) as well as patients suffering from GE: depression (GE vs PE): 11.8/5.1/24.7% vs 20.7/18.0/23.2%; anxiety (GE vs PE): 18.0/10.8/31.8% vs 24.0/15.6/31.0%; sleep disturbances (GE vs PE): 7.3/4.4/12.9% vs 15.1/11.7/17.5%).

Conclusion: Depression, anxiety and sleep disturbances are frequent neuropsychiatric problems, even in seizure free patients with epilepsy. Frequency and severity depend with respect to epilepsy type (PE > GE) and increase with seizure frequency.

p351

RISK FACTORS FOR PSYCHOTIC DISORDERS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Purpose: Temporal lobe epilepsy patients are at higher risk for acute and chronic psychotic disorders but the aetiology of this association is not clearly defined. The aim of this study was to determine risk factors for psychosis in temporal lobe epilepsy patients.

Method: 118 patients with neurological, neurophysiologic and neuroimaging criteria for temporal lobe epilepsy were included. Two groups of patients were determined: 61 patients (52%) with psychotic disorders codified in Axis I of DSM IV were compared with 57 patients (48%) without psychotic disorders. Psychotic disorders were defined by DSM IV criteria (SCDI I and II), and postictal and/or interictal psychoses were additionally diagnosed. Sex, age, age of epilepsy onset and epilepsy time duration, febrile convulsions, generalised seizures, status history, presence of unilateral and bilateral hippocampal sclerosis, and laterality of epileptic discharges diagnosed by video-EEG were determined. Student *t*-test and chi-square were carried out.

Results: The more frequent DSM IV psychotic disorders diagnosed were brief psychotic disorders (39%), schizophrenia (24%) and schizophreniform disorder (13%). Postictal psychotic episodes were reported in 29 patients with DSM IV psychotic disorders (47%). Topiramate in 4 patients and vigabatrin in 1 patient induced interictal psychosis (8%). Age of epilepsy onset was earlier and epilepsy time duration longer in the psychotic group, compared with the control group: $p = 0.04$ / $p = 0.017$. Status epilepticus history, and bilateral hippocampal sclerosis were more prevalent in psychotic patients $p = 0.02$ / 0.00.

Conclusion: In this study longer evolution, status epilepticus history, and bilateral hippocampal sclerosis (risk factors for epilepsy severity) were significantly more frequent in patients with psychotic disorders.

p352

NONEPILEPTIC SEIZURES AND OTHER FUNCTIONAL NEUROLOGICAL SYMPTOMS: PREDISPOSING, PRECIPITATING, AND PERPETUATING FACTORS

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Purpose: About 10% of patients presenting to neurologists have nonepileptic seizures or other functional symptoms. These patients are as disabled as patients with epilepsy or "neurologically explained" symptoms and experience higher rates of psychopathology and distress. This has prompted increased interest in treatment, especially with psychotherapy. This study describes the range and prevalence of predisposing, precipitating and perpetuating factors and explores whether different factors are related to particular symptoms.

Method: In this naturalistic study of 59 consecutive neurological outpatients referred for psychotherapy, aetiological factors were elicited by a single therapist during a semistandardised two-hour screening interview. The factors identified in the therapist's contemporaneous records were subjected to retrospective analysis.

Results: The most prominent predisposing or precipitating factors were trauma (78.0%), family dysfunction (62.7%) and bereavement (62.7%). The most prevalent perpetuating factors were family dysfunction (54.2%), affective disorder (42%) and health anxiety or hypochondriasis (23.7%). Trauma was more commonly identified in patients with nonepileptic seizures than in those with other functional symptoms ($p = 0.03$). Health anxiety was found more commonly in men ($p = 0.003$), family problems in women ($p = 0.033$).

Conclusion: Functional symptoms in neurology are heterogeneous. There are important aetiological differences between patients with nonepileptic seizures and other functional symptoms and between men and women. The results of this study suggest that trauma and anxiety are important targets for therapy but that treatment needs to be tailored to be appropriate for individual patients.

p353

INTERNATIONAL SURVEY OF PSYCHIATRIC DISORDERS AND PSYCHIATRIC SERVICE PROVISION FOR PATIENTS WITH EPILEPSY

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Purpose: To establish the perception among epileptologists of the role a psychiatric disorder plays in the lives of persons with epilepsy and the role of psychiatrists and other mental health professionals in service delivery.

Method: On behalf of the psychobiology subcommission of the ILAE, we conducted an e-mail based survey of the chapters of the ILAE. All chapter presidents and secretaries were sent an e-mail with an attached questionnaire to be circulated to up to 5 epilepsy centres represented by that chapter. Each centre was asked to describe its characteristics and estimate the burden of mental illness in its patient group. Responders were also asked to describe staffing and available treatments. Finally they were asked to comment on the ideal, in their view.

Results: Twenty-five replies were received from 18 countries. Estimates of the prevalence of psychiatric disorders ranged from 5% to 70%. Just under half said epilepsy specialists had training in psychiatry. Affective disorders and somatoform disorders were thought to be most common, with 50% of respondents estimating these affected more than 20% of their patients. Talking therapies were unavailable or of limited availability in most centres. More centres believed they were meeting the psychiatric needs of their patients than not.

Conclusion: The results show widespread recognition of the problems posed by mental illness or psychological problems for persons with epilepsy. Service provision is highly variable and clinicians have differing views on how the services should ideally be configured. To encourage further responses we have made the questionnaire available on-line at the ILAE website.

p354

ADOLESCENTS WITH EPILEPSY: NOT AT GREATER PSYCHOSOCIAL RISK?

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Purpose: To assess psychosocial risk factors for adolescents with epilepsy.

Method: We administered a questionnaire to 84 unselected adolescents attending outpatient service, and receiving mainstream education. Answers from 68 adolescents (R) were compared to those previously collected from 4260 healthy controls (C). Medical files were analysed for epileptological factors and comorbidity.

Results: R-rate was 81%. Mean age 16.4 yrs. Medical files: epilepsy onset mean age 10.4 yrs; family history + 20/68; focal 29, generalised 23, both focal and generalised 14, undetermined 2, photosensitivity 21. Mean epilepsy severity 2.4. (1–5). Mean seizure-freedom 29 mo (0–108). AEDs mean 1.25/patient, on at least one mood stabilising drug 61/68; taken regularly in 63/68. Comorbid medical complaints: 40%. Psychosocial problems: 46% had independent and/or epilepsy-related problems. 42% had been seen by mental health professionals. Questionnaire R:C. No significant difference*:* depression, self-esteem, suicidal behaviour. Suicidal attempts were detected in 9. In 8 this was ignored by the parents and not detected by the health service. Significant differences: R take *less* drugs, sedatives, alcohol, nicotine, have *less* stress, personal problems, *more* conflicts, easily discussed, emotional support, desire for a family, professional support. Within R: females less parental support, less sports, more suicidal (not significant).

Conclusion: Comparisons between R and C seem to indicate equal or even smaller risks in R. Possible reasons: milder epilepsy (study severe cases!), medication effects, other unexplained (family?). However, the risks are not negligible. Their having escaped parents' and professionals' attention requires better adjusted professional services for the unrecognised needs of the adolescent population. Proposals discussed.

p355

EPILEPSY AND DEPRESSION

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Purpose: Depression occurs in 25–55% of patients with epilepsy. We wanted to analyse the signs of depression and its dependence on number or type of seizures.

Method: A retrospective analysis of a group of 57 patients with epilepsy investigated from September 2005 to January 2006 using the questions of the PRIME-MD PHQ-9 Quick Depression Assessment. Patients were divided into groups according to number and type of seizure. Each group was correlated with the results from the questionnaire PRIME-MD PHQ-9, score from 0 to 27.

Results: We investigated 57 patients; 33 men, 24 women. Mean age 34.6 ± 12 years. Patients presented with partial seizures (PS) in 28 cases (49.12%), generalised tonic–clinic (GTCS) seizures in 14 cases (24.56%) and in 15 cases (37.93%) PS with secondary generalisation (PS + SG). The total number of PS in the last month was 1.3 ± 2.5, GTCS 2.7 ± 3.0. PRIME-MD PHQ-9 score was 0–17; median was 5 ± 3.8.

23% of the patients are treated with antidepressants. In the group of patients without seizures the median was PRIME-MD PHQ-9:4 and in the group of patients with seizures the median was PRIME-MD PHQ-9:7; $p < 0.01$ and Pearson's coefficient 0.53. Patients with PS had median PRIME-MD PHQ-9:5, patients with GTCS had median PRIME-MD PHQ-9:4, patients with PS +SG had median PRIME-MD® PHQ-9:6, $p > 0.1$.

Conclusion: In our group 55 patients (96.49%) suffered at least from minimal depression, the severity of which was dependent on the number of seizures. We did not prove the dependence on the type of seizure.

p356

POSTPARTUM DEPRESSION IN WOMEN WITH EPILEPSY VERSUS WOMEN WITHOUT EPILEPSY

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Purpose: The goal of this study was to verify whether there was a significant difference in the incidence of postpartum depression among patients with epilepsy and healthy controls. All patients were selected at the Epilepsy Center and at the Department of Obstetrics and Gynecology, University of Milan, St Paolo Hospital (Italy).

Method: 35 pregnant women with epilepsy and an equal number of pregnant women without epilepsy were assessed with the Edinburgh Postnatal Depression Scale (EPDS) to screen postpartum depression (PPD), a clinical interview, and a sociodemographic questionnaire. Patients receiving medication other than antiepileptic drugs (AEDs) and patients with a psychiatric background were excluded. None of the patients or controls had previously experienced mood and anxiety disorders.

Results: We found a statistically significant major incidence of PPD in patients with epilepsy compared with controls ($p < 0.05$). The results of the multiple linear regression analyses, in which the association of EPDS with demographic and clinical variables was explored, were not statistically significant. EPDS scores were not associated with age, education, type of epilepsy, duration of epilepsy, age at epilepsy onset, seizure frequency, aetiology or number of drugs.

Conclusion: It is very important to point out that pregnant women with epilepsy develop PPD more easily than those without epilepsy. In this regard, women at higher PPD risk can be identified earlier and treated as soon as possible to control this pathology and improve their quality of life.

p357

TWO CASES OF NONCONVULSIVE STATUS EPILEPTICUS (NCSE) WITH SCHIZOPHRENIA

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Purpose: We report 2 cases of patients with schizophrenia who developed stupor-like nonconvulsive generalised status epilepticus (NCSE).

Method: Case 1: A 40-year-old woman with schizophrenia who had been treated with neuroleptics since 18 years of age. She had a clinical history of diabetes mellitus (DM), but had no previous history of seizures. She developed constant myoclonic movements in her limbs and stereotypic movements such as stupor after one month's noncompliance with medication. On admission, her EEG showed a continuous rhythmic generalised 2–3 Hz spike-and-slow wave complex. This lasted for about 30 minutes, after which it gradually disappeared, with her EEG normalising.

Case 2: A 60-year-old man with schizophrenia who had been treated with neuroleptics since 27 years of age. He had a clinical history of DM and alcohol abuse, but had no previous history of seizures. He showed incoherent speech and psychomotor excitement. On admission, his EEG showed a continuous rhythmic generalised 3 Hz spike and slow wave complex. Intravenous injection of diazepam resulted in a rapid normalisation of the EEG, with disappearance of the clinical manifestations.

Results: At first, the symptoms that the patients presented with were believed to have resulted from aggravation of the symptoms of schizophrenia. Their EEGs, however, revealed that these symptoms were due to NCSE.

Conclusion: It is sometimes difficult to distinguish NCSE from stupor caused by other psychotic disorders, such as schizophrenia. We believe monitoring of the patient's EEG to be quite useful in confirming diagnosis of this condition.

p358

SUICIDAL AND HETERO-AGGRESSIVE BEHAVIOUR IN EPILEPSY PATIENTS

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Purpose: To analyse the occurrence and forms of hetero-aggression in epilepsy patients who had history of suicidal behavior (suicidal ideations, threats, attempts).

Method: The basic group of 150 adult epilepsy patients with a history of suicidal behaviour (suicidal ideas, threats, attempts) was compared to a control group consisting of 80 adult epilepsy patients who had never displayed suicidal behaviour. Occurrence and forms of hetero-aggression were investigated in each group. Groups were comparable in age, gender and psychiatric diagnoses. For statistical analysis Fisher's test $\phi^*$was used.

Results: Hetero-aggressive behaviour occurred significantly more often in the basic group—in 83 (55.3%) patients versus 18 (22.5%) patients in the control group ($p < 0.01$). Hetero-aggression had various forms in both groups: nonprovoked verbal aggression, threats, destructive behaviour, aggressive acts with assault and battery, violence and even murder attempts. Victims of these aggressive acts were mainly patients' relatives, but not infrequently chance persons and medical staff. Hetero-aggressive behaviour was more often connected with such psychopathologic conditions as dysphoric disorders, interictal and postictal psychoses, and twilight states. Statistically significant differences between the basic and control groups in types or heaviness of hetero-aggression were not revealed.

Conclusion: Epilepsy patients with a history of suicidal behaviour significantly more often committed hetero-aggressive acts. Probably, this fact testifies to substitution of object of aggressive emotions in epilepsy patients and mutual transformations of hetero- and self-aggression. Anyway, the problem of hetero-aggression in epilepsy patients expects much attention of psychiatrists and lawyers.

p359

TREATMENT OF PATIENTS WITH PSYCHOGENIC PSEUDO-EPILEPTIC ATTACKS: AN EVALUATION STUDY

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Purpose: This study was performed to evaluate the effect of a 3-month open clinical treatment programme for patients with psychogenic pseudo-epileptic attacks (PPEAs). The treatment was based on cognitive-behavioural theories and included individual and group psychotherapy, psychomotor therapy, creative therapy and family therapy.

Method: Twenty-eight patients with PPEAs (5 with coexistent epilepsy) participated in the study. Questionnaires measuring anxiety, depression, quality of life, psychological distress, dissociation and coping were administered at the start ($n = 28$) and the end ($n = 25$) of the treatment programme and 6 months after discharge ($n = 16$). Seizure frequency was also evaluated.

Results: At the time of discharge, statistically significant improvements were seen on all questionnaires and especially those concerning anxiety, depression and dissociative symptoms. Also, self-perceived quality of life was improved. 20% of the PPEA-only patients ($n = 20$) were seizure free and 50% of them had a seizure reduction of $>50\%$. After 6 months the improvements on all questionnaires were maintained and even increased in most cases. At that time 38% of the PPEA-only patients ($n = 13$) were seizure free.

Conclusion: The treatment programme results in an improvement of psychological functioning and a decrease of symptoms and seizures. It seems that what is learned during treatment is applied successfully in the normal life situation and leads to a healthier functioning and a further decrease of seizures.

p360

EPILEPSY SURGERY AND DEPRESSIVE DISORDERS: FURTHER DATA

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Purpose: Depression is the most frequent comorbid psychiatric disorder in patients with epilepsy. The objective of this study is to identify which patients may experience depression after surgery and if antidepressant therapy will be needed.

Method: 134 patient candidates for epilepsy surgery were evaluated by means of psychiatric interview and psychiatric rating scale presurgery. 116 and 91 have been evaluated respectively 6 months and 1 year after surgery. Relations between depression and localisation, lateralisation, crisis frequency, seizure duration, antiepileptic drugs, family and personal history for psychiatric disorders, were tested.

Results: 49 subjects had a DSMIV-TR psychiatric diagnosis presurgery, 57 six months and 42 one year after surgery. 9 subjects were depressed presurgery. After 6 months 7 patients were still depressed, 12 had a new diagnosis for depression (McNemar test $p < 0.003$). After 1 year, 9 patients were still depressed, 2 had a new diagnosis for depression. Lateralisation of focus was different with 8 of 9 depressed patients with left side focus ($p < 0.04$). After 6 months this correlation was not significant. A personal history for depression is more frequent in patients who have a depressive episode at the presurgical evaluation ($p < 0.00$) and 6 months after surgery ($p < 0.01$). Patients who were depressed worsened if they didn't receive antidepressant therapy.

Conclusion: Left-side seizure focus shows a higher incidence of depression. A personal history of depression seems to be a risk factor for depression at presurgical time and 6 months after surgery. For these patients an antidepressant therapy could be suggested at presurgery time.

p361

IS ICTAL DEREALISATION A TYPICAL SYMPTOM OF TEMPORAL LOBE EPILEPSY?

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Purpose: The psychiatric literature has been dominated by the concept that ictal dissociative symptoms like derealisation and depersonalisation are considered typical of temporal lobe epilepsy. The purpose of this study is to check if ictal dissociative symptoms occurred more frequently in temporal lobe epilepsy than in other localisations.

Method: 134 patients affected by epilepsy were evaluated by means of a psychiatric interview in order to cover ictal derealisation/depersonalisation information and interictal psychiatric disorders. Ictal depersonalisation/derealisation occurred in 22% of the sample. We compared 2 groups of patients: 54% affected by temporal lobe epilepsy, 46% affected by extratemporal lobe epilepsy. Relations between ictal depersonalisation/derealisation and localisation, lateralisation, presence of mesial temporal sclerosis and interictal anxiety disorders were tested by statistical analysis.

Results: Ictal depersonalisation/derealisation occurred in 24% of subjects affected by temporal lobe epilepsy and in 19% of those affected by extra temporal lobe epilepsy.

Relations between ictal depersonalisation/derealisation and TLE, lateralisation and mesial temporal sclerosis are not statistically significant. Ictal depersonalisation/ derealisation appears to be more common in patients with DSMIV-TR anxiety disorders ($p < .02$).

Conclusion: Ictal depersonalisation/derealisation doesn't appear to be more frequent in TLE. The relationship between ictal dissociative symptoms and interictal anxiety disorders suggests that the same anatomic structures are implicated in the development of both these disorders.

p362

EMOTIONAL DISORDERS: REFRACTORY VERSUS WELL-CONTROLLED EPILEPSY

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Purpose: Emotional disorders are very common in patients with epilepsy. The aim of the study was to investigate the prevalence and characteristics of emotional disorders in patients with refractory epilepsy in comparison with those whose epilepsy is well-controlled.

Method: For detection of emotional disorders we used Crown-Crisp Experience Index, which consist of 6 scales: generalised anxiety, phobic behaviour, obsessive behaviour, somatised anxiety, depression and hysteric behaviour. A group of 45 patients were analysed, 20 of them suffering from refractory epilepsy and 25 patients with well-controlled epilepsy.

Results: Results show a presence of emotional disorders in both investigated groups, but much greater in a group of patients with refractory epilepsy, statistically significant ($p < 0.01$) on scales of depression, phobic disturbances and somatised anxiety.

Conclusion: Our study confirms the presence of emotional disorders in epilepsy, especially refractory, and also emphasises the importance of their recognition.

p363

HANDEDNESS AND PSYCHOSIS IN EPILEPSY: REVISITED

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Purpose: Taylor reported a marked interaction between psychosis and left handedness in patients with psychomotor epilepsy (Taylor DC., *Psychological Medicine* 1975;5:249–254). However Oyebode and Davison found a significant reduction of mixed and left handedness in male epilepsy patients with psychosis (Oyebode F, Davison K., *Br J Psychiatry* 1990;156:228–230). Since there has been no established conclusion, we revisited this problem in a multicentre study in Japan (Matsuura M et al., *Epilepsia* 2005;46. (Suppl 1):11–14.).

Method: We examined 3 patient groups: 30 partial epilepsy with psychosis, 32 partial epilepsy without psychosis, and 25 schizophrenia. Handedness (right/ambidextrous/left) was determined with the Annette Handedness Schedule. We also investigated intelligence quotient (IQ) with the Wechsler Adult Intelligence Scale-Revised.

Results: The prevalence of each handedness was equivalent among the 3 groups (Fisher's exact test, $p = 0.86$). Although there was a significant difference in intelligence (one-way ANOVA, $p = 0.002$) among 3 groups, handedness was not significantly associated with the full-IQ (one-way ANOVA, $p = 0.6$).

Conclusion: Results of the current study suggest that handedness is not a risk factor to development of psychosis in patients with or without epilepsy.

p364

SCHIZOTYPAL PERSONALITY TRAITS AND TEMPORAL LOBE EPILEPSY: A CONTROLLED STUDY

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Purpose: To investigate the prevalence of schizotypal personality traits in patients with temporal lobe epilepsy (TLE) and to identify the main clinical features associated with schizotypy.

Method: Fifty-two consecutive patients with TLE referred to our Epilepsy Unit and a control group of 52 healthy subjects matched for age and sex, were assessed with the Schizotypal Personality Questionnaire (SPQ), the Beck Depression Inventory (BDI), and the State-Trait Anxiety Inventory (STAI). All subjects were also evaluated using the MMPI-2, with special attention to the Sch scale.

Results: TLE patients scored significantly higher for schizotypy than the control group. However, there were no correlations between total

SPQ scores and age, sex, duration of disease, localisation of EEG focus, or antiepileptic drug regimen. Total SPQ scores and subscores for Cognitive-Perceptual and Interpersonal (but not Disorganized) schizotypy dimensions correlated significantly ($p < 0.01$) with BDI and STAI scores. Comparing the MMPI-2 profile of the subgroup of patients with TLE and high schizotypy scores with the subgroup with TLE but low schizotypy scores, only the Sc scale was significantly different ($p < 0.01$).

Conclusion: Schizotypy was significantly prevalent in patients with TLE compared to healthy subjects and correlated with comorbid psychopathology. Our findings are consistent with shared pathoaetiological mechanisms underlying expression of specific schizotypal symptoms and comorbid affective disorder in TLE.

p365

EPILEPTIFORM ABNORMALITIES IN CHILDREN DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: CLINICAL CORRELATIONS, TREATMENT, AND OUTCOME

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Purpose: To investigate the frequency of different causes of epileptiform abnormalities (EAs), treatment implications and prognosis in a group of 526 children (82% males) with ADHD.

Method: 41 children (71% male) aged between 5–14 years, mean 9.6 ± 2.7, with ADHD and EAs were identified and followed for 3.7 ± 1.7 years. Different causes of EAs, treatment implications, epileptic seizure occurrence and prognoses were analysed. At least two EEGs were performed on all patients.

Results: 27 children (66% males) had no epilepsy comorbidity, whereas 14 patients (79% males) had epilepsy. Active epilepsy was diagnosed in 11 patients; of these, 8 had idiopathic and 3 had symptomatic epilepsies. Developmental disorders were diagnosed in 31 (76%) patients, conduct disorder in 8, depression/anxiety in 7, and Tourette's syndrome in 6. 38 of the 41 ADHD patients were treated with methylphenidate, 3 with dextroamphetamine and 2 with atomoxetine during the observation period. Two children who received only AEDs showed improved ADHD symptoms. AEDs were administered to 16 patients: monotherapy to 9 and polytherapy to 7 patients. No seizure exacerbation was observed in any patient with epilepsy. Seizure control was achieved in 9 of 11 patients. None of the 27 children who had only EAs developed epileptic seizures during follow up. At the end of the study EAs were still present in 16 patients.

Conclusion: The majority of our patients with ADHD and EAs have no epilepsy comorbidity. Medical treatment of ADHD is safe and not associated with an increased seizure frequency. Multiple comorbidities occur frequently and affect the clinical outcomes.

p366

INTERICTAL PSYCHOPATHOLOGY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY (TLE) AND EXTRA-TLE

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Purpose: This study was performed to investigate the relationship between symptoms of interictal depression, anxiety, personality traits and psychological dissociation with the localisation and lateralisation of the epileptogenic zone in patients with partial epilepsy.

Method: One hundred thirty one patients were diagnosed according to the localisation related concept of the 1989 ILAE Classification of Epilepsies and Epileptic Syndromes, and the localisation and lateralisation of the epileptogenic zone was established using the clinical criteria for noninvasive presurgical evaluation. This resulted in 67 patients with temporal lobe epilepsy (TLE) and 64 patients with extra-TLE. All patients were assessed on the various aspects of psychopathology using a comprehensive battery of standardised diagnostic instruments.

Results: The hypothesised excess of psychiatric symptoms in patients with (mesial) TLE was not found. We also found no differences between patients with the lateralisation of the epilepsy in the left versus the right hemisphere.

Conclusion: In spite of the strict diagnostic criteria applied to present-day epilepsy diagnosis and the wide variety of diagnostic instruments that were used, we found no evidence for associations between the different parameters of psychopathology and the localisation and lateralisation of the epilepsy syndromes. It seems that TLE per se cannot be considered as a risk factor in developing more and severer symptoms of psychopathology in patients with partial epilepsy. Concomitant factors, such as the duration of epilepsy, seizure frequency and frontal lobe dysfunction may play an additional role.

p367

SUBACUTE POSTICTAL AGGRESSION IN PATIENTS WITH EPILEPSY

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Purpose: Aggressive behaviour during postictal periods has been observed in some patients with epilepsy. We present 3 cases of patients who showed brief bouts of violent behaviour shortly after a seizure.

Method: Case 1: A 62-year-old man with a history of complex partial seizures (CPSs) and secondarily generalised tonic–clonic seizures (SGTCS) since the age of 18 years. Following CPSs he displayed aggressive behaviour toward his wife, both physically and verbally. This aggression lasted for approximately 30 minutes. He was not quite amnesiac, and was remorseful afterward. Case 2: A 59-year-old man with CPSs and SGTCS since the age of 17 years. Immediately after CPSs, he displayed aggressive behaviour toward his wife or nurse, both physically and verbally. This behaviour lasted for 10 minutes, and he regretted his behavior afterward. Case 3: A 38-year-old man with a history of simple partial seizures and CPSs followed by SGTCS since the age of 11 years. He showed aggression toward objects for 5 minutes several hours after a seizure. He regained consciousness immediately after, but was amnesic of his behaviour.

Results: Our patients were all male, and had both CPSs and SGTCSs. Postictal aggression occurred shortly after each seizure and lasted for 5 to 30 minutes. They regained consciousness immediately after, and then showed regret. These episodes appeared approximately 30 to 40 years after onset of epilepsy. Their EEGs showed temporal spikes.

Conclusion: These cases were consistent with the subacute postictal aggression reported by Gerard et al. (*Neurology*. 1998;50:384–388). A long duration of epilepsy and temporal lobe dysfunction may be associated with the occurrence of this phenomenon.

p368

COGNITIVE AND BEHAVIOURAL PROBLEMS IN CHILDREN WITH FRONTAL LOBE EPILEPSY

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Purpose: The purpose of the study was to find psychopathological behavioural features and cognitive characteristics in children aged 4 to 12 years old with frontal lobe epilepsy.

Method: 32 patients (15 boys/17 girls) with a confirmed diagnosis of frontal lobe epilepsy (clinical symptoms and EEG findings) were included in the study. All The children were investigated by a child psychiatrist and neuropsychologist with Achenbach's Child Behavior Checklist (CBCL) for Parents and Kaufman Assessment Battery for Children (K-ABC) to assess mental development and psychiatric disturbances. Wilcoxon-Mann-Whitey test for statistical analysis was used, statistically significant $p < 0.05$.

Results: K-ABC showed that the mean of the group for mental processing composite (MPC = IQ) was below the average mean of 87. There was a higher frequency of disturbance in simultaneous information processing than in sequential processing. Results in CBCL showed that there was no significant association between the age of patient, the age of the start of epilepsy, gender and behavioural problems. Internalising scale demonstrated problems (T score > 67) 12/32, externalising scale

16/32 of cases. The most prominent problem was delinquent behaviour and it was associated with right-sided frontal foci, $p = 0.0394$. Social and attention problems were associated with lower IQ ($p = 0.0091$; $p = 0.0208$).

Conclusion: The mental abilities of the children with frontal lobe epilepsy were lower than average. Externalising behavioural syndromes were more prominent than internalising behavioural syndromes.

p369

EFFECTS OF SOCIAL STRESS ON THE PROCESSING OF THREAT IN PATIENTS WITH PSYCHOGENIC-PSEUDO-EPILEPTIC ATTACKS

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Purpose: Psychogenic-pseudo-epileptic attacks (PPEAs) are widely considered as a stress related disorder. High rates of reported abuse are repeatedly found in this patient population. The main purpose of this study was to investigate the effect of stress on the processing of threat stimuli in patients with PPEAs.

Method: Eighteen patients and 20 healthy controls were administered a masked emotional stroop task in a rest and a social stress condition. This task measures the preconscious selective attention to threat by comparing colour-naming latencies for angry and neutral faces. Attentional bias scores were calculated by subtracting the reaction times for neutral faces from those for angry faces, with negative scores being indicative of avoidant reactions and positive scores indicating vigilance. Stress was induced by means of the Trier Social Stress Test.

Results: Whereas healthy controls showed an avoidant attentional bias in the rest condition, the PPEA patients were vigilant to angry faces in the rest condition. After stress induction, these group differences disappeared and both groups showed an avoidant attentional bias to angry faces.

Conclusion: These results indicate that in relative neutral conditions patients with pseudo epileptic attacks display an attentional bias toward threat stimuli, which can be interpreted as a tendency to scan the environment for signs of potential threat.

p370

ELECTROENCEPHALOGRAPHIC ASPECTS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

I. Dobrescu, I. Eparu, and O. Paun ("Al. Obregia" Psychiatry Hospital, Child and Adolescent Psychiatry Department, Bucharest, Romania)

Purpose: To investigate the eventual electroencephalographic (EEG) differences between children diagnosed with attention-deficit/hyperactivity disorder (ADHD) and children with ADHD and conduct disorder (CD), one of the most important comorbidities of ADHD, and to quantify the nature of these differences.

Method: We've compared 3 samples (ADHD, ADHD and CD, control), 40 boys each, 7–14 years old, inpatients in Child and Adolescent Psychiatry Department, "Al. Obregia" Psychiatry Hospital, Bucharest, from 2002-2005. For each child a standard 16 derivation EEG exam was performed, and a 15-second, eyes closed, without artifacts or pathological graphic elements fragment was analysed, counting different wave types. Student's *t*-test, Pearson's correlation and ANOVA were performed for statistical analysis.

Results: An increase in slow wave numbers (delta, theta) was observed, as well as a decrease of alpha and beta wave numbers for ADHD children. The derived quotients, theta/alpha and theta/beta, were much higher than in normal controls in all regions (frontal, central and posterior). Our data were able to discriminate, with statistical significance, between ADHD and normal subjects, with a few exceptions (frontal and central alpha and posterior beta). We could not detect a statistically significant difference between ADHD and ADHD + CD samples.

Conclusion: EEG can discriminate between ADHD and normal subjects. Conduct disorder does not modify EEG profile of ADHD. Though at the time being there is no recommendation for the routine use of EEG in ADHD, the potential of this method to discriminate ADHD suggests that further research should be done to certify its utility.

p371

ASSESSMENT OF DEPRESSION AND ANXIETY IN ADULTS WITH EPILEPSY

E. Navickiene, R. Mameniskiene, and D. Jatuzis (Department of Neurology, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania)

Purpose: To determine frequency of depression and anxiety in patients with epilepsy; to analyse the relationship between depression, anxiety and clinical characteristics of epilepsy, and patients' demographic and social characteristics.

Method: 193 patients (95 men, 98 women) with epilepsy were given a questionnaire regarding epilepsy characteristics, social issues and the fear of a recurrence of seizures. Depression and anxiety were measured by the Lithuanian version of Hospital Anxiety and Depression Scale (HAD Scale).

Results: 193 patients with epilepsy, aged 18–78 (39.65 ± 13.52), with mean duration of disease 14.1 ± 12.34 years were interviewed up to date. Mean frequency of seizures per month was 4.8 ± 8.3. Depression was determined in 38 (19.7%) patients, anxiety in 77 (39.9%). Both symptoms (depression and anxiety) were found in 32 (16.6%) patients without a significant difference between men and women. 84.2% of patients with depressive symptoms had significant anxiety symptoms. 87 (45.1%) patients notified about frequent or permanent fear of seizures. Depression and anxiety highly correlated with the fear of seizures ($p < 0.01$). Older age (>45 years), unemployment and shorter education of patients were associated with more severe depression, anxiety and fear of seizures ($p < 0.01$). Patients with generalised epilepsy or secondary generalised seizures had more severe anxiety than patients with partial seizures without secondary generalisation ($p < 0.01$).

Conclusion: Depression and anxiety are common and important interictal problems in patients with epilepsy. Severity of depression and anxiety were associated with older age, unemployment, shorter education of patients and the type of epilepsy and were highly related to the fear of a recurrence of seizures.

p372

ASSESSMENT OF PERSONALITY AND EMOTIVE PROFILE IN TEMPORAL DRUG-RESISTANT EPILEPSY PATIENTS: A FOLLOW-UP STUDY

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Purpose: We wanted to explore in the pre- and postsurgical stage the personality profile of drug-resistant temporal lobe epilepsy (TLE) patients. We investigated whether the hemispheric side of the epileptogenic area and surgery, age of onset, clinical outcome (Engel's Classification) relate to the personality profile.

Method: Thirty-three patients were studied before and after surgery (18 F, 15 M; 18 left TLE, 15 right TLE; mean age 32.5, SD 8.7; mean educational level 11.06 yrs, SD 2.6). Patients completed the Beck Depression Inventory (BDI) and the Minnesota Multiphasic Personality Inventory (MMPI-2). A semistructured interview was administered. This interview explored a subjective perception of epilepsy, awareness of severity of the disease per se and expectations about changes in quality of life after surgery. The post-surgical follow-up was staged at one year.

Results: We applied a repeated measures univariate ANOVA. Dependent variables: subjects' performance on 3 measures (BDI; MMPI-2; semi-structured interview). *Between*-subjects independent variables: hemispheric side of the epileptogenic area and surgery; age of onset; clinical outcome. *Within*-subjects independent variables: pre- vs post-surgical stage. No significant effects resulted from this analysis. We found a correlation between awareness of disease severity and depression from BDI (Spearman's Rho; B1-Beck, $r = 0.184$, $p = .03$; B1-D, $r = 0.188$, $p = .031$).

Conclusion: Scores on MMPI-2 and BDI were within the normal range. TLE patients did not show psychopathological indices as a group. No significant changes between the pre- and postsurgical personality were found independently of the clinical outcome. These results suggest that neurosurgery does not induce psychiatric morbidity per se. A significant correlation emerged between awareness of epilepsy severity and depressive symptoms as revealed by the BDI in the post-surgical follow-up.

p373
COPING STRATEGY IS A PREDISPOSITION FACTOR IN EPILEPSY PATIENTS WITH PSYCHOGENIC NON-EPILEPTIC SEIZURES?
B. Szuromi, Z. Hidasi, P. Salacz, and E. Csibri (Semmelweis University, Dept. Psychiatry, Budapest, Hungary)

Purpose: In spite of scientific and technical developments, diagnosis and management of psychogenic nonepileptic seizures (PNES) remains difficult, especially in the case of epilepsy patients. The purpose of our study was to investigate the psychological profile of epilepsy with PNES in order to provide better therapy.

Method: Eighteen consecutive epilepsy patients from our epilepsy outpatient clinic were recruited. Eight of them had only epilepsy (2 males and 6 females, mean age 31.4 $\pm$ 10.4) and 10 had epilepsy with PNES (2 males and 8 females, mean age 39.5 $\pm$ 12.6). Psychogenic seizures were documented by ictal observation. Patients answered Rosenberg Self-esteem Scale, Felton's Acceptance of Illness Scale and DISQ-H Questionnaire. Psychiatric diagnoses were based on DSM-IV. Data were evaluated using Student's *t*-test.

Results: Most of the patients showed an increased level on Rosenberg test, but there was no significant difference in self-esteem between groups. Patients with epilepsy and PNES had a significantly lower score on Felton's Scale concerning active coping strategies than patients with epilepsy alone (1.37 $\pm$ 0.52 versus 2.06 $\pm$ 0.55, $p = 0.008$). There was no significant difference between groups on DISQ-H Questionnaire. Opposite to patients with epilepsy alone, all the patients with epilepsy and PNES had a diagnosis on axis I or axis II of DSM IV.

Conclusion: The background of psychogenic seizures may be heterogeneous, not only a dissociative disorder that has a role in the mechanism of PNES. Our preliminary data suggest that appropriate coping strategies may be very important in prevention and therapy of PNES as well.

p374
PREVALENCE OF MOOD DYSFUNCTION IN EPILEPSY PATIENTS IN CROATIA
H. Hecimovic, S. Miskov, R. Covic-Negovetic, and V. Demarin (Zagreb Epilepsy Center, Croatia)

Purpose: To determine the prevalence of depressive symptoms in a tertiary epilepsy centre in Croatia.

Method: Fifty consecutive and consenting epilepsy patients from the Zagreb Epilepsy Center were examined for the presence of depressive symptoms using the Beck Depression Inventory (BDI). Clinical variables for age, gender, seizure factors and social and vocational factors were analysed.

Results: Mean age of the patients was 30.8 $\pm$ 13.5 years, and 60.4% were females. The majority of them were employed (72.9%) and single (62.5%), and 35.4% had a university degree. Most of the patients had complex partial seizures (n = 40, 80%), and 6 (12%) were diagnosed with idiopathic generalised epilepsy. The mean monthly seizure frequency was 2.0 $\pm$ 3.4. At the time of their office visit 31.3% were newly diagnosed patients, and of the remaining, 45.8% were on AED monotherapy, 18.8% on two, and 4.2% on three AEDs. Assessment with the BDI showed that 33.3% of patients had depressive symptoms: 6.3% had mild depressive symptoms, 8.4% moderate and 18.6% had severe depressive symptoms, with the total BDI score of $\geq$24. Three patients (6.4%) attempted suicide in the past, 2 of them had current suicidal ideation, and all of them were severely depressed.

Conclusion: This is the first study assessing mood dysfunction in epilepsy patients in Croatia. Increased prevalence of depression in epilepsy patients suggests specific approach and need for early treatment. This work was supported by the Epilepsy Foundation grant to HH.

p375
VIDEO-EEG MONITORING IN PAROXYSMAL EVENTS
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Purpose: Video-EEG monitoring with use of methods of EEG activations is a means to distinguish different types of seizures. The purpose of this study was to determine the utility and results of video-EEG examinations in paroxysmal events in children and adults.

Method: In the Department of Developmental Neurology, K. Marcinkowski University of Medical Science in Poznań, 302 video-EEG were performed from 2003-2005. Video-EEG monitoring was executed by means of computer electroencephalograph "Ceegraph" (Biologic-USA). The examinations involved a group of 302 patients with diagnostic doubtful paroxysmal events. In this group were 37 children aged 0–3 years, 216 children aged 4–18 years and 49 adults aged 19–56 years. During the examinations various EEG activation methods were used: hyperventilation, photostimulation, sleep deprivation and in patients with suspected psychogenic seizures, placebo application or psychogenic provoking test.

Results: In the group of younger children video-EEG allowed confirmation and more precise characteristics of seizures in 11 of 37 (29.7%) patients (epileptic seizures in 7, nonepileptic events in 4), whereas the corresponding number of older children was 93 of 216 (43%) patients (epileptic seizures in 27, psychogenic pseudoepileptic seizures in 51, syncope in 4, tics in 7, and others in 4). In the group of 49 adults paroxysmal events were recorded in 21 (42.8%) patients; among them psychogenic pseudoepileptic seizures in 18, tics in 1, generalised convulsions in 1, nonconvulsive epileptic status in 1 were diagnosed. Most of the psychogenic pseudoepileptic seizures were observed after placebo application (58%) or psychogenic provoking test (28%). Epileptiform activity in EEG was found in 44% patients, including 15% during clinical events.

Conclusion: Video-EEG monitoring is an efficient and valuable procedure in the diagnosis of paroxysmal events in children and adults. In the group of younger children the most frequent types of events were epileptic seizures. The largest group among older children and adults were psychogenic pseudoepileptic seizures.

p376
DEPRESSION IN EPILEPSY: HIGH PREVALENCE, RARELY TREATED
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Purpose: To determine the prevalence of major depression in epilepsy in Switzerland and the independent effects of antiepileptic medication, neurological and nonneurological comorbidity compared with demographic and clinical epilepsy variables.

Method: Adult subjects (n = 75), ambulatory and seen in 1 secondary and 1 tertiary centre of Epileptology in Switzerland completed the Beck Depression Inventory (BDI) questionnaire. (Jones JE et al., Screening for Major Depression in Epilepsy with common self-reported Depression Inventories. *Epilepsia* 2005;46(5):731–735.) Information was derived regarding the subject's epilepsy syndrome, last seizure, neurological and nonneurological comorbidity, medical treatment and demographic characteristics.

Results: Major depression defined by a BDI-Score > 11[1] was reported by 20 subjects (26.7%) of whom 3 are treated by antidepressants. Association between depression, clinical and demographic features were disclosed for taking antiepileptic polytherapy (chi-Quadrat 6.818, $p < 0.019$) and time of seizure freedom (Mann-Whitney, $p < 0.041$). No correlation was found for age, gender, seizure type, neurological or nonneurological comorbidity and antidepressant therapy. In unemployed

subjects the BDI Score was significantly higher (Mann-Whitney $p < 0.028$).

Conclusion: Depression is a frequent (26%) and often untreated comorbidity in adults with epilepsy in Switzerland. Factors reflecting epilepsy-related aetiological processes (poor seizure control), treatment related aetiological processes (antiepileptic polytherapy) and social aetiological processes (unemployment) are associated with depression.

p377
INTELLECTUAL FUNCTIONING IN POSTTRAUMATIC EPILEPSY PATIENTS COMPLICATED AND NON-COMPLICATED BY ALCOHOLISM
V. Sergeev, and P. Sergeeva (Ural State Medical Academy of Post-Diploma Education, Chelyabinsk, Russia)

Purpose: To study the character and the degree of influence of three reciprocal pathological processes: traumatic, epileptic and chronic alcoholism of cognitive abilities in patients with posttraumatic epilepsy complicated and noncomplicated by alcoholism in connection with their sociopsychological functioning.

Method: A comparative study of IQ by means of Raven's progressive matrices in 215 patients with paroxysms: 65 with consequences of CCT complicated by alcoholism (PTE + A); 65 with posttraumatic epilepsy non-complicated by alcoholism (PTE); 85 with no traumatic epilepsy without alcohol addiction (E-C) as a control group.

Results: In all groups the majority of patients had middle IQ in its low limits. The lower IQ index was in PTE + A patients, and significantly differed this group from others ($p < 0.01$) with no significant differences between PTE and E-C groups. A correlation was not found between IQ and heaviness of trauma in any group. In PTE + A group low IQ correlated with more duration of trauma, epileptic process, alcohol addiction, alcoholic psychosis in anamnesis, the number and frequency of alcoholic relapses ($r = 0.4–0.5$; $p < .01$). In PTE + A and E-C groups low IQ correlated with higher frequency of paroxysms, polymorphism, absences, secondary-generalised seizures and epileptic status: in the first one, vegetovisceral paroxysms, automatisms, twilight conditions; in the second one ($r = 0.3–0.5$; $p < .001$). The study determined the correlation between IQ indices and psychosocial adaptation of examined patients, revealing a correlation between low IQ and low level of education in PTE + A and PTE groups ($r = 0.35$; $p < 0.05$) and decreasing socio-professional status in all groups. Higher IQ showed PTE patients, who continued studies and kept a premorbid level of professional activity ($r = 0.3–0.45$; $p < 0.005–0.04$).

Conclusion: In most cases reducing intellectual abilities was observed in patients with mixed pathology: trauma, alcoholism, epilepsy. Their seriousness is connected with a number of clinicobiological factors, each of which depends on significance, interaction and progradience of indicated pathological processes. Features of psychosocial adaptation of the patients are mainly defined by clinicobiological factors.

p378
ANTICONVULSANTS IN SPORTS: ETHICAL CONSIDERATIONS
K. Kaufman, R. Aaron, and A. Prager (UMDNJ-Robert Wood Johnson Medical School, New Brunswick, USA)

Purpose: Antidoping codes in sport are intended to deter and sanction athletes using performance enhancing agents while promoting an even playing field for all competitors. Monetary rewards to athletes associated with superior performances have led to ingenious attempts to skirt these codes: erythropoietin, modafinil and designer steroids. Although the World Anti-Doping Code (WADC) permits anticonvulsants in general, harmonisation of antidoping permits international sport federations (IF) to prohibit specific medications within that IF. Anticonvulsants levetiracetam, tiagabine and lamotrigine may pose ethical dilemmas and could be considered violations of antidoping codes.

Method: Literature review with analysis.

Results: Lamotrigine, with antiglutaminergic and sodium channel properties, is FDA-approved for bipolar depression and has been used to treat major depression. Tiagabine, a selective GABA reuptake inhibitor, has mood stabilising and anxiolytic properties. Levetiracetam, whose unique mechanism involves modulators beta-carboline and zinc, has anxiolytic and mood stabilising properties. Anxiolytics and antidepressants are banned in archery; under strict liability, all three anticonvulsants violate WADC/IF for that specific sport and could result in disqualification unless therapeutic use exemptions (TUE) had been obtained. Ethical decisions regarding choice of anticonvulsant for athletes with epilepsy is addressed in addition to means of obtaining TUE.

Conclusion: WADC with harmonised IF policies are meant to prevent doping in athletes but not appropriate medical treatment. When anticonvulsants have other psychotropic properties, ethical issues arise. Athletes should list all medications taken with diagnoses, obtain TUE as indicated, and contact the appropriate IF or Olympic organisation to determine status of the proposed medication (banned, restricted, non-banned).

p379
POSTICTAL PSYCHOSIS: A RETROSPECTIVE STUDY OF PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY
M. Falip, A. Donaire, M. Carreño, I. Maestro, L. Pintor, N. Bargallo, T. Boiget, A. Raspall, J. Rumia, and X. Setoain (Hospital Clinic I Provincial, Barcelona, Spain)

Purpose: Postictal psychosis (PIP) represents 25% of the psychoses seen in epilepsy patients. A high frequency of bilateral independent epileptiform activity has been observed in patients with PIP. The objective of this study was to find the frequency of PIP in patients with temporal lobe epilepsy (TLE) who underwent video-EEG monitoring and to investigate possible differences between PIP and control patients.

Method: Clinical, electroencephalographic and neuroimaging data of 5 PPI patients with TLE were compared with data of 50 patients with TLE without psychotic antecedents. Patients with a past history of interictal psychosis were excluded.

Results: of 55 patients, 5 had PIP and 50 were controls. 31 (62%) were men, 9 (16.4%) had a history of encephalitis and 6 (10.9%) of status epilepticus. The mean age was 42.2 (SD 12.93). Mean age at epilepsy onset 16.95 (SD 12.93) and mean seizure frequency 5 seizures/month (SD 1.87). The frequency of PIP was 5/55 (9.1%). History of encephalitis was more frequent in PIP patients than in controls. ($p = 0.024$). PIP patients more frequently had a nonlateralising ictal EEG than controls ($p = 0.031$). Bitemporal lobe dysfunction revealed by neuropsychological studies was greater than expected by the observed lesion on MRI studies in patients with PIP. Moreover the presurgical study was less conclusive for PPI than for control patients ($p = 0.049$).

Conclusion: PPI is observed in up to 9% of patients undergoing video EEG monitoring and seems to be a marker of bitemporal lobe dysfunction.

p380
PSYCHOPATHOLOGY OF PSYCHOGENIC NONEPILEPTIC SEIZURES: CLINICAL OBSERVATIONS
[1]M. Valenti, [2]M. Mazza, [3]A. Martini, [4]M. Scoppetta, [5]M. Vaccario, [6]R. Rodriguez, [7]G. Ruggeri, [8]G. Della Marca, [9]P. Bria, and [10]S. Mazza ([1]Institute of Neurology, Epilepsy Centre, Neurophysiopathology, Università Del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [2]Institute of Psychiatry e Psychology, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [3]Institute of Psychiatry e Psychology, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [4]Institute of Psychiatry e Psychology, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [5]Institute of Neurology, Epilepsy Centre, Neurophysiopathology, Università Del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [6]Institute of Psychiatry e Psychology, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [7]Institute of Psychiatry e Psychology, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy, [8]Institute of Neurology, Epilepsy Centre, Neurophysiopathology, Università Del Sacro

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Purpose: Our aim is to examine the psychopathological features of patients with psychogenic nonepileptic seizures (PNES) in order to find useful patterns for differential diagnosis and to optimiSe psychological and psychopharmacological treatments.

Method: 17 patients with a diagnosis of PNES, confirmed by video-EEG recordings, were tested using the Hamilton Rating Scale for Depression (HDRS), Dissociative Experience Scale (DES), Minnesota Multiphasic Personality Inventory-2 (MMPI-2) and Short Form Health Survey 36 (SF-36). The same procedure was applied to 13 epilepsy patients and 16 healthy subjects matched for sex and age.

Results: Our data confirm previous studies showing that psychogenic seizures typically occur between 20 and 30 years of age, more frequently in women (70% of patients). Besides, these data confirm a pathogenetic role of dissociative mechanisms, traumatic experiences, conversion, and DSM–IV axis I disorders comorbidity. DES ratings are significantly higher in patients with PNES (Bonferroni test; $p < 0.05$), supporting the hypothesis of dissociative psychopathogenetic features. Conversion is an important aetiological mechanism: MMPI-2 profiles of patients with PNES revealed high scores on the hypochondriasis (Hs), conversion hysteria (Hy), schizophrenia (Sc), depression (D) and paranoia (Pa) scales and 3 patients showed a typical "Conversion V" pattern. Depression is an important aetiopathogenetic factor: HDRS scores are higher in patients with PNES ($p < 0.05$). Quality of life results are higher in patients with PNES compared with epilepsy patients: psychogenic seizures probably represent an outlet for emotional distress.

Conclusion: Our study confirms that complex psychosocial, environmental and intrapsychic mechanisms interact in the aetiology of psychogenic seizures.

Monday July 3, 2006
13:30–15:00
Poster Session 1
Social Issues/Nursing

p381

ANALYSIS OF COGNITIVE IMPAIRMENT AND INDEPENDENT RISK FACTORS OF PATIENTS WITH NEWLY DIAGNOSED CRYPTOGENIC EPILEPSY

C. Ziyi, Z. Liemin, Z. Jueqian, Z. Xia, and L. Weifeng (The First Affiliated Hospital of Sun Yatsen University, China)

Purpose: To evaluate the cognitive functions of patients with newly diagnosed cryptogenic epilepsy and to explore the effect of the related factors of epilepsy on cognition

Method: 60 registered patients met the criteria of the study, were arranged for the Wechsler intelligence scales and registered their clinical manifestations including onset age of seizure, seizure type, frequency, duration of seizure disorder, family history and the localisation of epileptic lesion before treatment. 60 healthy volunteer controls were paired.

Results: Epilepsy patients had lower FIQ, VIQ and PIQ than the healthy controls (99.96 ± 18.03 vs 116.80 ± 12.53, 103.92 ± 19.63 vs 120.68 ± 13.62, 95.32 ± 16.60 vs 108.85 ± 11.76, separately), with significant difference. Similar results were reported in the adult subgroup and child subgroup. The results on the risk factors showed that FIQ, VIQ and PIQ had a negative correlation with duration of seizure disorders (-0.478, -0.487, -0.406, separately, $p < 0.001$), and seizure frequency (-0.493, -0.474, -0.443 separately, $p < 0.001$);similar results were seen in the adult subgroup and child subgroup. No statistical difference in FIQ, VIQ and PIQ existed in analysis of other risk factors. Suggesting duration as a covariant, correlation index of FIQ and seizure frequency was -0.243 $p < 0.01$ while suggesting seizure frequency as covariant, the counterpart was -0.092 $p > 0.05$.

Conclusion: These findings indicated that IQs of patients with epilepsy were lower than those of the healthy population and that seizure frequency was the independent risk factor of impaired cognition in epilepsy.

p382

EPILEPSY NARRATIVES: THE DIFFERENCES IN BEING DIFFERENT

D. Snape (University of Liverpool, Liverpool, UK)

Purpose: By exploring the nature of having epilepsy and issues of related stigma from the perspective of people with epilepsy (PWE), this qualitative study seeks to enhance understanding about the impact of this condition on daily living and life trajectories and to represent the heterogeneity of the meaning of having epilepsy. The overall aim is to contribute to both stigma theory and to the debate on the need for holistic care for PWE.

Method: Drawing upon research on illness narratives, the subjective experiences of living with epilepsy are explored in order to identify how conceptions of self evolve over biographical time. Using theoretical sampling a series of life history interviews are being conducted with 12 participants attending epilepsy out patient clinics. Interview transcripts are subjected to content and paradigmatic analysis to examine thematic similarities and differences between the narratives provided.

Results: Early findings relate to perceptions about the causes of epilepsy, knowledge, understanding and treatment choice. How PWE feel about and see themselves in relation to their epilepsy provides insight into the element of epilepsy stigma and serves to highlight how individuals perceive the (positive/negative) influence of their epilepsy in different phases of their life (past, present, future).

Conclusion: The research has implications for theories of stigma, healthcare intervention and policymaking. It is essential for health care professionals and "significant others' to understand the lived experiences of PWE and their individual needs; and identify the diversity of approaches to helping them improve their coping mechanisms.

Acknowledgement: This research is partially funded by a Postgraduate Research Bursary from Epilepsy Action.

p383

EDUCATION IMPROVES SOCIAL KNOWLEDGE ABOUT EPILEPSY: EDUCATION, EPILEPSY AND SOCIETY IN SPAIN.

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Purpose: Spanish society still has a very low level of knowledge about epilepsy and its social repercussions on the patient's quality of life. This is mostly due to lack of information among the general population, plus low educational levels. AEAE together with the Epilepsy Unit at Hospital Clínico, San Carlos, have researched the general population with the aim of testing the degree of knowledge about epilepsy and its consequences on the patient's social environment. The research results show that the higher the level of education, the better the understanding of epilepsy and its social consequences.

Method: We carried out a poll on a sample of 237 people from the metropolitan area of Madrid. Individuals were of both sexes, aged between 19 and 73. We classified the educational levels on three categories: primary education, high school level and university level. The questionnaire had 14 questions related to epilepsy and its consequences on the patient's environment.

Results: Most representative data extracted from the answers are shown on the graphics. Individuals from the youngest group and the highest educational level know and better understand epilepsy and its repercussions on different aspects of the patient's daily life.

Conclusion: People understand and accept epilepsy better due to 2 different factors: high education and youth. Following this direction, epilepsy will get rid of the stigma associated to it, because of lack of information and social prejudices. Thus, all actions to give information and develop educational policies about epilepsy from childhood will

be to the advantage of a promising, gratifying and better future for the general population and for epilepsy patients and their environment in particular.

p384
EXPLORING PATIENT VIEWS OF CONSULTANT NEUROLOGIST AND EPILEPSY SPECIALIST NURSE INTERVIEW AT FIRST SEIZURE PRESENTATION: WHO WOULD THE PATIENT PREFER TO SEE?
M. Goodwin (Northampton General Hospital, Northampton, UK)

Purpose: Historically medical diagnoses are made by medical practitioners. However, the development of specialist/advanced nursing practice blurs the boundaries of medicine and nursing. Were nurses to diagnose epilepsy how might the patient feel? Would patients identify differences between the doctor and specialist nurse and would they prefer one to the other?

Method: As part of an exploratory study to compare consultant neurologist (CN) to epilepsy specialist nurse (ESN) opinion at first seizure presentation patients were asked their views of the interviews with the CN and ESN. Participants consisted of 20 consecutive referrals to the first seizure clinic, following at least one suspected seizure. Patients were randomly allocated to see either CN or ESN first, and then swapped. Following both interviews and prior to diagnosis patients underwent a third interview. This interview used open-ended questions to explore patient's feelings about the two previous interviews. Interviews were tape recorded and transcribed verbatim. Individual interviews were analysed for common themes then compared across cases to identify commonalities. Patients were finally asked whom they would recommend to a friend with a similar medical problem.

Results: The common themes raised focus on 1) Personality 2) Gender 3) Language and terms 4) Note taking 5) Speed/time 6) Number of questions. Six patients recommended the ESN, 4 recommended the CN and 8 would opt for either. (2 were not asked specifically).

Conclusion: This study compares patient views of the CN and ESN interviews. It suggests most patients liked the ESN interview and would accept a diagnosis made by a specialist nurse.

p385
FOLLOW-UP OF PATIENTS REJECTED FOR EPILEPSY SURGERY: HOW ARE THEY DOING?
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Purpose: To describe the medical and social status and quality of life of patients rejected for epilepsy surgery.

Method: We approached 70 patients from a national database, who were rejected for epilepsy surgery between 2001 and 2005, were older than 16 and capable of filling in questionnaires. For 50 patients we checked medical charts, recent social status and quality of life by means of three questionnaires: EQ5D, Qolie-31 and RAND-36. Relatives completed questionnaires as well. The outcomes were cross-compared and compared to earlier studies on quality of life in epilepsy and to the general population.

Results: Two patients had been seizure-free for more than six months. Averaged EQ5D-score was 81.8 ± 0.26, which is lower than the score of the general population, corrected for age and sex ($p = 0.03$ 1-tailed). In all domains except for physical functioning, the RAND-36 scores were lower compared to those for unselected Dutch patients with epilepsy. The employment ratio was 56%, compared to 67.2% for a comparable Dutch general population. It was not lower than for unselected Dutch patients with epilepsy (51%). The experienced care load by relatives was greater with lower quality of life scores (Qolie-31: R-square 0.24), but not dependant on seizure frequency (R-square 0.00).

Conclusion: 4% of patients rejected for epilepsy surgery became seizure-free and in retrospect would not to have needed surgery. The group of rejected surgery candidates forms a particular group within the group of patients with epilepsy in general, with comparatively low scores on quality of life in spite of equal employment ratios.

p386
MONO- AND POLYTHERAPY FOR IDIOPATHIC AND SYMPTOMATIC FORMS OF EPILEPSY TREATMENT IN CHILDREN
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Purpose: To determine treatment efficacy for idiopathic and symptomatic forms of epilepsy in children (6 months–16 years).

Method: Analysis of treatment of the children's epilepsy group (153) has been carried out.

Results: The group consisted of 153 children with different forms of epilepsy. The idiopathic group, 72 children: 61 from this group underwent monotherapy (84.7%). The monotherapy of the group mostly consisted of valproic acid (Depakine) 78%, topiramate (Topamax) 12%; polytherapy (11 children 15.3%) mostly consisted of combinations: valproic acid and Topamax (topiramate) and valproic acid and lamictal (lamotrigine). The symptomatic group treatment (81): monotherapy was used for 41 children (50.6%), 51% of children were on carbamazepine, 25% on valproic acid, and 24% on Topamax. Polytherapy consisted of combinations of valproic acid and topiramate (Topamax) for 11 children; and valproic acid and lamotrigine (Lamictal), 8 children; carbamazepine and valproic acid, 4 children; carbamazipine and lamotrigine (Lamictal), 4 children; also rare combinations of valproic acid, carbamazepine and benzodiazepine (clonazepam, antilepsin) for 2 children or VPA, CBZ and phenobarbital for 1 child.

Conclusion: The study confirms the recommendations of ILAE of superiority of monotherapy for treatment of idiopathic forms of epilepsy (the drug of choice is depakine). The symptomatic forms need rational polytherapy (mostly combinations of valproic acid and topiramate or lamotrigine).

p387
SEIZURE PRECIPITATION IN UNCONTROLLED EPILEPSY
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Purpose: To explore the pattern of seizure precipitating factors in patients with uncontrolled epilepsy.

Method: One hundred and thirteen patients were asked to indicate situations with an increased risk of seizures, first by report of their own experience and then by ranking 10 specific items.

Results: 88% of patients identified one or several precipitating factors, with a mean of 3. The most frequent single factors were sleep deprivation (66%), stress (54%) and missing drug intake (40%). No significant differences between partial and generalised epilepsy were found. The percentage of patients reporting each factor increased when they were introduced to the list of the 10 items, a finding that emphasises the importance of addressing single factors directly in clinical practice.

Conclusion: Most patients with uncontrolled epilepsy are aware of circumstances which may contribute to the initiation of seizures. Their frequency varies among individuals, and many represent a cascade of dependent factors which may relate to psychosocial difficulties. The most frequent single factors are stress, lack of sleep and treatment noncompliance. Any complete epilepsy program must consider the relationship between seizures and behaviour. An increasing number of epilepsy specialist nurses are now involved in the educational and social support of patients with uncontrolled epilepsy. Assessment of the individual seizure precipitant profile may be a useful approach in this intervention. This study underscores that the interaction between seizure precipitation and epilepsy-related psychosocial difficulties should receive ample attention.

p388

PSYCHOSOCIAL REHABILITATION IN EPILEPSY: AN OVERVIEW OF A THREE-YEAR PRACTICE

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Purpose: Social and psychological support have been shown to participate in the improvement of epilepsies (Oosterhuis 1994, Collings 1995, Ogata 2000) in adjunction of drug therapy or surgery. To cure patients with epilepsy, give them the wish to improve their quality of life and also give the epileptologists the duty to help patients to improve their psychosocial condition. The authors report in the present study on a 3 year experience of comprehensive care in epilepsy.

Method: Three hundred patients with psychosocial disability were enrolled in a special programme of rehabilitation driven in a multidisciplinary approach by a medico-psycho-social network. Patients were evaluated by an epileptologist, a psychologist, a neuropsychologist and social workers specialised in occupational rehabilitation.

Results: Epilepsy patients with heavy socio-professional disability are most often of poor educational level (level V to VI according to educational scale = 78%). 57% have no occupational activity from 1 to 2 years or more. Epilepsy is not at all the main cause of poor social integration. The main grounds for unemployment and/or poor social life are in increasing frequency order: the severity of epilepsy; incorrect treatment; lack of professional qualification; stigmatisation in occupational environment; associated handicap (mainly cognitive and psychiatric) and psychological disturbances (self-esteem and confidence, ambivalence in relation with work, social life . . .).

Conclusion: To help patients to improve their social conditions one needs to take into account the cognitive status of the patients, their ability to take care of themselves and to built up a project for their life.

p389

HUMANISTIC IMPACT AS ASSESSED BY QUALITY OF LIFE, DEPRESSION, ANXIETY, AND HEALTH STATUS IN PATIENTS WITH REFRACTORY EPILEPSY: A CROSS-SECTIONAL EVALUATION IN SPAIN

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Purpose: To assess the humanistic impact of disease (quality of life, depression, anxiety and health status) in adult patients with refractory epilepsy in Spain.

Method: A cross-sectional study was carried out in both neurology outpatient clinics and epilepsy units between March and September 2005. Consecutive male and female adult patients (over 18 years) with refractory epilepsy were enrolled. Health-related quality of life (QoLIE-10), anxiety and depression (HADS), and health status (0–100 mm VAS) were assessed.

Results: A total of 762 consecutive patients [728 valuables, (95.5%); 50.8% males, 40.5 (13.5) years, 24.3 (13.4) years of evolution] were included by 169 neurologists. Mean overall scoring in QoLIE-10 was 58.0 (19.5), with dimensions ranging between 50.9 (26.8), energy domain, to 64.2 (23.7) in emotional well-being. Any degree of anxiety was showed by 43.5% of patients; 21.2% mild, 15.8% moderate and 6.5% severe according with HADS scoring, while this scale detected any degree of depression in 32.0% of patients; 16.3% mild, 11.8% moderate and 3.9% severe. Mean health status on the 0–100 VAS was scored at 57.2 (19.9) mm. Women showed worst emotional well-being and seizure-worry than men; 61.8 (24.6) vs 66.5 (22.7), $p = 0.012$, and 47.1 (31.3) vs 56.8 (31.5), $p = 0.0003$, respectively. More women than men showed any degree of anxiety; 47.9% vs 39.2% ($p = 0.004$).

Conclusion: Refractory epilepsy impacts negatively on a patient's quality of life, health status and level of anxiety and depression, particularly in women who showed slightly worse scoring on anxiety and two dimensions of health-related quality of life. This study was financed by Pfizer Spain.

p390

EPILEPSY IN MOTION: WHAT'S ON IN A WEEK?

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Purpose: Awareness and knowledge of the Portuguese population concerning epilepsy is insufficient and some misjudgments about people with epilepsy still prevail.

The "aim a week" for epilepsy in Portugal was to promote knowledge, to contribute to demystification and to improve integration of people with epilepsy into society.

Method: The main goals were local and national media, schools and cultural institutions. With support of social partners and motivation and work of members of self-supporting groups and health technicians the 1st week of epilepsy was held.

Results: An exhibition of paintings and drawings by people with epilepsy was open to the public at the Zoo Auditorium in Lisbon, ending in a party that joined self supporting groups and the general population. Workshops about "Epilepsy and Learning" and "Living with Epilepsy" were held in schools and cultural centres. A group of children with epilepsy lived the unique experience of "Sleeping with the Sharks" in Lisbon Aquarium. Wearing the T-shirt and cap of the week: "Epilepsy in Motion," people with epilepsy, their families and friends ended the week participating in the "15th Mini-Marathon of Lisbon." All the events were reported by the media and many people with epilepsy were interviewed.

Conclusion: We accomplished the objective of epilepsy being the focus of interest of the media in Portugal for a whole week, resulting in a national impact. A week for epilepsy is a must every year and contributes to reduce social stigma and to improve self-esteem of people with epilepsy and their families.

p391

PREVALENCE AND BURDEN OF ILLNESS IN PATIENTS WITH REFRACTORY EPILEPSY IN SPAIN: THE PATIENT/FAMILY PERSPECTIVE

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Purpose: To ascertain prevalence and family/patient burden of illness in adult patients with refractory epilepsy in Spain.

Method: A two-phase (prevalence and burden) cross-sectional and retrospective study was designed. Consecutive adult patients (over 18 years) with epilepsy attending neurology outpatient clinics and epilepsy units in the year 2005 were enrolled. Refractory epilepsy was considered as a patient not seizure-free after being treated with, at least, three different antiepileptic drugs, as monotherapy or in combination, for a minimum time of one year, and having, at the least, a seizure within the last three months. Caregiver need, disease burden on caregivers and family were assessed.

Results: A total of 1,448 (22.7%) out of 6,374 screened patients fulfilled the criterion for refractory epilepsy; males (22.9%), females (22.5%), outpatients (18.9%) and epilepsy units (36.3%), $p < 0.001$ between level of care. 762 patients [728 valuables, (95.5%); 50.8% males, 40.5 (13.5) years, 24.3 (13.4) years of evolution] were included in burden-of-illness assessment. Only 56.0% were workers and 44.7% reduced the workday duration. Absenteeism was showed by 33.3% [mean yearly absence; 72.6 (73.0) days]. 8% needed house-adaptations and 3.4% were institutionalised. An informal caregiver was needed by 36.4% of whom 40.2% reduced their workday by a daily mean of 4.0 (2.5) hours. Mean monthly out-of-pocket spent was 251.4 (566.5). Absenteeism and

institutionalisation were higher in men; 60% vs 44% ($p < 0.0001$) and 5% vs 2% ($p = 0.036$), respectively.

Conclusion: Refractory epilepsy is prevalent and constitutes a considerable burden to family and patients in Spain. A substantial portion of costs are paid by own patient/family. This study has been financed by Pfizer Spain.

p392

HEALTH CARE AND NON–HEALTH CARE RESOURCES USE IN PATIENTS WITH REFRACTORY EPILEPSY: A COST OF ILLNESS STUDY IN SPAIN

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Purpose: To ascertain health and non–health care resources use and to estimate the cost of illness in adult patients with refractory epilepsy in Spain.

Method: A cross-sectional and retrospective study was designed. Male and female adult patients (over 18 years) with refractory epilepsy were enrolled in neurology outpatient clinics and epilepsy units between March and September 2005. Health care and non-health care resources were collected.

Results: 762 consecutive patients [728 valuables (95.5%); 50.8% males, 40.5 (13.5) years, 24.3 (13.4) years of evolution] were included. Yearly health care use included any type of EEG (56.5% of patients), MR scans (33.8%), spectroscopy (3.7), SPECT (4.3%), PET (1.9%), medical visits (4.3 per year), emergency visits (0.8 per year), hospitalisations (15.3%) and drugs (mean number: 2.2). Only 56% of subjects were workers, with 44.7% reducing the workday and absenteeism being present in 33.3%. Total yearly costs were 6,838 (8,100): health costs; 4,977 (6,490), and non–health costs; 1,873 (4,921). Emergency visits were higher in women: 1.1 (2.9) vs 0.7 (1.3); $p = 0.021$, and institutionalisation needs in men: 5% vs 2%; $p = 0.036$. Males showed significantly higher annual health care costs [5,528 (7,516)] than females [4,431 (5,259)], $p = 0.024$ yielding to near significant total costs: [7,414 (8,979)] and [6,279 (7,097)], respectively ($p = 0.061$).

Conclusion: Health care, and to a lesser extent non health care, resources use are high in patients with refractory epilepsy in Spain, yielding a considerable cost to both the National Health System and Society. This study has been financed by Pfizer Spain.

p393

IMPACT OF IDIOPATHIC EPILEPSY ON MOTHERS AND FATHERS: STRAIN, BURDEN OF CARE, WORRIES AND PERCEPTION OF VULNERABILITY

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Purpose: To examine a) strain, burden of care, worries (regarding stigma, academic underachievement, uncertainty of future) and perception of child's vulnerability in parents of children with newly diagnosed "epilepsy only," compared with parents of healthy children who had an acute illness during the last 6 months before the beginning of the study; b) changes in every variable after 12 months; c) relationships among strain (dependent variable), and the other variables in parents of children with epilepsy at baseline (T0) and 12 months after (T1).

Method: Twenty-seven parental couples of children with epilepsy and 27 parental couples of controls filled out: two questionnaires on parents' burden of care and worries; the Family Strain Questionnaire (FSQ) and the Child Vulnerability Scale (CVS). Statistical analysis included *t*-test, ANOVAs, stepwise regression analysis.

Results: a) At baseline parents of children with epilepsy had significantly higher CVS scores ($F_{1,52} = 7.607$; $p = 0.008$) and higher levels of worries (stigma $F_{1,52} = 17.186$; $p = 0.000$ and academic underachievement $F_{1,52} = 14.09$; $p = 0.000$) than controls; in each group, mothers had sustained a greater burden of care ($F_{1,52} = 67.186$; $p = 0.000$) and exhibited higher FSQ scores than fathers ($F_{1,52} = 9.075$; $p = 0.004$); b) after 12 months, the FSQ and CVS scores significantly diminished both for mothers (respectively $T_{26} = 3.253$; $p = 0.0034$ and $T_{26} = -3.499$; $p = 0.0018$); and fathers (respectively $T_{26} = 2.731$; $p = 0.0117$ and $T_{26} = -3.153$; $p = 0.0043$), while burden of care, worries and relationships among variables remained stable; c) the strain was significantly associated with perception of child's vulnerability (mothers $R^2_{(T0)} = 0.331$; $R^2_{(T1)} = 0.29$) and uncertainty (fathers $R^2_{(T0)} = 0.19$; $R^2_{(T1)} = 0.277$).

Conclusion: Diagnosis of epilepsy "only" induces a perception of vulnerability and worries (uncertainty of future) which in turn associate with the parents' strain.

p394

LIVING CIRCUMSTANCES OF PERSONS WITH SEVERE EPILEPSY AND AN INTELLECTUAL DISABILITY

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Purpose: Epilepsy affects approximately 25% of people with an intellectual disability and is more common in those with an IQ below 50. There is a lack of knowledge about the effect of epilepsy on living circumstances and consequently on quality of life in this population. In this study we will explore a) the relationship between the severity of the epilepsy, the intellectual disability and living conditions; b) the role of epilepsy in this relationship: is epilepsy a modulating or inhibitory factor with respect to living conditions and quality of life? How do the different aspects of the severity of epilepsy contribute to this role?

Method: The study is a clinical descriptive, nonrandomised study. During 18 months aspects of living conditions, quality of life and epilepsy are monitored. In this we follow Felce (*Journal of Intellectual Disability Research* 1997;41:126–135) who developed a model for measuring quality of life, defining it as an overall general well- being that comprises objective factors and subjective evaluations of physical, material, social, productive, emotional and civic well-being all weighted by a personal set of values. Aspects of the severity of their epilepsy are obtained in order to compute a score.

Results: 98 patients have been included and all assessments were carried out. All participants have epilepsy and are on antiepileptic drug treatment (on average 3 AED's). 40% have to deal with permanent restrictions due to their epilepsy, such as protective helmet or fixation. Five aspects of epilepsy are gathered to a score.

They have a mild to severe intellectual disability (IQ ranging 30 to 60). Most of them have comorbid problems (somatic, behavioural, physical handicaps). The participants all live in groups (mean size 11.2 persons) in units of the long-stay department of the epilepsy centre outside the community. The mean length of stay is 28 years. Their possibilities to control their own living circumstances are limited. Nonetheless most of them (89%) are satisfied with their life (QOL interview).

Conclusion: Living conditions of a group of 98 institutionalised adults with epilepsy and intellectual disability are described. Compared to persons with an intellectual disability without epilepsy (Bowley et al., 2000;44:529–543) their quality of life seems to be less). The role of epilepsy will be further explored.

p395

MEASURING STIGMA IN CHILDREN WITH EPILEPSY AND THEIR PARENTS

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Purpose: This study aims to assess the application of a promising tool for measuring stigma developed by Austin et al. (Austin J et al., *Epilepsy*

& Behaviour 2004;5:472–482). Although stigma is recognised in both children with epilepsy and their parents, levels of such have not been measured extensively. The questionnaires will be tested for suitability in a clinical setting, and will determine the value of the resulting data.

Method: The questionnaires were developed for children with epilepsy and their parents; they included Austin et al.'s stigma scales, and questions gathering sociodemographic data (child/parent age, child gender, residential area, age of diagnosis, epilepsy duration, seizure frequency and social class). Patients will be recruited from specialist paediatric epilepsy clinics in Swansea NHS trust, UK. All patients up to 19 years old will be included. If children are unable to complete the questionnaire, parent's questionnaires will still be collected.

Results: Twenty-nine children and 38 parents completed the questionnaires. The average stigma score for children was 1.82 (SD 0.86) and 2.61 (1.08) for parents. No correlations were found between child and adult stigma scores, or between stigma and the sociodemographic data collected.

Conclusion: The questionnaires were easily implemented in the clinical setting. Problems encountered included parental influence over the children's answers and collecting data from children with learning difficulties. The stigma scores were lower than those collected in the Austin et al. study. Although no significant correlations were found when considering sociodemographic factors, it is hoped that with the collection of further data, correlations will become apparent.

p396

SELF-SUPPORTING GROUPS: PSYCHOSOCIAL INTERVENTION

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Purpose: Epilepsy is a neurological chronic disease affecting the well being of patients and their families, with repercussions in psychosocial adjustment and quality of life. The self-supporting groups promote social interactions, intercommunication, sharing of feelings and positive relational experiences increasing self-esteem and emotional stability. The aim of this work is to demonstrate the importance of self-supporting groups for people with epilepsy and for their families and to estimate their evolution along time.

Method: A 12 item questionnaire was applied, to each member of the 3 self-supporting groups of the South Delegation of LPCE (2 groups of parents/family and 1 group of people with epilepsy). The results were submitted to a descriptive analysis by SPSS 11.0.

Results: Our sample is composed of 23 subjects (14 female; 9 male) between 21 and 68 years of age. Most of the individuals were informed of these groups by the neurologist or neuropaediatrician. 83% answered that their initial expectations concerning the groups were accomplished. 56% realise they need another kind of psychological support besides the self-supporting group. 72% affirmed that the groups had a positive psychological impact in their lives and in helping to accept epilepsy as a chronic disease. To inform others about epilepsy, to divulge and to expand the self-supporting groups are the aims of these individuals.

Conclusion: This work demonstrates that interacting with self-supporting groups promotes positive personal and psychological changes and determines a call to action attitude of their members in society.

p397

QOL IN ADOLESCENTS WITH EPILEPSY: RESULTS OF SEMI-STRUCTURED IN-DEPTH INTERVIEWS WITH SWEDISH TEENAGERS

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Purpose: It is a challenge to treat chronic disease in adolescents, especially epilepsy with unpredictable seizures. In a previous study based on a questionnaire sent to 86 13–19y old teenagers with epilepsy we found that >50% were not seizure free, experienced side effects from the anticonvulsant medication, and had low self-esteem. In order to improve the medical and psychosocial caretaking we performed semistructured indepth interviews with 8 adolescents with epilepsy in mainstream schooling.

Method: Semistructured in-depth interviews, analysed with a computerised aid (open code).

Results: Three boys and 5 girls were interviewed; only 1 teenager knew the exact diagnosis. Six had GTC, and 2 absences, 6/8 had experienced seizures during the last six months, 1 of them had daily seizures. There were 9 categories of concern in the interviews: seizures (debut, diagnosis) (n = 65), obstacles (n = 51), medication (n = 50) (side effects, treatment), feelings (n = 20), friends (n = 24), family (n = 19), (spare time), schooling (n = 17), and future (n = 13). On the question of what kind of care-giving, the adolescent wanted a less childish waiting area, they wanted to talk to the physician without the parents, they wanted information on rules for a driving licence, and work opportunities.

Conclusion: This group of patients need special care with emphasis on both medical care with information directly from the physician but also help to cope with the psychosocial situation, help to focus on the salutogenetic factors from the epilepsy nurse, possibilities of find information on and possibilities to chat with the nursing staff on the Internet.

p398

GENERAL KNOWLEDGE AND ATTITUDES TOWARD EPILEPSY AMONG PRIMARY LEVEL TEACHERS IN MACEDONIA

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Purpose: The study was conducted to determinate the knowledge regarding epilepsy among primary level teachers in Bitola, Macedonia, their knowledge regarding management of seizures in children, and the influence by the degree of knowledge to the attitudes toward epilepsy.

Method: A self-administered questionnaire was answered by 101 teachers, in three primary schools, with different levels of education (university 81 (80.2%), academy 20 (19.8%)) and different work experience (15 teachers up to 5 years, 33 from 5 to 15 years, 17 from 15 to 25 and 36 with more than 25 years work experience).

Results: All the teachers had heard about epilepsy. Forty-five of them (44.6%) have had a pupil with epilepsy (usually teachers with longer work experience) and 44 (43.6%) have witnessed a seizure. All knew that epilepsy is not contagious. Most information was from family/friends and TV (movies). Regarding the aetiology 78.2% answered that epilepsy is a brain disorder, 29 (28.7%) answered that epilepsy is a psychiatric disorder, 33 (32.7%) hereditary and 4 accepted it as "good punishment" (multiple choice question). Fifteen teachers (14.9%) answered that death can frequently occur during a seizure. They all knew that epilepsy isn't contagious. Some of the elements of the GTCS were recognised by almost all of them, but no one recognised the description of an absence seizure. 89% (91 teachers) thought that seizures could be controlled, 75.2% elected medications as treatment (17 in combination with psychotherapy, two medications and diet, two medications and an operation). 63% judged themselves as educated about what to do if a seizure occurred, but unfortunately only 15 (14.8%) answered correctly. Almost 84% chose pulling the tongue and putting an object between the teeth as first aid. Twenty teachers (19.8%) thought that pupils with epilepsy have to be isolated (special schools), mostly from the teacher group with longer work experience (attitudes). Eleven (10.9%) had objections if they had a pupil with epilepsy in the class (stigma). More than 33% had different criteria during the evaluation.

Conclusion: Almost all the teachers had heard about epilepsy, but their awareness did not equate with acceptance and understanding of epilepsy. Negative attitudes and bias towards epilepsy was still deeply ingrained among them, especially among teachers with longer work experience.

p399

TUBEROUS SCLEROSIS RESOURCE CENTRE IN NORWAY: AN EVALUATION OF FAMILY AND NETWORK COURSES

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Purpose: Tuberous Sclerosis Resource Centre (TSRS) in Norway is, to our knowledge, the only registered resource centre for tuberous sclerosis complex (TSC). The Centre was established in 1998 to: 1) inform patients and family members with a newly diagnosed TSC about the disease; 2) organise network courses for the social and health services in the patient's residential area. The main purpose of this study was to evaluate the participants' satisfaction with the courses provided by TSRC. A secondary objective was to assess any geographical variation in satisfaction with the network courses.

Method: 168 participants at either family (n = 14) or network courses (n = 154) during 2004 and 2005 filled in a questionnaire. Overall satisfaction with the courses was measured on a five-point response scale, with score = 1 indicating dissatisfaction and score = 5 indicating a high degree of satisfaction. We used Fischer's exact test, Kruskal Wallis, and Pearson's chi-square to analyse the relation between type of course, geographical region and the percentage of patients with maximum satisfaction scores (score = 5).

Results: The satisfaction rates (= 5) were somewhat higher for the family courses compared to the network courses (77% versus 62%), but not statistically significant. The mean total satisfaction scores were 4.77, 4.63, and 4.45 respectively ($p = 0.009$). The percentage scoring 5 (maximum score) were significantly higher in West/Central (80%), and South/East (67%) compared to Northern (47%).

Conclusion: The participants expressed a high degree of satisfaction with both courses. The variation in satisfaction rates between geographical regions indicates a potential for quality improvement of the courses provided in Northern Norway.

p400

THE PAMs EXPERIENCE: AN UPDATE

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Purpose: A learning partnership has been set up which aims to mobilise resources and improve competence among the partners for training and education of adults working in the medical field with an interest in epilepsy (PAMs). This project would provide European professionals allied to medicine (PAMs) with tools and methods to improve knowledge and expertise for prevention, diagnosis and treatment in epileptology and thus help to improve the quality of care to patients with epilepsy.

Method: This project is being realised from two sides: 1) A working group consisting of ILAE and IBE members is working out the content of this curriculum: essential knowledge about epilepsy, diagnostics of epilepsy, and principles of epilepsy treatment, therapy of epilepsy: pharmacological treatment; living with epilepsy; and communication and interaction. 2) Funding has been obtained as an EU Grundtvig 2 project which involves development of pedagogical skills needed for both individual and organised learning and the promotion of strategies for change in this educational sphere of adult learning, which to date has been very fragmented. The partners were from Malta, Hungary, Germany, and Eurepa. The main methods used were e-learning, elements of the moderation method, group work and problem-based learning.

Results: While the first year of the project was mainly dedicated to get an overview of already existing PAMs programmes, and to try out and evaluate teaching methods on their usability in different settings, in the second year, the first year results' are related to the content being worked out by the ILAE/IBE Working Group.

Conclusion: The project has been extremely successful with PAMs in member countries and an application has been made for a third year (2006–2007) in order to be able to finalise the basic curriculum. According to the action plan of the project, the curriculum should then be published and disseminated as well as a system for Train-the-Trainers courses and certification should be worked out.

Tuesday July 4, 2006
13:30–15:00
Poster Session 2
Clinical Neurophysiology

p401

VALPROATE TREATMENT IS SUCCESSFUL IN PATIENTS WITH PHOTOSENSITIVE EPILEPSY: IS IT TRULY SUSTAINED EFFICACY OR MERELY AGE-RELATED SPONTANEOUS REMISSION?

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Purpose: To determine whether the sustained therapeutic effect of sodium valproate (VPA) in treating patients with photosensitive epilepsy is due to its intrinsic pharmacodynamic effect or to natural disease remission. Although evidence exists that demonstrates VPA's continued positive clinical and EEG effect, determination of its true long-term effect is confounded by evidence indicating spontaneous remission. The mere finding of continued suppression of a photoparoxysmal response (PPR) with VPA use after serial testing over time is not sufficient evidence of its sustained efficacy.

Method: A chart review of patients with annual serial testing with standardised intermittent photic stimulation (IPS) was conducted. Those selected had IPS during VPA monotherapy without interruption for $\geq$ 2 years, and after withdrawal of VPA. Spontaneous remission meant no change in PPR range 30 days after the discontinuation of VPA.

Results: Fourteen patients (11F/3M) met our criteria, age = 10 to 69 yrs. The VPA monotherapy total daily dose (13 as Na salt) ranged between 150 and 1800 mg with a median of 600 mg. The suppressive effect of VPA continued up to 12 years (median = 4 yrs). In 1 patient with abolition of the PPR on VPA 600 mg, no change was seen after withdrawal of VPA at age 32; most likely, this is an age effect.

Conclusion: Repeat IPS PPR testing well after VPA withdrawal indicated spontaneous remission of photosensitivity had not occurred in all but 1 patient selected. VPA has proven sustained efficacy (median = 4 years, up to 12 years).

p402

LOBAR LOCALISATION INFORMATION: COMPARISON OF EEG AND MEG

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Purpose: The aim of this study was to describe the contribution of MEG in presurgical focus localisation compared to video-EEG-monitoring. The study concerns the precision of focus information and the additional benefit of MEG in cases of no or not clearly localised EEG findings.

Method: Eighty-four patients with presurgical video-EEG-monitoring and MEG investigation, who underwent surgical treatment between 1998 and 2004, were included. The anatomical lobe(s) of localisation results were compared to the resection affected lobe(s). Postsurgical outcome was used for validation. Data were analysed in respect of: 1) percentage of the results located in one anatomical lobe, 2) number of patients for whom MEG provided a localisation result within only one lobe, when interictal and/or ictal EEG localised to two or more lobes or yielded no localisation at all.

Results: 1) MEG results localised in 84% (n = 48 of 57 patients with spikes) within one anatomical lobe. Ictal EEG in 70% (n = 51 of 73), interictal EEG in 64% (n = 49 of 77).

2) In 20 (of all 84) patients a clear localisation within one lobe was not found either in interictal or in ictal EEG. In 10 of these cases MEG

provided a unilobar localisation which matched the resected lobe. These 10 patients became seizure free or achieved a reduced seizure rate.

Conclusion: MEG localised within one anatomical lobe in more cases compared to video-EEG-monitoring. MEG provided a unilobar beneficial localisation result in half the patients with no or multilobar video-EEG-findings. MEG yields additional information to video-EEG monitoring in the workup for epilepsy surgery and shows higher precision in presurgical focus localisation.

p403

SEIZURE PREDICTION ALGORITHM ON SCALP EEG IS SENSITIVE TO CHANGES IN STATE OF VIGILANCE

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Purpose: To evaluate a novel prediction algorithm on scalp-EEG of patients with temporal lobe epilepsy in order to preventively treat seizures in real time.

Method: We analysed data from 5 patients with a total of 19 seizures. We initially used the nonlinear measure of permutation entropy (PE) (*Bandt & Pompe Physical Review Letter* 2002;88:174102–6) to predict epileptic seizures online on the basis of scalp-EEG. PE is known to be similar to the Lyapunov Exponent, which is often suggested for seizure prediction. Permutation entropy was calculated over time using a moving window technique. ROC analysis was applied to evaluate the separability of amplitude distributions of PE resulting for preictal and interictal phase. The possibility to use a unique threshold for seizure prediction was tested. An additional analysis was undertaken to control for a possible dependency of PE on vigilance state.

Results: We found a good separability of interictal and preictal phase by means of PE. PE was also found to be sensitive to changes in the vigilance state. The changes of PE during the preictal phase were in most cases found to coincide with changes in the vigilance state.

Conclusion: This forecasting method shows firstly, that detection and real time prediction of the epileptic seizure on the basis of scalp-EEG can be done with a high performance. However, the dependency of the algorithm on vigilance state extremely restricts its possible application.

p404

EXPLORATION OF MOTOR CORTEX EXCITABILITY IN PATIENTS WITH AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY: A TRANSCRANIAL MAGNETIC STIMULATION STUDY

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Purpose: Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) has been found to be associated with five distinct mutations in the two genes coding for the alpha4 or beta2 subunits of the neuronal nicotinic acetylcholine receptor, which lead to altered receptor properties. We aimed to elucidate the origin of the epileptic seizures and to clarify the major structural features responsible for the induction of convulsions in the ADNFLE.

Method: Transcranial magnetic stimulation (TMS) was performed on 2 patients with ADNFLE, and on 10 control subjects. Measures of cortical excitability included the resting and active motor thresholds to TMS, the duration of the cortical silent period, the short latency intracortical inhibition (SICI) and intracortical facilitation using a paired-pulse TMS technique.

Results: SICI was significantly reduced in ADNFLE patients ($p < 0.05$, Mann-Whitney test). The other TMS parameters did not differ significantly between patients and controls ($p > 0.05$).

Conclusion: SICI is thought to depend on GABAergic inhibitory mechanisms; since cortical interneurones containing GABA have nicotinic as well as muscarinic receptors and receive rich cholinergic afferents, projecting principally from the brainstem and basal forebrain, the changes in SICI here described in ADNFLE patients may be due to an altered nicotinic receptor function. It could be hypothesised that an impaired nicotinic activity may deprive inhibitory GABAergic neurons of a source of excitatory inputs and thus reduce intracortical inhibition.

p405

ECHOENCEPHALOGRAPHY MIDLINE SPIKE SHIFT AT ICTUS AS STRONG EVIDENCE OF A FOCAL EPILEPTIC SEIZURE

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Purpose: The aim of the present work is to study the midline echo-spike shift (MESS) at the focal epileptic ictus. This work was intended to find a reliable method of bedside diagnostic of focal epileptic seizures.

Method: This study was carried out with an ULTRAMED A-mode cranioscope echoencephalograph. A 1.5 mega Hz ultrasound transducer was fixed to an area above the root of the ear. We observed 12 patients with focal epileptic adversive seizures, 14 patients with epileptic hemiclonic seizures, and 6 patients with hemiclonic psychotic seizures. The age range was 17 to 46. The problem has been studied for 2 years at our neurotraumatology department.

Results: The 4–7 mm MESS occurred towards an undamaged brain hemisphere. The maximum MESS was during hemiclonic epileptic seizures. The minimum MESS occurred during focal adversive epileptic seizures. During psychotic hemiclonic seizures no MESS was observed. In focal adversive epileptic seizures the MESS was in 10 patients (83%). During epileptic hemiclonic seizures the MESS was in 13 patients (92%).

Conclusion: A-mode MESS at focal ictus may be strong evidence of an increase in the cerebral regional blood flow. At the same time there is evidence of focal epileptic seizures. Our results are coincident with the findings of a functional transcranial dopplerography. The MESS method can be used to identify the side of the epileptic focus. This MESS method of application is covered by patent 2182463 (2001) registered in the Russian Federation.

p406

AUDITORY BRAINSTEM RESPONSE, MIDDLE-LATENCY RESPONSE, AND SLOW CORTICAL POTENTIAL IN EPILEPSY PATIENTS WITH ANTICONVULSANT TOXICITY

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Purpose: Auditory evoked potentials (AEPs) under anticonvulsant neurotoxicity have rarely been investigated. The aim of the present study was the inspection of AEPs in patients suffering from antiepileptic drug toxicity.

Method: Auditory brainstem responses (ABRs), middle-latency responses (MLRs), and slow cortical potentials (SCPs) have been estimated in 14 epilepsy patients of 14–44 years age, 3 females and 11 males. All subjects possessed symptoms of anticonvulsant neurotoxicity. Out of 14 patients, 8 were treated by monotherapy, carbamazepine-2, phenytoin-5, valproate-1, and 6 by polytherapy, various combinations with valproate-2, phenytoin-2, and clonazepam-2. The AEP parameters in individual patients were compared with the respective data in 33 age- and gender-matched healthy individuals.

Results: ABR abnormalities were revealed in 6 of 14 patients, 42.8%. Five patients from those were under phenytoin monotherapy. MLR abnormalities were detected in 10 patients, 71.1%. In all of them peak-latency prolongations have been observed. SCP alterations were detected in 13 patients, 92.8%, and were similarly manifested in latency lengthening. In 6 patients, individual SCP components were missing additionally. In 5 patients, exhibiting no clear EEG signs of drug toxicity, AEPs also demonstrated abnormal parameters. In 3 patients from those, SCP abnormalities were rough. After 1–4 weeks of drug or dose adjustments and, as a result, recoveries from intoxication, the occurrence and severity of AEP abnormalities decreased. In some cases, nevertheless, abnormalities remained unaltered.

Conclusion: Anticonvulsant neurotoxicity is reflected in AEP parameters. SCP alterations seem particularly characteristic. ABR shifts appear selectively typical for PHT intoxication. AEP measurements thus permit objectifying and proper monitoring of anticonvulsant neurotoxicity.

p407

STUDY OF THE MORPHINE EFFECT ON FREQUENCY OF HIPPOCAMPAL SEIZURES IN MICE

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Purpose: This study was designed to determine the effect of morphine on the frequency of different components of seizures induced by low Mg^{2+}ACSF in whole hippocampus preparation of mice.

Method: C57/BL6 mice 11 to 19 days of age were used. The animals were anaesthetised and the brain was removed (n = 25) and placed in ice-cold, continuously oxygenated ACSF for 3 min. Then the hippocampi were dissected and incubated in normal ACSF at room temperature for one hour before electrophysiological recording. Seizure activity was induced by perfusing the hippocampus with low $Mg2^{+}$ACSF. Extracellular recordings were performed mainly in the CA1 pyramidal cell layer. Seizure activity was quantified by measuring the frequency of ictal events.

Results: All applied concentrations of morphine and naloxone 10 μM decreased the frequency of seizures, more effectively in the tonic part of the seizure. Naloxone 10 μM not only did not inhibit the inhibitory effects of morphine on seizures but also markedly suppressed the frequency of epileptiform activities. Also, the combined application of morphine and naloxone completely blocked the bursting activity.

Conclusion: Our results indicate that morphine may decrease the frequency of hippocampal seizures through different receptors than opioid receptors, because naloxone, the opioid receptors antagonist, cannot block the effect.

Key words: hippocampus, naloxone, morphine, seizure, epilepsy, frequency, low Mg^{2+}ACSF.

p408

PROPAGATION TIME COURSE OF CONTRALATERAL AND IPSILATERAL SYNCHRONISED SPIKES: HIGH-DENSITY ELECTRICAL MAPPING COMPARISON

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Purpose: In some patients with localisation-related epilepsy, focal primary discharges activate the contralateral homologous cortex as a mirror focus. On the other hand, some patients with parietal and occipital lobe epilepsies show apparently synchronised spikes within the ipsilateral cortex. Although these intrahemispherically synchronised spikes might be generated by a mechanism resembling that of a mirror focus, their actual basis has not yet been explored. To investigate the nature of these spikes, we analysed their peak latency disparity and propagation patterns of the spikes.

Method: Subjects were 5 patients with a temporal mirror focus and 3 patients with intrahemispherically parietofrontopolar synchronised spikes. We estimated the time lags between the peak latency of the interictal synchronised spikes and determined how the spikes were propagated over the scalp recording using 64-channel spherical spline mapping with a sampling rate of 1000 Hz.

Results: Mean time lags of peak latency of temporal mirror foci were 20.9 to 69.2 ms. In 3 cases, mirror foci appeared in both temporal areas. Parietal spikes were always followed by frontopolar spikes. Mean time lags of peak latency were 20.6 to 27.1 ms. Spherical spline mapping demonstrated that spikes originating in the parietal area were propagated directly to the frontopolar area without cortical spread.

Conclusion: Parietal spikes were always directly followed by ipsilateral frontopolar spikes without cortical spread, while temporal mirror foci were produced in both directions in some patients.

p409

TIME-FREQUENCY DYNAMICS OF SPIKE-WAVE DISCHARGES IN ABSENCE EPILEPSY PATIENTS USING WAVELET TRANSFORM

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Purpose: Time-frequency structure of spike-wave discharges (SWDs) of absence epilepsy is sparing investigated. Recently the modified wavelet Morlet transform was developed by us and used for SWD time-frequency analyses in animal model of absence epilepsy (Bosnyakova et al., *J. Neurosci Methods* 2006, in press). Now we present the results of SWDs time-frequency analyses in patients with different forms of absence-epilepsy.

Method: SWDs of 22 patients were investigated. EEG was registered from 16 electrodes placed by scheme 10×20. For the registration Neurocartograph (MBN, Moscow) was used. The time-frequency dependence in SWDs was analysed using modified wavelet Morlet transform.

Results: In 12 of 22 patients SWDs' time-frequency dynamics were of the same type. The discharge's beginning had the largest frequency (5.7 ± 1.3Hz). This frequency decreased fast up to 3.9 ± 0.4 Hz and then it reduced slowly with the periodicity 1–2 sec. By the end of the discharges the frequency decreased up to 3.5 ± 0.5 Hz. In the case of short discharges (1-2 sec) the frequency dropped up to 2.6 ± 0.2 Hz and the discharge abruptly ended. In the remaining 10 patients the SWDs' time-frequency dynamics differed from those described above and were of various types.

Conclusion: Some types of SWDs' time-frequency dynamics were revealed and compared with neurological patients' examination. New information about this kind of paroxysmal activity was found. Some assumptions could be made about mechanisms of discharges abrupt cessations on the basis of obtained data in absence epilepsy patients and animal models.

p410

FOCUS DIAGNOSIS USING ELECTROCORTICOGRAPHY ANALYSIS SOFTWARE AND THREE-DIMENSIONAL RECONSTRUCTED MRI IN PATIENTS WITH MULTICHANNEL INTRACRANIAL ELECTRODES

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Purpose: Invasive intracranial recording provides dynamic neuronal activity in patients with neocortical epilepsy. However, it is not always easy to define the epileptic focus on electrocorticography (ECoG) because ictal discharges are recorded simultaneously on many channels or rapidly propagate to the surrounding cortex. We investigated the usefulness of computerised voltage topographic mapping analysis of ictal spikes on multichannel grids using three-dimensional reconstructed MRI (3-D MRI), which enhanced spatial and time resolution.

Method: We studied 3 neocortical epilepsy patients with long-term ECoG monitoring. We took photographs of cortical surface electrodes by digital camera and then took CT scans immediately after surgery to create a 3D electrode template with MRI. After ictal recording, spike voltage topographic maps were created with review and analysis programmes (Insight and Prism) on the electrodes template of the grid of cortical surface and 3-D MRI. In 1 patient, we also analysed ictal spikes with continuous wavelet.

Results: In 2 cases, ictal discharges appeared on many channels simultaneously. We had difficulty in identifying the epileptogenetic area by conventional assessment. Voltage topographic mapping showed the extent of ictal discharges, which enabled us to recognise visually the ictal onset zone and its time course. In one patient, ictal ECoG showed bilateral synchronised spikes and voltage map of a preceding spike represented broad activated area. With the detail wavelet analysis of the preceding spike, the ictal onset zone was more clearly localised.

Conclusion: Application of electrocorticography analysis software and three-dimensional reconstructed MRI is useful to visualise and

detect the ictal onset zone in patients with multi-channel intracranial electrodes.

p411
K COMPLEX AS A TRIGGERING FACTOR FOR SEIZURES IN AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY (ADNFLE)
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Purpose: Seizures in ADNFLE occur preferentially during cyclic alternating patterns (CAP) of NREM sleep [Zucconi et al., *J Clin Neurophysiol* 2000;17:77–86]. The precise relation of seizures to CAP events is not yet well described. Our purpose is to study the relationship between K complex and seizures in a case of genetically confirmed ADNFLE.

Method: Four day video-EEG monitoring of an ADNFLE case with CHRNA4 gene mutation.

Results: We report the case of an 18-year-old woman presenting an ADFNLE with a *CHRNA4* gene mutation, who had nocturnal motor seizures, starting with head extension, mouth opening, dystonic movements of the right then left arm, oro-alimentary automatisms, associated with athetotic movements of right then both arms followed by apnea or vomiting-like movements. They ended with an intense snoring sound. The video-EEG monitoring showed that most episodes took place during a CAP in different stages of NREM sleep. They started just after a K complex. Interestingly, many were triggered by a sound that induced the appearance of a K complex which was immediately followed by the motor episode. The ictal EEG showed anterior bilateral rapid low voltage rhythms (10–11 Hz), followed by slower high voltage waves in the anterior midline region. Episodes lasted 20 to 30 seconds. Interictal EEG recordings showed no abnormalities.

Conclusion: K complex is one of the possible triggering factors of seizures in ADNFLE.

We will discuss the role of the different sleep stages in the occurrence of seizures in this disease.

p412
CLINICAL AND NEUROPHYSIOLOGICAL ASPECTS OF EPILEPSY WITH STIMULUS-INDUCED SEIZURES
V. Karlov, and O. Andreeva (The Moscow State Medico-Stomatological University, Russia)

Purpose: To study the trigger factors, clinical and neurophysiological comparisons of patients with epilepsy seizures that are always induced by various stimuli.

Method: 191 patients (134 children, 57 adults) from 5 to 45 years (mean 16.7 $\pm$ 6.9) were studied. All had different types of epileptic seizures, induced by various stimuli. Idiopathic epilepsy was diagnosed in 59 patients (31.0%), cryptogenic epilepsy in 105 patients (54.9%) and symptomatic epilepsy in 27 patients (14.1%). Clinical, MRI, EEG, including, if needed, video EEG sleep monitoring, the method of multistep dipole localisation (MDL) of spike activity and visual evoked potentials (VEP) were used.

Results: The patients with photosensitive epilepsy; 158 (82.7%) were predominant. 8 (4.2%) patients had pattern-sensitive seizures, 10 (5.2%) patients had seizures induced by eye-closing (FOS-seizures). There were 5 (2.6%) patients with seizures induced by thinking, 2 (1.1%) patients, with seizures induced by eating. In single patients the trigger factors of the seizures were: fright (startle-seizures), sound, music, walking, reading and hot water. We also, for the first time, described 2 patients (1.1%) with epileptic seizures precipitated by laughter. Two patterns of epileptiform activity have been revealed in thinking-epilepsy: the first started from the left hemisphere (thinking-speech) and the second started from the right hemisphere (thinking space). In photosensitive epilepsy two different variants of VEP responses were revealed. The first: early components transformation into spike-slow wave form and late components of alpha-theta diapason; the second: absence of spike-wave pattern and alpha-diapason oscillations. In 7 of 10 patients with FOS epilepsy the focuses of spike activity were identified in the mediobasal frontal lobe by MDL's method.

Conclusion: This study demonstrates epileptic systems that realise stimulus sensitive responses by involving one or another part of the neural network and have a complex and nonsynonymous character. In this connection, the term "stimulus-dependent seizures" is more adequate.

p413
DIAGNOSTIC VALUE OF INVASIVE RECORDING FOR TEMPORAL LOBE EPILEPSY: THE HOMOLKA EXPERIENCE
T. Procházka, Z. Vojtìch, I. Mareèková, and M. Kalina (Na Homolce Hospital, Prague, Czech Republic)

Purpose: Temporal lobe epilepsy (TLE) is the most common type of surgically remediable epilepsy. In the majority of cases, only noninvasive evaluation is required before surgery. However, invasive monitoring with intracranial EEG electrodes is sometimes necessary. The objective of this study was to determine the correlation of invasive video EEG (VEEG) recordings with data obtained during noninvasive evaluations.

Method: We retrospectively reviewed data of all adult epilepsy surgery candidates who had undergone invasive EEG monitoring at the Epilepsy Center na Homolce from 1999 to 2004 ($n = 53$). Only those patients with suspected TLE were included in the study ($n = 33$). For each patient we compared invasive VEEG result with hypothesis based on noninvasive methods.

Results: There were 13 patients with nonconvergence of imaging with scalp EEG, 10 patients with nonlesional TLE, 5 patients with suspected bitemporal epilepsy and 5 patients with lesional TLE. The concordance between invasive VEEG and noninvasive hypothesis was seen only in 22 (66%) patients. Among 11 nonconcordant patients, 4 were from bitemporal group, 5 were imaging/EEG nonconvergent and 2 were nonlesional. Noninvasive hypothesis was accurate in all patients with unilateral hippocampal sclerosis with contralateral scalp ictal onset and in those with MRI-negative PET-positive TLE. 27 patients underwent resective surgery with >12 months follow-up. Of those, 56% were seizure free and 26% were without significant improvement.

Conclusion: In our series of adult patients with TLE, the value of invasive recording in presurgical evaluation was surprisingly high.

p414
FRONTAL AND PARIETAL INTERHEMISPHERIC INTEGRATIVE INTERACTIONS IN THE MODEL OF EPILEPSY
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Purpose: The aim of the study was to analyse the interaction of frontal areas with parietal, temporal, and occipital areas of contralateral hemispheres in patients with symptomatic epilepsy.

Method: The changes of higher integrative (mental) functions were evaluated in 4 groups (26 patients in each, mean age 32.5, S.D. 6.5 years) with different lateralisation and localisation of epileptic focus. The mapping of EEG spectral power and coherence was used for the analyses of the brain bioelectrical activity and was analysed with Program Statistical Package WinStat-7.0.

Results: Controversial data in the literature and our examinations deserve special attention. There is numerous evidence for separate right- and left-hemisphere epilepsies: clinical examinations and literature data mainly confirm this viewpoint. Our results (electrophysiological, psychological, clinical) displayed that in a number of cases in epilepsy, functional communications between the frontal area and somatosensory area of contralateral hemispheres may cause the "additional" clinical and behavioural events symptomatic of epilepsy, which is affected by contralateral hemisphere dysfunction. The statistical analysis of the brain bioelectrical activity showed the increase of spectral power and coherence in the EEG delta band in the frontal area of one hemisphere and in the parietal brain regions of the contralateral hemisphere. The data obtained testify to functional integrative interactions between fontal and parietal areas of opposite hemispheres.

Conclusion: The data obtained testify to functional integrative interactions between frontal and parietal areas of opposite hemispheres. The results permit us to assume it may be it possible to explain a number of uncleared clinical cases, the formation of nonmirror foci, heteronymous

to the epileptic focus clinical picture, and inefficiency of antiepileptic drug therapy. The features of cortical interhemispheric associations according to data in the literature data is not pathognomonic for epilepsy and reflects one of the forms of functional flexibility causing a new level of the reorganisation of integrative activity.

p415
EYE MOVEMENTS AND ANTIEPILEPTIC DRUGS
C. Lo, and S. Shorvon (Institute of Neurology, University College London, UK)

Purpose: The aim of this study was to test the hypothesis that saccade velocity (or other saccadic parameters) can be used as a surrogate marker to predict/evaluate the clinical effects of antiepileptic drugs (AEDs). This abstract presents the findings of initial proof of the principle stage of this study.

Method: Epilepsy patients on monotherapy with carbamazepine (CBZ) and other AEDs were recruited. A package of eye movement examinations was performed, related to serum drug levels measured before and after taking the morning dose. The responsiveness of eye movement to changes in serum level (trough and peak) was correlated to clinical responsiveness.

Results: Saccadic velocities were presented in a series of patients showing the marked variation within individuals to changing drug doses. 30% differences were noted in some patients between different serum levels, with conversely little change in others. For carbamazepine, epoxide levels also influence velocity and are included in carbamazepine measures. Latency of saccades is less sensitive to the changes of serum concentration. The relation of saccadic changes to clinical effect is shown in terms of effectiveness.

Conclusion: The computerised measurement of eye movements is robust and easily applied to routine clinical settings. In this study, the reliability and variance of changes in eye movement measures in relation to drug responsiveness was explored. As the molecular and neuronal mechanisms which underpin the effect of drugs on eye movements is similar to those involved in the antiepileptic effect, it seems possible that this simple clinical test will be a useful predictor of the therapeutic effect.

p416
SERIAL EVOLUTION OF PLEDS
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Purpose: Periodic lateralised epileptiform discharges (PLEDs) are defined as spikes or sharp waves occurring at approximately regular intervals. According to Reiher'sclassification, PLEDs can be subdivided into benign PLEDs proper (including class 1, 2, and 3) and malignant PEDs plus (including class 4 and 5). This study was performed to investigate 1) the serial pattern of PLEDs. 2) the evolution of malignant PLEDs plus to benign PLEDs proper, and 3) to suggest a more benign form in the same PLEDs class.

Method: Thirty-seven patients who had two or more available EEGs were included in this study. All patients had structural brain lesions identifiedin the brain CT/MRIs. Patients with hypoxic brain damage or uncertain diagnosis were excluded. 237 EEGs from 37 patients were retrospectively analysed and the pattern of PLEDs classifiedaccording to Reiher's classification.

Results: One hundred and two PLEDs were identified out of 237 EEGs. (PLEDs proper: 100 EEGs, PLEDs plus: 12 EEGs). Seventy one EEGs belonged to class 3. We subdivided them into 1) simple group, 2) benign group, 3) vigorous group, and 4) suppressed group. Most PLEDs started with a vigorous or suppressed pattern of class 3 evolving into class 3 of simple or benign pattern, and then changing to class 1 or class 2. During the course, medium to high amplitude, complex sharp waves became lower amplitude and broader basis, simple sharp waves (class1/2). And finally they buried into theneighboring background waves. PLEDs started with class 3 of benign or simple pattern rapidly changing into class 1 or 2 and patients whose EEG started with class 1 or 2 showed the most rapid improvement in the EEGs and better prognosis.

Conclusion: PLEDs have five distinguished classes. As time goes by, with proper treatment, they evolved from a malignant class to a benign class and finally disappeared. Class 3 had more diverse patterns and we suggest a vigorous and suppression pattern in more malignant forms of PLEDs in this class.

p417
DIFFERENCES BETWEEN INTRACEREBRAL ACTIVITIES OF PATIENTS WITH IDIOPATHIC GENERALISED EPILEPSY BEFORE AND AFTER CHRONIC VALPROATE THERAPY
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Purpose: EEG background activity was localised by LORETA to test the possible differences between brain electrical activities of untreated and valproate-treated patients with idiopathic generalised epilepsy (IGE).

Method: 19-channel EEG data of 15 IGE patients before and after chronic valproate therapy were studied. For source localisation of brain electrical activity LORETA, a new tomographic method was applied, where localisation is based on images of standardised current density. The method is able to localise electrical generators in 3 dimensions in four frequency domains: delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25 Hz). For the analysis 42 (S.D.: 1.7) artifact-free, 2 sec epochs were selected from the filtered raw EEG (1.5–25.0 Hz) and were processed by LORETA. Statistical differences between pairs of conditions were computed as images of *t*-values. To assess the possible differences in background EEG activity, voxel-by-voxel dependent *t*-tests were computed. The *t*-statistic images were examined to localise regions showing statistically significant effects thresholded at 1% probability level.

Results: All patients became seizure-free. Valproate caused a statistically significant ($p < 0.01$) decrease of delta and theta band EEG activity in the frontal cortex, and in part of the temporal cortex. Valproate did not alter the activity of the parietal and occipital cortex, and in the remaining areas of the temporal cortex.

Conclusion: The selective effect of valproate is related to areas of the cortex that might be responsible for the initiation of the seizures in IGE. The relationship between clinical and EEG effect of valproate might be suggested.

p418
ELECTRICAL SOURCE IMAGING OF SPATIAL RELATIONSHIPS BETWEEN LESIONAL AND IRRITATIVE ZONES IN MEDICALLY INTRACTABLE POSTERIOR PARTIAL EPILEPSIES
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Purpose: Medically intractable posterior partial epilepsies (MIPPE: occipital, parietal, TPOJ) remain a challenge in term localising the irritative zone (which generates interictal spikes) and the epileptogenic zone (which generates seizures). This may directly explain the low rate of success of surgery compared with temporal or frontal lobe epilepsies. Recent development of high resolution EEG (HR-EEG) which allows electrical source imaging of generators of spikes could help to localise the irritative zone and to study its relationships with MRI lesion.

Method: Prospective, multicentric (Nancy, Reims) study of patients with MIPPE. Each patient had a comprehensive presurgical evaluation comprising video-EEG recordings of seizures, HR-EEG (64 channels and dipole modelling with ASA, ANT) and cranial MRI.

Results: Since the beginning of the study, 3 patients have been included. In patient EN, the generator of interictal spikes (IIS) is centered on the left lateral occipitotemporal sulcus, overlapping the lesional zone (regional subcortical atrophy). In the patient PN, IIS are localised in

the right inferior parietal gyrus outside but next to the lesional zone (periventricular nodular heterotopia) suggesting a pathological connection between these two distant neuronal assemblies. In the last patient, IIS have a right temporal pole generator related to the ispilateral hippocampal atrophy but distant from the occipital dysplasia.

Conclusion: In MIPPE, relationships between the lesions and the irritative networks are complex. HR-EEG is a promising tool to study these relationships and take a place in presurgical investigations.

p419

FRACTAL DYNAMICS OF THE THETA RHYTHM IN EPILEPSY

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Purpose: The purpose of the present study consisted of in investigation of fractal dynamics of the theta rhythm at initial and later stages of epileptogenesis during the absence of paroxysmal discharge (PD).

Method: The examination was carried out with 30 healthy subjects, 32 patients with a preclinical stage of epilepsy who had a single unprovoked seizure and no PD, 29 epilepsy patients with a clinical stage of epilepsy (CSE), but without PD on the routine EEG, 34 patients with CSE and PD. The power spectrum of the theta rhythm envelope were calculated for monopolar EEG on the 3 min recoding devoid of PD. Power spectrum form had the appearance of $1/f^{\beta}$ where f = frequency, β = fractal index. Fractal indexes were calculated within the range of low-frequency ($\beta 1$) and medium-frequency ($\beta 2$) fluctuations of the theta rhythm amplitude.

Results: In case of discovery of paroxysms on the EEG in epilepsy, a sharp change of the theta activity fractal characteristics more marked with $\beta 2$ takes place. The appearance of PD in epilepsy leads to that in the range of the theta rhythm. The values of $\beta 1$ reach the greatest magnitudes in F3, F4, C3, F7, F8 and T3 as compared with all other groups of examinees ($p < 0.05$). The same changes occur with the values of $\beta 2$, but already over all the cortical areas ($p < 0.01$).

Conclusion: Thus, increase in stability, and regularity and decrease in complexity of the theta rhythm represent an indicator of a high probability of paroxysms appearance, a precursor of the development of PD on the EEG.

p420

ACHIEVING SLEEP STATE DURING EEG IN CHILDREN: SEQUENCE OF ACTIVATION PROCEDURES

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Purpose: Hyperventilation (HV) during an EEG is often followed by drowsiness. The effect of intermittent photic stimulations (IPS) on awake/sleep state is unclear. The current study was conducted to determine if the sequence of activation procedures have an impact on acquisition of sleep during a routine, non–sleep deprived EEG.

Method: Children, scheduled between 9 to noon, who were not sleep deprived and able to hyperventilate, were included in a 3-month prospective study undertaken at the Neurophysiology Laboratory of a tertiary children's hospital. In the first 48 children evaluated, IPS was started 5 minutes into the EEG recording and HV was elicited at the end of the session (group I). For the next 48 children, HV was started 5 minutes into the EEG recording and IPS were presented at the end of the EEG (group II). Both groups were assessed for the presence or absence of sleep during their EEG recording.

Results: Only 3 of the 48 (6.2%) children in group I versus 17/48 (35.5%) in group II attained sleep ($p < .0001$, OR = 8.68, 95% CI 2.34-32.22). Therefore, the children who hyperventilated at the beginning of the session had an 8-fold increase chance to attain sleep in comparison with children who received IPS at the beginning of the recording followed by HV at the end.

Conclusion: We recommend that when performing routine non-sleep deprived EEGs in children, HV be performed first with IPS at the end of the EEG in order to maximize the yield of attaining sleep recording during the study.

p421

HYPNOGENIC PAROXYSMAL DYSTONIA: DOES IT EXIST?

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Purpose: Nocturnal or hypnogenic paroxysmal dystonia (HPD) are rarely reported complex motor attacks occurring abruptly during sleep, especially NREM sleep. The existence of HPD as a distinct nosological entity has been the cause of much discussion. Many authors consider these nocturnal motor attacks to be frontal lobe epileptic seizures (FLS). In many of the patients presented to support the hypothesis that HPDs are in fact FLS the dystonia is mostly only a minor part of what is obviously an epileptic seizure and should not be a point of discussion. The majority also have in addition to their nocturnal "dystonic" attacks, seizures of obvious epileptic origin or epileptiform activity in the interictal EEG. However, patients do exist who experience pure HPD that show no other semiology which would relate them to FLS. In the EEG during such episodes the typical delta arousals pattern that is otherwise associated with NREM parasomnias is seen.

Method: A retrospective review was made of all patients who were referred for unclear nocturnal events. All night polysomnographic-video EEG recordings were performed utilising all 10–20 electrodes.

Results: We found a total of 12 patients who had pure nocturnal dystonic attacks, during which the EEG showed delta arousals. On complete awakening the semiology abruptly ceased. There was no additional semiology that would support a diagnosis of epilepsy.

Conclusion: Our findings support the fact that HPD as a distinct nosological entity does exist. We suggest that it be considered, in analogy to confusional arousals, an incomplete motor awaking with associated delta arousal in the EEG.

p422

POSTLESION FOCAL NEOCORTICAL EPILEPSY IN HUMANS: THE ROLE OF THE BLOOD–BRAIN BARRIER

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Purpose: Recent studies in experimental animals suggest that lesions of the blood–brain barrier (BBB) play a key role in the pathogenesis of focal neocortical epilepsy (Seiffert et al., *J Neurosci* 2004;24:7829–36). The purpose of the present study was to evaluate possible correlations between areas of enhanced BBB permeability and areas with abnormal neocortical electrical activity in human patients suffering from lesion-related seizures.

Method: Included in this study were patients with mild-moderate blunt head trauma. Patients underwent standard magnetic resonance brain scan sequences, as well as dynamic studies aimed at evaluating the integrity of the BBB. In addition, a postgadolinium T1 sequence was used to evaluate statistically significant changes in cortical signal, suggesting diffusion of the contrast material across an altered BBB. EEG was recorded from subjects using a clinical EEG unit (CEEGRAPH IV, Bio-logic Systems Corp., Mundelein, Illinois). Areas of aberrant power spectra slowing and interictal like events were localised using low resolution electrotomography (LORETA) and statistical parametric mapping.

Results: Increased BBB permeability following focal brain trauma can be measured and localised in the neocortex. In some cases BBB permeability may last up to several months following the traumatic event. In ca. 30% of the patients (n = 21) examined under this study, spatial correlation was found between regions with enhanced BBB permeability and regions with localised focal cortical slowing or inter-ictal activity.

Conclusion: Our data suggest that a prolonged increase in BBB permeability following head trauma may be associated with abnormal, hypersynchronised neocortical activity, perhaps predisposing to epileptic seizures.

p423

INTEROBSERVER RELIABILITY OF VIDEO-POLYSOMNOGRAPHIC DIAGNOSIS OF NOCTURNAL FRONTAL LOBE SEIZURES

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Purpose: The diagnosis of nocturnal frontal lobe epilepsy (NFLE) is mainly based on video-polysomnographic examination. Paroxysmal sleep-related disturbances distinguishing NFLE are characterised by one or all of the following movement-related subtypes: 1) paroxysmal arousals (PA–brief and sudden recurrent motor paroxysmal behaviour), 2) supplementary motor area seizures (SMAs–motor attacks with dystonic features), 3) hypermotor seizures (HMs–motor attacks with complex dyskinetic features) 4) episodic nocturnal wanderings (ENW–stereotyped, agitated somnambulism). The aim of this study was to estimate interobserver reliability of video-polysomnographic diagnosis in patients with suspected NFLE among sleep medicine experts, experts in epileptic disorders and trainees in sleep medicine.

Method: Sixty-six patients referred to our sleep centre for suspected NFLE were included. All underwent nocturnal video-polysomnographic recording. Six doctors (3 residents and 3 trainees) independently classified each case as "NFLE ascertained" (according to the above specified subtypes: PA, SMAs, HMs, ENW) or "NFLE excluded." Interobserver reliability was calculated by means of Kappa statistics, and interpreted according to standard classification (0.0–0.20 = slight agreement; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; 0.81–1.00 = almost perfect).

Results: The observed raw agreement on the diagnosis of NFLE ranged from 63% to 79% between each pair of raters; the interobserver reliability ranged from "moderate" (kappa = 0.50) to "substantial" (kappa = 0.72). The major source of variance was the disagreement in interpreting arousal movements as PA or not. There were no differences in the level of agreement between residents and trainees.

Conclusion: Among sleep medicine/epileptologist residents and trainees, interobserver reliability of diagnosis of NFLE on the basis of videotaped observation of sleep motor phenomena is not satisfactory. One of the sources of variance is probably the interpretation of motor phenomena resembling simple arousals or PA. Explicit video-polysomnographic criteria for the classification of paroxysmal sleep motor phenomena are needed.

p424

CLINICAL, MRI AND DIPOLE LOCALISATION ANALYSIS IN DIFFERENT SUBTYPES OF MALFORMATIONS OF CORTICAL DEVELOPMENT (MCD)

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Purpose: MCD represent the second cause of refractory epilepsy in adults. Clinical, epidemiological and localisation of the epileptogenic zone, through dipole localisation of the different subtypes, were compared.

Method: For dipole localisation, our work group developed software that allowed optimisation of the application of Polhemus and BESA. The EEG (10-10 system) were obtained for 3 hours with 64 channels (Stellate). The patients were divided in 3 groups: G1: abnormal proliferation (cortical focal dysplasia and neoplasias), G2: abnormal migration (heterotopias), and G3: abnormal organization (polymicrogyria). We analysed different variables, particularly the occurrence of gradient of divergence (GD) clinical-MRI-dipole localisation.

Results: We included 80 patients. The significance data, in G1 (n = 40): women 42.5%, neurological deficit (ND) 7.5%, GD 12.5%. G2 (n = 24): women 75%, ND 8.3%, GD 16.7%. G3 (n = 16): women 43.7%, ND 75%, GD 31.2%.

Conclusion: We found between the subtypes of MCD a significant difference in relation to sex, women's majority in G2, neurological deficit in G3. And we observed a gradient of divergence minor in G1 and most important in G3, corresponding with the worst postsurgical prognostic in the last group. The clinical information, MRI and the source localisation methods proved useful in distinguishing the differences and the prognosis in the patients with MCD.

p425

DYNAMIC CHANGES OF ICTAL HIGH FREQUENCY OSCILLATIONS IN NEOCORTICAL EPILEPSY: USING MULTIPLE BAND FREQUENCY ANALYSIS

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Purpose: To characterise the spatial and temporal course of ictal high frequency oscillations (HFOs) recorded by subdural EEG in children with intractable neocortical epilepsy.

Method: We retrospectively studied 9 children (4 girls and 5 boys, 4 to 17 years) who presented with intractable extrahippocampal localisation-related epilepsy and underwent extraoperative video subdural EEG and cortical resections. We performed multiple band frequency analysis (MBFA) to evaluate the frequency, time course and distribution of ictal HFOs. We compared ictal HFO changes before and after clinical onsets, and postsurgical seizure outcomes.

Results: Seventy-eight of 79 seizures presented HFOs. MBFA distinguished multiple band and sustained single band HFOs. Three patients with partial seizures alone and 4 with epileptic spasms showed multiple band HFOs. Three patients with partial seizures with secondary generalisation had multiple band HFOs before clinical onset and following sustained single band HFOs after clinical onset. In 4 patients with postoperative seizure freedom, there were more electrodes with HFOs and faster HFOs inside the resection area than outside both before and after clinical onsets. In 5 patients with residual seizures, after clinical onsets, there were more electrodes with HFOs and faster or equal frequency of HFOs outsides.

Conclusion: In partial seizures with secondary generalisation, multiple and sustained single band ictal HFOs were confined to a small area. In partial seizures alone and epileptic spasms, multiple band HFOs were presented in a larger area. When the surgical resection included all ictal HFOs present throughout the seizure, post-surgical seizure freedom was obtained. The area of confined ictal HFOs correlated to the discrete epileptogenic zone.

p426

INTRACRANIAL ELECTROPHYSIOLOGICAL FINDINGS SUGGESTING PRIMARY EPILEPTOGENIC REGION IN NONLESIONAL SECONDARY GENERALISED EPILEPTIC ENCEPHALOPATHY

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Purpose: To characterise electrophysiological features suggesting primary epileptogenic region to differentiate from irritative zone in nonlesional secondary generalised epileptic encephalopathy.

Method: We retrospectively reviewed the long-term intracranial EEG's in 6 patients of nonlesional infantile spasm or Lennox-Gastaut syndrome, who became seizure free after surgery. We compared the ictal and interictal characteristics differentiating the primary epileptogenic region from the secondary irritative area by visual review for 10 randomised 2 minutes of interictal recordings during patient's non-REM sleep.

Results: 1) Interictal features such as repetitive spikes, paroxysmal fast activities, high voltage rhythmic sharp and slow wave discharges, electrodecrements, and interictal localised rhythmic slow waves are significantly prominent in the primary epileptogenic region. 2) Localised

paroxysmal fast activities are the most significant finding for localising the epileptogenic region. 3) The frequency of isolated spike activities are not significantly different between these areas. 4) Ictal patterns of repetitive spasms or atonic seizures were repetitive spiking, rhythmic sharp and waves, or paroxysmal fast activities followed by slow waves or electrodecrements. 5) All these ictal features were significantly more prominent in the primary epileptogenic region.

Conclusion: Interictal findings such as repetitive spikes, paroxysmal fast activities, high voltage rhythmic sharp and slow wave discharges, electrodecrements, and localised slow rhythmic waves as well as more prominent ictal features in intracranial EEG recording can be critical electrophysiological features to determine the primary epileptogenic region in nonlesional cases of secondary generalised epileptic encephalopathy.

p427

POSTERIOR ALPHA RHYTHM IS ACTIVATED BY DISAPPEARANCE OF A VISUAL FIXATION STIMULUS

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Purpose: Activation and suppression of the posterior alpha rhythm (AR) by eye closure and opening is a commonly known phenomenon. The underlying neurophysiological mechanisms are not clear. This study investigates the relationship between AR and fixation.

Method: 10–20-EEG was recorded from healthy individuals (n = 8). Via a monitor (dark room) subjects were presented black objects on white background for 5sec: (1) randomly distributed small squares (0.6° size), (2) regularly distributed small squares (0.6°), (3) large squares (6°), (4) large diamonds (6°). Following each object, a homogenous light-grey screen was presented for 5 sec. Screen luminance remained constant throughout the experiment. The protocol was repeated with fixation eliminated by Frenzel lenses. The amplitude of AR (peak-to-peak, O1-T1/O2-T2) was determined for the first (S1) through fifth seconds (S5) following object disappearance. Statistical comparisons were made using Wilcoxon's test.

Results: AR was present in all individuals. During object presentation, AR was suppressed. Disappearance of objects (presentation of grey screen) resulted in AR activation (ARA). There was no correlation with eye blinks. ARA was more robust after disappearance of larger (3.4), compared to smaller objects (1.2): average amplitudes 64 μV and 24 μV ($p < 0.05$). After disappearance of larger objects, AR was more pronounced in S1, compared to S5 ($p < 0.05$). Eliminating fixation abolished ARA.

Conclusion: Eye closure is not required for ARA. AR can be generated while a subject is looking at a homogenous bright background. AR is facilitated by a sudden disappearance of structured visual input. Disappearance of large objects leads to more robust ARA than disappearance of smaller objects. ARA is abolished when visual fixation is eliminated.

p428

DESCRIPTIVE ELECTROENCEPHALOGRAPHIC STUDY OF EYELID MYOCLONUS

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Purpose: Epileptic eyelid myoclonia (ELM) are repetitive and short shakes of palpebral muscles with simultaneous epileptiform discharges on surface EEG. ELM is a frequent manifestation of epileptic myoclonus and has been described associated to different brain pathologies. Epileptogenic zone location and physiopathology of ELM are still controversial. Trying to contribute to ELM knowledge, we describe the clinical features and EEG characteristics of a population with ELM.

Method: We reviewed patients with epileptic or other brain disorders whose main symptom was ELM.

Results: Our study population (29 patients: mean age: 25.1 ± 5; 55% female) had heterogeneous disorders: 20% juvenile myoclonic epilepsy, 20% absence, 20% symptomatic epilepsy, 10% generalised criptogenetic; 7% Lennox-Gastaut, drug induced seizures and Lance-Adams; 3% West, Angelman's and progressive myoclonic epilepsy. Most patients had generalised seizures (85%). ELM was associated to simultaneous segmentary or generalised myoclonia (32%). ELM most common triggers were hyperpnoea (39%) and wake-up (35%). EEGs showed generalised synchronous spikes, polyspike and sharp waves of variable duration (0.5 to 58 seconds), predominantly over frontocentral areas (80%). 33% of patients showed impairment of consciousness related to the duration of the epileptic discharges ($p = 0.003$) and independently of pathologic background activity, absence of alpha rhythms.

Conclusion: Generalised EEG patterns were the most electroencephalographic features associated to ELM. Impairment of consciousness in patients with ELM was associated to long EEG generalised discharges, independently from the background activity or the underlying pathology. Participation of oculomotor nerves and the occasional loss of consciousness suggest the involvement of brainstem and reticular ascendant system in the genesis of ELM.

p429

TMS IN TREATMENT OF DEPRESSION: AN ATTEMPT AT EXPLAINING THE POOR EFFECTIVENESS OF THE METHOD

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Purpose: In 1992, Zyss suggested the application of prolonged rapid-rate transcranial magnetic stimulation as an alternative to electroconvulsive therapy.

Method: TMS was regarded as the method that could bring about an antidepressant effect without evoking seizures.

Results: In our own examinations 18 patients with a diagnosis of depressive disorders were subjected to rTMS (1.5T, 5 Hz, 5 min, n = 8–10; left DLPF cortex). The effects of therapy in the rTMS group were compared with those obtained in the groups receiving only pharmacotherapy and those treated with pharmacotherapy and ECT.

The effects in the rTMS group were similar to those in pharmacotherapy group. The ECT treatment resulted in a significant acceleration of recovery–disappearance of depressive symptoms. In a subsequent 2 patients a different frequency parameter was applied (50 Hz). In both patients generalised discharges in EEG were observed during the first stimulation, causing termination of the experiment.

Conclusion: The results confirm that antidepressant effects of nonconvulsive TMS are little or absent. Application of higher parameters (frequency) of the magnetic field may induce a seizure, i.e., the effect that was initially to be avoided. The seizure seems to be a condition sine qua non of an effective antidepressant therapy.

Our computed model investigations confirm that the density of the stimulating current in ECT technique is significantly higher (10–100×) than in TMS technique. Increasing both the amplitude of the magnetic field and its frequency seems extremely difficult from the construction point of view. Neither does it seem that we could expect any special advantages of a seizure obtained in magnetic stimulation as compared to one obtained in ECT.

p430

STUDY OF EVENT-RELATED POTENTIALS (ERP) IN PATIENT WITH PARTIAL EPILEPSY (PE)

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Purpose: To evaluate the auditory ERP (P300) in patients with partial epilepsy.

Method: Auditory P300 was analysed in 64 patients with PE (age 36.09 ± 9.63 years). Forty-four patients had uncontrolled seizures, 20

patients were seizure-free. Fifteen healthy volunteers were also included as controls. All the patients with PE were diagnosed as having epilepsy according to the criteria of Commission on Classification and Terminology of the International League against Epilepsy. All patients were using antiepileptic drugs. All patients and controls were administrated the Mini-Mental State Examination.

Results: P300 amplitudes at Pz were higher in patients with epilepsy (11.59 ± 5.84 uV) than in the control group (5.76 ± 4.18 uV) ($p < .05$). P 300 latency also were higher in patients with epilepsy (392.26 ± 59.14 ms and 315.84 ± 92.43 ms, $p < .05$). The mean P300 latency in patients with uncontrolled seizures (391.16 ± 47.14 ms) was significantly prolonged compared with that of seizure-free patients (335.14 ± 52.53 ms) ($p < .05$). However, P 300 amplitudes decreased in the group of patients with uncontrolled epilepsy (6.65 ± 3.72 uV) compared with the seizure-free group (10.16 ± 4.18) ($p < .05$).

Conclusion: The effects of antiepileptic drugs on P300 latency prolongation have been intensively studied and controversial results have been reported. The results of our study suggest that prolongation of P300 latency in patients with resistant epilepsy possibly depends on higher doses of antiepileptic drugs in this group.

p431

LATERALISATION OF CHANGES IN EEG PATIENTS SUFFERING FROM EPILEPSY AND PSYCHOSOMATIC REACTIONS

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Purpose: A pilot examination of psychosomatic reactions in patients suffering from epilepsy in relation to the lateralisation of changes in EEG.

Method: We used Lüsher short colour test (LCT) and analysed psychosomatic reactions of 15 patients suffering from epilepsy, then we compared results with changes in EEG.

Results: Patients of both sexes (11 females and 4 males), aged between 20 and 63 years, had the following lateralisation of EEG changes: left, 8 patients (LCT showed psychosomatic reactions for all of them), right, 4 (for 3 of them LCT did not show psychosomatic reactions), generalised EEG changes:3 patients (LCT did not show psychosomatic reactions in any of them).

Conclusion: The sample was small, but we noticed that patients suffering from epilepsy with changes in EEG left, showed a tendency to psychosomatic reactions and that the patients with changes in EEG right and generalised did not show a tendency to psychosomatic reactions. We are inclined to think that the LCT makes it possible to follow a relationship between lateralisation of changes in EEG patients suffering from epilepsy with psychosomatic reactions.

p432

INTEREST OF SYSTEMATIC HYPERVENTILATION DURING EEG-VIDEO MONITORING FOR PRESURGICAL EVALUATION OF DRUG-RESISTANT TEMPORAL LOBE EPILEPSY (TLE)

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Purpose: Hyperventilation (HV) is an activation method that provokes physiological slowing of brain rhythms, interictal discharges and seizures, especially in generalised idiopathic epilepsies. The aim of this study was to assess the effectiveness of HV in inducing temporal seizures during video-EEG monitoring in drug-resistant TLE patients.

Method: We included 4 patients with medically intractable temporal lobe epilepsy in our study. Patients performed HV for 4 minutes, 5 times daily. Interictal epileptic discharges (ED) during HV were evaluated according to Celesia and Paulsen criteria (*Arch Neurol* 1972;27:361–363). Antiepileptic drugs were progressively tapered during monitoring. All patients underwent brain MRI, SPECT and FDG PET to localise the epileptogenic zone.

Results: Only 1 patient had increased frequency of ED during HV. There was a greater activation of ED in sleep stage II than during HV (2 patients of 4). Five of the 9 recorded seizures occurred during HV. Three patients had positive seizure activation.

HV induced seizures occurred earlier than spontaneous seizures in the video-EEG recording. Most spontaneous seizures took place in the morning, whereas most activated seizures occurred during the afternoon. Spontaneous and activated seizures were clinically similar.

Conclusion: HV seems to be a safe and effective method of seizure activation in temporal lobe epilepsy during EEG monitoring. Sleep seems to be more interesting in the diagnosis step (inducing interictal discharges), whereas HV is useful for localisation of the epileptogenic zone by inducing seizures. HV could help to shorten this presurgical evaluation, thus facilitating access of candidates to epilepsy surgery.

p433

MORNING SESSION RECORDING INCREASES THE SENSITIVITY OF THE EEG IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY (JME)

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Purpose: In each laboratory of neurophysiology the EEG can be recorded in either morning or afternoon sessions. Both myoclonic and generalised tonic–clonic seizures in patients with JME have a typical circadian pattern; they occur almost exclusively on or soon after awakening. In this study we evaluated whether the EEG abnormalities follow the same clinical circadian pattern.

Method: We recruited 29 consecutive epilepsy patients (23 females, mean age 22.3 ± 6.3yr; age at onset 15.7 ± 3.5yr) from August 2004 to August 2005 referred to our clinic. All patients received a diagnosis of JME. In detail, 5 patients were untreated, 23 were taking a monotherapy (8 lamotrigine, 9 valproate, 6 levetiracetam), and only 1 was taking a bitherapy (valproate and phenobarbital). Two interictal EEGs acquired during the same day at 9 a.m. and at 3 p.m. were reviewed in each subject. The interictal EEG investigation was a routine awake with no sleep deprivation and without withdrawing medications.

Results: In 22/29 patients (76%) the morning recording showed epileptiform abnormalities (general spike and waves (GSW), photosensitivity response (PPR), only PPR). In these patients the afternoon recording was normal (18/22; 82%), or showed dramatic reduction of the epileptiform abnormalities (4/22). Overall 25 patients out of 29 had normal EEG during the afternoon session ($p < 0.001$).

Conclusion: We found that in patients with JME a morning EEG recording is more sensitive to detect epileptiform abnormalities than the afternoon recording. Therefore, our results suggest that EEG features follow the same circadian pattern as clinical features.

p434

EPILEPTIC ACTIVITY IN TWO CHILDREN WITH PRENATAL UNILATERAL BRAIN INFARCT AND CSWS: AN EEG SOURCE IMAGING STUDY

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Purpose: Electrical source imaging (ESI) was used to study 2 children with a MCA infarct and early epilepsy (7 and 32 months). Case 1 developed right parietal-occipital activity and right sided CSWS at 5 years. Case 2 developed at age 4 left central-parietal epileptic and frontal-central epileptic activity and generalised CSWS.

Method: Several single spike wave complexes, selected from standard EEG, were analysed using a distributed linear inverse solution in the patients own magnetic resonance. Then a statistical parametrical mapping approach was used to determine which areas were significantly more active during the different phases of the spike wave complex compared

to a baseline period. In this way a measure over time of spike propagation could be obtained.

Results: Case 1: ESI showed right occipital activity with propagation to the right hemisphere parietal, temporal and frontal region, correlating with attention deficit and stagnation of visual-spatial skills. Case 2: ESI showed left parietal-occipital activity with propagation to the left frontal and central regions and right temporal, frontal-temporal and parietal regions, correlating with severe mental deterioration.

Conclusion: In these 2 cases, with similar lesions but very different clinical pictures, interictal ESI, showed different propagation patterns of epileptic activity that seemed to correlate with the neuropsychological evolution. FNS grant number 3200–068105.

p435

LOCALISATION OF THE NEOCORTICAL EPILEPTIC FOCUS FROM SEIZURE-FREE SUBDURAL EEG BY ANALYSIS OF LONG-RANGE TEMPORAL CORRELATIONS

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Purpose: Video-EEG monitoring is a standard procedure for presurgical evaluation of localisation-related epilepsies. Long-term intracranial recordings, however, often involve significant burdens to patients and health care. We tested whether the neocortical epileptogenic area could be circumscribed by analysing the temporal properties of ongoing seizure-free EEG activity.

Method: We recorded 5 neocortical epilepsy patients with subdural grids during 20 min rest period. Detrended fluctuation analysis (DFA) was applied to quantify long-range temporal correlations (LRTC). We compared the distribution of LRTCs to seizure foci found with standard clinical methods, and confirmed by postsurgical outcome. Two patients were remeasured after administering 2 mg of lorazepam, a widely used antiepileptic drug.

Results: We found that the LRTCs are stronger at the focus of seizure onset than in surrounding cortical areas. The effect was most salient in ß-frequency band (significance for correlation of LRTC vs distance-to-focus: $p = 0.009 \pm 0.015$, $n = 5$). Additionally, we found that lorazepam otherwise increases LRTCs, but selectively decreases the ß-band LRTC in the area of the epileptic focus.

Conclusion: Our findings show that the brain activity close to the epileptic focus presents abnormally strong temporal correlations during seizure-free periods, and suggest that LRTC analysis may be utilised as an additional tool in focus localisation efforts. The observations are corroborated by the finding that the seizure-preventing effect of lorazepam is reflected in focal decay of LRTC. This decorrelation originates in renormalisation of local network activity. Our approach may also open new possibilities for noninvasive localisation of seizure foci with electro- and magnetoencephalography.

p436

TOPOGRAPHIC MOVIE OF ICTAL HIGH-FREQUENCY OSCILLATIONS ON THE BRAIN SURFACE USING SUBDURAL EEG IN NEOCORTICAL EPILEPSY

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Purpose: To understand the rapid dynamic changes of ictal intracranial high-frequency oscillations (HFOs) in neocortical epilepsy.

Method: We integrated multiple band frequency analysis and brain-surface topographic maps of HFOs from ictal subdural EEG (SDEEG) recordings. We used SDEEG to record partial seizures consisting of right arm jerks with secondary generalisation in a 17-year-old right-handed girl. We selected 20-second EEG sections that included preclinical seizure recordings. We averaged the HFO power between 60–120 Hz for 25 selected electrodes, made topographic maps from these averaged powers, and superimposed the maps on the brain-surface image. We filmed consecutive HFO maps at a 10 ms frame rate.

Results: Before clinical seizure onset, high-power HFOs emerged at the superior portion of the left precentral gyrus, then appeared in the middle of the left postcentral gyrus, and subsequently reverberated between both regions as well as the posterior portion of the left postcentral gyrus. Right arm extension and facial grimacing started as the HFO power decreased. As generalised tonic–clonic seizures evolved, HFO power increased but remained within the central region.

Conclusion: Topographic movies of intracranial HFOs on the brain surface allow visualisation of the dynamic ictal changes in neocortical epilepsy.

p437

ANATOMICAL DEGENERATION AND FUNCTIONAL DETERIORATION IN THE RAT EPILEPTIC CORTEX

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Purpose: Recent studies in experimental animals have shown that lesions of the blood–brain barrier (BBB) in the rat neocortex may lead to focal epileptiform activity (Seiffert et al., *J Neurosci* 2004;24:7829–36). The purpose of the present study was to evaluate molecular, anatomical and functional long-term alterations in the BBB-disrupted epileptic neocortex.

Method: BBB disruption (using bile salts) or sham operation was performed on the motor cortex of 85 adult male Wistar rats. Animals were followed for up to 11 months, and were tested repeatedly for motor and behavioural capabilities. Epileptiform activity was recorded in the in vitro slice preparation. Changes in specific neuronal and astrocytic markers were identified using immunostaining and confocal microscopy.

Results: Epileptiform activity was recorded from the 4th day following treatment. However, motor functions showed increasing deterioration from the 4th week onwards. This was associated with a reduction in total cell numbers. Specifically, we found a reduced number of neurons (immunolabelled with MAP2) together with fewer dendritic branching (labelled with biotin). In addition, in GFAP labelled astrocytes, glutamine synthase (GS) immunolabelling was significantly reduced both in the neuropil and the perivascular area.

Conclusion: While epileptiform activity can be observed in the presence of an apparently anatomically intact cortex, with time it may be associated with neuronal damage and functional deterioration. Astrocytic changes including reduced GS may play a role in neuronal excitotoxicity.

p438

SEIZURE IN TAKAYASU ARTERITIS AS A FIRST SYMPTOM

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Purpose: Takayasu arteritis is a chronic granulomatous inflammatory arteritis affecting large vessels, predominantly aorta and its main branches. The symptoms of Takayasu arteritis are related with end organ ischemia. The main clinical symptoms are weakness, fever, arthralgia, skin rash, hypertension, intermittent claducation, cardiac diseases (cardiac failure, valvular or ischemic heart disease, pulmonary hypertension, pericarditis), and impaired renal functions. Cerebrovascular manifestations which can also be seen in Takayasu arteritis consist of transient ischemic attack, stroke, hypertensive encephalopathy, spastic paraplegia, and elevated intracranial pressure. According to our knowledge, convulsion is not commonly reported in this disease.

Method: A Case report.

Results: We wanted to present a 15-year-old girl with the diagnosis of Takayasu arteritis. She was admitted to our hospital with generalised seizures which had begun 15 months previously. She was healthy, and her family history was unremarkable. Although no pathology was detected in

neurological examination, brachial artery pulse was decreased and blood pressure couldn't be measured. High sedimentation and CRP levels were also found. With detailed radiological diagnostic approaches, she was diagnosed as Takayasu arteritis. After steroid therapy (1 mg/kg/day), her complaints improved within 10 days.

Conclusion: Our patient is a rare case of Takayasu arteritis suffering from seizures. Despite the well known characteristics of this disease, the first symptom can be a convulsion.

p439

CORTICAL MOTOR EXCITABILITY IN UNVERRICHT-LUNDBORG AND LAFORA DISEASE

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Purpose: To test cortical motor excitability in progressive myoclonus epilepsy using transcranial magnetic stimulation.

Method: We assessed the cortical threshold in 10 patients with Unverricht-Lundborg and Lafora types of progressive myoclonus epilepsy and in a group of healthy subjects and we applied paired-stimuli protocols aimed at evaluating short interval intracortical inhibition and facilitation, as well long interval intracortical inhibition.

Results: Patients had a significant increase of cortical threshold (Kruskal-Wallis test; $p < 0.05$). Short-interval intracortical inhibition was reduced at all interstimulus intervals (ISI) and statistically different from healthy subjects at 1 and 2 ms ($p < 0.05$). Lafora patients, but not Unverricht-Lundborg patients showed a significantly decreased intracortical facilitation at 10 ms ISI ($p < 0.05$). Long interval intracortical inhibition was similar in patients and controls.

Conclusion: Paired magnetic stimuli protocols revealed a defect of intracortical inhibition in all patients with progressive myoclonic epilepsies; however, Lafora patients only had an extensive impairment of the intracortical modulation profile. These findings suggest a more severe and widespread disruption of the cortical network in Lafora patients.

p440

ELECTROPHYSIOLOGICAL PROFILING OF BASAL AND LATERAL AMYGDALOID NUCLEI NEURONS RESISTANT TO STATUS EPILEPTICUS–INDUCED DAMAGE

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Purpose: To probe altered membrane properties of neurons resistant to status epilepticus induced damage in kainic acid (KA) model by using whole-cell patch-clamp technique.

Method: Amygdala-hippocampal projection was identified by injecting retrograde axonal tracer Fluoro-Gold into the CA1/Subiculum. Eight male Wistar rats were treated with kainic acid (10 mg/kg, i.p) and 5 with saline. After 3 and 4 weeks coronal slices comprising amygdaloid complex at 1.3–3.3 mm posterior to bregma were prepared. Target neurons were identified by using fluorescence illumination, and whole-cell measurements were performed in current-clamp mode. Nissl staining was used to assess the injection site and the recorded nuclei. Six KA and three control neurons were included.

Preliminary Results: The resting membrane potentials were -65.6 ± 1.2 mV in KA and -64.5 ± 3.5 mV in control group indicating that KA neurons were not depolarised/hyperpolarised compared to control neurons. The maximum input resistance and steady-state resistance were 159 ± 29 MOhm and 145 ± 30 MOhm in KA and 159 ± 12 and 143 ± 15 in the control group; therefore passive membrane potential responses did not differ between groups. Thresholds to rectangular currents were -49.9 ± 2.2 mV in KA and -56.6 ± 2.9 mV in control, but changed during ramp current pulses to -38.3 ± 3.2 in KA compared to -53.3 ± 1.8 ($p < .05$) in control.

Conclusion: The action potential threshold depends on the functional history of the neuron. In KA neurons, the threshold was higher than in control cells, indicating a change in sodium channel inactivation properties, which might help the neurons to endure the decreased inhibition due to the loss of GABAergic interneurons.

p441

SUCCESSFUL SCREENING OF NEOCORTICAL EPILEPSY USING ROUTINE MEG RECORDINGS

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Purpose: It is well known that the diagnosis of a large percentage of the initial awake routine EEG records is inconclusive. In such cases additional sleep deprived EEG is required. Since it has recently been shown that in the case of neocortical epilepsy spike sensitivity is higher for MEG then EEG, we investigated whether with optimal procedures for screening and localising interictal epileptiform MEG discharges (MEG spikes) additional EEG recordings could be avoided.

Method: Twenty eight ($n = 28$) patients with a suspicion of localisation bound neocortical epilepsy whose routine EEG records were inconclusive underwent routine MEG recordings. This MEG was visually reviewed following the standard procedures of the routine EEG records. Furthermore, equivalent dipole analysis was applied, which enabled the localisation of MEG spike clusters.

Results: Visual inspection of routine MEG records yielded for 17 of the 28 patients studied (60.7%) ten or more detected interictal events. For 15 of these patients (53.6%), the clustering algorithm revealed subclasses of spikes corresponding clearly to dipolar magnetic field maps. Inverse computations applied on the selected spike subaverages yielded anatomical plausible localisations for 8 of the patients studied (28.6%).

Conclusion: Although routine EEG records of the patients studied were inconclusive, the MEG yielded a significant number of interictal events in many of these patients. Moreover, a reliable categorisation of these spikes was obtained or even a plausible localisation. However, further evaluation in relation to the patients' epilepsy is needed to decide whether routine MEG records may replace additional EEG investigations.

p442

CORRELATION BETWEEN REGIONAL GLUCOSE METABOLISM AND INTRAOPERATIVE ELECTROCORTICOGRAPHY IN TEMPORAL LOBE EPILEPSY

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Purpose: To determine the relation between cerebral regional metabolism and epileptiform activity in patients with temporal lobe epilepsy (TLE).

Method: We analysed interictal [^{18}F]FDG-PET and rate of epileptiform discharges (ED) in the acute electrocorticography (ECoG) in 30 TLE patients who underwent standard anterior temporal lobectomy. We correlated regional [^{18}F]FDG uptake and ED rate in the hippocampus, anterior and posterior infratemporal cortex by regions of interest (ROI) and voxel-based statistical parametric mapping (SPM). Patients were grouped into those with the highest ED rate at the hippocampus (group H) and those with highest ED rate outside the hippocampus (group exH).

Results: Among all patients and in group H, there was no correlation between ROI values from each structure and ED rates. In exH patients, there was a positive correlation between the hippocampal ED rates and ROI metabolic values in ipsilateral medial, lateral and infratemporal areas, ipsilateral basal ganglia and thalamus bilaterally ($r = 0.624$ to 0.771, $p < 0.05$). SPM analysis showed correlations only in group exH, between hippocampal ED rates and metabolic rates in ipsilateral amygdala and anterior hippocampus, anterior portion of ipsilateral superior and mid temporal gyri, and contralateral amygdala and hippocampus ($p < 0.001$).

Conclusion: A positive correlation was found between ED and metabolic rates in several ipsilateral temporal regions among patients with the highest ED rate outside the hippocampus. This may be due to increased surround inhibition. Correlations with metabolism in ipsilateral temporal, subcortical regions and contralateral medial temporal

structures may reflect the involvement of these structures in propagation or generation of ED.

p443

INTRACTABLE FOCAL EPILEPSY DUE TO CORTICAL DYSPLASIA IS ASSOCIATED WITH INCREASED CORTICAL MOTOR THRESHOLD: A NAVIGATED BRAIN STIMULATION STUDY

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Purpose: Navigated brain stimulation (NBS) combines transcranial magnetic stimulation (TMS) with accurate guidance by individual MRI. NBS allows noninvasive study of local cortical inhibition-excitation. Simultaneous EEG monitoring adds the safety required for studies of epilepsy patients.

Method: We determined the motor threshold (MT) in 2 patients (Case 1: 11 y left-handed female, Case 2: 13 y right-handed male) with intractable focal epilepsy due to a single area of cortical dysplasia beyond primary motor cortices. Patients received normal individual AEDs. Optimal stimulation sites to activate abductor pollicis brevis muscle were localised on the motor strip (M1) and MT for these sites was determined. MT was defined as the lowest stimulation intensity which elicited a motor-evoked potential (MEP) of 0.1 mV or greater in surface EMG for at least 4 out of 10 consecutive pulses. Single monophasic pulse was delivered out with Magstim 200 via figure eight coil. Simultaneous EEG recording was performed.

Results: Case 1: left hemisphere MT ipsilateral to seizure onset was 75% of maximum intensity, right MT was 43%. MTs on the seizure onset hemisphere were fluctuating during assessment. Case 2: right hemisphere MT ipsilateral to seizure onset was 56% of maximum intensity, left MT was 58%.

Conclusion: We found that MT is increased outside the actual seizure onset zone. MT increase was marked only ipsilaterally to seizure onset (Case 1), or was seen bilaterally (Case 2). Possible mechanisms include remote effects of focal epileptogenic pathology (cortical dysplasia), very active interictal epileptiform EEG activity (Case 1), and maximal tolerated AED dosages due to medical intractability.

p444

MEG DIPOLES FROM MESIAL TEMPORAL STRUCTURES IN THE ABSENCE OF LATERAL TEMPORAL CORTEX

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Purpose: The lateral temporal cortex has a great influence on magnetoencephalography (MEG) because of the location between detecting coils and mesial temporal structures. To reveal patterns of magnetic fields from mesial temporal structures alone, we analysed temporal spike discharges in a patient with intractable seizures secondary to porencephaly.

Method: We analysed mesial temporal discharges on MEG in a 12 year old boy with intractable epileptic seizures. MRI showed a left porencephalic cyst of temporoparietooccipital regions including most of the lateral and anterior temporal cortices but mesial temporal structures left. We recorded 151 channels MEG (VSM MedTech. Canada) and simultaneous international 10-20 EEG. We analysed MEG dipoles, using MEG single moving dipole models. We placed synthetic aperture magnetometry virtual sensors (SAM-VS) in left mesial and lateral temporal structures to reconstruct the current density waveforms from MEG data.

Results: We captured MEG dipoles with two F7-T3 spikes (group-A) and ten T5 spikes (group-B) on EEG. Dipoles were estimated in the anterior mesiobasal temporal region with vertical orientation in group-A and in posterior temporal basal cortex with vertical orientation in group-B. SAM-VS analysis of group-A showed spikes on the adjacent area of the hippocampus and fusiform gyrus.

Conclusion: By dipole modeling, Ebersole divided magnetic fields of temporal spikes into 3 types including anterior temporal horizontal, anterior temporal vertical (ATV) and posterior temporal vertical. ATV dipoles are probably correlated to mesial temporal discharges including basal temporal region in this case with left temporoparietal porencephaly. SAM-VS projected mesial and basal temporal discharges associated with these dipoles with vertical orientations.

p445

ICTAL TACHYCARDIA CAN BE USED FOR AUTOMATED SEIZURE DETECTION DURING VIDEO-EEG MONITORING

B. Schreiner, B. Steinhoff, and C. Kurth (Epilepsy Centre Kork, Kork, Germany)

Purpose: It is well known that temporal and extratemporal epileptic seizures may cause a significant increase in heart rate. This shift in frequency seems to precede the seizure onset in EEG up to several seconds. The aim of this study was to demonstrate that computerised evaluation of heart rate change can be used for automated seizure detection.

Method: 317 hours of EEG/ECG-recordings of 3 patients with focal epilepsies of temproal or extratemporal origin were evaluated. A LABVIEW based software measured the RR-interval in ECG continously. If the heart rate was in a range between 120 and 230 beats per minute for more than 15 heart beats a seizure was indicated. Seizure detections within the next 2 minutes were ignored to prevent repeated signaling of the same seizure. The results of the detection algorithm were compared to evaluation of the video-EEG recordings. Sensitivity and rate of false positives were calculated.

Results: Eight complex partial or secondary generalised tonic–clonic seizures could be analysed. Sensitivity was 100% in 2 patients and 80% in 1 patient. Rate of false positive detections ranged between 1 within 2h–4h 42min. Seizures were detected between 1min 24s before and 12s after seizure onset in EEG. In 1 patient 7 auras without accelaration of heart frequency occurred and, of course, were not detected.

Conclusion: Automated evaluation of heart rate is a sensitive method for seizure detection with an acceptable rate of false positives in a video-EEG monitoring setting. Therefore we started with online evaluation of ECG in our monitoring unit.

p446

SLEEP DEPRIVATION: A SIMPLE METHOD SPECIFICALLY FOR EPILEPSY PATIENTS

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Purpose: To evaluate how much EEG sleep deprivation became positive after a negative EEG at rest in patients affected by epilepsy, making a comparison with patients affected by other neurological pathologies.

Method: We conducted a retrospective study on our database of 292 patients who came to our EEG service at the Second Faculty of Medicine of the University of Rome "La Sapienza" from 2001 until the present. We focused on those patients who performed a sleep deprivation after attending a normal EEG at rest. All of the patients investigated underwent a partial sleep deprivation; in fact, they were allowed to sleep from midnight to 3.00 a.m. Because of the wide variety of our population, we decided to study a group of 146 patients known as suffering from epilepsy with a consecutive group of 146 patients affected by head injury, syncope, paraesthesia, vertigo, dementia and Parkinson's disease. All patients were investigated with a longitudinal montage with 21 channels according to the 10–20 International System both for EEG at the rest and for partial sleep deprivation. We compared the results of the 2 groups of patients using the *t*-test.

Results: From our statistical analysis we found out that there is a significant difference ($p < 0.005$) between the EEG that became positive after partial sleep deprivation in the patients affected by epilepsy and the other group of patients, in favour of the first group.

Conclusion: We empathise with this retrospective study the specificity of a simple neurophysiology method that can discover in a simple way anomalies that otherwise could be hidden.

p447
USEFULNESS OF VIDEO-EEG MONITORING IN PAROXYSMAL EVENTS IN THE ELDERLY
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Purpose: The incidence of seizures increases with age, however, because of diverse clinical manifestations on the one hand and other paroxysmal events mimicking seizures on the other hand, the diagnosis can be difficult. Surprisingly, very few papers relate to video-EEG monitoring (VEEGM) as a diagnostic aid in the elderly. The study's aim was to determine the importance of VEEGM in elderly patients with various paroxysmal events.

Method: Out of 834 consecutively admitted persons to our Video-EEG unit from 1997-2005, we identified 16 elderly ($\geq$60) patients (1.9%). We evaluated their demographic, clinical, EEG and imaging data.

Results: There were 7 females and 9 males, ages 67.8 $\pm$ 7.7 years; disease onset 51.1 $\pm$ 21.4 years, disease duration 16.6 $\pm$ 17.6 years. The number of events during VEEGM was 5.3 $\pm$ 4.3, and the duration of VEEGM was 6.9 $\pm$ 5.3 days. In 7 patients, epilepsy was verified and antiepileptic drug (AED) treatment was adjusted. In 8 patients, non-epileptic seizures (NES) were diagnosed, 1 patient had both epileptic and NES, and 2 patients had nonconclusive events. Following hospitalisation, the frequency of monthly events decreased for the whole group from 26.3 $\pm$ 16.2 to 4.7 + 8.3 ($p < 0.001$); reduction for NES patients was from 22.8 $\pm$ 12.2 to 5.8 $\pm$ 10.6 ($p < 0.027$); in patients with epilepsy, the rate was from 31.2 $\pm$ 21.1 to 1.8 $\pm$ 1.6 ($p < 0.031$). VEEGM impacted diagnosis and treatment in 14/16 (88%) patients.

Conclusion: VEEGM in these elderly patients lead to verification of diagnosis as well as to better AED treatment in the vast majority of our patients. Our experience shows that this diagnostic tool is underutilised in this population group.

Tuesday July 4, 2006
13:30–15:00
Poster Session 2
Drug Therapy

p448
CLINICAL DECISION MAKING REGARDING THERAPY ADJUSTMENT USING SYSTEMATIC SCREENING OF ADVERSE ANTIEPILEPTIC DRUG EFFECTS
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Purpose: To evaluate the clinical application of the Adverse Events Profile questionnaire AEP (Gilliam et al., *Neurology* 2004;62:23–27) for systematic screening of adverse AED effects, and to propose potential improvement.

Method: Patients were recruited from a consecutive sample of eligible, consenting outpatients in the adult university epilepsy clinics. Enrolment criteria included age >17 years, $\geq$2 seizures that required AED treatment at the time of evaluation, ability to give informed consent and complete self-report documents, and absence of symptomatic chronic illness or use of medications with significant potential for side effects. Patients were randomly assigned for examination by two investigators. Primary outcome measure was correlation between clinical decision and AEP score, as well as improvement in adverse effects reporting for 4 months. Also, we developed a fuzzy model which simulates clinical decision making using AEP in a more complex manner, which was tested on 30 patients.

Results: For a majority (38/42) of patients with AEP score of >45, a clinical decision was made adjust therapy. However, for 10/18 patients with an AEP score of $\leq$45, a clinical decision was also directed to a dose adjustment. In 40/48 patients we observed significant improvement in adverse effects. The developed fuzzy inference model demonstrated a high compliance with clinical decisions, producing expected judgment in a great majority of patients.

Conclusion: We found good specificity and moderate sensitivity of the AEP score in clinical judgment, which could be better simulated by fuzzy logic principles, rather than by binary logic based on a simple threshold value.

p449
DEVELOPMENT AND IMPLEMENTATION OF EPILEPSY DATABASE AND REGISTRY (EDAR)
M. Spasic and S. Lukic (University Clinical Centre Nis, Serbia and Montenegro)

Purpose: The purpose of this research is to develop and implement a unique, specialised Windows-based epilepsy management and research tools, for supporting the daily registration and storage of clinical events in epilepsy clinics.

Method: The collection of patient-specific clinical data forms the patient database. The database contains structured terminology of seizure types, syndromes, epilepsy type, aetiology, therapy and follow up procedures. Developed Visual Basic 6.3 modules allow editing and personal adjustment of tool items. The database has been written in English to allow international use. Epilepsy database and registry (EDAR) has been developed without any involvement or help from the sponsor company.

Results: Adult epileptologists have provided the knowledge of diagnostics and treatment of epilepsy for the basis of the application. Data on over 500 adult epilepsy patients have been entered and used for routine and research purposes at the University Epilepsy Department. The system offers the possibility to easily access all patient data at a local level, without the need of looking for paper files. Moreover, it allows the collection of anonymous data via the internet.

Conclusion: EDAR is a novel method for collecting and storing clinically relevant data from epilepsy patients. EDAR allows the standardisation of patient data, and a better organisation of the patient management process. It can be used as a comprehensive and powerful resource to provide routine practice and clinical management as well as for epilepsy research and an information exchange channel.

p450
INFLUENCE OF MATERNAL EPILEPSY AND ITS TREATMENT ON THE DEVELOPMENT OF THE CHILD: PREGNANCY, LABOUR AND THE NEWBORN
M. Briggs (Central Manchester University Hospitals NHS Trust, UK)

Purpose: To report early findings in a longitudinal study of child development from pregnancy to school years.

Method: Prospective, controlled, observational study of pregnancy and its outcome in 292 women with epilepsy and 339 matched controls receiving hospital antenatal care. Clinical data came from mothers and case records. Minor congenital abnormalities were excluded (Eurocat 2005). Development of children was assessed at intervals. Statistical analysis: chi-square or unpaired *t*-test.

Results: Mothers with epilepsy left school earlier and had less further education ($\chi^2$35.3; $p < 0.001$). Seizures in pregnancy: free 53%, non-convulsive 29%, convulsive 18%. Drug therapy: none 22%, mono 61% (CBZ 25%; VPS 20%; LTG 11%), poly 16%.

Pregnancies with complications were similar (patients 26.4%, controls 27.1%, $\chi^2$0.05, $p = 0.83$). Most patients had normal deliveries (65.9%, controls 58.1%, $\chi^2$3.06, $p = 0.08$) although breech presentation was more common (8.3%, controls 4.1%, χ^2 3.83; $p < 0.05$). There was no difference in gestational age at birth (patients 38.8 (0.3) weeks (SEM), controls 38.9 (0.4), $t = 0.08$; $p = 0.93$) or in admissions to the special baby care unit (patients 7.4%, controls 9.6%, $\chi^2$0.78; $p = 0.38$). Patients had more prenatal scans and a small increase in major congenital

abnormalities (4.1% controls 2.6%, $\chi^2 0.92$; $p = 0.34$). They were less likely to breast-feed (37.0%, controls 52.9%, $\chi^2 11.7$; $p < 0.01$).

Conclusion: Differences in maternal education, seizures during pregnancy, drug exposure in utero and breast-feeding are expected to influence neuro-behavioural development. The likelihood of an uncomplicated pregnancy and normal delivery will reassure the would-be mother with epilepsy.

p451

HOW WELL ARE NEURAL TUBE DEFECTS DIAGNOSED PRENATALLY WHEN THE MOTHER IS TAKING ANTIEPILEPTIC DRUGS?

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Purpose: 1) To describe the clinical spectrum in 56 cases of neural tube defects (NTDs) when the mother was on antiepileptic drugs (AEDs) during pregnancy; 2) to evaluate the reliability of prenatal diagnosis in The Netherlands.

Method: We collected data on congenital malformations, maternal disease, use of AEDs and folic acid, and prenatal testing.

Results: From AED prescription rates and NTD risks specific to AED, we estimated that, since 1970, there should be ~150 NTD cases associated with maternal AED use in The Netherlands. Our first 56 NTD cases included 52 (93%) spina bifida aperta (SBA), 1 spina bifida occulta, and 3 anencephaly, with 46 (82%) lumbar/sacral NTDs. Other CNS abnormalities were: hydrocephalus (37), Arnold-Chiari II malformation (17), and microcephaly (4). Non-CNS abnormalities occurred in 17 cases (30%), predominantly urogenital (4) and cardiac (4) malformations. The mothers took valproate (30), carbamazepine (10), phenobarbital (1), or polytherapy (15) that included valproate or carbamazepine in 14/15 cases. 19/56 (34%) used folic acid supplements (0.5–5 mg/day). Some form of prenatal testing was performed in 36/56 (64%) cases. Open NTDs were detected by measuring maternal serum alpha-foetoprotein (AFP) in only 3/8 (38%), but foetal ultrasound identified 30/36 (83%) and measuring amniotic fluid AFP detected 20/22 (91%). Five live-born SBA babies were missed by prenatal ultrasound.

Conclusion: NTDs were almost exclusively associated with valproate or carbamazepine treatment, despite supplementary folic acid being taken in one-third of these cases. Maternal serum AFP proves to be unreliable for diagnosing NTDs associated with maternal AED use. Funding: National Epilepsy Fund (grant 03-18).

p452

EFFECT OF AED AND ENDOCRINE FACTORS ON SEIZURE REDUCTION AND SUSTAINED REMISSION IN WOMEN WITH EPILEPSY

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Purpose: The current study was carried out in order to find the optimal combinations of AED and endocrine factors for maximal seizure reduction and support of remission in women with epilepsy.

Method: One hundred thirty women with epilepsy (23 with catamenial and 107 with noncatamenial epilepsy) were recruited into the study. MANOVA was performed for the purposes of the study, and AED, thyroid and gynecologic data were used as fixed factors, while the data on reduction (%) of each type of seizure and duration of sustained remission were used as dependent variables.

Results: The isolated factor of reproductive dysfunction has no effect on reduction of any seizure type, although catamenial epilepsy was characterised as a whole by poor seizure reduction. The isolated factor of thyroid pathology has significant influence on reduction of simple partial seizures (SPS). Their maximal reduction was observed in diffuse thyroid enlargement in noncatamenial epilepsy under topiramate (TPM) treatment. The maximal reduction of SPS was under carbamazepine (CBZ) treatment, while the maximal reduction of primary generalised (PGS) and secondary generalised (SGS) was revealed for TPM-CBZ combination. The valproates (VPA) had the maximal effect on absences and myoclonus reduction, while the combination of VPA-CBZ was optimal for sustained remission in catamenial epilepsy.

Conclusion: The AED type, comorbid endocrine pathology and catameniality should be taken into account in the treatment of female epilepsy in order to achieve maximal efficacy.

p453

CONGENITAL MALFORMATIONS IN CHILDREN OF MOTHERS WITH EPILEPSY

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Purpose: The incidence of congenital malformations (CM) in children of mothers with epilepsy (EM) is higher than in the general population, and has a multifactorial origin. We investigated the frequency of CM in children of EM and some related risk factors.

Method: A prospective study of 370 children of EM was carried out from January 1995 to January 2005. A form was designed to record demographic, clinical and genetic data. Final results were recorded on a data base to make statistical analysis. Results were compared to those of a control group of 500 children from mothers who did not have epilepsy (NEM).

Results: CM were diagnosed in 9.85% of children from EM (36/370), 4.20% (21/500) in children from NEM (odds ratio = 2.7; IC of 95% = 2.0–3.3). The rate of CM with only one antiepileptic drug (DAEs) was 3.1% to 1.2% of the control (RR = 2.1; IC 95%; 1.3–3.5%). The rate was 4.9% when taking 2 DAEs (RR = 3.6; IC 95%; 2.1–6.5%) and 9.7% if taking 3 or more DAEs (RR = 6.3; IC 95%; 2.5–16.3). The most common CM were cardiac defects (1.63% to 0.4%), cleft palate (1.15% to 0.18%), urogenital abnormalities (1.80% to 0.61%) and defects of the neural tube (1.30% to 0.50%). CM were more frequent in children under valproic acid (14.38%) than those under other DAEs (2.7%) ($p < 0.001$). The daily dose of valproic acid was higher in children with CM than those without CM (1750 to 1000 mg; $p < 0.01$). 37.5% of MC were diagnosed in children from EM with tonic–clonic seizures during the first trimester of pregnancy.

Conclusion: CM were more frequent in children from EM use of DAEs in pregnancy. Polytherapy, high doses and seizures during the first trimester are some risk factors of CM in children from EM.

p454

ANTIEPILEPTIC DRUGS AND BONE MASS IN MENOPAUSE

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Purpose: The purpose of our study was to determine the effects of anti epileptic drugs (AEDs) on mineral metabolism and whether use of them had an adverse effect on bone mass, particularly in women during menopause, who have been suffering from epilepsy and have been taking AEDs for 5 years and more.

Method: We analysed 25 women with epilepsy, in menopause, on long-term antiepileptic drug therapy (carbamazepine, valproate, phenobarbital), for a five-year period (2001–2005). Their urine levels of minerals and serum level of calcium, magnesium, phosphor, alkaline phosphatase, liver enzymes, testosterone, estradiol, FSH and prolactin hormone were measured, including bone density measurement.

Results: The results showed that only one, a 35-year-old woman, who was taking AEDs (carbamazepine, valproate, and phenobarbital) for 20 years and was in post ovariectomy menopause for five years, had low calcium concentration in serum and in urine, high levels of alkaline phosphatase in serum, and osteoporosis.

Conclusion: With our study we cannot confirm that long-term antiepileptic therapy causes changes in calcium concentration levels and increases possibility of osteoporosis development. The literature describes these long-term side effects in patients who were taking mostly phenytoin. In our case only one woman, who has entered early menopause because of an ovariectomy, was taking different kinds of antiepileptic drugs in mono or polytherapy during her life. Did she get osteoporosis because of early menopause induced by prematurely removing her ovaries or because of long-term treatment with AEDs, or is it a combination of those two factors?

p455

A HUMANISED IN VITRO BLOOD–BRAIN BARRIER MODEL TO SCREEN FOR BRAIN PENETRATION OF ANTIEPILEPTIC DRUGS

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Purpose: We compared the transendothelial permeation properties of sucrose, phenytoin and diazepam in three humanized blood-brain barrier (BBB) models based on cocultures of human astrocytes and different types of endothelial cells (HUVEC, AVM_EC, HBMEC/D3) differentiated in a BBB phenotype under dynamic conditions (DIV-BBB) .

Method: EC and astrocytes were cocultured for 14 days using polypropylene capillaries inside a sealed chamber. EC were exposed to physiological levels of shear stress generated by intraluminal medium flow. Permeability to ^{3}H sucrose ^{14}C phenytoin and ^{14}C diazepam were measured and compared to BBB integrity by transendothelial electrical resistance (TEER) measurements.

Results: The TEER was $\approx$1200 Ohm cm^2 for AVM_EC and HBMEC/D3 DIV-BBB based models while only 800 Ohm cm^2 for HUVEC. Sucrose permeability (n = 3) was 5.7×10^{-8} cm/sec in HBMEC based cartridges against 1.06×10^{-7} cm/sec in AVM and 4.93×10^{-7}cm/sec in HUVEC. Phenytoin permeability ranged from 3×10^{-5} cm/sec in HBMEC and AVM-EC models to 1.24×10^{-4} cm/sec in HUVEC. Permeability to diazepam was $\approx 3 \times 10^{-4}$ cm/sec in both AVM-EC and HBMEC but twice as permeable in HUVEC.

Conclusion: These results demonstrate that the humanised DIV-BBB recapitulates the in vivo rank order for AED permeability thus making it an ideal vector to study brain penetration of new CNS drugs. HBMEC models achieved the highest reliability for drug screening application.
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p456

PROFILE OF ANTIEPILEPTIC PHARMACOTHERAPY IN TERTIARY REFERRAL CENTRE IN SERBIA: A PHARMACOEPIDEMIOLOGICAL STUDY

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Purpose: To study current practices of pharmacotherapy of epilepsy in a developing country in economic transition (Serbia).

Method: Current practices of pharmacotherapy of epilepsy were analysed retrospectively at the Institute of Neurology in Belgrade, Serbia, for two consecutive years (2004 and 2005).

Results: We analysed 177 inpatients (females 55.9%; mean age 41.1 ± 14.8 years), the majority of which were treated at the Department of Epileptology. There were 75 patients (42.3%) with newly diagnosed and 102 patients with previously diagnosed epilepsy. Symptomatic cause of epilepsy was found in 26.7% of cases. Among the previously diagnosed patients the most frequently used drugs on admission were valproate (51.9%, average dose 1255 ± 525 mg), carbamazepine (43.1%, average dose 785 ± 400 mg), lamotrigine (39.2%, average dose 275 ± 183 mg), phenobarbital (35.2%, average dose 96 ± 29 mg) and topiramate (21.5%, average dose 264 ± 155 mg). Newly diagnosed patients were initially treated with valproate (50.6%), lamotrigine (13.3%), and carbamazepine (13.1%) or with various combinations. In the previously treated group different antiepileptic drugs (AED) were introduced in 55% of patients, among which the most prevalent were valproate (38.8%), lamotrigine (31.4%), topiramate (20.3%), levetiracetam (1.7%), oxcarbazepine (1.7%), and various combinations (9% of patients). Epileptic seizures were controlled in 74.6% (easily in 7%, and with difficulty in 67.6%) and pharmacoresistant in 25.4% of patients. Polytherapy at the end of hospitalisation was registered in 39%, mostly prevalent in pharmacoresistant (100%), difficult to treat (44.5%), and symptomatic cases (29%). Most frequently discontinued drugs were phenobarbital and carbamazepine.

Conclusion: Profile of AED therapy in the Serbian tertiary referral centre is approaching the standards in developed countries.

p457

LONG-TERM MONITORING FOR LEUKOPENIA IN EPILEPSY PATIENTS ON ANTIEPILEPTIC DRUGS

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Purpose: Patients with epilepsy are typically required to take antiepileptic drugs (AEDs) for many years. Leukopenia, a reduction in blood leukocytes, is a common side effect of AEDs. We evaluated leukopenia in epilepsy patients on long-term AED treatment for more than 20 years.

Method: We retrospectively evaluated records from epilepsy patients who received AED and white blood cell (WBC) counts two or more times a year for over 20 years. Patients with other diseases that may contribute to leukopenia were excluded. We defined severe leukopenia as WBC<3000/. We further examined the course of WBC counts in patients who showed severe leukopenia more than once during this monitoring period.

Results: 183 patients were examined (mean age = 48.5 years, mean duration of follow-up = 26.2 years). Severe leukopenia was detected in 43 patients (23.5%) at least once during the monitoring period. However, 27 out of 43 patients (62.8%) recovered to WBC.3000 by their next blood test. 8 patients showed continued WBC.3000 (or 3500) after a display of leukopenia (duration = 2 to 20 years; mean duration; 11.4 years). Four patients were required to reduce AEDs due to severe leukopenia.

Conclusion: This is the first report to evaluate leukopenia in patients with long-term AED treatment. We found that leukopenia is very common in patients with epilepsy during long follow-up. However, in most cases, AED reductions were unnecessary. Even patients who exhibited repeated leukopenia eventually showed recovery. Future studies will investigate the mechanisms by which AEDs contribute to leucopenia.

p458

EFFECT OF ANTIEPILEPTIC DRUGS ON HOMOCYSTEINE LEVEL

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Purpose: In the last decade the theory was established on the cytotoxic effect of homocysteine excess and its high level was recognised as a risk factor for vascular diseases. Recently it was found that patients taking anticonvulsant drugs have a higher homocysteine level. It is thought that a higher homocysteine level might be connected with taking epileptic drugs which are the inducers of cytochrome P 450.

Method: The aim of the study was to measure the plasma homocysteine level of 60 patients with epilepsy. We also measured the level of vitamin B12 and folic acid. These measurements were made in 4 groups: the 1st group consisted of 20 patients after the first epileptic seizure; the 2nd group 21 patients on monotherapy, the 3rd group 19 patients on polytherapy, and the 4th was a control group of 20 patients suffering from low back pain.

Results: 21% of patients treated for epilepsy had higher mean homocysteine levels. The highest homocysteine level was in patients on monotherapy with inductors of cytochrome P450 (14.02 ± 5.56) and it was higher than in the control group (10.05 ± 2.03) and was statistically significant. Also, a higher mean homocysteine level was in patients on polytherapy (12.24 ± 3.78).

Conclusion: Current results show that higher homocysteine levels in epilepsy patients are connected with treatment. The study was financed by Medical University in Lodz program Nr 502-15-386.

p459
ENZYME INDUCING ANTIEPILEPTICS: CONCERN FOR DRUG INTERACTIONS IN GENERAL PRACTICE
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Purpose: Up to 6% of all hospitalisations are due to adverse drug reactions and 20% of these are caused by drug-drug interactions. Some antiepileptic drugs (AED) have enzyme inducing properties with potentially life-threatening adverse effects as comedication. These drug-drug interactions are published in detail (Patsalos PN et al., The importance of drug interactions in epilepsy therapy. *Epilepsia* 43(4) 2002; 365–85). In spite of this, no data is available on adult epilepsy concerning the implementation of this knowledge in general practice of prescription.

Method: We included 192 adult subjects consecutively seen ambulatory in one secondary and one tertiary centre of Epileptology in Switzerland. Information was derived regarding prescription of enzyme-inducing (CBZ/PHT/PBT) and other AEDs as well as comedication. We screened for potentially dangerous interactions. Subject's epilepsy syndrome, neurological and nonneurological comorbidity and demographic characteristics were collected.

Results: Eighty-two (42.7%) were female. Mean age was 45.2 years (range 16 to 84). 132 (68.8%) received comedication. 67 (34.9%) had enzyme-inducing AED, of whom 46 (68.7%) had comedication. Potentially dangerous combinations (Patsalos PN et al., The importance of drug interactions in epilepsy therapy. *Epilepsia* 43(4) 2002; 365–85) were seen in 35 patients (18.2%) concerning 52.1% of patients treated with enzyme-inducing AED; including 4 subjects on Warfarin, 2 using contraceptives and 1 on chemotherapy.

Conclusion: Two-thirds of our patients with epilepsy receive polymedication with various AEDs and non-AEDs. Potentially dangerous drug-drug interactions (mainly due to enzyme inducing AEDs) were disclosed in 18% of patients. This subgroup is particularly at risk of developing adverse events if their medication regime is changed.

Reference

p460
SEIZURE CONTROL IN EIGHT PATIENTS WITH CORTICAL DEVELOPMENT MALFORMATIONS AFTER SHIFTING FROM OLD TO NEW AEDS
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Purpose: Cortical development malformations (CDM) are a major aetiology of chronic drug-resistant epilepsy. Evolution from high resolution neuroimaging techniques allows easier diagnosis of partial epilepsy due to CDM thus reducing the number of cases of "Cryptogenetic" partial epilepsy. Complete pharmacological control of seizures in partial epilepsy due to CDM is rarely obtained and neurosurgical treatment becomes mandatory. We report our experience with 8 patients whose electroclinical and MRI data pointed out diagnosis of drug-resistant partial epilepsy due to CDM; in these patients the shift from old antiepileptic drugs (AEDs) to new AEDs made patients seizure-free after a mean follow-up of 17.33 months.

Method: Eight patients, 3 males, 5 females, with a mean age of 27.37 years (range 19–46), came to our ambulatory clinic for persistent partial seizures while treated with old AEDs. Neuroimaging studies showed cortical dysplasia in 6 patients, band heterotopia in 1 patient and dysembryoplastic neuroepithelial tumour (DNET) in 1 patient. Electroclinical studies confirmed matching between type of seizure and lesion topography.

Results: All patients obtained benefit from a therapeutic shift and are seizure-free after a mean follow-up of 17.33 months (range 8–56). Three of the 6 patients with cortical dysplasia are on monotherapy with topiramate, 2 are on topiramate plus valproic acid, 1 on topiramate plus oxcarbazepine. The remaining 2 patients, 1 with band heterotopia and 1 with DNET are both on monotherapy with oxcarbazepine.

Conclusion: In 100% of our patients where old AEDs failed, we achieved total seizure control with new AEDs. The possibility of complete pharmacological seizure control in patients with CDM is not yet assessed. Rationalisation and simplification of pharmacological therapy might obtain excellent results in these patients, usually destined to neurosurgery.

p461
INFLUENCE OF ANTIEPILEPTIC THERAPY ON STRUCTURE OF SLEEP IN PATIENTS WITH PARTIAL EPILEPSIES
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Purpose: To establish the influence of antiepileptic therapy (AET) on sleep in patients with different types of partial epilepsies.

Method: Sleep was recorded in 37 male and female patients (mean age: 28.72 years) with cryptogenic partial epilepsy (PE), prior to and approximately 3 weeks after the initiation of AET (carbamazepine, valproic acid, phenobarbital and clonazepam). Statistics included 9 hours of night sleep. Neurological and radiological findings were normal.

Results: AET fragments sleep period time (SPT) in PE, prolongs it in PSSG and shortens it in PCSG. AET has a positive effect on wake after sleep onset (WASO $\geq$ 120 sec) in PS and PSSG: it is shortened and less fragmented; it is more fragmented only in PCSG. AET has a positive effect on WASO $<$ 120 sec in PSSG: it is shortened and less fragmented. AET has no influence on any parameter (SPT, WASO $\geq$ 120 sec, WASO $<$ 120 sec and MT) in PC epilepsy. AET has no influence on sleep stage I in patients with different types of PE; it worsens the quality of sleep stage II (shortens it) in PC and PCSG. It has no influence on PE as a group, or on PS and PSSG. AET both prolongs and fragments sleep stage III in PEs as a group, PS and PSSG. It has no influence on PC and PCSG.

Conclusion: In patients with different forms of partial epilepsy AET prolongs the duration of sleep, but it also fragments it by increasing the number of sleep stage shifts.

p462
RISK FACTORS FOR SEIZURE RECURRENCE DURING TREATMENT
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Purpose: To investigate the rate and factors for seizure recurrence after one year effective response.

Method: 1098 patients with partial epilepsy with secondary generalisation were treated with VPA (285), LTG (222), TPM (192), OXC (123), CBZ (84) and polytherapy (192). Seizure recurrence was scored after a one year seizure free period without dose alteration.

Results: Seizure reappearance was established in 352 patients (32.1%) treated with individually adjusted dose monotherapy in 273 (30.1%) and polytherapy in 79 (41.1%) patients. The seizure free period varied from 12 to 42 months, 20 months average. The most frequent reason suspected for relapse was abrupt AED withdrawal in 74 (21.0%) patients, followed by illness in 34 (9.7%), alcohol intake in 31 (8.8%), sleep deprivation in 29 (8.2%), combined factors (TV, workload, discotheques, basking in the sun) in 57 (16.2%). The reason is unknown for 102 patients (29.0%) and in only 25 (7.1%) patients there was epilepsy progression. For different AEDs the percentage of the seizure reappearance varied from 17.9% for CBZ, 25.3% for VPA to 30–40% for LTG, TPM and OXC (AED choice depended on clinical severity).

Conclusion: Omitted doses are the most important factor for seizure relapse, followed by intercurrent illness, alcohol intake, sleep deprivation and extreme lifestyle. The aggravation of the disease affected an insignificant number of patients.

p463
EFFICACY OF NEW ANTIEPILEPTIC DRUGS IN REFRACTORY FOCAL EPILEPSY

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Purpose: Adult focal epilepsy is often drug-resistant. Unfortunately there is little information on the comparative efficacy of new antiepileptic drugs (AEDs) concerning this group.

Method: An oobservational study based on 96 Patients from our new Epilepsy Unit Data Bank. We included consecutive adult outpatients with refractory focal epilepsy RFE. We studied the efficacy of lamotrigine LTG, levetiracetam LEV and topiramate TPM. AED dosages must be stable for at least three months. AED efficacy was classified as: 1: seizure free; 2: reduction of 50–99% in seizure frequency; 3: reduction of 1–49%; 4: no changes or worsening.

Results: Ninety-six patients with RFE were studied; 51 of them on LTG, LEV or TPM. Epileptic Syndromes were: temporal lobe epilepsy TLE with hippocampal sclerosis, 30 patients (61%); frontal lobe epilepsies, 10 (20%); nonlesional TLE, 10 (20%); lesional neocortical TLE, 8 (16%); parietal lobe epilepsy, 2 (4%); occipital lobe epilepsy and Rasmussen syndrome, 1 (2%). LMT: 24 patients (47%) 2 on monotherapy MT. Average time on LTG: 1270 days (range 259–2155 days). Average dosage: 300 mg/day (range: 100–450). Efficacy: 1:2 patients; 2:2; 3:12; class 4:8.

LEV: 29 patients (49%) 1 MT. Average time: 576 days (range: 188–967 days). Average dosage: 2,500 mg/day (range: 1000–3000). Efficacy: 1:1 patient; 2:2; class 3:10; class 4:13 patients. TPM: 9 patients (17.6%) 1 MT. Average time: 415 days range: 296–1037 days). Average dosage: 225 mg/day (range 100–400). Efficacy: 1:0; 2:2; 3:3; 4:4 patients.

Conclusion: LMT, LEV and TPM have a similar efficacy in RFE. In our study, the frequency of patients being seizure free or with a significant reduction in seizure frequency was low (3–25%).

p464

SAFETY AND LONG-TERM EFFECTIVENESS OF NEW ANTIEPILEPTIC DRUGS IN SYMPTOMATIC LENNOX-GASTAUT SYNDROME

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Purpose: Treatment of Lennox-Gastaut syndrome consists of polytherapy, which usually fails to achieve a significant control on seizures: our aim is to evaluate safety and long-term effectiveness of new antiepileptic drugs (AEDs) as add-on therapy in patients affected by symptomatic Lennox-Gastaut syndrome.

Method: This is an open label, observational study. Patients underwent accurate anamnesis, EEG and neuroimaging. During the 3 months preceding the introduction of new AEDs, the mean number of seizures was 60/month. New AEDs (lamotrigine LMT, levetiracetam LEV and topiramate TPM) were introduced, reaching a mean dosage of 160 mg/die, 1344 mg/die and 182 mg/die, respectively. Every 3 months, patients underwent a neurological examination and routine laboratory tests. Therapeutic response was assessed in a semiquantitative way, as a percentage of reduction in number of seizures ($<50\%$, $>/=50\%$, $>/=75\%$, seizure-free, stationary, worsened). Adverse effects were collected by clinical interview.

Results: We collected data from 13 adults (7 males and 6 females), with a mean age of 37 years. New AEDs as add-on therapy were distributed as follows: 5 patients were administered TPM, 4 patients LMT and 4 patients LEV. Mean observational period length was 36 months. Nine of 13 patients over a reduction in number of seizures equal or greater than 50%; 2 patients are presently seizure-free as regards atonic seizures. Only 2 patients complained of adverse effects, mostly attributable to central nervous system (dizziness, sedation).

Conclusion: In our patients, new AEDs demonstrated to be effective and safe in long-term treatment of symptomatic Lennox-Gastaut syndrome, particularly in case of hypoxic encephalopathy.

p465

HYPERHOMOCYSTEINEMIA AND FOLATE SUPPLEMENTATION IN PATIENTS WITH EPILEPSY: INFLUENCE OF MTHFR POLYMORPHISMS AND OF CONVENTIONAL AND NEW ANTIEPILEPTIC DRUGS

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Purpose: To compare the influence of conventional and new antiepileptic drugs (AEDs) on plasma homocysteine and folate and to determine the therapeutic schedule of folate supplementation on the basis of the antiepileptic medication and the methylenetetrahydrofolate reductase (MTHFR) mutation.

Method: One hundred twenty-two patients, 70F/52M, 19–61 years of age, were screened for plasma homocysteine, folate and MTHFR polymorphisms. Forty-four of these were on conventional AEDs, 38 on new AEDs and the remaining 40 on different drug combinations. Patients exhibiting plasma hyperhomocysteine (i.e.>13 μmol/L) and low (i.e.$<$ 3.4 nmol/L) folate were treated with folate supplementation (5 mg/day) for 30 days and monitored every two months for six months. Statistical analysis was carried out by student *t*-test for independent data and analysis of variance (one-way, ANOVA).

Results: 46 patients on conventional drugs (mono-/polytherapy) but none on new drugs exhibited hyper-homocysteinemia and low folate levels. These patients had the diplotypes TT677/AA1298 (26) and CT677/AC1298 (20). Following folate supplementation, homocysteinemia fell within the physiologic range in all patients and returned to the basal values six months after discontinuation of folate therapy in 37 patients. In the remaining 9 patients, treated with CBZ or PHT and exhibiting the 677TT/1298AA genotype, homocysteinemia exceeded the normal values already at 2–4 months after folate discontinuation.

Conclusion: The risk of hyperhomocysteinemia, very low/absent in patients on new AEDs, is highest in patients on CBZ or PHT therapy exhibiting the 677TT/1298AA genotype. These patients need a more frequent folate supplementation over time to maintain homocysteine levels within the normal values.

p466

EFFECT OF ENZYME-INDUCING AEDS ON THE CHOLESTEROL AND LIPOPROTEIN PROFILE OF ADULT EPILEPSY PATIENTS: EVIDENCE FOR ELEVATED GGT ENZYME AS A KEY DISCRIMINATOR OF THE HIGH LIPID PATIENTS GROUP

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Purpose: Serum total cholesterol (TC), low-density lipoprotein (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TG) have been shown, albeit not consistently, to be increased in those epilepsy patients taking enzyme-inducing antiepileptic drugs (AEDs). Recently, gamma-glutamyl transferase has been found to be an indicator of cardiovascular disease death risk. The aim of this study was twofold: to investigate the effect of AEDs on the lipid and lipoprotein levels in adult epilepsy patients and evaluate the role played by elevated GGT enzyme concentrations as an indicator of high lipid risk epilepsy patients.

Method: A total of 108 patients with epilepsy on long-term AED treatment attending the outpatient epilepsy department, S. João Hospital, Porto, Portugal, were investigated. Serum total cholesterol (TC), LDL-c, HDL-c, TG, GGT, AST, ALT, and the body mass index (BMI) were measured.

Results: Patients on carbamazepine monotherapy showed significantly higher TC, LDL and TG, which was found to be correlated to elevated GGT (respectively $p = 0.0001$; $p = 0.002$ and $p = 0.01$).

Conclusion: Our findings showed that enzyme-inducing AEDs increase total cholesterol and LDL-c but additionally provide evidence supporting that only those patients with elevated GGT are truly likely to have a significant increase in these lipid serum concentrations. Therefore, the increase in serum GGT may have clinical relevance with respect to the

incidence of atherosclerosis in patients with epilepsy receiving enzyme-inducing AEDs, mediated, at least in part, by the increase in cholesterol levels.

p467
REFLEX EATING SEIZURES IN SYMPTOMATIC EPILEPSY
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Purpose: Reflex eating seizures are rare, difficult to control and are usually related to symptomatic epilepsy. We enlighten the clinical context and drug responsiveness of these seizures.

Method: We report patient histories, EEG and neuroradiological findings of two paediatric patients. Video EEGs are available for demonstration.

Results: Patient 1, aged 8 years was born at term. After birth he needed a shunt operation for congenital hydrocephalus. He is multiple disabled. At 5 months of age he began to have focal clonic seizures, and later focal seizures with automatisms and arrest. Daily serial epileptic spasms provoked by eating appeared at 6 years of age. Ictal EEG showed bilaterally and frontally slow wave complexes followed by suppression or fast activity. MRI revealed aqueduct stenosis, polymicrogyria, periventricular heterotopia, hypoplastic corpus callosum and cerebellum. Epileptic spasms did not respond to AEDs. Corticosteroid treatment was added and epileptic spasms stopped. He has been seizure free for 9 months. Patient 2, aged 14 years, was born prematurely. Psychomotor development was normal but later she showed learning difficulties. At 7 years of age she began to have focal seizures with arrest and version and asymmetric tonic posturing. Seizures have been resistant to multiple AEDs. Right frontal lobe is atrophic on MRI. During the last catastrophic phase of seizures (seizures up to 136/day) she had short focal seizures with arrest and slight head deviation and eye blinking spontaneously and similar seizures triggered by eating. Ictal EEG showed progressive epileptiform discharge in right central-centrotemporal region. Phenytoin as add-on combined with corticosteroids left her seizure free until now.

Conclusion: Both patients had symptomatic epilepsy with spontaneous seizures and disabling reflex eating seizures. Seizures were resistant to conventional AEDs. Patients with eating seizures may benefit from corticosteroids when neuronal network is highly excitable.

p468
MEDICAL DECISION MAKING IN EPILEPSY: EXPLORING PATIENTS' REASONING AND UNDERSTANDING OF RECENT AED DECISIONS MADE WITH A HEALTH CARE PROFESSIONAL
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Purpose: Antiepileptic (AED) decision making has not previously been explored from the patients' perspective. Understanding AED decision making is important because: 1) treatment failure is increasingly used as a primary outcome for many randomised control trials; and in defining a treatment failure patients almost always involve health care professionals; 2) shared decision making has been advocated as an ethically desirable approach, leading to improved clinical outcomes (Coulter, A. Paternalism or partnership? Patients have grown up-and there's no going back. *BMJ* 319(7212), 719–20. 99); but levels of participation the clinician or patient adopt have not been examined in epilepsy.

Method: Fifty-nine individuals with epilepsy were recruited from the Mersey regional epilepsy clinic (49) and a major trial (SANAD) of AED treatment (10). All individuals were taking AEDs and had recently seen a health professional. In depth qualitative interviews were conducted by a researcher (DM) using a semistructured approach. The interviews were recorded and transcribed. Using NVIVO software, recurring data themes were examined using content analysis; grounded theory methodology was used to construct a model of decision making.

Results: Dominant themes included that (i) patients consider doctors as the decision makers (ii) potential AED dose or drug changes are rarely considered prior to the consultation (iii) the language of decision making is universally "they decided" rather than "I" or "we" decided.

Conclusion: The individuals studied considered that it is doctors who make decisions about AED changes. A paternalistic rather than shared decision making model is suggested. Ongoing analysis involves examination of tape-recorded consultations between patients with epilepsy and their health care professionals.

p469
UTILISATION OF HISTORICAL DATA IN ACTIVE-CONTROL MONOTHERAPY STUDIES WITH ANTIEPILEPTIC DRUGS
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Purpose: There are no randomised placebo controlled monotherapy trials for standard antiepileptic drugs such as carbamazepine. The effectiveness of carbamazepine in actively controlled trials has differed, implying underlying differences in newly diagnosed populations. This hinders the interpretation of actively controlled trials, particularly equivalence and noninferiority trials and creates major problems for drug regulatory authorities. Modeling data from patients taking standard treatments in existing trials may identify predictors of response and provide evidence of assay sensitivity, and hence aid trial interpretation.

Method: Data from 7 antiepileptic drug monotherapy trials are used to model the outcome for patients prescribed carbamazepine. For the analysis of time to first seizure and time to 12 month remission, Cox regression models are used to explore within and between trial relationships for patient characteristics: age, sex, number of prerandomisation seizures, time from first pre-randomisation seizure, epilepsy type, neurological signs, EEG/CT scan results.

Results: Individual patient data are available for 552 newly diagnosed epilepsy patients treated with carbamazepine within 7 randomised trials. The patient factor that consistently has a significant influence upon outcome is the number of prerandomisation seizures, and this factor may account for up to 40% of the variability in some trials (for the outcome time to first seizure). Full clinical results will be presented.

Conclusion: First seizure occurs more rapidly for individuals that have experienced more seizures before randomisation and 12 month remission occurs more rapidly for individuals with less seizures. Future equivalence or noninferiority trials restricting entry according to number of seizures may have greater assay sensitivity.

p470
LIVER ULTRASONOGRAPHY CHANGES DURING THE LONG ANTICONVULSANT THERAPY
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Purpose: We did an investigation that was going to prove the idea that long anticonvulsant therapy could lead to the pathological changes of liver structure.

Method: 40 patients were studied, all diagnosed with different forms of epilepsy. All of them received anticonvulsants longer than 2 years; average duration of therapy was 8 years. Average age of patients was 26.2 years.

We excluded patients with smoking, chronic alcohol intoxication, prolonged usage of any pharmacological medicaments, endocrinological pathology, hematological diseases, diseases with any metabolism shift, occupational diseases.

Design of experiment included standard ultrasonograpy study of liver, its size, structure, portal system's vessels and liver veins; also we measured the activity of alaninaminotranspherase and aspartataminotransferase.

Results: 26% of patients had no pathological changes of liver. 38% had moderate pathological changes, including changing of liver's size and structure without involving of portal vein system and other liver vessels. 36% of patients had ultrasonography symptoms of chronic hepatitis.

ALT and AST activities were close to normal parameters in 90% of cases.

Conclusion: Thus we did the conclusion that long anticonvulsant therapy could have side effects on liver, chronic hepatitis can develop in 36% of cases.

p471

ANALYSING THE PRACTICE OF ANTIEPILEPTIC AND CONCOMITANT MEDICAL TREATMENT AMONG EPILEPSY OUTPATIENTS IN EASTERN HUNGARY

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Purpose: Epilepsy needs chronic medical treatment throughout life. The patients can suffer from different concomitant neurological and psychiatric disorders. This is why, besides management of epilepsy, the concomitant drug therapy also has an important role in the clinical practice.

Method: We analysed 60 parameters of 986 adult outpatients with epilepsy in the Eastern-Hungarian Database at the Department of Neurology, from 1992–2005. We collected and analysed the data that are connected to epilepsy treatment and concomitant drug therapy.

Results: The mean age was 44.8 years. During the examination period 720 patients took antiepileptic treatment: 78.6% monotherapy, 17.4% bitherapy and only 4% polytherapy. More than half of the patients took carbamazepine (53.5%) and 16.5% valproate monotherapy. AE side effects were only 8.4%. The concomitant drug therapy investigation was surprising, since at the onset of the registration 30.0% of the patients took different drugs affecting the CNS and which may also influence the AEs metabolism. After carefully analysing the anamnesis and the concomitant disorders, we could decrease the use of the concomitant drugs (diazepam, antidepressants, minor and major tranquillants, alprazolam) to 15.5% of patients. The compliance was good in 77.0% of patients.

Conclusion: The analysis of the Epilepsy Database may give useful information for clinical practice. The analysis, and if possible, also elimination of concomitant drug therapy may decrease side effects and drug interactions. These will improve the compliance and the quality of life in patients with epilepsy.

p472

POTENTIAL DRUG INTERACTIONS IN PATIENTS WITH EPILEPSY: CONCOMITANT MEDICATION USE BY AGE AND GENDER

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Purpose: While prevalence of antiepileptic drug–non-antiepileptic drug comedication and interactions is described for the elderly, few data exist regarding gender and age patterns of potentially important interactions. We describe patterns of cardiovascular and psychotropic comedication in epilepsy patients.

Method: A retrospective cohort study was conducted in epilepsy patients using a US claims database (1/2001-12/2004). Patients were sub-grouped: enzyme inducing AEDs (EIAEDs) or noninducing (NEIAEDs).Usage of comedications was compared for: children (C)(0-17yo), young adults (YA)(18-34 yo), adults (A)(35-54yo), older adults (OA)(55-64yo), elderly (E)(65+yo).

Results: of n = 15,869 epilepsy patients (43%men/57%women), n = 9,296 received EIAEDs (54%women), NEIAEDs (61%women). Overall comedication exposure was 4.3 drugs/person, increasing with age: C = 2.6, YA = 3.4, A = 5.5, OA = 7.1, E = 7.0. Many patients used more than 5 prescription medications: 18–44 yrs 31%, 45–64 yrs 54%, 65+ yrs 64%. Statin use was high in those >35yo (EIAED/NEIAED; A = 12.9/13.9%, OA = 29.6/31.0%, E = 34/36%). Calcium channel blocker (all AEDs: C = 0.5%, YA = 2.8%, A = 9.2%, OA = 17.46%, E = 27.1%) and warfarin use were also common (all AEDs: C = 0.9%, YA = 1.32%, A = 4.24%, OA = 8.3%, E = 14.2%). Overall SSRI use was 28.6% for those >34 yo while TCA use was most common in A (10.4%). Antipsychotic use was 11.1%, (EIAED/NEIAED C = 5.7%/12.4%, YA = 8.9%/12.6%, A = 10.9%/14.4%, OA = 12.8%/12.8%, E = 16.9%/15.2%). SSRI and TCA use was higher in women 24.7%–9% respectively vs 16%–4.6% in men.

Conclusion: Discrimination in drug selection based on potential drug-drug interactions was not found. Importantly, concomitant drug use leading to potential interactions occurs across all age groups, not simply the elderly. No specific gender differences were seen with cardiovascular medications, but possibly with antidepressants. These findings suggest more caution be used when prescribing an EIAED.

p473

LONG-TERM EFFICIENCY OF ANTIEPILEPTIC DRUGS IN ADULTS

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Purpose: Due to the pharmacological advantages of some of the new antiepileptic drugs (AEDs) the question of the long-term efficacy and safety of classical AEDs becomes more and more important. We prospectively investigated a consecutive group of 197 adult outpatients treated in our centre for more than 10 years in order to assess the efficiency of their chronic AED therapy.

Method: From April to June 2005 we consecutively assessed the demographic data, epilepsy syndromes, seizure types, seizure frequency, EEG findings, medication schedules and the adverse effects as well as the therapeutic consequences such side effects had. The main target was the rate of seizure-free patients and the probability that a highly efficacious treatment with classical AEDs may be complicated by tolerability problems.

Results: One hundred and ninety-seven patients were analysed (94 women, 103 men, mean age 41.1 ± 14.7 years, range 18–83 years). One hundred thirty patients (66%) were seizure-free for more than 3 months, 70 patients (36%) more than 5 years. Long-term seizure freedom was achieved with one AED in 60%, with two AEDs in 33% and with three AEDs in 4%. 3% of the long-term seizure-free patients were off medication. The most frequently used AEDs were valproate and carbamazepine. Among the new AEDs levetiracetam had the highest proportion (13% of all seizure-free patients). Potential long-term side-effects occurred under classical AEDs exclusively and were found in 14% of the seizure-free patients. Polyneuropathies were the most frequent of those side effects. 70% of the patients suffering from long-term adverse effects refused any dose change or the offering of a complete medication change because of their fears of risking seizure freedom.

Conclusion: It is possible to achieve seizure freedom in a high percentage of adult patients even in a specialised Epilepsy Centre whose referrals should reflect more complicated cases. The long-term prognosis is good once seizure freedom is achieved. Clinically relevant side effects are relatively rare even under treatment with classical AEDs. Seizure freedom is such a spectacular achievement for patients that the majority accept side effects more than risking a seizure relapse during the process of AED changes.

p474

REDUCTION OF MOTOR CORTEX EXCITABILITY BY THE ANTICONVULSANT DRUG SULTHIAME: A TMS STUDY

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Purpose: Sulthiame (STM), a carbonic anhydrase inhibitor, is a widely used drug for treatment of partial and myoclonic seizures especially in children. However, the mechanisms of the anticonvulsant effect of sulthiame in humans are insufficiently characterised.

Method: Transcranial magnetic stimulation (TMS) was performed on 11 healthy adults (age 28.7 ± 7.9). Motor-evoked potentials were recorded using Ag/AgCl electrodes placed over the m. abductor pollicis

brevis of the nondominant left hand. The EMG signal was amplified (Nihon Kodhen), bandpass-filtered (1 Hz–2 kHz), digitised (5 kHz) and recorded using Signal 3.0 software (CED Co., UK). TMS was delivered through a figure-of-eight-shaped coil connected to two Magstim 200 stimulators. In a randomised single-blind placebo-controlled crossover study, the effects of the single oral doses of 5 mg/kg STM on motor thresholds (MT), recruitment curves, cortical induced silent period (CSP), intracortical inhibition (ICI) and facilitation (ICF) were studied.

Results: The only significant ANOVA effect was the interaction "Change × Group" for the motor threshold ($F(1, 11) = 13.57$; $p = 0.004$). Sulthiame induced a significant increase of MT compared with placebo. No other effects and interactions for recruitment curve, ICI, ICF, CSP, were found to be significant.

Conclusion: Because the changes in MT are related to ion-channel function (sodium-mediated), it seems likely that sulthiame exerts its antiepileptic effect through modulation of this function and reduction of cortical excitability. GABAergic or glutamatergic mechanisms seem to be less important in vivo as measured by TMS.

p475

CONTROLLED TRIAL OF LAMOTRIGINE FOR THE TREATMENT OF REFRACTORY PARTIAL SEIZURES

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Purpose: Lamotrigine is an inhibitor of dihydrofolate reductase, an approach based on the folic acid deficiency seen in patients with a long history of phenytoin or phenobarbital treatment. Tested in 1985 in the USA and approved for use in 1994, lamotrigine is a triazine derivate of pyrimethamine, poorly soluble in water, not related to other AEDs. Lamotrigine basically has an inhibitory effect on sodium, and possibly potassium channels. Acting similarly to phenytoin and carbamazepine, lamotrigine differs in better blocking the release of glutamate. Lamotrigine is also more efficacious on slow inactivation of the sodium channel, avoiding fast inactivation and consequently possibly provides better neuroprotection and less behavioural effects. Experience in USA and UK on reducing Sz frequency has been good on partial and generalised epilepsy. Dizziness, blurred vision, somnolence, ataxia and diplopia were the most frequent adverse effects, but the most serious side effect is thrush, which is more probable when used together with VPA, and can be potentially lethal.

Method: In this group of epilepsies, partial seizures are of multiform semiology, with more or less conscious affectation, mixed motor-cognitive-sensitive-autonomic symptoms, and all intent to classify as a syndrome (exception made of localisation criteria), are naive, according to our criteria, because clinical modifications and EEG showed initial site activation of a system of neurons in a specific brain area (usually deep temporal lobe), with different propagation of the discharge in different brains, (aetiology being so wide that is impossible to describe here), excluding idiopathic partial seizures, which are not included in our group. Focusing on a heterogeneous group of 47 patients, cognitive functions basically normal, with different minor focal abnormalities, all belonging a to crypto-remote symptomatic group, aged 14–27 years, with at least 6 yrs of disease duration, gender prevalence of males (wide variability between authors), all with simple partial, complex partial and secondary generalised tonic–clonic seizures, having been treated with at least 3 different programmes of efficient drug therapy, most frequently a combination of DPH, CBZ, VPA, PB or VGB, never alone, always in a different pattern of combination. These patients were enrolled with written consent, into an add-on programme of LTG, starting with very low doses, especially those with previous treatment with VPA. A randomised, double-blind, placebo-controlled trial enrolling 47 patients with at least 4 partial remote symptomatic seizures/month sometimes going to generalisation on different plans of therapy, was conducted at 4 Argentine sites to assess lamotrigine efficacy and dose response as adjunctive therapy for refractory partial-onset seizures. Lamotrigine dosages were elevated by 25 mg/d each week. The study design allowed parallel comparisons with placebo for 3 dosages and a final crossover to 400 mg/d of lamotrigine fsor all patients. The primary efficacy comparison was a change in seizure frequency from a 4-week placebo baseline to weeks 4 through 10 on double-blinded therapy.

Results: At 400 mg/d, lamotrigine reduced the median frequency of all seizures by 46% from baseline, compared with a 6% reduction ($p = 0.0007$) with placebo treatment, and produced a 60% seizure reduction (responder rate) in 56% of patients. A dosage of 100 mg/d produced a 22% reduction in median seizure frequency ($p = 0.043$ compared with placebo) and a dosage of 200 mg/d produced a 28% reduction in median seizure frequency ($p = 0.005$ compared with placebo). Dropouts from adverse events (10%) did not differ from placebo (11%). The only adverse event differing significantly from placebo was thrush, weight loss, though blurred vision, somnolence, anorexia, and ataxia were slightly more common with lamotrigine treatment, as long as placebo shows mostly digestive discomfort.

Conclusion: Lamotrigine is effective and well tolerated as an adjunctive agent for refractory partial-onset seizures. The minimal effective dosage was 100 mg/d, but 400 mg/d was the most effective dosage.

p476

THE INCIDENCE OF COMPONENTS OF POLYCYSTIC OVARY SYNDROME IS HIGHER IN YOUNG WOMEN WITH EPILEPSY TREATED WITH VALPROATE VERSUS LAMOTRIGINE

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Purpose: To evaluate the development of components of polycystic ovary syndrome (PCOS) in women with epilepsy (WWE) initiating either valproate (VPA) or lamotrigine (LTG) therapy.

Method: This prospective, randomised, open-label, multicentre study (LAM30007) enrolled WWE ages 13–40 years with regular menstrual cycles, and either newly diagnosed or inadequately controlled epilepsy (1 chronic AED). Subjects were randomised to VPA or LTG and were treated for up to 12 months. Serum androgen levels were measured every 3 months, and urinary pregnanediol glucuronide levels were measured weekly to assess ovulation for two 3-month periods. The primary endpoint was development of components of PCOS (hyperandrogenism or ovulatory dysfunction) during the study. To exclude the confounding effect of puberty on the results, a post hoc analysis was conducted in women who were >2 years post menarche.

Results: 363 women (177 LTG, 186 VPA) aged 12 to 40 years were evaluated in the post-hoc analysis. The incidence of components of PCOS was higher in the VPA group than the LTG group (36% VPA vs 23% LTG; $p = 0.007$). The high incidence of components of PCOS was evident in the VPA group if the medication was started at 25 years of age or younger (44% VPA vs. 23% LTG, $p = 0.002$), whereas the incidence was similar if the medication was started after age 25 (24%VPA vs. 22% LTG).

Conclusion: This large, multiethnic, prospective, randomised study shows that a greater proportion of WWE receiving VPA than LTG develop components of PCOS symptoms, especially if the medication is started before age 26 years.

p477

THERAPEUTIC DRUG MONITORING OF LAMOTRIGINE IN A PAEDIATRIC POPULATION

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Purpose: Therapeutic drug monitoring is important for drugs that exhibit interindividual variability in pharmacokinetics, and where drug-drug interactions, concurrent disease or age alters the kinetics of that drug. This is of particular importance in a chronic neurological condition such as epilepsy. In this study, the value of therapeutic drug monitoring for lamotrigine, a novel antiepileptic drug, was investigated in a group of paediatric patients.

Method: Plasma lamotrigine levels in 20 paediatric patients (mean ± S.D., age 8.85 ± 3.47 years and weight, 32.22 ± 20.81 kg) were measured using a novel validated high performance liquid chromatography (HPLC) technique that gave a retention time for lamotrigine and internal standard

of 1.258 min and 2.30 min respectively. The method proved to be linear, precise and reproducible over the plasma concentration range of 0.08–20 mg/.

Results: Plasma lamotrigine levels at steady state (mean ± S.D.) in epilepsy patients were thus measured using this novel analysis. The levels thus estimated were 10.1 ± 4.95 mg/L in the lamotrigine monotherapy group. In the valproate co-medication group; carbamazepine co-medication group; clonazepam comedication group; and valproate and clonazepam comedication group, these were 8.11 ± 5.48, 1.89 ± 1.55, 8.33 ± 0.91 and 8.86 ± .98 mg/L respectively. A statistically significant difference ($p < 0.05$) was obtained between the valproate co-medication group and carbamazepine comedication group, between the valproate comedication group and clonazepam comedication group, and between the valproate comedication group and valproate, clonazepam comedication group.

Conclusion: Overall, the results thus obtained from the studies in this research indicate the important need to streamline pharmacokinetic data for the use of antiepileptic drugs in children. Most physicians use ad hoc reasoning in the design of therapeutics and dosage regimens for these drugs in children. Our studies have shown that there are too many variables that could influence the plasma drug concentrations obtained. There is still a lack of satisfactory models and software packages that will allow accurate predictions of drug levels with these drugs in these populations

p478

EURAP GERMANY: SEIZURE CONTROL AND DOSE MODIFICATIONS DURING PREGNANCY UNDER TREATMENT WITH VALPROATE, CARBAMAZEPINE, AND LAMOTRIGINE IN MONOTHERAPY

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Purpose: Antiepileptic drugs (AED) underlie modified pharmacokinetics during pregnancy. A clinically relevant decrease of serum concentration levels has been reported with lamotrigine (LTG). In the 2nd and 3rd trimester compared to the 1st trimester the best seizure control has been shown for valproate (VPA)-monotherapy. A significantly high number of dose changes were performed in patients with LTG-monotherapy (EURAP study group, Neurology 2005). EURAP is a prospective study to investigate pregnancies with AED exposition.

Method: In 37 patients with completed pregnancies who were treated with VPA (n = 13), carbamazepine CBZ (n = 14) or LTG (n = 10) in monotherapy we retrospectively investigated seizure control and dose modifications 1 year preconception and 3 months postpartum in addition to the data of the EURAP Registry.

Results: There was no relevant change in seizure frequency in the VPA- and CBZ-groups, whereas in the LTG-patients we found a favourable development with a continuous decrease of seizure frequency during pregnancy (percentage of patients with seizures: 75% preconception, 50% 1st trimester, 40% 2nd trimester, 30% 3rd trimester, 50% postpartum). In 80% of LTG-patients dose modifications were performed during pregnancy. In 2/3 of these patients the dose was increased due to low serum concentration levels, in 1/3 the dose was raised because of seizures.

Conclusion: The seizure situation of patients with LTG-monotherapy shows a favourable development with decrease of seizure frequency in the course of pregnancy. A causal relation to prophylactic increases of dosages seems likely. We plan to extend the retrospective analysis to other EURAP centres.

p479

PATIENTS WITH PSYCHOSIS UNDER LAMOTRIGINE

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Purpose: Lamotrigine (LTG) is an antiepileptic drug (AED) with a broad efficacy, also licensed in Germany for the prevention of depressive episodes in patients with bipolar affective disorder. Only a few cases are reported with psychoses under lamotrigine, mainly due to alternative psychosis with the EEG finding of forced normalisation (Clemens 2005).

Method: To our knowledge, there are only 6 patients who developed psychoses among 1,400 treated with LTG up until now in our centre. These cases are presented below.

Results: Five patients suffered from symptomatic partial epilepsy (left-sided hippocampal sclerosis in 2, both-sided in 1, bilateral posterior gliosis in 1), one from idiopathic generalised epilepsy with an additional focal component after traumatic brain-injury. One patient had a history of postictal psychoses, another of bipolar disorder, another of pseudologia phantastica. We found LTG-serum levels of 3.5–9.8 μg/ml before the onset of the psychotic episodes, during the psychoses up to 21.8. At least 1 patient suffered from disturbed night-sleep. There were no signs of alternative or postictal psychosis in any case. LTG had to be withdrawn in 3 cases, dose reduction was sufficient for remission of symptoms in the others. Five patients had to be treated with neuroleptics.

Conclusion: Psychoses are a very rare side effect under LTG treatment. A toxic or substance-specific cause of the psychoses has to be discussed, but more cases with additional EEG-recordings are necessary.

p480

TOLERABILITY OF LAMOTRIGINE (LTG), LEVETIRACETAM (LEV), AND TOPIRAMATE (TPM) IN INTRACTABLE FOCAL EPILEPSY

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Purpose: Focal epilepsy is the most common type of epilepsy in adults. The high rate of drug resistance in this group is well known. This drives usually to polytherapy and to use new AEDs. Medical Treatment Guidelines published in the US and Europe agree on the efficacy, safety and tolerability of new AEDs and recommend their use as add-on treatment in refractory epilepsies.

Method: An observational study using Epilepsy Unit Databank. Consecutive adult outpatients included (1995–2006). We studied the tolerability of three new AEDs (lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM)), as monotherapy or add-on therapy, in patients with refractory focal epilepsy (RFE). Tolerability was studied in terms of withdrawal due to adverse effects.

Results: Ninety-six patients with RFE. Epileptic syndromes: temporal lobe epilepsy (TLE) with hippocampal sclerosis, 52 patients (61%); frontal lobe epilepsy, 16; lesional neocortical TLE, 14; non lesional TLE, 10; parietal lobe epilepsy, 2; occipital lobe epilepsy and Rasmussen syndrome,1. LTG, 42 patients (44%); 2 on monotherapy (MT). Withdrawal, 12 (28%); seizure frequency increase, 1; rash, 5; dizziness, 2; tremor, 1; diplopia, 2; constipation, 1. LEV, 38 patients (39%); 2 on MT. Withdrawal, 13 (34%); cognitive disturbance, 4; rash, 2 (and LTG); weight-loss, 2; mammary glands volume increase, 1; tremor, 1; somnolence, 1; not specified, 2.

TPM, 31 patients (32%) 1 on MT. Withdrawal, 14 (45%). Seizure increase, 4; weight loss, 3; cognitive disturbances, 1; diplopia, 1; somnolence,1; nephrolithiasis, 1; not specified, 3.

Conclusion: It is said that new AEDs are well tolerated. In our study, LMT, LVT and TPM, mostly used as add-on therapy in RFE, have a withdrawal rate between 28–41%. LMT appears to be the best tolerated. TPM has the highest withdrawal rate.

p481

COMPARATIVE DAILY PROFILES OF VARIOUS LAMOTRIGINE PREPARATIONS

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Purpose: To discuss the purpose and methodology of comparative daily profiles of Lamotrigine (LTG).

Method: In Denmark, since 2005, legislature requests that pharmacies always deliver the cheapest of several preparations of any drug regardless of the doctors' prescriptions. The prices of preparations are

evaluated every 2 weeks which results in multiple changes of preparations for drugs with multiple marketed preparations. This legislation coincided with the end of patents for branded lamotrigine (Lamictal), and at present 7 different generic preparations are available. Doctors can apply for patients to be exempt from preparation shifts but the health authority requires comparative plasma level data to consider an exception. We have started to determine comparative daily profiles of LTG as only these provide sufficiently detailed data which include C_{max}, C_{min}, t_{max}, $C_{max/min}$ and C_x. Our data are observational, and generated with patients who reported problems with shifts of preparation. There are no standard methods to establish such profiles. Ideally, blood sampling would have to take place at 30–60 min intervals after drug intake, followed by slightly longer intervals until the next dose. But compromises are necessary because blood sampling needs to be integrated into daily hospital routine. Another question is the adequate interval between the two comparative profiles. In addition, possible pharmacokinetic interactions with comedications need to be considered.

Results: We present preliminary findings with sampling intervals of 3 and 4 hours, and with intervals between profiles of 1 and 3 weeks. The 3 hour schedule appears to provide reasonably informative data, whereas a 4 hour schedule may fail to detect differences in t_{max} and carries a risk of rather imprecise C_{max} measurements from which other calculations depend. Significant deviations were detected in profiles collected 1 week apart, but these may become clearer after 3 weeks especially but not only in cases with a long half-life where readjustment to a new steady state may take more time. Although the Danish authorities have set a range of 90–110% in the bioequivalence studies for acknowledgment of equivalence of a new antiepileptic drug preparation, larger deviations could be observed with continuous medication. These were not necessarily apparent, when only morning trough levels were compared.

Conclusion: Comparative daily profiles provide differentiated information on the bioequivalence of different LTG preparations. In clinical conditions, deviations outside the accepted bioequivalence range were observed. For clinical purposes, a 3 hour sampling schedule seems to be adequate. It is recommended to determine the comparative profiles at an interval of 3 weeks.

p482

ONSET OF EFFICACY WITH LAMOTRIGINE IN PRIMARY GENERALISED TONIC–CLONIC SEIZURES (PGTCS): A RANDOMISED, PLACEBO-CONTROLLED STUDY

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Purpose: This abstract reports efficacy, including time to onset, and tolerability results from a study with LTG as adjunctive therapy in patients with primary generalised tonic–clonic seizures (PGTCS).

Method: LTG-naive patients (≥2 years, ≥13 kg) with inadequately controlled PGTCS, receiving a regimen of 1 or 2 AED(s) and an electroencephalogram (EEG) with evidence of generalised epileptiform discharges or no evidence of interictal expression of partial seizures were enrolled in a randomised, double-blind, placebo-controlled trial. Patients having ≥3 PGTCS over an 8 week baseline were randomised to receive LTG or placebo (PBO). Treatment period: escalation phase (12 weeks for patients 2–12 years, 7 weeks for patients >12 years) and maintenance phase (12 weeks).

Results: of the 184 patients enrolled, 117 were randomised to LTG or PBO. LTG group: n = 58, 50% male, median age = 27 years, 50% with 1 concurrent AED, median PGTCS during baseline = 2.4. PBO group: n = 59, 56% male, median age = 25 years, 59% with 1 concurrent AED, median PGTCS during baseline = 2.9. The median percent decreases from baseline in PGTCS were 56% and 30% ($p = 0.036$) 5 weeks after treatment initiation with LTG and PBO, respectively; in patients >12 years, the decreases were 63% and 33% ($p = 0.045$) 3 weeks after treatment initiation. The median percent decreases from baseline in PGTCS were 82% and 43% ($p = 0.006$) during maintenance, and 66% and 34% ($p = 0.006$) during the entire treatment phase, for LTG and PBO, respectively. The median PGTCS counts per month were 2.4 and 2.9 during baseline for LTG and PBO, respectively, 1.0 and 2.3 ($p = 0.013$) during escalation, and 0.4 and 1.6 ($p = 0.001$) during maintenance, and 0.8 and 2.0 ($p = 0.003$) during the entire treatment phase.

Conclusion: The results from this study, combined with the efficacy of LTG for partial seizures, demonstrate that LTG is a broad spectrum AED for patients with either partial or generalised seizures.

p483

PARADOXICAL SEIZURES INDUCED BY GABAPENTIN: A CASE REPORT

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Purpose: We describe a status epilepticus (SE) due to accidental overdosing by incorrect prescription of gabapentin (GBP) up to 5400 mg/day in a patient with epilepsy due to previous meningoencephalitis. After sequential titration down of GBP dosage, the SE phenomenon subsided and the series of EEG recordings suggested successful treatment with clinical improvement.

Method: A 34-year-old female had suffered from meningoencephalitis with epilepsy since 8 years old. Her anticonvulsant included Deparkin (1200 mg/day), Sabril (4 gm/day) and GBP (3600 mg/day). One week before admission, her dosage of GBP was increased to 5400 mg/day. Sudden onset of twitching over right side of face and upper limb evolved, lasting for more than one hour. An EEG done on admission revealed evidence of SE. On examination, she was intubated with a ventilator. She was comatose and unresponsive. Fundi were normal. Pupils were 5 mm and nonreactive. Corneal reflexes were absent. All four limbs were mildly spastic.

Results: A CT scan of her brain was performed without contrast enhancement and revealed atrophy of bilateral cerebral hemispheres, more severe in the frontal and temporal lobes. The cerebral ventricles are moderately dilated. Titration of GBP from 5400 mg/day to 3600 mg/day in two weeks; the last EEG showed poor sustained background alpha rhythm of 8 Hz without epileptic waveform. The patient recovered and was discharged three weeks after admission.

Conclusion: High doses or rapid increase of GBP could result in SE. Careful reduction of GBP was a mandatory treatment in this case.

p484

LEVETIRACETAM VERSUS GABAPENTIN: COMPARISON OF HEALTH CARE UTILISATION, COSTS, AND INCIDENCE OF ADVERSE EVENTS IN EPILEPSY PATIENTS USING A RETROSPECTIVE CLAIMS ANALYSIS

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Purpose: To investigate health care utilisation and costs, and to compare the incidence of adverse events (AEs) in commercially insured epilepsy patients initiating levetiracetam (LEV) or gabapentin (GBP).

Method: A retrospective cohort analysis of epilepsy patients was conducted using a large US claims database (July 2001–December 2003). Patients with a 6-month baseline period were classified into mutually exclusive treatment groups based on their first LEV or GBP prescription, propensity-matched on a 1:1 basis and followed between 3 and 12 months. Utilisation and cost were analysed using non-parametric Wilcoxon rank-sum tests. Risk of AEs was assessed using Cox proportional hazards models.

Results: Treatment groups (n = 816 each) were comparable regarding clinical and demographic characteristics. Patients received more prescriptions for LEV compared to GBP (mean/patient/year: 8.3/6.0, $p < 0.001$), which generated higher LEV pharmacy costs ($1,319/$648, $p < 0.001$). Health care utilisation was significantly (all $p < 0.05$) lower in LEV patients for number of physician office visits (18.1/20.8), emergency-room visits (8.5/11.0), other outpatient visits (35.7/40.6) and medications other than antiepileptic (24.4/36.5). Costs were significantly in favour of LEV for emergency-room visits ($880/$1,094, $p < 0.01$) and medications other than antiepileptic ($1,995/$2,396, $p < 0.001$). The percentage of patients with AEs was significantly lower for LEV (62%/71%, $p < 0.001$). Median time to first AE was longer for LEV (42/28 days). The hazard ratio for time to first AE (LEV vs GBP) was 0.76 (95% CI: 0.68, 0.86).

Conclusion: In a commercially insured setting, increased persistency generates higher LEV pharmacy costs. However, LEV was associated with significantly less utilisation and costs of common health care services and lower risk of AEs than GBP.

p485

LEVETIRACETAM IS AN EFFECTIVE ADD-ON TREATMENT FOR ADULTS WITH EPILEPSY AND INTELLECTUAL DISABILITIES

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Purpose: Evaluate the effect of levetiracetam both in terms of its efficacy as well as its adverse effects on adults with intellectual disabilities and epilepsy.

Method: This is a prospective audit of case notes based data collected from a tertiary clinic for the treatment of epilepsy among adults with intellectual disabilities at the University of Birmingham, UK. The study includes 21 patients with epilepsy and intellectual disabilities of various degrees for whom levetiracetam has been prescribed as an add-on therapy for the first time. Of them 10 were also treated with lamotrigine simultaneously. Data were collected at baseline before starting levetiracetam and then at 3, 6, 9 and 12 months follow-up. The patients were on an average of 2.3 antiepileptic drugs prior to starting add-on levetiracetam. Data were analysed using an intention to treat (ITT) analysis at the 12-month follow up.

Results: 14% (n = 3) became totally seizure free. An additional 43% (n = 9) showed >50% reduction in seizure frequency, 19% (n = 4) showed <50% reduction in seizure frequency, 5% (n = 1) showed improvement which was not quantified and 14% (n = 3) did not show any change in seizure frequency but 5% (n = 1) showed an increase in seizure frequency. Overall in 81% (n = 43) of cases there was an improvement in seizure frequency. Seizure improvement was observed for complex partial seizures (71.5%), primary or secondarily generalised tonic–clonic seizures (77%), and absence seizures (58%). Some patients have experienced a positive effect on mood and behaviour.

Conclusion: Levetiracetam is an effective add-on therapy for adults with intellectual disabilities and epilepsy.

p486

EFFICACY OF LEVETIRACETAM AS ADD-ON TREATMENT FOR PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Purpose: The efficacy of levetiracetam in the treatment of partial seizures is already confirmed by many studies. However, its efficacy has not been evaluated specifically for temporal lobe epilepsy (TLE) until now.

Method: In a retrospective analysis the effect of levetiracetam as add-on treatment on seizure frequency was studied in 38 TLE patients (15 males, 23 females). Levetiracetam was used with a median dose of 2290 mg/day (range: 500 to 6000 mg/day) in combination with various other antiepileptic drugs. The frequency of seizures was assessed 1 (n = 38), 6 (n = 33), 12 (n = 26) and 24 (n = 14) months after starting the adjunctive therapy with levetiracetam and related to the baseline median seizure frequency.

Results: We found a statistical significant reduction of seizure frequency at each control (1, 6, 12 and 24 months). After 1 month 12 of 38 patients (31.6%) had no seizures, after 24 months 1 of 14 patients (7.1%) was still seizure free. In addition, levetiracetam led to a more than 50% seizure reduction in 7 patients (18.4%) within the first month, and after 2 years in 5 patients (35.7%). There was a reduction of the number of patients over 24 months because of discontinuation of levetiracetam as a result of side effects like fatigue and increasing aggressiveness (n = 3), non–compliance (n = 5) or shorter treatment with levetiracetam (n = 16).

Conclusion: This retrospective study demonstrates an excellent therapeutic response of levetiracetam in patients with TLE. Prospective studies to confirm these results are recommended.

p487

ANTIMYOCLONIC EFFECT OF LEVETIRACETAM IN MERRF SYNDROME

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Purpose: To test the efficacy and safety of levetiracetam (LEV) in MERRF syndrome. The treatment of progressive myoclonic epilepsy (PME) is largely empirical, even though valproic acid (VPA) is considered the drug of first choice. However, VPA should be used with caution in PME due to mitochondrial dysfunction, i.e. in MERRF (myoclonic epilepsy with ragged-red fibers) syndrome, because of its interaction with mitochondrial respiration and metabolism.

Method: LEV treatment was started in combination with VPA in a patient with MERRF due to a mutation on the tRNA-phenilalanine gene (G611A). A detailed simplified myoclonus rating scale was administered, and repeated screening of side effects and overall well-being was performed. The effect of LEV was assessed at follow-ups (six and ten months) and compared with the patients' status at initiation of LEV. The Holter-EEG was performed before, after 2 months of treatment with LEV as add-on and in monotherapy with LEV.

Results: The patient before LEV experienced disabling refractory action-induced myoclonus, with significant impairment in activities of daily living. With less than 1500 mg of LEV, the average myoclonus score improved dramatically, as well as the quality of life and no side effects were observed, even after having withdrawn VPA. The initial Holter-EEG showed generalised spikes and spike-and-wave complexes with background slowing. After 2 months of add-on therapy, those complexes disappeared, and did not reappear after another 6 and 8 months.

Conclusion: LEV may benefit myoclonus in PME of mitochondrial origin without altering mitochondrial function, and it could be considered the drug of first choice for the treatment of myoclonus in MERRF.

p488

LEVETIRACETAM IN IDIOPATHIC GENERALISED EPILEPSY AND PORPHYRIA CUTANEA TARDA: A CASE REPORT

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Purpose: Many drugs inducing hepatic metabolism, in particular the cytochrome P-450 system, can exacerbate latent porphyrias because they increase heme synthesis. Consequently, noninducing antiepileptic drugs (AEDs) are usually considered a safe choice in epilepsy patients with porphyrias. However, there are several reports which describe porphyrinogenic activity in noninducing AEDs as well. Treatment of epileptic seizures in patients with porphyrias may consequently be a challenge.

Method: In this case report we are the first to describe levetiracetam usage in porphyria cutanea tarda, the most common form of porphyria. So far, only two reports of levetiracetam use in porphyria are found in the literature, one describing use in coproporphyria and the other in acute intermittent porphyria. Our patient is a 50 year old male affected by idiopathic generalised epilepsy and porphyria cutanea tarda. Valproate and phenobarbital controlled seizures but exacerbated porphyric symptomatology, while clobazam, clonazepam and lamotrigine were safe on porphyric disturbances but did not control seizures.

Results: Levetiracetam monotherapy was accompanied by complete control of seizures and normal liver function and blood count.

Conclusion: Lack of hepatic metabolism in levetiracetam might represent an indicator of its safety in porphyric patients. However, evaluation of experimental models of porphyria is warranted for levetiracetam and for all new AEDs.

p489

SIX MONTH FOLLOW-UP OF LEVETIRACETAM TREATMENT IN ELDERLY PATIENTS: AN INITIAL APPROACH FOR AN OBSERVATIONAL STUDY

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Purpose: To perform a pilot study of efficacy of levetiracetam as monotherapy in elderly patients.

Method: Longitudinal, observational study. Participants were elderly patients initiating monotherapy with levetiracetam. Number of seizures (NS), levetiracetam daily dose and adverse events were recorded at 1, 3 and 6 months from treatment initiation.

Results: Mean age was 73.9 years; 4 patients were female. 8 patients had generalised seizures (GS) and 1 patient had partial and generalised seizures (P&GS). In GS patients, at month 1, the dose ranged from 500–2000 mg/day (mean: 1125 mg/day) and mean NS was 0.57. At month 3, mean NS between study visits decreased to 0.33 and the dose was increased in only 1 patient experiencing 2 seizures. At month 6, mean NS was 0.20, and the dose was increased in 1 patient (dose rank: 1000–3000 mg/day, mean: 1600 mg/day). The P&GS patient was taking a 1000 mg/day dose by month 1, with 1 partial seizure recorded during this period; from month 1–month 3 no seizures were registered, though the dose was increased to 2000 mg/day at month 3. During months 3–6, no seizures or dose modifications occurred. None of the patients discontinued treatment with LEV or presented AE during the 6 month follow-up period.

Conclusion: This pilot study indicates that monotherapy with LEV may be an effective and safe therapeutic option in elderly patients with epilepsy. A longer term study in a larger group of patients is needed to confirm these results.

p490

EFFICACY OF LEVETIRACETAM AS MONOTHERAPY TREATMENT IN PATIENTS OF ALL AGES

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Purpose: LEV is a new antiepileptic drug used as add-on therapy in the treatment of refractory partial epilepsy seizures. The aim of this study was to evaluate the efficacy of LEV as monotherapy in patients with partial and generalised epilepsy.

Method: This is a retrospective study where 10 patients (5 males and 5 females) were evaluated. Mean age was 38.5 (age range 12–84) years. They were followed for a mean duration of LEV treatment of 8.5 (range 1–12) months. Six patients had acryptogenic epilepsy and 4 patients had a secondary epilepsy. LEV was added to other AEDs (TPM; CBZ; LTG) for 5 patients, and then they were progressively switched to LEV monotherapy. The other 5 patients received LEV as the initial AED. LEV was used at doses of 1000–3000 mg/a day with a low titration for 4 weeks. The monthly frequency of seizures was 3.6.

Results: Six of 10 patients became completely seizure free (5 patients were affected by CPC and 1 patient was affected by CGTC). Reduction in seizure frequency >50% was seen in 3 patients (30%). One patient reported some adverse events of irritability and aggressiveness; so LEV treatment was interrupted.

Conclusion: LEV showed itself effective in 90% of patients with CGTC and CPC. It was generally well tolerated. This study confirms the high efficacy of LEV as monotherapy treatment.

p491

PLASMA LEVEL MONITORING OF LEVETIRACETAM IN ADULT PATIENTS WITH EPILEPSY

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Purpose: The aim of this study was to investigate the influence of LEV dosage, age, and comedication on LEV serum concentration.

Method: Plasma levels of LEV were evaluated in 157 patients with epilepsy, 89 females and 68 males, mean age 36.98 years, range 17 to 71 years; 113 patients received enzyme inducing comedication and 44 patients received comedication considered not enzyme inducing. The LEV serum concentration in relation to LEV dose per body weight (level-to-dose ratio, LDR) was calculated and compared for patients receiving enzyme inducing and not enzyme inducing antiepileptic drugs (AEDs).

Results: In our patient population, the mean LEV dosage was 2156 $\pm$ 818 mg/day, the mean LEV dose per body weight was 33.29 $\pm$ 12.63 mg, the mean LEV serum concentration was 12.64 $\pm$ 7.06 μg/mL, the mean LDR was 0.41 $\pm$ 0.26.

The LEV dose per body weight was significantly correlated with LEV serum concentration ($r = 0.37$, $p < 0.001$); the LDR did not correlate with age ($r = 0.17$, $p > 0.1$); although there was a trend for the LDR to be lower among patients on enzyme inducers. The LDR for patients receiving enzyme inducing comedication did not differ significantly from the LDR for patients receiving comedication considered not enzyme inducing ($0.05 < p < 0.1$).

Conclusion: These results suggest that determination of LEV serum concentration seems not to be necessary to adjust LEV dosage in patients on co-medication with or without enzyme inducing AEDs.

p492

EFFECTS OF LEVETIRACETAM ON MOTOR ACTIVITY AND SLEEP ARCHITECTURE: AN ACTIGRAPHIC STUDY

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Purpose: Levetiracetam-treated patients commonly report daytime sleepiness, somnolence, tiredness, and asthenia. However, objective data on the character and/or severity of these findings with levetiracetam (LEV) are missing in the literature. So this prospective, open-label study was conducted to evaluate the effects of levetiracetam (LEV) on motor activity and sleep architecture.

Method: At least 2 days before treatment and 7 days after 3 weeks of treatment, sleep architecture and motor activities of the 22 levetiracetam-treated patients (10 monotherapy, 12 add-on therapy) were evaluated by Epworth Sleepiness Scale (ESS), sleep log and the actiwatch (Mini-Mitter Co., Inc., Bend, OR). Actiwatches are small, rugged, actigraphy-based data loggers that record a digitally integrated measure of gross motor activity and automatically collect all data for sleep parameters. In evaluating nocturnal sleep, the following sleep parameters were estimated: bedtime, wake-up time, sleep-onset time, sleep-offset time, sleep latency (SL), sleep period time (SPT), total sleep time (TST), wake time after sleep onset (WASO), and sleep efficiency (SE). Each subject gave written informed consent for this investigation.

Results: After treatment with LEV (in particular with add-on therapy), motor activity scores statistically significantly decreased and napping episodes statistically significantly increased. But ESS, sleep log, SL, TST and SE weren't different from before treatment.

Conclusion: These results suggest that LEV (in particular add-on therapy) decreases daytime vigilance but does not have major effects on sleep structure.

p493

TWO YEARS CLINICAL EXPERIENCE OF LEVETIRACETAM IN A RUSSIAN ADULT EPILEPSY CLINIC

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Purpose: To evaluate the efficacy of levetiracetam (LEV) as adjunctive therapy in adult patients with pharamacoresistant partial epilepsy (PE) and idiopathic generalised epilepsy (IGE).

Method: Open-label prospective study of patients enrolled from 1 February 2004. LEV up-titration was performed at a rate of 500 mg/day to a maintenance dose of 1000–3000 mg/day. Seizure frequency and adverse events (AEs) were analysed after 1 and 2 years' follow-up.

Results: 101 patients, aged 19-51 (mean 25.3 $\pm$ 2.3) years, with an epilepsy duration ranging from 3-27 years were included. Of these, 84 patients had PE, 17 had IGE. LEV was dosed at 1000-3000 (mean 1500) mg/day. 72 (PE 55, IGE 17) patients received 1 year of LEV treatment and 29 (all PE) received 2 years LEV treatment. After 1 year, 76.5% (13/17) IGE patients achieved 100% seizure freedom, 11.8% (2/17)

demonstrated a ≥75% and 5.9% (1/17) a ≥50% seizure frequency reduction; 5.9% (1/17) showed no change. 25.5% (14/55) PE patients achieved 100% seizure freedom, 12.7% (7/55) demonstrated a ≥75%, 47.3% (26/55) a ≥50% seizure frequency reduction, 14.5% (8/55) showed no change. After 2 years, 24.1% (7/29) PE patients achieved 100% seizure freedom, 17.2% (5/29) demonstrated a ≥75%, 55.2% (16/29) ≥50% and only 3.4% (1/29) showed no change. AEs led to LEV discontinuation (at 500 mg/day) in 2 patients (agitation, dizziness, nausea, tremor). Other AEs were mild somnolence, asthenia and nervousness, reported during LEV titration.

Conclusion: Our data confirm the efficacy and tolerability of LEV adjunctive therapy in pharamacoresistant PE and IGE patients.

p494

COMPARATIVE CNS TOLERABILITY OF NEW ANTIEPILEPTIC DRUGS: AN EVALUATION OF DATA FROM PLACEBO-CONTROLLED STUDIES

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Purpose: To compare CNS adverse effects (CNS-AE) of new antiepileptic drugs (AEDs) through an evaluation of key double-blind studies.

Method: All published placebo-controlled clinical studies conducted in adults using new AEDs, were selected for descriptive analysis. The number of patients reporting CNS-AEs when treated with an active drug (by dose level) or placebo was extracted from each study and the percentage of patients (receiving active drug or placebo) was calculated. The complaint rate of each CNS-AE (ie percentage of CNS-AE patients receiving the active drug minus the percentage of CNS-AE from patients receiving a placebo) was then calculated according to Cramer JA et al. (*Epilepsia,* 1999). Finally, complaint rates were summed to calculate a "summary complaint score" (SCS) for each different class of CNS-AEs.

Results: Thirty-four studies were included in our analysis. The respective SCS for 4 classes of CNS-AEs (somnolence, tremor, vestibular-cerebellar [ataxia, dizziness, diplopia, blurred vision and lack of gait coordination] and cognitive impairment) were as follows: gabapentin 9.6%, 2.3%, 21%, 0%; lamotrigine 0%, 0%, 69%, 0%; levetiracetam (LEV) 7%, 0%, 7%, 0%; pregabalin 11.6%, 4%, 41%, 9%; oxcarbazepine 14.8%, 4.6%, 76%, 0%; tiagabine 0%, 26%, 17%, 5%; topiramate 30.3%, 0%, 94%, 67.8%; zonisamide 6.3%, 0%, 9%, 0%. Overall, LEV had the best CNS tolerability profile. The SCS of these AEs will also be presented for different dose levels for each drug.

Conclusion: Although only a descriptive analysis of these data could be performed, there are clear differences in the CNS tolerability profiles of the AEDs evaluated; of these LEV appears advantageous.

p495

FULL SEIZURE CONTROL AFTER LEVETIRACETAM ADD-ON IN DRUG-RESISTANT PATIENTS WITH EPILEPSY

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Purpose: To examine the factors underlying the unexpected response to levetiracetam (LEV) add-on therapy in patients with a history of drug resistance.

Method: Case review of patients with partial refractory epilepsy achieving full seizure control with LEV, despite not responding to ≥3 polytherapies (combination of 2 or 3 AEDs). Clinical, neurophysiological and neuroimaging data were reviewed.

Results: Fifteen patients (7 males, aged 19-75 [mean 42] years) were selected from 250 consecutive patients. All patients suffered from partial epilepsy (cryptogenic [12/15] and symptomatic [3/15]). Mean daily LEV add-on dose was 2000 (range 1500–3000) mg. All patients achieved seizure freedom on LEV therapy, on average, within the first 2 weeks. Mean follow-up was 26 (range 18–36) months. Analysis of clinical, neurophysiological and neuroimaging data predominantly showed: cryptogenic aetiology (12/15), frontal (8/15) or temporal (5/15) seizures. EEG data showed generalised spike-and-wave discharges as expression of secondary bilateral synchrony (12/15). The AEDs to which LEV was most commonly added were carbamazepine, valproate and phenobarbital, although no specific association showed superior efficacy.

Conclusion: Our results suggest that LEV's effectiveness in this population may be related to its pharmacological profile circumventing some of the drug-resistance mechanisms, avoiding the excessive expression of multidrug transporter and the related removal of AEDs from epileptogenic tissue. LEV's mechanism of action may offer new opportunities of synergy when used in combination with old AEDs.

p496

SELETRACETAM SINGLE RISING DOSE SAFETY: TOLERABILITY AND PHARMACOKINETICS IN HEALTHY SUBJECTS

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Purpose: Seletracetam (UCB 44212) is an investigational antiepileptic drug (AED) with high affinity toward the synaptic vesicle protein SV_{2A}. This first human study investigated its safety, tolerability and pharmacokinetics in healthy subjects.

Method: Single rising oral doses were administered in a randomised, double-blind, placebo controlled manner to healthy male subjects. Three alternating panels of 9 subjects (6 active, 3 placebo) received 2, 4, 10, 20, 50, 100, 200, 400, and 600 mg of seletracetam. Food effect was assessed in an additional group of 8 subjects. Bond and Lader, ARCI-49 and DSS tests were used to explore CNS effects. Plasma and urinary concentrations were determined by LCMSMS.

Results: The maximum dose of 600 mg was not intolerated. Adverse events at all doses were of mild to moderate severity, resolved quickly and were mostly CNS in origin, including dizziness, somnolence, nausea, euphoria, feeling drunk, fatigue and headache. There were no laboratory abnormalities. Seletracetam was rapidly absorbed and followed first-order monocompartmental kinetics, with a half-life of 8 hours. Pharmacokinetics were linear from 2 to 600 mg. Coadministration with a high fat meal resulted in a 39% reduction in C_{max} and no change in AUC. Urinary excretion was 60% of the dose in 48 hours (approximately 20% as parent and 40% as a carboxylic acid metabolite).

Conclusion: The MTD of seletracetam was greater than 600 mg after a single oral dose. Absorption was rapid and pharmacokinetics linear over more than two orders of magnitude. Food had no effect on the extent of absorption. UCB funded.

p497

SELETRACETAM MULTIPLE DOSE SAFETY, TOLERABILITY, AND PHARMACOKINETICS IN HEALTHY SUBJECTS

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Purpose: Seletracetam (UBC 44212) is an investigational antiepileptic drug (AED) with high affinity toward the synaptic vesicle protein SV_{2A}. This study investigated its safety, tolerability and pharmacokinetics in healthy subjects, following 2 weeks of multiple oral dosing.

Method: Three different panels of 12 male subjects (9 active; 3 placebo) received 40, 120 and 400 mg/day in 2 daily doses for 2 weeks. CNS effects were explored using psychomotor tests, rating scales and neurological assessments. PK profiles were obtained after the first dose, and after 7 and 14 days of twice daily dosing.

Results: Treatment emergent adverse effects (TEAEs) occurred in 44%, 89%, 78% and 100% of subjects receiving placebo, 40, 120 and 400 mg/day, respectively, the most frequent being dizziness, drowsiness, euphoria and feeling drunk. Their onset was generally within 1 hour of the seletracetam first dose and was resolved within 24 hours and of mild to moderate severity. There were no serious adverse events (AEs), nor

changes in laboratory, vital signs, ECGs or neurological examinations. Seletracetam pharmacokinetics were linear, dose-proportional and time invariant, with a plasma half-life of 8.0 hours.

Conclusion: The maximum dose of seletracetam in this study (400 mg/day for 2 weeks) was well tolerated, with AEs limited to mild to moderate CNS effects at initial dosing. UCB funded.

p498

PHARMACOKINETICS AND METABOLISM OF 14C-SELETRACETAM IN HEALTHY SUBJECTS

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Purpose: Seletracetam (UCB 44212) is an investigational antiepileptic drug (AED) with a high affinity for the synaptic vesicle protein SV_{2A}. This study investigated the excretion balance and metabolism of orally administered [^{14}C]-seletracetam in healthy male volunteers.

Method: Six subjects received a single oral dose of 100 mg seletracetam labelled with 3.7 MBq of radiocarbon. Plasma, whole blood and expired air samples were obtained serially and urine and faeces were collected for 7 days and analysed for total radioactivity, seletracetam and metabolites (plasma and urinary levels). Ex vivo plasma protein binding was also determined.

Results: Radioactivity excretion was rapid (>90% in 48 hours) and almost complete (92% in urine and 3.2% in faeces) within 168 hours. Main urinary components were seletracetam (25%) and UCB-101596-1 (53%), a carboxylic acid formed by hydrolysis of the amide moiety. Two minor metabolites were also detected, each representing less than 2% of the total radioactivity. No radioactivity was found in exhaled air. Peak plasma concentrations were reached 3 hours postdose. Approximately 90% of plasma radioactivity was identified as seletracetam over the 24 hour period postadministration, while the remainder was associated with ucb-101596-1. Respective half-lives were 8.7 and 9.8 hours. Protein unbound fraction was 95%.

Conclusion: The oral bioavailability of seletracetam is >90%. Plasma protein binding is negligible. Rapid and complete recovery of radioactivity indicates a lack of retention in the body. Seletracetam is eliminated by urinary excretion as the unchanged compound and as the carboxylic acid metabolite ucb-101596-1. UCB funded.

p499

LONG-TERM EFFECTIVENESS OF LEVETIRACETAM IN THE TREATMENT OF EPILEPSY ASSOCIATED WITH LIVER DISEASES

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Purpose: Levetiracetam (LEV) has a good pharmacological profile. This study investigated LEV's efficacy in patients with comorbid liver diseases.

Method: Patients affected by partial or generalised epilepsy associated with liver disease (chronic or acute hepatopathies), where treatment with old antiepileptic drugs (AEDs) produced complications, were included. EEG, clinical and blood parameters were assessed before LEV initiation and existing AED therapy withdrawn. Clinical, EEG and laboratory assessments were performed again at 3, 6, 12 and 18 months. LEV's efficacy was assessed by seizure frequency reduction; tolerability by adverse event (AE) reporting.

Results: Eighteen epilepsy patients were recruited (partial n = 12, generalised n = 6). In 15/18 (83%) patients, seizures were not fully controlled by previous AED therapy. Concomitant liver pathology comprised hepatitis C virus chronic hepatopathies (13/18) and acute toxic hepatitis (5/18). AED therapy was changed for liver failure or increased hepatic values in those patients in which acute or chronic hepatotoxic effects were documented, and/or interactions observed with specific medication (i.e. interferon) with enzyme inducing AEDs. LEV mean daily dose was 2000 (range 1000–3000) mg. LEV was effective and after 18 months follow-up, seizure recurrence was not observed, and an improvement in basal medical conditions was confirmed. LEV's efficacy was particularly evident in patients in whom previous poor seizure control was due to drug interactions or low dose AED monotherapy. No significant side effects were reported.

Conclusion: LEV is effective and well tolerated and should be considered as a first choice AED in the treatment of epilepsy associated with acute or chronic hepatopathies.

p500

SAFETY OF LEVETIRACETAM 1000–3000 mg DAILY AS ADJUNCTIVE THERAPY IN ADULT PATIENTS WITH PARTIAL EPILEPSY (SKATE STUDY): THE GREEK EXPERIENCE

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Purpose: To evaluate the safety and efficacy of levetiracetam (LEV) as adjunctive therapy in patients with epilepsy experiencing partial seizures, with or without secondary generalisation, in daily clinical practice.

Method: A 16 week, prospective, multicentre, open-label, phase-IV pharmacovigilance study of LEV in an adult population receiving at least one concomitant antiepileptic drug (AED). A 2-week baseline and/or 4-week titration schedule was used; LEV was uptitrated from 1000 mg/day to 3000 mg/day (maximum). The intention-to-treat (ITT) population was used for safety and efficacy analysis.

Results: Thirty-five patients (16 male, 19 female), mean age 40.1 (range 17.0–69.8) years were included. LEV mean dose was 1382.1 mg/day. 10/35 (29%) patients achieved seizure freedom and 25 (71%) ≥50% seizure reduction (23.5% and 61.8% for partial seizures respectively) with a median seizure reduction of 79.5% (78.2% partial). Of 24/35 (68.5%) responders, 22 (63%) achieved marked or moderate improvement on a Global Evaluation Scale. LEV 16 week retention was 82.9%. AEs were reported in 10/35 (29%) patients; most mild to moderate, with 1 serious AE considered drug-related. Nonserious drug-related AEs were: vertigo (n = 1), diarrhoea (n = 1), nausea (n = 2), anorexia (n = 2), dizziness (n = 1), impaired balance (n = 1), headache (n = 5), somnolence (n = 6). AEs caused LEV discontinuation in 1/35, LEV dose change or temporary discontinuation in 2/35 patients. Lack of efficacy caused LEV discontinuation in 3/35 patients.

Conclusion: LEV add-on therapy was effective and well tolerated in managing partial seizures, with or without secondary generalisation, with a retention rate of 82.9%. The majority of patients were identified as CGI-responders

p501

SAFETY PROFILE OF LEVETIRACETAM INTRAVENOUS INFUSION (1000–3000 mg/day IN BID ADMINISTRATION) IN PATIENTS WITH PARTIAL-ONSET SEIZURES

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Purpose: To assess the safety profile of intravenous (IV) levetiracetam (LEV, 1000–3000 mg/day), a new formulation intended for patients temporarily unable to take oral LEV. Bioequivalence between oral and IV formulations is previously demonstrated.

Method: A multicentre, open label, single arm study. Patients taking oral LEV were switched to the equivalent IV dosage (mg-by-mg substitution, without washout). 1 to 3 LEV ampoules (500 mg/5 mL) were injected into 100 mL pouches 0.9% saline and 15 minute infusions

administered BID for 4 days. Adverse events (AEs), vital signs, physical and neurological examinations, and LEV and other AED plasma concentrations were recorded. On days 1 and 4, 2 electrocardiograms (ECGs) were performed (predose and end of morning infusion). On day 5 patients were switched back to oral LEV. Any seizure occurrence was recorded.

Results: Twenty-five adults with partial-onset seizures (12 male, 13 female; mean age 40.8 ± 10.6 years, age at epilepsy onset 0–46 years) completed the study. AEs, mostly mild or moderate, were consistent with LEV's known AE profile. Eleven subjects (44%) experienced at least one treatment-emergent AE. Most frequently reported AEs were headache (n = 5) and fatigue (n = 3). No serious AEs or deaths occurred, nor clinically relevant vital sign, ECG or clinical laboratory changes noted. No temporal relationship between IV infusion and AE onset was observed, nor infusion site reactions. No seizure worsening was reported during the study or brief follow-up.

Conclusion: IV LEV appears well tolerated and may be a useful alternative for patients with partial-onset seizures temporarily unable to take oral LEV. Supported by funds from UCB.

p502

LEVETIRACETAM AS MONOTHERAPY FOR EPILEPSY IN ADULTS: A CASE SERIES

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Purpose: To evaluate efficacy and tolerability of levetiracetam (LEV) monotherapy in adult patients with epilepsy, both newly diagnosed and converting from another antiepileptic drug.

Method: Adult patients affected by partial or generalised epilepsy, with idiopathic, cryptogenic or lesional aetiology, received LEV monotherapy. Patients were either newly diagnosed or converting from add-on therapy. All patients underwent objective neurological and psychological examination, EEG, and encephalic CT/MRI at baseline; EEG, neurological examinations and routine laboratory tests were performed every 3 months.

Results: Fifty-four patients (25 male, 29 female), aged 15–71 (mean 37) years, mean baseline seizure frequency 4.4/month, received LEV monotherapy 1000–3000 (mean 2120) mg/day for between 6 and 33 (mean 13.3) months. Twenty-four patients were newly diagnosed, 30 converted from add-on therapy (46.6% from carbamazepine, 10% from oxcarbazepine, 20% from phenobarbital, 10% from topiramate, 13.3% valproate). Overall responder rates (≥50% seizure reduction) were 45/54 (83%) at 6 months and 43/54 (79%) at 12 months. Seizure freedom was achieved in 21/54 (39%) of all patients both at 6 and 12 months. 16/24 (66.6%) patients in the newly diagnosed group and 5/30 (16.6%) patients who converted from add-on therapy achieved seizure-freedom. 9/54 (17%) patients showed no significant improvement in seizure frequency. Adverse events reported were somnolence, anxiety, depression, vertigo. LEV was otherwise well tolerated, with no clinically relevant changes in laboratory parameters.

Conclusion: In this case series, LEV showed good efficacy as monotherapy and was well tolerated, with initial monotherapy appearing more effective than conversion to monotherapy.

p503

EFFICACY OF LEVETIRACETAM AS PROPHYLAXIS TREATMENT IN COMPLEX FOCAL STATUS EPILEPTICUS: A CASE REPORT

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Purpose: To evaluate the efficacy of levetiracetam (LEV) as prophylactic treatment in a patient with complex focal status epilepticus.

Method: This case concerns a female aged 65 years with partial status epilepticus whose EEG showed focal paroxysmal anomalies which disappeared after treatment with intravenous (IV) diazepam (DZP). Two weeks before this episode, she had experienced a confusional state for a few minutes. Her initial symptoms of meningism, right hemiparesis and fever could be attributed to other diseases (eg encephalitis). Investigations performed 12 after symptoms appearing; CT scan, MRI and cerebrospinal fluid analysis were normal. After IV DZP administration as acute treatment, LEV was selected as the antiepileptic drug (AED) for prophylactic treatment. This patient has Hepatitis C hepatopathy and so the use of AEDs metabolised by the liver would be contraindicated; LEV was thus chosen since it does not undergo any significant hepatic metabolism. LEV was uptitrated over a 5 week period with a starting dose of 250 mg/day, and increased by 250 mg/day every week to a target dose of 2000 mg/day.

Results: After 3 months of LEV treatment (2000 mg/day) the patient remained seizure-free without the occurrence of adverse events. A control EEG performed during the follow-up visit showed no abnormalities.

Conclusion: This case study suggests that LEV may be safe and effective when used as prophylactic treatment to prevent complex focal status epilepticus. Larger studies are needed to confirm this preliminary finding.

p504

LONG-TERM EFFICACY AND TOLERABILITY OF LEVETIRACETAM IN PATIENTS WITH EPILEPSY WITH SEVERE CONCOMITANT DISEASES

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Purpose: To evaluate the long-term efficacy and safety of levetiracetam (LEV) in patients with focal epilepsy and other severe concomitant neurological and/or clinical diseases.

Method: Retrospective study of patients with focal epilepsy and partial seizures with or without secondary generalisation, who also had concomitant diseases including neurological copathologies such as: cerebrovascular disease, Alzheimer's disease and posttrauma outcomes; and/or other conditions such as: cardiopathy (atrial fibrillation), nephropathy and hepatopathy. All patients received additional drugs for these copathologies. LEV was administered either as monotherapy or as add-on to existing antiepileptic drugs (AEDs) eg PB, CBZ, VPA, LTG, GBP. At end of follow-up period, seizure reduction, safety and drug-drug interactions between AEDs and other concomitant drugs were evaluated.

Results: Fifty-four patients (33 Males, 21 Females), mean age 57.2 (range 23–91) years were included. LEV mean dose was 1420 (range 1000–4000) mg/day. Mean follow-up was 20 (range 6–44) months. 9/54 (16.7%) patients who were seizure-free with previous AEDs and who were switched to LEV (5 monotherapy, 4 add-on) due to adverse effects of previous therapy, remained seizure-free. Of the remaining patients 17/45 (37.8%) achieved seizure freedom. Seizure reductions of ≥75% were achieved by 11/45 (24.4%), and ≥50% by 5/45 (11.1%). 8/45 (17.8%) achieved seizure reduction <50%. 4/45 (8.9%) patients discontinued LEV due to AEs (drowsiness, migraine, restlessness, rash). Other reported AEs, not requiring discontinuation were transient somnolence and restlessness.

Conclusion: These data confirm LEV's good efficacy and safety profile in patients with specific therapeutic needs such as those on polytherapy for other copathologies.

p505

CLINICAL AUDIT OF 218 PATIENTS TREATED WITH LEVETIRACETAM

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Purpose: To assess the safety and efficacy of levetiracetam (LEV) in patients with uncontrolled partial (focal) seizures.

Method: A clinical audit of adults and children (≥14 years) treated with LEV for partial onset seizures between 2002 and May 2005. Main outcome parameters were retention rate (Kaplan-Meyer analysis), seizure frequency reduction/month, AED treatment changes and adverse events (AEs).

Results: Two hundred and eighteen (92 male, 107 female) patients, aged 14–68 (mean 37.2 ± 12.1) years, epilepsy duration 0–54 (mean 18.5

± 11.4) years were included. LEV was initial monotherapy in 8/218 patients and as add-on to: 1 AED 85/218, 2 AEDs 113/218, 3 AEDs 12/218. LEV retention rates after 6 months, 1, 2 and 3 years were 84.8%, 72%, 62% and 50%, respectively. Mean seizure frequency/month decreased from 19.2 at baseline to 12.7 and 7.1 after 6 months and 3 years respectively. Mean percentage seizure reductions were 45.7% and 64.2% after 6 months and 3 years and responder rates (≥50% seizure reduction) 51.5% and 62.2% after 6 months and 3 years respectively. Seizure freedom (100% seizure reduction) was achieved by 18.6% and 6.2% after 6 months and 3 years. Concomitant AED use decreased; 25 patients received LEV monotherapy, 94, 97 and 2 patients received 1,2 and 3 concomitant AEDs. AEs were experienced by 18.3% (40/218) patients; mild to moderate, commonly somnolence (24/218), dizziness (8/218) and mood changes (11/218). 6.4% (14/218) patients discontinued LEV due to AEs.

Conclusion: LEV add-on therapy demonstrated long-term efficacy and favourable tolerability in patients with refractory focal epilepsy and its use decreased substantially concomitant AED requirements.

p506

LEVETIRACETAM IN MESIAL TEMPORAL LOBE EPILEPSY

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Purpose: To evaluate the efficacy and safety of Levetiracetam in mesial temporal lobe epilepsy.

Method: Thirteen patients (6 males+7 females, aged between 21–53 years old), all diagnosed, during adolescence, with mesial temporal lobe epilepsy have been included in this retrospective study. At adult age and after several years of seizure freedom, all patients showed recurrence of seizures (from 2–3 seizures/month to a maximum of 15–20). At baseline, all patients were already on treatment with 2 or more AEDs (CBZ, VPA, PB, PHT, CLB). Considering our prior positive experience with levetiracetam in symptomatic epilepsy, we tried to optimise patients' therapy to improve their outcome in terms of efficacy (seizure freedom, seizure reduction, seizure intensity) and in terms of safety (less AEs) and therefore shifted all patients to CBZ+LEV therapy. Levetiracetam mean dosage was: 1750 mg/die (range 1000–3000 mg/die). Patients were followed up to 15–28 months.

Results: Five patients (38.4%) were seizure free. Four patients (30.8%) had a 50% reduction of seizure frequency and seizures are now less intensive (only minor oral automatism and/or a prolonged epigastric aura). Four patients had no improvement (30.8%). The main adverse event reported by patients was somnolence (mild to moderate).

Conclusion: Even if our experience is limited because of the small population, we believe that levetiracetam, in association with CBZ, is effective and well tolerated and represents a valid alternative in the treatment of MTLE, a pathology where surgical treatment is an important therapeutic choice.

p507

LEVETIRACETAM: A POTENTIAL TREATMENT OPTION IN REFRACTORY CANINE EPILEPSY

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Purpose: Epilepsy is the most common chronic neurological disorder in dogs. In veterinary medicine approximately 33% of dogs with epilepsy are refractory to pharmacological treatment. Refractory canine epilepsy was discussed as a model for pharmacoresistant human epilepsy. As in humans, new pharmacological treatment options with greater efficacy are urgently needed. The aim of this study was to find a well tolerated antiepileptic drug, which reduces seizure frequency by more than 50% in pharmacoresistant canine epilepsy patients.

Method: The second generation antiepileptic drug (AED) levetiracetam was administered to 6 pharmacoresistant epileptic dogs as an adjunct to standard treatment protocols with phenobarbital and potassium bromide. The seizure frequency, pattern, severity and side effects were recorded. Dogs received 10 mg/kg 3 times daily for 2 months. If no response was obtained 20 mg/kg 3 times daily was used.

Results: One dog showed no response, 5 dogs had a decrease of seizure frequency by 80% (responders). Four responded to the lower dose of levetiracetam, 1 to the higher dose. Three responders had days with cluster seizures. The number of days with clusters was reduced by 90% on treatment. Four of the responders had complex focal seizures with secondary generalisation prior to levetiracetam. In 3 of these dogs 65% of the seizures did not generalise during the drug period. One dog was severely sedated on levetiracetam, no other side effects were observed.

Conclusion: Preliminary data suggest that levetiracetam is well tolerated in dogs and reduces seizure frequency and severity in 83% of cases.

p508

LEVETIRACETAM ALTERNATIVE MONOTHERAPY FOR ELDERLY PATIENTS WITH DIFFICULT TO TREAT EPILEPSY

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Purpose: This open-label 1 year follow-up study was designed to evaluate levetiracetam (LEV) as a possible alternative for patients who previously failed other antiepileptic drug monotherapy.

Method: Patients aged 60 years or more with partial seizures with or without secondarily generalisation, were eligible if they were receiving a major antiepileptic drug and needed to discontinue it because of unacceptable side effects or inadequate seizure control. The study protocol comprised: 1) an 8 week retrospective screening phase; 2) a dose-escalation phase lasting up to 12 weeks; 3) an open treatment phase. For the dose-escalation phase, LEV was started at a dose of 250 mg b.i.d., increased to 500 mg b.i.d. in 3–4 weeks and then based on patients' clinical response up to 3000 mg/day or up to seizure freedom. Concomitant antiepileptic drug was gradually discontinued after week 4 of the beginning of the dose-escalation phase. The treatment phase began when patients had achieved an initial maintenance dose of LEV monotherapy. Baseline assessments obtained during the screening visit included historical seizure frequency, vital signs, physical examination, medical history, health-related quality of life measured with the Quality of Life in Epilepsy Inventory (QOLIE-31) and the self-report Adverse Events Profile (AEP). At each follow-up visit, which occurred every 12 weeks, patients compiled the QOLIE-31 and AEP questionnaires and investigators rated patients' global clinical status according to seizure (frequency, duration, and intensity), adverse events, and cognitive, psychic, motor, and social functioning with the 7-point scale Clinical Global Impression (CGI).

Results: Twenty-four patients agreed to participate and 17 entered the treatment phase. Six patients failed by discontinuing concomitant antiepileptic drug for seizure recurrence. Seven patients reported adverse events within two weeks of starting LEV. Of these patients, 1 discontinued LEV while the others continued with LEV. At the 6 months visit 3 patients were lost to follow-up and an additional 2 patients discontinued treatment for lack of efficacy. Remaining 12 patients completed 1 year of follow-up. The CGI, the QOLIE-31 and the AEP scores showed that LEV monotherapy was perceived by both physicians and patients to have more benefits than monotherapy with previous antiepileptic drugs.

Conclusion: LEV is a promising alternative monotherapy for elderly patients as a substitution of other ineffective or poorly tolerated antiepileptic drugs.

p509

LEVETIRACETAM FOR THE TREATMENT OF "NOT SO BENIGN" PARTIAL EPILEPSIES OF CHILDHOOD WITH CENTROTEMPORAL SPIKES (BECTS)

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Purpose: This currently ongoing prospective open study aims to define the efficacy and safety of LEV in children with BECTS who did

not respond to sulthiam (STM) and to assess its effect on interictal EEG activity and cognition.

Method: Children are consecutively recruited from the Vienna university paediatric epilepsy outpatient department. Diagnosis is based on clinical and EEG criteria (including prolonged sleep recordings) by using the ILAE criteria. LEV is administered after STM failure. In case of treatment success, STM is tapered. EEG and comprehensive neuropsychological assessments are conducted before treatment and then periodically. Study end points are the electroclinical state and cognitive performance after 12 months' continuous treatment with LEV monotherapy.

Results: We present pilot data on 15 children who were recruited between September 2003 and December 2004. Data so far demonstrate that all of these children remained seizure-free and are experiencing no reported side effects. In 2 cases, nonconvulsive status epilepticus (oromotor dyspraxia with speech deterioration and drooling) was promptly interrupted. In addition EEG spikes diminished in all of them and have not reoccurred so far. No further cognitive and/or behavioural decline has been found.

Conclusion: LEV seems to be an effective and safe alternative treatment option to STM in children with BREC. Further studies will have to compare both drugs concerning first-line treatment. Strict syndrome diagnosis is crucial, as the same positive effect was not seen by us in other idiopathic localisation-related epilepsy syndromes, especially benign epilepsy with occipital paroxysms and familial frontal lobe epilepsy.

p510

EFFICACY OF LEVETIRACETAM IN THE TREATMENT OF CHILDREN WITH BECTS: A PROSPECTIVE, OPEN-LABEL PILOT TRIAL PRIOR TO A CONTROLLED, RANDOMISED, DOUBLE-BLIND GERMAN MULTICENTRE STUDY (HEAD-STUDY)

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Purpose: To conduct a prospective, open-label pilot trial to evaluate the efficacy and tolerability of levetiracetam (LEV) monotherapy in a cohort of 10 children with benign childhood epilepsy with centrotemporal spikes (BECTS), paying special attention to effects on cognitive function.

Method: To date 8 patients aged 3 to 12 years with BECTS were recruited. LEV was titrated up to 20 mg/kg. Efficacy was assessed by seizure freedom and alteration of electroencephalogram (EEG) findings over a 6 month period. Neuropsychological testing of 7 patients took place before the start of treatment and after 6 months of treatment. Tolerability was assessed by evaluation of adverse events (AE).

Results: All 8 patients are seizure-free under treatment. EEG abnormalities showed significant reduction. Neuropsychological assessment before the start of treatment revealed average performance in 5 and below average performance in 2 patients. In 4 patients who have reached the endpoint of the trial by now no changes in test results were seen. Mild AEs were reported in 2 patients (n = 1: mild temporary behavioural changes within the first week of treatment, n = 1: mild weight loss). In both cases no adjustment or discontinuation of LEV dosage was necessary.

Conclusion: These preliminary data show that LEV seems to be an effective and well-tolerated option in the treatment of children with BECTS. Concerning effects on cognitive function preliminary data are promising, but the complete data of retesting are to be awaited. Based on these encouraging results a controlled, randomised, double-blind multicentre trial to evaluate the application of LEV in a representative cohort of 120 children with BECTS is going to start in Germany in spring 2006 (HEAD-Study).

p511

DETERMINATION OF LEVETIRACETAM IN PATIENTS WITH EPILEPSY AND INTELLECTUAL DISABILITY

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Purpose: Levetiracetam (Keppra) is a new drug that has a therapeutic application in epilepsy and disorders involving cognitive disturbances. We measured twice the concentrations of levetiracetam in sera of 8 patients with epilepsy and intellectual disability.

Method: We used an isocratic high performance liquid chromatography (HPLC) method for the quantification of levetiracetam. Chromatograms were run at 35°C with Zorbax Eclipse XDB-C8 column. A mobile phase of acetonitrile/38 mM potassium phosphate buffer (pH 4.3., 12:88 vol/vol) at a flow rate of 1.0 ml/min was used and it was monitored at 220 nm (Contin et al 2004. Therapeutic Drug Monitoring 26(4):375–379). All chromatograms were run with Agilent 1100 equipment. The patient population consisted of 8 patients with difficult-to-treat epilepsy and intellectual disability who were on antiepileptic multidrug therapy including levetiracetam.

Results: The mean value of levetiracetam concentrations in these samples was 130 μmol/l (from 60 to 255). The dose of levetiracetam in these patients was 2000–4000 mg per day.

Conclusion: This HPLC method is rapid and simple for the determination of levetiracetam in patients with epilepsy. It seems that the dose 2000–4000 mg per day will give the necessary therapeutic level. The detailed relationship between efficacy and the concentration of levetiracetam in serum is under analysis.

p512

EFFICACY OF LEV IN POSTSURGICAL PATIENTS WITH CONTINUING SEIZURES

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Purpose: To evaluate the efficacy of levetiracetam (LEV) newly introduced in postoperative patients still experiencing seizures.

Method: At the University Hospital, Freiburg, in Germany patients with ongoing seizures after elective brain surgery were identified. From 2001 to 2005 LEV was started in 32 of these patients after surgery. LEV treatment was started after up-titration of preexisting AEDs. A retrospective chart review was performed to assess seizure freedom and responder rates.

Results: Thirty-two patients were analysed. In 31 patients LEV was started as add-on therapy (1-3 preexisting AEDs), in 1 patient as monotherapy. 21/32 patients (69%) became seizure free and an additional 6 patients (19%) experienced a seizure reduction of at least 50% after administration of LEV 500–4000 mg/d. The follow-up period ranged from 3 to 41 months (mean 16.5 months) per patient. Eight of the patients had been treated preoperatively with LEV without success. Seven of these patients became seizure free post-operative when the treatment with LEV was started again.

Conclusion: LEV proved highly effective (69% seizure freedom) in the post-operative treatment of brain surgery patients still experiencing seizures. Epilepsy surgery, although not leading to seizure freedom, rendered some patients pharmaco-responsive to LEV.

p513

EEG EFFECTS OF LEVETIRACETAM IN PATIENTS WITH EPILEPSY

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Purpose: To study EEG changes during Levetiracetam (LEV) as add-on therapy in patients with epilepsy.

Method: The study included 23 patients with refractory epilepsy (partial with secondary generalisation) treated with LEV as add-on therapy. The basic antiepileptic drug was kept constant during the evaluated period. The EEG findings after 3 months of treatment were compared to the baseline period.

Results: Fifteen (65.22%) patients achieved more than 50% seizure control, and 8 (34.78%) showed insufficient effect. Two (8.7%) patients

reported on sleep and mood disturbances. In the EEG no changes were found in the organisation of background activity during LEV. The initial diffuse slowing in 4 (17.39%) patients was reduced in 3 (13.04%) of them. Focal activity was found in 11 (47.83%) patients before LEV followed by reduction in 2 (8.7%) and aggravation/provocation in 7 (30.43%) patients. Paroxysmal activity showed in 7 (30.43%) patients initially. During LEV reduction was found in 2 patients (8.7%), no change in 3 (13.04%) and activation/new in 4 (17.39%) patients. No correlation was found between the evolution of focal and paroxysmal activity and seizure control.

Conclusion: LEV does not affect the background activity in patients with epilepsy. No correlation was found between clinical efficacy and evolution of focal and paroxysmal activity. Investigations are needed to study the EEG changes in patients with epilepsy treated with LEV as monotherapy.

p514

LEVETIRACETAM SERUM LEVELS ARE INFLUENCED BY ENZYME-INDUCING AND NON–ENZYME-INDUCING CO-MEDICATION

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Purpose: Levetiracetam (LEV) is a new antiepileptic drug (AED) approved for add-on therapy up until now. As there is no major metabolism of LEV, its serum levels are usually considered not to be influenced by other AEDs, especially enzyme-inducing AEDs (EI-AEDs).

Method: To evaluate the effect of AEDs on serum levels of LEV we retrospectively analysed data of 541 in- or outpatients of the Swiss Epilepsy Center between January 2002 and May 2005. 2007 measurements (188 with LEV as monotherapy, 410 with EI-AEDs as co-medication, 1179 with non–enzyme-inducing AEDs (NEI-AEDs) and 230 with both EI-AEDs and NEI-AEDs were processed. Repeated measurements in the same patient were considered only if the drug regimen or dosages were changed.

Results: Serumlevel-to-dose ratios of LEV are significantly lower when AEDs are administered simultaneously (median 3.22 vs 3.86, $p = 0.003$). This effect is primarily induced by EI-AEDs as indicated by significant differences in this group (median 3.10, $p = 0.001$) comparing to a nonsignificant difference in combination with NEI-AEDs (median 3.26, $p = 0.591$). When only fasting values were taken into account (LEV monotherapy $n = 47$, LEV & EI-AEDs $n = 212$, LEV & NEI-AEDs $n = 559$) significantly lower LEVserum level-to-dose ratios were also seen in combination with EI-AEDs (median 2.32 vs 2.52, $p = 0.022$), whereas simultaneous application of NEI-AEDs lead to significantly higher LEV-serum level-to-dose ratios (median 2.56 vs 2.16, $p = 0.003$).

Conclusion: Serum levels of LEV are influenced by other AEDs. Whether these findings are of clinical significance has to be evaluated in further studies. More data on fasting values in monotherapy should be available soon, as LEV is about to be approved for monotherapy.

p515

EFFICACY OF LEVETIRACETAM AS AN ADD-ON THERAPY IN PATIENTS WITH STARTLE EPILEPSY

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Purpose: Our aim is to evaluate the use of levetiracetam as an add-on therapy in patients with startle epilepsy.

Method: Thirteen patients suffering from seizures triggered by unexpected stimulus were evaluated. Touching or striking any part of the body was the main triggering stimulus. Sudden noise in 2, touching and noise in 7, touching in 4 patients were the stimuli. Onset of seizures in 4 male and 9 female patients varied from birth to 13 years. Head trauma in 3, birth injury in 4, febrile or nonfebrile convulsions in 3 and epilepsy in a family of 3 patients was found in their stories. Neurologic examination abnormality was found in 10 and mental retardation in 9 patients. Neuroimaging studies showed abnormality in 10 patients. EEG abnormalities were seen in 12 patients, and normal in 1. Levetiracetam was started as an add on therapy to other antiepileptic drugs and doses could be adjusted individually.

Results: Thirteen patients were enrolled, data were analysed for 9 patients. The frequency of seizures increased in 1 patient, 1 was unresponsive and levetiracetam therapy was stopped in 2. The response rates were 100% in 1, 70–99% in 2, 50–70% in 2, and 0–20% in 2 patients.

Conclusion: Levetiacetam can be an alternative treatment as an add on therapy in startle epilepsy. This study may serve as pilot data for trials of levetiracetam for startle induced seizures.

p516

EFFICACY AND TOLERABILITY OF LEVETIRACETAM AS AN ADD-ON THERAPY IN 40 PATIENTS WITH EPILEPSY

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Purpose: Our aim is to evaluate the efficacy and tolerability of levetiracetam as an add-on therapy in patients with epilepsy.

Method: Levetiracetam was administered to 40 patients with epilepsy older than 16. Onset of seizures of 21 males and 19 females patients varied from birth to 74 years. Head trauma in 11, birth injury in 3, febril or nonfebril convulsions in 7 were found in their stories. Four patients had a history of status epilepticus and 6 patients had other systemic disorders. Neurologic examination abnormality was found in 22 and mental retardation in 16 patients. Neuroimaging studies showed abnormality in 22 patients. EEG abnormalities were seen in 34 patients, and normal in 6. The seizure pattern was different: 35 generalised or partial intractable epilepsy, 5 generalised or partial epilepsy. Two patients with progressive myoclonic epilepsy, 2 with Jacob Creutzfeldt Disease were also evaluated. Levetiracetam was started as an add on therapy to other antiepileptic drugs and doses could be adjusted individually.

Results: 40 patients were enrolled; data were analysed for 26 patients. The patients included in this study were studied prospectively and these are the early results of this study. Five patients were seizure free, 50–90% decrease in 6, 25–50% decrease in 6, no change in 9, and more seizures were seen in 1. Five of 9 startle epilepsy patients had good response. Lack of efficacy in 7%, and adverse effects in 17.5% of patients were seen.

Conclusion: Levetiracetam was effective and well tolerated as an add-on therapy in patients with partial, generalised, startle epilepsy and JCD myoclonies.

p517

RETROSPECTIVE STUDY OF LEVETIRACETAM TREATMENT AS MONOTHERAPY FOR PATIENTS WITH EPILEPSY

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Purpose: To evaluate the efficacy and safety of levetiracetam (LEV) as monotherapy for patients with epilepsy.

Method: A retrospective analysis of patients treated with LEV monotherapy, either as first-line antiepileptic drug (AED) therapy, or having previously been treated unsuccessfully with other AEDs.

Results: 25 patients were identified (11M/14F, age 19–80 years); 52% (13/25) with partial seizures and 48% (12/25) with generalised seizures. Aetiologies were symptomatic (52%; 13/25), idiopathic (36%; 9/25) and cryptogenic (12%; 3/25). 32% (8/25) patients received LEV as first-line therapy, having presented with monthly or multi-monthly seizures; 68% (17/25) patients converted to LEV monotherapy having been treated unsuccessfully with valproate (VPA; $n = 5$), lamotrigine (LTG; $n = 5$), oxcarbazepine ($n = 2$), phenobarbital (PB; $n = 2$), carbamazepine (CBZ; $n = 1$), CBZ + PB ($n = 1$) and VPA + LTG ($n = 1$). In patients treated as first-line therapy, LEV was uptitrated to 1500–2000 mg/day; after 6 months ($n = 2$) and 2 years ($n = 6$) follow-up, all patients achieved seizure freedom, without adverse events (AEs). In patients converted from other AEDs, LEV was uptitrated to 1500–3000 mg/day; 94.1% (16/17) patients achieved seizure freedom after 6 months follow-up without AEs;

1 patient (5.9%), who had cryptogenic epilepsy with absences, discontinued treatment due to lack of efficacy.

Conclusion: This analysis suggests that LEV monotherapy is effective and well tolerated both as first-line therapy and in patients converting from previously unsuccessful treatment with other AEDs. Retention rate was good, with many patients continuing LEV treatment for >6 months. AEs occurring before conversion to LEV monotherapy (eg., weight gain, pruriginous exanthema, intense tremor) disappeared after conversion.

p518

NEUROPSYCHOLOGICAL AND PSYCHIATRIC IMPACT OF ADD-ON TITRATION OF PREGABALIN VERSUS LEVETIRACETAM: A COMPARATIVE STUDY

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Purpose: Cognitive and behavioural impairments are common in patients with epilepsy. Multiple factors may contribute to these difficulties; among them is antiepileptic drug (AED) treatment. We examined the impact of two new add-on AEDs, pregabalin (PGB) and levetiracetam (LEV), on cognition and psychiatric states in 20 adult patients with medically refractory partial epilepsies.

Method: According to an open, prospective comparative trial add-on PGB was titrated to 300 mg or LEV to 1000 mg in 10 patients each. Patients were assessed before (T1) and two weeks after (T2) the addition of the AED.

Results: During the short trial the seizure frequency did not change significantly in either group. PGB seemed to impair episodic memory of verbal and visual information, although it did not influence psychiatric states. With LEV treatment we saw improvements of visual short-term memory, attention span and psychiatric states (i.e., interpersonal sensibility, depression and anxiety).

Conclusion: This study suggests a favourable neuropsychological and psychiatric impact of add-on LEV. The somewhat disappointing results with PGB may reflect temporary effects under titration, but still they did not confirm the promising profile concerning psychiatric co-morbidity factors that have been emphasised by other reports.

p519

EFFICACY OF LEVETIRACETAM AS MONOTHERAPY IN SUPPRESSING INTERICTAL DISCHARGES IN FOCAL AND GENERALISED EPILEPSY

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Purpose: To assess the efficacy of levetiracetam as monotherapy in suppressing interictal EEG epileptiform activity.

Method: In this open retrospective trial 20 patients (9 males and 11 females, aged 10–70 years, mean 38) affected by partial or generalised epilepsy, with idiopathic, cryptogenic or lesional aetiology, received LEV monotherapy (doses: 1000–4000 mg daily, mean 2250). 8 patients were newly diagnosed; the remaining 12 were converted to LEV monotherapy from add-on therapy (4 VPA, 5 CBZ, 2 OXC, 1 LTG). At baseline the mean seizure frequency was 4.0/month and all patients showed EEG interictal epileptic activity (strictly following the IFCN definition). The efficacy was tested by evaluating suppression of such epileptic activity after 3 and 6 months of therapy and by calculating the rate of patients with significant (>50%) reduction of baseline seizure frequency (responder rate).

Results: After 3 months of therapy we observed a complete disappearance of interictal epileptic activity with normal EEG in 13 patients (65%); 5 patients (25%) showed a marked improvement of EEG with disappearance of epileptic activity and persistence only of slow and non specific abnormalities. In 2 cases (10%) the EEG showed no significant modifications of epileptic activity. After 6 months these results were unchanged. Overall responder rate (≥50% seizure reduction) was 18/20 (90%) at 3 and 6 months. We observed the lack of clinical response in the same two patients who didn't show EEG improvement.

Conclusion: In our case series, LEV as monotherapy showed a good efficacy both in suppressing interictal EEG epileptic activity and controlling seizures.

p520

THERAPEUTIC DRUG MONITORING IN NONRESPONDING AND RESPONDING PATIENTS TREATED WITH KEPPRA

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Purpose: The purpose is to study the possibilities of identification and clinical characterisation of subgroups of patients that will respond to Keppra after exhibiting nonresponding features to a number of medical treatments. The hypothesis is that such an investigation may elucidate an epilepsy patient's disposition for intractable epilepsy and the risk of a patient to develop drug resistance.

Method: Retrospective studies of therapeutic drug monitoring values of children with a well-characterised epilepsy diagnosis were performed. Investigation of drug profiles was limited to children either receiving Keppra medication or children withdrawn from Keppra due to non response or accumulation of side effects. The subjects were identified among patients at the Danish Epilepsy Centre and the patients were characterised as nonresponders to at least three previously tested medical treatments prior to introducing Keppra therapy. For each patient the diagnosis, seizure type, seizure frequency and level of Keppra efficacy was characterised and compared to seizure types and frequencies observed during earlier therapeutic regimes.

Results: Children characterised in terms of seizure control, adverse drug reactions, and manifestation of the epileptic syndrome were subgrouped into responders exhibiting 100% seizure control and partial responders exhibiting either >50% or <50% reduction in seizure frequency. Based on these data a cohort with full seizure control and a cohort without seizure control were defined.

Conclusion: Responding patients becoming seizure free on Keppra therapy after at least 3 insufficient drug treatments were found as were patients that did not respond to Keppra. These preliminary results are the background for further characterisation of both subgroups and finding potential responders to Keppra therapy.

p521

COGNITIVE EFFECTS OF LOW-DOSE TOPIRAMATE: A COMPARATIVE STUDY WITH LAMOTRIGINE IN EPILEPSY PATIENTS

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Purpose: Cognitive effects of topiramate (TPM) during low-dose monotherapy have not been established. We evaluated the cognitive effects of low-dose TPM compared with lamotrigine (LTG), because LTG has not been shown to negatively affect cognitive function.

Method: This retrospective study comprised 60 epilepsy patients who had undergone two sets of neuropsychological tests (baseline and a year of medication) who were newly diagnosed, or untreated in the preceding 6 months. The results of cognitive function of 30 patients with low-dose TPM monotherapy (50–100 mg/day) were compared with those of a random sample of 30 patients with LTG monotherapy. Groups did not differ with respect to epilepsy relevant variables. Their neuropsychological tests at baseline did not differ. After a year of treatment, an average daily dose of TPM and LTG were 75 mg and 100 mg, respectively.

Results: TPM group showed a significant difference in the performance of list learning ($p < 0.05$), forward digit span ($p < 0.05$), backward digit span ($p < 0.05$), and verbal fluency ($p < 0.01$) compared with the LTG group. TPM group showed worse performances of digit span and verbal fluency. LTG group showed a better performance of list learning. The incidence of cognitive complaints was higher in TPM group (50%) than LTG group (20%) ($p < 0.05$). These cognitive effects shown in the TPM group were dose-related. The cognitive dysfunction was trivial for patients taking 50 mg/day TPM.

Conclusion: Even low-dose TPM monotherapy certainly has a negative effect on short-term memory and speech compared with LTG.

p522
TOPIRAMATE IN BRAIN-TUMOUR ASSOCIATED EPILEPSY: OUTCOME AND TOLERABILITY
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Purpose: In patients with brain tumours, conventional antiepileptic drugs (AED) may interact with chemotherapeutics and corticosteroids, leading to reduced efficacy and/or more frequent side effects. Topiramate is a newer well-tolerated broad-spectrum AED with low potential for interactions. The aim of this study was to investigate its efficacy and tolerability in brain-tumour associated epilepsy. We selected topiramate because of its favourable pharmacokinetics.

Method: In this single-centre, open-label, observational study, 46 patients (mean age 48 years, 20M/26F) with epilepsy related to brain tumours received topiramate according to the dose recommendations in the label. Twelve patients were treatment-naive, 34 were converted from other AEDs to topiramate add-on or monotherapy because of poor seizure control or intolerable side effects. Seizure frequency was captured retrospectively (baseline) for up to 12 months prior study entry and at the final follow-up visit (mean (range): 13.1 (5–43) months).

Results: During topiramate (67.4% monotherapy, 32.6% add-on), 54.4% of patients were seizure-free; at least 50% seizure reduction was observed in another 23.9%. Seizures remained unchanged in 17.4% and worsened in 4.3% (increasing less than 50%). Seizure control remained stable during tumour progression. The overall responder rate was 78%; 75% with versus 83% without tumour progression. Side effects during topiramate (1 paraesthesia, 1 weight loss, 1 confusion) were mild and didn't lead to changes in therapies.

Conclusion: Topiramate appears to be a good choice for patients with brain-tumour associated epilepsy: the data support adequate seizure control (also stable during tumour progression) and paucity of adverse events.

p523
EFFICACY AND SAFETY OF TOPIRAMATE MONOTHERAPY IN ELDERLY EPILEPSY
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Purpose: In the elderly with epilepsy we need to consider better-tolerated and less toxic drugs than those classically used. Topiramate is a wide spectrum antiepileptic drug which is effective in the treatment of all types of seizures and offers considerable advantages (approved in monotherapy, absence of interactions in patients generally polymedicated) over other antiepileptic therapies for the treatment of the elderly. The goal of the present study is to assess the efficacy and tolerance of a low dose of topiramate as monotherapy for elderly patients with epilepsy.

Method: A prospective, descriptive, observational study was carried out on a total of 31 patients over 65 years old. All patients started with a single daily dose of 25 mg of topiramate. Their dosages were adjusted to treatment response. Where further seizures arose, the dose of topiramate was increased. Efficacy and tolerance checks were carried out after one month, three and six months.

Results: Median daily dose was 90 mg. At the end of the study 23 (74.2%) patients continued to be seizure free. The drug was withdrawn in 2 cases. Median reduction in seizure frequency from baseline to study end was 91%. The most common adverse events (19.3%) were dizziness and somnolence. One patient discontinued because of adverse events.

Conclusion: Topiramate is an effective therapy for the control of epilepsy in elderly patients at low doses, with good tolerance and a low rate of adverse effects.

p524
EFFECTS OF TOPIRAMATE (TOPAMAX) IN PATIENTS WITH REFRACTORY EPILEPSY
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Purpose: Topiramate (TPM), a novel AED of broad spectrum, is often used in the treatment of patients with refractory epilepsy. The effects of TPM have not yet been investigated in patients with epilepsy in Georgia. The aim of the study was to evaluate the effects of TPM in patients with refractory epilepsy.

Method: The effect of TPM was observed in 12 patients (4 females, 8 males; age range 6–54 years, MD = 25.3 years) with seizures resistant to old generation AEDs. Five patients with temporal lobe, 5 with frontal lobe, and 2 with unclassified seizures were investigated (seizure frequency by individual calendars, EEG, neuropsychological testing, MRI) before starting and 6 months after starting TPM-therapy. Three patients from those remained on TPM monotherapy, while 9 patients remained on polytherapy. The initial daily dose of TPM was 25 mg and titration rate 25 mg per week. Average dosage of TPM varied between 50–400 mg/day.

Results: With a dose of TPM under 50–200 mg/day, 6 patients, 50%, (3 with temporal, 2 with frontal, and one with unclassified seizures) became seizure free. In 4 patients seizure frequency was reduced by $>50\%$, in 2 cases by $<50\%$. Observed side effects of TPM were weight loss in 2 cases and cognitive impairment (concentration problems and word finding difficulty) at high dosage (400 mg/day) of TPM in 1 patient.

Conclusion: Topiramate is very effective in the treatment of refractory epilepsy in patients with focal seizures.

p525
OBSERVATIONAL STUDY OF THE OUTCOME OF EPILEPSY FOLLOWING USE OF TOPIRAMATE AS A BROAD-SPECTRUM ANTIEPILEPTIC DRUG IN ROUTINE CLINICAL CARE
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Purpose: Controlled clinical trials support the efficacy and safety of topiramate in various types of epilepsy. This survey documents its outcome as a broad-spectrum antiepileptic drug (AED) in a Romanian population of epilepsy patients.

Method: Open-label observational study in patients ($\geq$2 years old) with epilepsy (newly diagnosed, unresponsive to previous AEDs because of insufficient efficacy/tolerability, or responding but with unacceptable weight gain). Patients were titrated to optimal dose according to usual regimen over 2 months and then maintained for 6 months. Concomitant AEDs were discontinued if possible. Seizures and adverse events were documented. Monthly seizure rate was calculated at baseline (3 months retrospectively) and during month 8 in trial completers.

Results: 607 patients (44.8% children $\leq$18years; 74.5% refractory to prior AEDs, various seizure types) were started on topiramate monotherapy (14.5%) or combined therapy (85.5%); 460 patients (231 children) completed the study, 58.7% receiving monotherapy. During month 8, 86.1% of children and 71.9% of adults were seizure-free; in the other completers, monthly seizure rates decreased significantly ($p < 0.001$) from 24.5 at baseline to 3.6 in children ($n = 71$), and from 5.3 to 1.0 in adults ($n = 65$). Median topiramate dose was 100 mg/day in children, 150 mg/day in adults. The most common treatment-emergent adverse event was weight decrease ($n = 26$). Topiramate was discontinued due to adverse events in 1.5% (1 child, 8 adults).

Conclusion: The findings corroborate those of randomised clinical trials: they support topiramate as an effective and well-tolerated broad-spectrum AED; at month 8, complete seizure control can be achieved by topiramate monotherapy in a substantial portion of patients. Funded by Janssen-Cilag.

p526

EFFICACY AND TOLERABILITY OF TOPIRAMATE IN PATIENTS WITH EPILEPSY PREVIOUSLY TREATED WITH CARBAMAZEPINE OR OXCARBAZEPINE

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Purpose: To evaluate seizure frequency and tolerability in patients with epilepsy treated with topiramate (TPM) after transition from carbamazepine (CBZ) or oxcarbazepine (OXC).

Method: Interim analysis of a multicenter open-label non-interventional study. Patients with epilepsy ≥12 years of age previously unsuccessfully treated (lack of efficacy and/or lack of tolerability) with CBZ (71% of patients) or OXC (29%) were prospectively followed for 26 weeks after initiation of, and transition to, TPM. A 12 week retrospective seizure frequency was used as baseline.

Results: Seventy-five patients (64% female, mean age 46 ± 17 years) were enrolled. The most frequent seizure types at baseline were generalised tonic-clonic (48%), complex partial (28%), and simple partial (17%). Main reasons for CBZ/OXC discontinuation were side effects in 81% (reported side effects: somnolence 74% and dizziness 55% (CBZ); somnolence 64% and concentration difficulties 42% (OXC) and lack of efficacy (73%). At endpoint, the median TPM dose was 100mg/day. Mean seizure frequency decreased from 4.5/month at baseline to 0.9/month at endpoint ($p < .00001$). The responder rate (≥50% seizure reduction) was 90%, and 64% of patients remained seizure-free for more than the last 3 months of the study. 83% of patients completed the study. 9% discontinued TPM prematurely due to an adverse event (AE), 1% due to lack of efficacy. The only AEs reported in ≥5% were paraesthesia (11%) and weight decrease (11%).

Conclusion: After transition from CBZ or OXC, topiramate was associated with a substantial reduction in seizure frequency, including a high seizure-free rate, and was well tolerated.

p527

EFFICACY AND TOLERABILITY OF TOPIRAMATE IN PATIENTS WITH EPILEPSY AFTER TRANSITION FROM VALPROATE

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Purpose: To seizure and tolerability in patients with epilepsy treated with topiramate monotherapy (Topamax; TPM) after transition from valproate (VPA).

Method: Interim analysis of a multicenter open-label non-interventional study. Patients with epilepsy independent of seizure type, age 12 and above and previously unsuccessfully treated with VPA (lack of efficacy and/or lack of tolerability) were prospectively followed for 20 weeks after initiation of, and transition onto TPM.

Results: One hundred patients (66% female, mean age 42 ± 20 years) were enrolled. Most frequent seizure types at baseline were generalised tonic–clonic (46%), complex partial (20%) and absence seizures (13%). Reasons for VPA discontinuation were side effects in 82% (reported side effects: tremor 44%, somnolence 34%, cognitive symptoms 28%) and lack of efficacy (57%). At end point, the median TPM dose was 100mg/day, with 23% of patients receiving less than 100 mg TPM/day. Mean seizure frequency decreased from 14.3/month at baseline to 4.4/month at endpoint ($p < .0001$). The responder rate (≥50% seizure reduction) was 76%, and 51% of patients remained seizure-free for at least the last 3 months of the study. 85% of patients completed the study. 7% discontinued TPM prematurely due to an adverse event (AE), 2% due to lack of efficacy. The only AEs reported in ≥5% were paraesthesia (6%) and weight decrease (5%).

Conclusion: After transition from VPA, topiramate was associated with a substantial reduction in seizure frequency including a high seizure-free rate, and was well tolerated.

p528

SAFETY AND TOLERABILITY OF TOPIRAMATE IN ELDERLY PATIENTS WITH EPILEPSY: RESULTS FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Purpose: To observe safety and tolerability in elderly individuals with epilepsy age 65 and above treated with topiramate (TPM) monotherapy in a naturalistic setting.

Method: Multicenter, open-label, observational study. Individuals with epilepsy independent of seizure type aged 65 and above were prospectively followed for 6 months after first ever initiation of TPM. Seizure frequency was recorded for a 6-month retrospective baseline and prospectively. Adverse events (AEs) were assessed at each visit.

Results: One hundred and forty-five patients (mean age 72.7, range 64–100, 49% women) were documented prospectively and followed for up to 6 months. Median duration of epilepsy was one year (range, 0–33). The most frequent aetiologies were cerebrovascular (68%) and degenerative disease (14%). Overall, 93% patients had a least one concomitant disease and 90% had at least one other non–anticonvulsant concomitant medication. TPM doses ranged between 50 and 100 mg/day in most patients. Seizure frequency decreased from 2.9 ± 15.8 at baseline to 0.5 ± 1.7 at endpoint. 73.1% of patients had at least a 50% seizure reduction compared to the retrospective baseline, and 40.7% remained seizure-free throughout the study. 5.5% of patients had an AE, with dizziness being the only AE reported in ≥2% of patients (2.1%). The only cognitive adverse event was psychomotor slowing in 1 patient (0.7%). In 89.7% of patients investigators rated the tolerability of TPM as very good or good.

Conclusion: In this naturalistic setting topiramate was safe, well tolerated and associated with a substantial seizure reduction in elderly patients with epilepsy.

p529

EFFICACY AND TOLERABILITY OF TOPIRAMATE IN THE TREATMENT OF EPILEPSY IN ELDERLY PATIENTS: RESULTS OF A PHASE IV CLINICAL TRIAL

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Purpose: To assess seizure reduction and tolerability of topiramate (Topamax, TPM) in mono- or combination therapy in elderly patients with epilepsy.

Method: In this multicenter phase IV clinical trial, patients ≥60 years of age were prospectively followed for 12 months. Doses of TPM and concomitant antiepileptic drugs (AEDs) could be adjusted individually. Seizure frequency and adverse events were documented at each visit.

Results: One hundred and seven patients (53% male, mean age 69 ± 7 years) were enrolled. The most frequent seizure types at baseline were generalised tonic-clonic (58%) and complex partial (25%). After enrollment, 49 patients received TPM as monotherapy, 58 in combination with at least one other AED. The number of patients on TPM monotherapy increased from 49 to 70 during the study at the discretion of the investigator. At endpoint, the mean TPM dose as monotherapy was 98mg/day and 153 mg/day as add-on. The mean monthly seizure frequency decreased from 3.5 ± 14.6 to 1.6 ± 7.7 ($p < .0001$ versus baseline). 78% of patients were responders (seizure reduction ≥50%), and 44% remained seizure-free throughout the study. 46 patients (43%) had at least one treatment emergent adverse event (TEAE). TEAEs ≥5% were somnolence (9.4%), dizziness (7.5%) and paraesthesia (5.6%). Main reasons for study discontinuation (40% overall) were a TEAE (15.9%) or loss to follow-up (12.2%).

Conclusion: In elderly patients with epilepsy, TPM was well tolerated and is associated with a significant decrease in seizure frequency.

p530

LONG-TERM SEIZURE FREEDOM IN REFRACTORY PARTIAL EPILEPSY TREATED WITH LEVETIRACETAM AS COMPARED WITH TOPIRAMATE

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Purpose: To compare the efficacy of levetiracetam and topiramate add-on long-term treatments in obtaining seizure freedom in adults with refractory partial epilepsy.

Method: Patients with ≥2 focal seizures over an 8 week baseline period received LEV or TPM in two distinct open-label, add-on, prospective phases. LEV was titrated up to 1000 mg/day (2 weeks) and TPM up to 100 mg/day (4 weeks) or 200 mg/day (with inducers, 6 weeks). Follow up lasted 24 months. Efficacy evaluation started after titration: number of seizure-free patients over the study period and during the last six months of observation; retention rate. Tolerability was evaluated recording type, duration and intensity of AEs

Results: LEV group: 157 patients (90 F, mean age 41 years, range 11–77, 61% remote symptomatic, mean dose 2200 mg/day). TPM group:103 patients (66 F, mean age 37 years, range 15–71, 50.4% remote symptomatic; mean dose 430 mg/day). Mean follow-up duration was 15 (0-24) and 12 months (0-24) respectively. 16 (10.2%) patients with LEV and 3 (2.9%) with TPM were seizure-free over the study period (21.6m. LEV, 14.6m. TPM). 30 (19.1%) with LEV and 7 (6.8%) with TPM were seizure-free during the last 6 months of observation. 100 (63.7%) and 62 (60.2%) patients, respectively, still remain in the study. 25 (15.9%) patients on LEV and 16 (15.5%) on TPM dropped out for AEs, 57 (32 (20%) LEV, 25 (24.3%) TPM) for other reasons.

Conclusion: This study showed a better long-term efficacy of levetiracetam in the treatment of refractory partial epilepsy with three-fold patients achieving a seizure remission over the study period compared to topiramate.

p531

WITHDRAWAL TO MONOTHERAPY: A PRACTICE-BASED STUDY ON TOPIRAMATE

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Purpose: Withdrawal to monotherapy may, in a clinical setting, uncover specific indications for new anticonvulsants, which are usually used as add-ons for a long period.

Method: Over a one year period, of 114 patients on topiramate (TPM), 18 had reached monotherapy (10 men, 8 women, aged 10–60 years); 14 had refractory focal epilepsy and 4 had idiopathic generalised epilepsy (IGE). At each visit, the treatment and seizure logs were studied, and routine biology and peak TPM blood levels were assessed.

Results: Eleven patients continued TPM monotherapy after 1 to 7 yrs. Seven were seizure-free: 3 patients with idiopathic generalised epilepsy, 2 patients after successful epilepsy surgery, and 2 with cryptogenic focal (frontal lobe) epilepsy. Five patients had a worthwhile improvement, with seizure reduction ≥ 75% in 4 (3 with symptomatic focal epilepsy; parietal in 1 and temporal in 2, and 1 with IGE), and ≥ 50% in 1 with cryptogenic frontal lobe epilepsy. TPM monotherapy was discontinued in 6 due to inefficacy and in 1 because of side effects. Age, sex and peak blood levels did not influence efficacy, side effects or retention time.

Conclusion: TPM monotherapy was successfully maintained (1) in patients with idiopathic generalised epilepsy when weight loss was necessary, (2) as the last drug after successful epilepsy surgery, (3) in various cases of symptomatic focal and (4) in cryptogenic focal epilepsy of frontal lobe origin. Retrospective demonstration of successful withdrawal to monotherapy may highlight possible promising selective indications.

p532

SAFETY AND TOLERABILITY OF TOPIRAMATE WITH CURRENT VERSUS MORE RAPID TITRATION

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Purpose: To evaluate the safety and tolerability of two different titration regimens of adjunctive topiramate (Topamax, TPM) in a specialised epilepsy center.

Method: During this single-center noninterventional study, refractory epilepsy patients (≥12 years) were prospectively followed for 12 weeks. Based on seizure frequency and severity, adjunctive TPM was titrated either according to current prescribing information (NT = normal titration, 100 mg TPM/day was attempted at day 12) or more rapidly (RT, 100 mg TPM/day was attempted at day 3) per investigator's discretion.

Results: Fifty patients (58% female, mean age 35 years, 86% partial epilepsy) were followed for a median of 102 days (range 6–278). Twenty-nine patients were in the RT group, 21 in the NT group. Age and gender showed no significant difference. In the RT group, significantly more patients had symptomatic epilepsy (81 vs 48%), and preexisting cognitive deficits (71 vs 59%). Mean TPM maintenance was 136 mg/day (NT) versus 213 mg/day (RT), $p < 0.05$. Median seizure frequency (all patients) decreased from 7.5 (baseline) to 2.0 (end point), 46% had a 50% responder rate and 14% remained seizure free without significant differences for both groups. Thirty-two patients had a treatment-emergent adverse event (AE), and 15 patients (30%) discontinued TPM due to an AE with no statistically significant difference between RT (29%) and NT (31%). Only paraesthesia occurred more frequently in the RT group.

Conclusion: In this study patients with treatment resistant epilepsy titrated more rapidly with topiramate and had comparable tolerability and efficacy profile compared to those titrated using currently recommended regimen.

p533

LONG-TERM TREATMENT WITH ZONISAMIDE: RESULTS OF A 2 YEAR OPEN-LABEL EXTENSION STUDY

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Purpose: To demonstrate the long-term safety and efficacy of zonisamide in patients with refractory partial onset epilepsy.

Method: A total of 243 patients (aged ≥12 years, on 1–3 AEDs) who had previously received placebo or zonisamide 100, 300 or 500 mg/day for 18 weeks on a fixed-dose study, were enrolled in a 2 year, open-label extension study. Following a 6 week titration phase all patients received zonisamide 500 mg/day, then commenced the 104 week flexible dosing (100–600 mg/day) phase, during which zonisamide dose was adjusted to optimum effect (mean dose 500 mg/day). Concomitant AEDs were adjusted as required. Efficacy evaluations (every 3 months; n = 240) included reduction in seizure frequency (complex partial seizures and total seizures) and time on study. Safety assessments (n = 243) included reporting of adverse events (AEs).

Results: 104 (44%) patients remained in the study for 2 years, 35 patients (14.6%) showed a reduction in concomitant medication and 11 (4.6%) achieved zonisamide monotherapy. Adverse events and treatment related AEs were reported by 196 and 103 patients, only 28 (11.5%) patients discontinued due to AEs. The majority of AEs (81%) were considered mild to moderate; the most common treatment related AEs were weight loss (8.6%), somnolence (6.6%) and dizziness (6.6%).

Conclusion: Long-term treatment (up to 2 years) with zonisamide for partial refractory epilepsy is well tolerated, with a safety profile consistent with that reported in double-blind trials, and allows some patients to reduce concomitant medications or achieve monotherapy.

This study was supported by Eisai Ltd.

p534

DOSE RESPONSIVE EFFICACY OF ZONISAMIDE MONOTHERAPY DURING 40 WEEKS TREATMENT OF PARTIAL SEIZURES IN PATIENTS WITH NEWLY DIAGNOSED EPILEPSY

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Purpose: To evaluate the relationship between efficacy and dose of zonisamide (ZNS) as monotherapy in patients with newly diagnosed epilepsy (complex partial seizures [CPS] with and without secondary generalisation).

Method: 167 patients (aged ≥16 years) received ZNS 25 (n = 56), 100 (n = 52) and 300 (n = 59) mg/day in a double-blind, randomised, 42 week trial with a 40 week treatment period. The primary efficacy endpoint was time from first dose of study drug to occurrence of two CPS or one generalised tonic–clonic seizure (GTC). Secondary endpoints included the proportion of patients seizure free for ≥6 months, and the proportion completing 40 weeks of treatment.

Results: All patients were included in the efficacy analyses and baseline demographics were similar across treatment groups. There was a trend to dose-dependent seizure frequency reduction ($p = 0.06$); fewer patients receiving ZNS 300mg/day experienced endpoint seizures (22.0% compared with 41.1% and 40.4% for ZNS 25 and 100 mg/day). A similar trend was observed for seizure freedom (≥6 months), 33.9%, 30.8% and 50.8% for the 25, 100 and 300 mg/day groups ($p = 0.06$), respectively. The proportion of patients treated for 40 weeks was similar for all treatment groups, 41.1%, 40.4% and 40.7% for ZNS 25, 100 and 300mg/day, respectively.

Conclusion: ZNS was suitable as monotherapy for patients with newly diagnosed epilepsy. ZNS displayed a trend towards dose dependent efficacy and at 300 mg/day reduced the proportion of patients experiencing CPS or GTC seizures and increased the proportion remaining seizure free at ≥6 months, compared with ZNS 25and 100mg/day. This study was supported by Eisai Ltd.

p535

EPILEPSY IN THE OLDER PATIENT: US EXPERIENCE WITH LONG-TERM ZONISAMIDE THERAPY

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Purpose: To provide a retrospective review evaluating the efficacy and safety of long-term zonisamide therapy for older patients with epilepsy.

Method: Neurology clinic records were reviewed to identify patients aged ≥60 years treated with zonisamide for ≥3 months. Efficacy was assessed via reduction in seizure frequency during zonisamide therapy, and safety was evaluated by adverse events (AEs), based on physicians' notes and patient reporting.

Results: Sixty patients (mean age 76 [range 60–97] years) were identified and 53 were included in the efficacy analysis. For patients on monotherapy (n = 37), mean zonisamide dose and duration were 200.0 mg/day and 28.2 months; 20 patients (54.1%) achieved seizure freedom; seizure frequency was reduced by ≥50% in an additional 5 patients (13.5%) and by <50% in 2 patients (5.4%). For patients receiving adjunctive therapy (n = 16), mean zonisamide dose and duration were 268.8mg/day and 35.3 months; 5 (31.2%) were seizure-free; seizure frequency was reduced by ≥50% in an additional 7 patients (43.8%) and by <50% in 3 patients (18.8%). Zonisamide had no effect in 3 patients and 8 patients were lost to follow-up. AEs included gastrointestinal upset, mild sedation, and rash (n = 2 each), anorexia, vision changes, headache and lightheadedness (n = 1 each). Six patients discontinued zonisamide, 5 due to AEs. Positive neurological effects reported with zonisamide therapy included increased alertness (n = 2) and improvements in parkinsonian tremor (n = 2), postherpetic neuralgia, mood and restless legs syndrome (n = 1 each).

Conclusion: Long-term zonisamide was effective as monotherapy and adjunctive therapy and was well tolerated in older patients with epilepsy. This study was supported by Eisai Ltd.

p536

LONG-TERM EFFICACY OF ZONISAMIDE IN PAEDIATRIC PATIENTS: AN OPEN LABEL STUDY

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Purpose: To assess the long-term efficacy of zonisamide in paediatric patients with various types of epilepsy.

Method: This open-label study included 134 paediatric patients (mean age 8.2 [range 2–16] years) experiencing ≥4 seizures per month while on a stable dose of 1 or 2 concomitant antiepileptic drugs (AEDs). Efficacy was evaluated by change in "all seizure" frequency (average number of seizures per week) and global assessments for each 3-month follow-up period, until study end or discontinuation (final assessment). Baseline seizure counts were only available for patients new to zonisamide (n = 109).

Results: In the overall study population, the median seizure frequency for "all seizures" significantly decreased over the study period (–1.5; $p = 0.025$), for patients (n = 86) who provided start-of-study and final assessment data. The median seizure frequency decreased from 5.85 for months 1–3 (n = 92) to 3.15 in months 19–21 (n = 24) and was 3.70 (n = 93) at the final 3-month assessment. Similarly, for patients new to zonisamide, there was a progressive decrease in median seizure frequency over time, the median seizure frequency was 8.95 at baseline (n = 106), then decreased from 5.90 in months 1–3 (n = 69) to 0.60 in months 19–21 (n = 16). For new patients, the median seizure frequency decreased by 50% on average relative to baseline by months 7–9 (median seizure frequency 1.4 per week). Global assessments also indicated improvement in response to zonisamide.

Conclusion: Long-term zonisamide add-on therapy significantly improved seizure rates in children with epilepsy. This study was supported by Eisai Ltd.

p537

SHORT-TERM AND LONG-TERM EFFICACY AND SAFETY OF RUFINAMIDE AS ADJUNCTIVE THERAPY IN PATIENTS WITH INADEQUATELY CONTROLLED LENNOX-GASTAUT SYNDROME

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Purpose: To evaluate the short- and long-term efficacy and safety of adjunctive rufinamide therapy for patients with inadequately controlled Lennox-Gastaut syndrome (LGS).

Method: This was a multicentre, double-blind, placebo-controlled, randomised, parallel-group study followed by a long-term extension study. During the double-blind study, patients were randomised to receive either adjunctive rufinamide (10 mg/kg per day of rufinamide titrated to 45 mg/kg per day) or placebo; those who completed all study visits could enter the 3 year long-term study. Efficacy was evaluated by the percent change in total and tonic-atonic seizure frequency per 28 days and the change in seizure severity rating. Safety analysis included adverse events (AEs), laboratory parameters, physical examinations, vital signs, and electrocardiogram recordings.

Results: Patients, mean age 14.1 years (range 4–37 years), received either rufinamide (n = 74) or placebo (n = 64); median dose at each visit was 42.16 mg/kg per day (range, 4.17–60.10 mg/kg per day). Rufinamide, versus placebo treatment, was associated with a greater median percent reduction in total seizure frequency (32.7% vs 11.7%, $p = 0.0015$), tonic-atonic seizure frequency (42.5% vs –1.4%, $p < 0.0001$), and improved seizure severity ($p = 0.0041$). Eligible patients (n = 124) entered an open-label, long-term, extension study of rufinamide therapy. Efficacy of rufinamide observed in the short-term study was maintained during long-term treatment. The majority of AEs were mild or moderate and were similar in both the short- and long-term studies. The most common AEs were somnolence, vomiting, pyrexia, and diarrhea.

Conclusion: Adjunctive rufinamide therapy was effective and generally well tolerated as short- and long-term therapy in patients with inadequately controlled LGS. This study was supported by Eisai Inc.

p538

EFFICACY AND SAFETY OF RUFINAMIDE AS ADJUNCTIVE THERAPY IN ADULT PATIENTS WITH INADEQUATELY CONTROLLED PARTIAL SEIZURES

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Purpose: The objective of this study was to assess the efficacy and safety of rufinamide as adjunctive therapy in adult patients with inadequately controlled partial seizures.

Method: Adult patients (aged ≥16 years) with partial seizures, taking stable doses of ≤2 other antiepileptic drugs, were enrolled in this multicentre, double-blind, placebo-controlled, randomised, parallel-group study. Patients were randomised to receive either rufinamide (3200 mg/d) or placebo for the duration of the 91-day double-blind phase. Efficacy was evaluated by the percent change in partial seizure frequency during the double-blind phase relative to the baseline phase and the percentage of treatment responders (patients with ≥50% reduction in partial seizure frequency). The safety assessment included monitoring of adverse events (AEs), laboratory parameters, vital signs, physical examinations, and electrocardiogram recordings.

Results: A total of 313 adult patients were randomised to receive either rufinamide (n = 156) or placebo (n = 157). Rufinamide treatment was associated with a 20.4% median reduction in partial seizures, per 28 days relative to baseline, compared to a 1.6% median increase with placebo treatment ($p = 0.0158$). Furthermore, a significantly higher percentage of rufinamide-treated patients (28.2%) were treatment responders compared to placebo-treated patients (18.6%) ($p = 0.0381$). The majority of AEs were mild to moderate in severity; the most commonly reported AEs were headache, dizziness, nausea, diplopia, somnolence, and fatigue. Study discontinuations due to AEs occurred in 14.1% of rufinamide-treated patients and 3.2% of placebo-treated patients.

Conclusion: Rufinamide (3200 mg/d) demonstrated a significant reduction in seizure frequency compared to placebo and was generally well tolerated as adjunctive therapy for adult epilepsy patients. This study was supported by Eisai Inc.

p539

DOSE-RANGE RELATIONSHIPS OF RUFINAMIDE IN PATIENTS WITH INADEQUATELY CONTROLLED PARTIAL SEIZURES

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Purpose: The objective of this study was to assess the dose-dependant efficacy and safety of rufinamide in patients with inadequately controlled partial seizures.

Method: This was a multicenter, double-blind, randomised, placebo-controlled, parallel-group study involving patients who received 1 to 3 concomitant antiepileptic drugs (AEDs). Patients with ≥9 seizures on stable AED dosages were randomised to 1 of 5 treatment groups: rufinamide 200, 400, 800, and 1600 mg/d, or placebo. The primary efficacy variable was total seizure frequency per 28 days in the double-blind treatment phase; the secondary efficacy variables included the seizure frequency ratio (seizure frequency per 28 days in the double-blind treatment phase divided by that in the baseline phase) and response to treatment. Safety was evaluated by adverse events (AEs), vital signs, electrocardiogram recordings, and laboratory tests.

Results: A total of 737 patients were enrolled; 647 patients were randomised to the 5 treatment arms. Rufinamide demonstrated a statistically significant linear trend of dose response for seizure frequency per 28 days ($p = 0.003$) and for ≥50% treatment responders ($p = 0.0319$). The median seizure frequency ratio was significantly reduced in patients treated with rufinamide 400 mg/d (11%, $p = 0.0274$), 800 mg/d (16%, $p = 0.0123$), and 1600 mg/d (17%, $p = 0.0163$) compared to placebo. The occurrence of AEs was similar to placebo for all rufinamide doses ≤800 mg/d. At 1600 mg/d, dizziness, somnolence, diplopia, and nystagmus were reported.

Conclusion: Rufinamide demonstrated a significant reduction in seizure frequency with increasing dosages in patients with inadequately controlled partial seizures and was generally well tolerated.

p540

SHORT-TERM AND LONG-TERM SAFETY OF RUFINAMIDE IN PATIENTS WITH EPILEPSY

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Purpose: The aim of this analysis was to evaluate the safety of rufinamide during short-term (placebo-controlled) and long-term (extension or open-label) therapy in patients with epilepsy.

Method: Safety data from short-term, double-blind, placebo-controlled studies and long-term, open-label, extension studies of adjunctive rufinamide therapy were integrated into a single database for analysis. All patients who received at least 1 dose of rufinamide were included in the analysis. Adverse events (AEs) were analysed using the Medical Dictionary for Regulatory Activities and were presented by preferred term. Serious adverse events (SAEs) and clinical laboratory test results abnormalities were also identified.

Results: Safety data were derived from 23 studies involving patients with epilepsy. Short-term therapy safety data were derived from 11 studies involving 1875 patients treated with rufinamide (n = 1240) or placebo (n = 635). The most frequently reported AEs for rufinamide included headache, dizziness, fatigue, somnolence, and nausea; most AEs were mild to moderate in severity. The time to onset of these AEs was comparable between the groups. Serious adverse events occurred in 6.3% of rufinamide-treated and 3.9% of placebo-treated patients. During long-term therapy, safety of rufinamide was assessed in 1978 patients. The most frequently reported AEs with long-term follow-up were headache, dizziness, and fatigue; 13.1% of patients discontinued rufinamide treatment due to AEs. The rates of AEs generally increased with increases in median dose of rufinamide. The most common SAEs were convulsion, status epilepticus, and pneumonia.

Conclusion: Rufinamide was well tolerated in patients with epilepsy during short- and long-term therapy.

p541

EFFECTS OF VALPROATE EXPOSURE IN UTERO TO BEHAVIOUR AND NEED FOR EDUCATIONAL SUPPORT IN SCHOOL-AGE CHILDREN

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Purpose: An increasing amount of information is available concerning the teratogenic effects of antiepileptic drugs (AED) exposure in utero but less is known about the long-term cognitive and behavioural effects of AEDs. We compared in a controlled, blinded study the effects of valproate (VPA) and carbamazepine (CBZ) monotherapy exposures in utero to behavioural and cognitive development of the child.

Method: We identified from the community-based pregnancy registry of Kuopio University Hospital area (1989–2000) all children who had been exposed to VPA monotherapy in utero and were first-born and of school age (N = 13). Age and gender-matched children of mothers with epilepsy and with CBZ exposure or without AED exposure served as controls. Neurological and neuropsychological assessments were made clinically and behavioural problems were assessed with the Conners' Teacher Rating Scale (CTRS) questionnaire.

Results: Eight children (61.5%) exposed to VPA and 2 (15.4%) in both CBZ and no-exposure group ($p = 0.022$) had needed educational support. Minor dysmorphic features were noted in 8 children (61.5%) exposed to VPA and in 3 children (23.1%) in both CBZ and no-exposure groups. In CTRS there was a systematic tendency of children exposed to VPA to score higher indicating more behavioural problems. This was seen especially in domains representing social problems ($p = 0.07$) and cognitive problems/inattention, $p = 0.09$.

Conclusion: Children exposed to VPA in utero seem to have more behavioural problems and need for educational support than CBZ exposed and unexposed controls. This difference is seen clearly when assessing each child individually but many confounding factors explaining at least some of this difference are difficult to control.

p542

ENDOCRINE EFFECTS OF VALPROATE IN GIRLS WITH EPILEPSY

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Purpose: Valproate has been associated with weight gain, hyperandrogenism and polycystic ovaries. The objective of this study was to investigate whether valproate or epilepsy itself causes these adverse effects.

Method: Anthropometric measurements, pubertal stage, waist-hip ratio, bioelectrical impedance, levels of fasting insulin, androgens, sex hormone-binding globulin, and thyroid function and transabdominal pelvic ultrasound were compared between girls with epilepsy receiving valproate and girls with epilepsy with no treatment.

Results: The sample included 88 girls with epilepsy aged 6–20 years (14 prepubertal, 26 pubertal, 48 postpubertal), 45 treated with valproate for 3.5 years (range 1–9.5) and 43 untreated. The treated postpubertal subgroup had higher testosterone levels than the postpubertal controls (2.12 ± 1.74 vs 0.91 ± 0.25 $p = 0.007$). However, no significant differences were found in biochemical, hormonal, anthropometric, or ultrasound parameters, either in comparison of the groups as a whole or by pubertal stage. BMI-SDS was 0.75 in the treated group and 0.63 in the untreated group; rates of obesity were 16.3% and 15.5% respectively. There were no between-group differences in menses irregularities, hirsutism, or acne. No correlation was found between duration of treatment or dosage and BMI-SDS, height SDS or androgen level. The treated group had higher levels of TSH and lower levels of free T4 than the untreated group, although still within normal range.

Conclusion: Long-term treatment with valproate for girls with epilepsy is associated with increased testosterone levels in the post pubertal period, without clinical hyperandrogenism, PCOS or an increase in BMI-SDS. Careful endocrine observation is recommended in postpubertal girls taking valproate.

p543

SAFETY AND EFFICACY OF INTRAVENOUS VALPROATE IN COMPARISON WITH DIAZEPAM IN ADULT STATUS EPILEPTICUS

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Purpose: To evaluate the safety and efficacy of intravenous infusion of valproate in comparison with diazepam in status epilepticus.

Method: A cohort study was carried out by dividing 90 status epilepsy patients into 2 groups: VPA group ($n = 38$) and diazepam group ($n = 42$). 15 adult patients in SE with generalised tonic–clonic seizures (GTCS) and 13 with simple partial motor seizures were administered IV VPA (Depakine injectable 400 mg, Sanofi corp.) in a bolus dose of 15 mg/kg and then 30 min later as a continuous infusion of 1 mg/kg/h for 24 h. 42 patients with SE were administered diazepam in a bolus dose of 10 mg and then a continuous infusion of 0.1 mg/kg/h for 24 h. The therapeutic effect was evaluated by response latency time and seizure cessation rate. Safety was evaluated by monitoring ECG, blood pressure, serum concentration and adverse reactions before, during, and after infusion.

Results: Response latency time is 24 ± 7 min in VPA group and 9 ± 4 min in diazepam group ($p < 0.01$). Seizure cessation rate is 62% in VPA group and 83% in diazepam group ($p > 0.05$). There is no significant difference on efficacy of IV VPA between different seizure types. No significant changes in ECG or blood pressure were found in either group before, and after infusion. Postinfusion plasma VPA levels ranged from 46∼147g/mL(86 ± 19 g/mL). Times taken to regain normal mental state were 2 ± 1.3 hours in VPA group and 8 ± 2.4 hours in diazepam group.

Conclusion: IV valproate can be administered safely and rapidly for SE patients. Efficacy between VPA and diazepam is similar. Diazepam acts more quickly while VPA is less mentally disturbing.

p544

EFFICACY OF MONOTHERAPY AND POLYTHERAPY BY TOPIRAMATE AND VALPROATE IN CHILDHOOD EPILEPTIC ENCEPHALOPATHY (LENNOX-GASTAUT SYNDROME)

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Purpose: To define the comparative efficacy of monotherapy and polytherapy by topiramate and valproate in childhood epileptic encephalopathy (the Lennox-Gastaut syndrome) (LGS).

Method: Thirty-eight children, age 1–8 years were investigated. The research was divided into 2 phases: for 28 days patients received the same doses of standard antiepileptic drugs, then, for carrying out comparative control research, four groups of patients were formed: 1) receiving valproate; 2) receiving topiramate; 3) receiving no more than 100 mg topiramate + valproate (300–900 mg); 4) receiving no more than 600 mg valproate + topiramate (100–300 mg).

Results: In the groups receiving monotherapy by topiramate and valproate, the reduction in the number of total seizures was 19% and 22%, for atonics seizures, 19% and 12%. Monotherapy by valproate showed no change; with topiramate some of the children had an increase in generalised convulsions. Of the patients receiving topiramate in common with valproate, the degree of reduction of number of total and atonic attacks changed, and varied from 30% to 40%, generalized convulsions made 73%. Side effects from monotherapy by topiramate and valproate and polytherapy topiramate (100–200 mg) + valproate (100–600 mg) for children with LGS did not differ statistically.

Conclusion: Polytherapy by topiramate at a dose of 100–200 mg per day and valproate at a dose of 600–1000 mg per day is more effective than monotherapy by topiramate at an average dose of 100–300 mg per day and monotherapy by valproate at its maximum transferable dose in the treatment of children with LGS.

p545

VALPROATE DOES NOT ELIMINATE EPILEPTIC KK

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Purpose: To evaluate the effect of valproate therapy on the epileptic K complexes (e-KK).

Method: Long-term EEG (LT-EEG) was applied 3 times in a period of 5 years to investigate the frequency of epileptic events in 1 patient with primary generalised epilepsy. His first LT-EEG was recorded when he was 29. More than 177 epileptic paroxysmal discharges in one night have been revealed when he was under phenobarbital therapy. Because his epileptic seizures were not under control, his therapy was changed from phenobarbital to slow-releasing valproate medication.

Results: The conversion from phenobarbital to valproate therapy was performed successfully. Neither rebound epileptic seizures nor new seizures have happened while taking 2000 mg slow releasing valproate separated in 2 daily doses. Three years later the second LT-EEG has revealed 23 e- KK in one night. After slow reduction of therapy 2 years later a series of 3 epileptic seizures occurred. There were 56 e-KK obtained during the one night.

Conclusion: Valproate therapy eliminated the epileptic paroxysmal discharges of 3/s spike-and-slow-wave complexes completely, but was unable to push out e-KK in our patients with primary generalised epilepsy. It seems there exists a dose dependent suppression of e-KK with valproate therapy.

p546

RETENTION RATE OF PREGABALIN IN PATIENTS WITH REFRACTORY EPILEPSY

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Purpose: Pregabalin (PGB) was licensed as an add-on treatment for partial epilepsy in adults in Germany in 09/2004. Controlled clinical trials demonstrated that PGB is an efficient and well tolerated antiepileptic drug (AED). The aim of this study (open label, mostly phone interviews) was to evaluate the efficacy and the tolerability of PGB in patients with refractory epilepsy under clinical conditions.

Method: We included all patients of the Bethel Epilepsy Centre who started with PGB from 09/2004 to 12/2005. The patients were interviewed after 3, 6 and in some cases after 12 months. We assessed the discontinuation of PGB, type of epilepsy, seizure type and frequency, comedication etc. The retention rate of PGB was the primary parameter for efficacy and tolerability.

Results: One hundred and nine adult patients were treated with PGB, on average in combination with 2.1 AED. Twelve patients had a vagus nerve stimulator. The mean observation period was 158 days. 51% of the patients continued PGB with the following outcome: 5% seizure free, 19% 50%-responders, in 27% seizure frequency remained unchanged or increased. Reasons for withdrawal were lack of efficacy (33%) or side effects (17%). Weight gain was the most frequently mentioned adverse effect (19 patients, 17.4%). Other adverse effects mentioned were tiredness (9.2%, n = 10), dizziness (5.5%, n = 6) and allergic skin reactions (5.5%, n = 6).

Conclusion: The retention rate of 50% indicates that add-on treatment with PGB is effective and well tolerated even in patients with refractory epilepsies.

Development of a questionnaire used for this study was partly supported by Pfizer.

p547

PREGABALIN IS EFFECTIVE AND WELL TOLERATED AS ADD-ON TREATMENT FOR PATIENTS WITH HIGHLY REFRACTORY PARTIAL EPILEPSY: A TERTIARY CENTRE EXPERIENCE

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Purpose: Pregabalin (PGB) is a new antiepileptic drug (AED) that has shown a high efficacy as add-on therapy in controlled trials, with responder rates close to 50%. The objective of our study was to analyse the efficacy and tolerability of PGB in clinical practice when used as add-on therapy in highly pharmacoresistant epilepsy patients.

Method: We retrospectively identified patients who received PGB as add-on treatment from March 2005 until November 2005. We analysed the efficacy to decrease seizure frequency and the emergent adverse effects. A patient was considered a responder if ≥50% seizure reduction was attained.

Results: We identified 50 patients (31 women) who received PGB. Mean age was 37.31 (SD9.7); mean time of epilepsy evolution was 25 (0.5–53; SD 11.5). The mean number of previous AEDs tried was 7. Twenty patients had a history of clusters of seizures or previous status epilepticus, which prevented them from participating in controlled trials. Patients received a mean dose of 384 mg (150–900; SD181). Dose of concomitant AEDs were decreased in 25 patients to improve tolerability. Twenty-three patients (46%) were responders and 7 patients (14%) became seizure free. Two patients reported seizure worsening. Adverse effects were reported by 23 patients (46%), the most common being weight gain (12 patients), ataxia/dizziness (8), somnolence (5), blurred vision (3), and malleolar edema (3). Adverse effects were generally mild to moderate, but caused treatment discontinuation in 4 patients (8%).

Conclusion: In clinical practice, PGB is effective and generally well tolerated as add-on treatment in patients with highly refractory partial epilepsy.

p548

SAFETY AND TOLERABILITY PROFILE OF PREGABALIN IN THE LONG-TERM TREATMENT OF PATIENTS WITH PARTIAL-ONSET SEIZURES

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Purpose: To evaluate the long-term safety and tolerability profile of pregabalin as add-on treatment in adult patients with partial seizures.

Method: Three long-term, open-label (OL) add-on trials enrolled 1057 patients (386 de novo; 671 from double-blind randomised, placebo-controlled trials). Patients took pregabalin 150–600 mg/day, BID or TID, and kept seizure diaries. Results for patients receiving pregabalin treatment for 30 months (n = 344) are presented.

Results: Mean age was 40 years; mean epilepsy duration was 27 years. All patients were taking at least 1 concurrent AED, 91.9% took ≥2 AEDs. Baseline median seizure rate was ∼11/28d. Approximately half of patients received pregabalin 600 mg/d; one-third received 450 mg/d; and the remainder received 150 or 300 mg/d. Dosing remained relatively stable throughout the 30 month period, as did the 50% responder rate (6 months: 49.1%; 30 months: 64.8%). The most common AEs reported during the first 6 months of OL treatment were dizziness and somnolence, which tended to resolve over time. Overall AE incidence and intensity resolved or diminished over time. At 30 months, the most common AEs were dizziness (3.5%), asthenia (3.2%), somnolence (1.8%), and weight gain (0.6%). Over the 30 months of treatment, 64.5% patients discontinued for any reason, with 8.4% withdrawing due to AEs that included weight gain and dizziness.

Conclusion: Long-term pregabalin treatment is well tolerated and the safety profile is favourable in patients treated for up to 30 months, at doses up to 600 mg/d. Most AEs were mild-to-moderate and resolved with continued treatment. Supported by Pfizer Inc.

p549

PHARMACODYNAMIC COMPARISON OF PREGABALIN AND GABAPENTIN

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Purpose: To compare the dose-response (seizure frequency) relationship of pregabalin and gabapentin add-on treatment in patients with refractory partial epilepsy. Preclinical studies with pregabalin and gabapentin indicate similar anticonvulsant pharmacological profiles; however, pregabalin shows 3- to 6-fold greater potency. Pregabalin, unlike gabapentin, exhibits linear absorption with observed maximum plasma drug concentration (C_{max}) and area under the plasma drug concentration-time profile (AUC) increasing proportionally with dose. In contrast, the extent of gabapentin absorption decreases with increasing dose.

Method: Data from 3 pregabalin clinical trials (1042 patients) and 6 gabapentin trials (551 patients) were analysed using a nonlinear mixed-effects model to characterise the relationship between seizure frequency and pregabalin and gabapentin dose. Percent of responders among patients was estimated.

Results: Pregabalin (50–600 mg/d) and gabapentin (600–1800 mg/d) showed an asymptotic dose-related decrease in seizure frequency. Both pregabalin- and gabapentin-treated patients demonstrated a dose-response relationship; however, the maximal decrease in seizure

frequency from baseline with pregabalin was 100%, while the maximal decrease with gabapentin therapy was only 24.5%. Based on this information, pregabalin was estimated to be 4 times more effective than gabapentin in patients who responded to treatment. Pregabalin was also 2.5 times more potent than gabapentin in responding patients, as measured by the dose that reduced seizure frequency by ≥50%.

Conclusion: The observed improvement in potency and effectiveness combined with the pharmacokinetic and pharmacodynamic properties of pregabalin relative to gabapentin offer distinct advantages over standard gabapentin therapy for the treatment of refractory partial seizures.

p550

PREDICTIVE PERFORMANCE OF WEIGHT CHANGE ASSOCIATED WITH PREGABALIN ADMINISTRATION

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Purpose: Validate a pharmacodynamic model characterising change from baseline weight over time following pregabalin administration.

Method: Open-label pregabalin-treated patients (n = 141) received daily dosage of 75 mg per week up to 300 or 450 mg per day after 4-6 weeks, respectively. Dosage was increased in some patients after 3 months based on clinical outcome using similar regimen to 900 mg/d maximum dose (n = 2). Expected fractional change from baseline weight was estimated using baseline weight, age, time, and average pregabalin exposure for this cohort using a pharmacodynamic model. Bias was assessed using median error (median of observed minus predicted weights) and variability, or precision, was assessed using median absolute error, after 6 months of treatment. For subjects with observations at 3 months only (drop outs), posterior predictions were generated for 6 month exposure.

Results: Mean pregabalin exposure was 279.5 mg/day. The median error (bias) was 0.84 kG at 6 months (n = 93). The median absolute error (variability) was 2.6kG at 6 months. Comparison of model-predicted weights to observed weights suggested that the model slightly underpredicted 6 month weights. Subjects with observations at 3 months only had median predicted 6 month weights of 1.017 times their baseline weight. Subjects observed at 6 months had median weights of 1.037 times their baseline value.

Conclusion: Overall, the model was relatively unbiased and reasonably precise. The predicted values were not significantly different from those observed. The substantial intersubject variability in weight change remains to be explained. Differences in weight trajectories between subjects lost to follow-up and those who completed warrant investigation.

p551

MODELLING OF WEIGHT CHANGE ASSOCIATED WITH PLACEBO AND PREGABALIN ADMINISTRATION

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Purpose: To characterise change from baseline weight over time for pregabalin and placebo administration.

Method: Asymptotic fractional change from baseline weight was modelled with a nonmixture model and a mixture model as a function of baseline weight, exposure, time, covariate effects, and subject-specific random effects. Model fit was assessed using standard diagnostic plots. Predictive performance was assessed using both data similar to the original data, and open-label data.

Results: The nonmixture model indicated that a typical patient (baseline weight, 82 kg) receiving placebo or 300 mg/day pregabalin approached an asymptotic fractional increase from baseline weight of [mean (95% prediction interval for typical individual)] 0.7% (−5.5% to 7.4%) or 2.5% (−3.8% to 9.1%), respectively, with a "half-life" of 17 days. Substantial between-subject variability is observed, with some drug-treated subjects remaining weight neutral or losing weight, at all levels of exposure. Structural fixed effects parameters for the two submodels (mixture model) were in close agreement with each other and with those for the nonmixture model. The mixture model described two subpopulations differing in interindividual variability. No significant interindividual-varying covariates influencing the mixture probabilities were identified other than exposure. Both models had adequate fit; both models performed well during external validation. Predictive performance (nonmixture model) was adequate to ∼900 days.

Conclusion: Though substantial between-subject variability exists, the weight of a typical 82-kg patient receiving placebo or pregabalin (300 mg/day) approaches an asymptotic fractional increase from baseline weight of 0.7% or 2.5%, respectively, with a "half-life" of 17 days.

p552

LONG-TERM RESPONSE IN PATIENTS WITH PARTIAL-ONSET SEIZURES TREATED WITH ADD-ON PREGABALIN

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Purpose: To evaluate the long-term efficacy and safety of pregabalin as adjunctive therapy in adult patients with partial-onset seizures

Method: 671 patients completed three 12 week, randomised, placebo-controlled, double-blind pregabalin trials and entered open-label (OL) trials. Patients took pregabalin up to 600 mg/day, BID or TID, and kept seizure diaries. Data from those treated for ≤30 months were evaluated.

Results: 261/671 patients received OL pregabalin treatment for 30 months. Median baseline seizure rate was ∼11/28d, despite use of 1–5 concomitant AEDs. Mean age was 40 years; mean duration of epilepsy was 27 years. Most patients received pregabalin 600 mg/d or 450 mg/d. At 30 months, 64.8% of patients experienced a ≥50% reduction in seizure frequency (SF); 84 patients (32.2%) attained a 76–100% decrease in SF; 85 (32.6%) attained a 51–75% decrease; and 83 (31.8%) decreased SF up to 50%. Nine patients (3.4%) worsened, with 8 reporting an increase in SF of ≤50%. Response rates remained relatively consistent throughout the 30-month period. The mean number of seizure-free days/28d among responders was 25.5 (± 2.7), compared with 22.8 (± 4.5) among nonresponders. With ongoing treatment, somnolence, weight gain, and dizziness were observed most frequently and were generally considered to be mild-to-moderate. Adverse events led to discontinuation in 8.4% patients over the 30 months, with weight gain and dizziness cited most often.

Conclusion: After 30 months of pregabalin treatment, two-thirds of patients were responders and demonstrated maintenance of seizure-frequency reduction throughout the observation period. Long-term pregabalin treatment was safe and well tolerated. Supported by Pfizer Inc.

p553

EFFICACY AND TOLERABILITY OF PREGABALIN IN REFRACTORY PARTIAL SEIZURES ARE NOT ALTERED BY BACKGROUND ANTIEPILEPTIC DRUGS

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Purpose: To assess the response and tolerability of pregabalin relative to types of background antiepileptic drugs (AEDs) in add-on trials of patients with refractory partial-onset seizures.

Method: In this post hoc analysis, pooled data from 4 large pregabalin add-on trials in patients with partial seizures were analysed. Analyses were restricted to the greatest pregabalin dose (600 mg/d) and placebo. The type of AED comedication was classified into 3 groups based on presumed mode of action: (1) Na^+-channel blocker AEDs; (2) GABAergic

AEDs; and (3) multimodal-action AEDs. Outcome in the ITT population (n = 899) was analysed by type of AED comedication.

Results: The response rates (proportion of patients with ≥50% reduction from baseline in seizures) for pregabalin-treated groups (45.9% to 47.2%) were significantly greater than those for patients who received placebo (6.6% to 10.7%), irrespective of class of background AED. There were no significant differences in placebo-corrected responder rates in patients who received pregabalin and were comedicated exclusively with either Na^+-channel blockers, GABAergic AEDs, or multimodal-action AEDs. Similarly, there were no significant differences in responder rates between pregabalin-treated patients who received different combinations of classes of background AEDs (eg, Na^+-channel blocker AEDs plus multimodal-action drugs; Na^+-channel blocker AEDs plus GABAergic AEDs; a combination of all three classes). Differences in placebo-corrected withdrawal rates (18.9% to 20.5%) were similar when comparing patients treated with the different classes or combinations of background AEDs.

Conclusion: Pregabalin is effective and well-tolerated as add-on treatment for partial seizures, and was not altered by background AEDs.

p554

LONG-TERM SEIZURE FREEDOM IN PATIENTS WITH PARTIAL SEIZURES TREATED WITH ADD-ON PREGABALIN: ANALYSIS OF OPEN-LABEL STUDIES

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Purpose: To evaluate differences over time in measures of seizure freedom among adults with poorly controlled partial-onset epilepsy treated with pregabalin.

Method: Three long-term, open-label, add-on trials enrolled 1057 patients (386 de novo and 671 from double-blind randomised, placebo-controlled trials). Patients took pregabalin 150–600 mg/d, BID or TID, and kept seizure diaries. Results at 30 months are reported.

Results: 344 patients received OL pregabalin treatment for 30 months. Mean age was 40 years; mean epilepsy duration was 27 years. All patients were taking ≥1 concurrent AED; 92% were taking ≥2 AEDs. Most patients received pregabalin 600 mg/d or 450 mg/d. The proportion of patients seizure-free for the last 6, 12, 18, 24, and 30 months of treatment was 8.0%, 5.1%, 4.6%, 2.9%, and 2.6%, respectively. The median maximum seizure-free interval was 12 days at baseline. At 1 year, the seizure-free interval was 62 days, and was 98 days in patients treated for 30 months. The median number of seizure-free days/28d for this 30-month cohort was 25.6. Pregabalin was generally well tolerated. Most AEs were mild-to-moderate and tended to resolve over time. The most common AEs at 30 months were dizziness (3.5%), asthenia (3.2%), and somnolence (1.8%). Over the 30-month treatment period, 8.4% patients discontinued due to AEs.

Conclusion: In patients with treatment-refractory epilepsy who received add-on pregabalin up to 600 mg/d, nearly 10% were seizure-free for the last 6 months of treatment, with seizure-free intervals of 3.5 months for patients treated for 30 months. Pregabalin was generally well tolerated. Supported by Pfizer Inc.

p555

OXCARBAZEPINE FOR ELDERLY EPILEPSY PATIENTS

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Purpose: In the elderly with epilepsy we need to consider better-tolerated and less toxic drugs than those classically used. Oxcarbazepine is a modern antiepileptic drug (AED) used as both monotherapy and adjunctive therapy for the treatment of partial seizures with and without secondary generalisation in adults and children. The goal of the present study is to assess the efficacy and tolerance of oxcarbazepine in elderly patients with epilepsy.

Method: A prospective, descriptive, observational study was carried out in a total of 40 patients over 65 years old. All patients started with a double daily dose of 150 mg of oxcarbazepine. Their dosages were adjusted to treatment response. Where further seizures occurred, the dose of oxcarbazepine was increased. Efficacy and tolerance checks were carried out after one month, three months and six months.

Results: Median daily oxcarbazepine dose was 832.5 mg. Thirty-one patients (77.5%) were taking low doses (less or equal to 900 mg/day). At the end of the study 28 (70%) patients continued to be seizure-free. The drug was withdrawn in 2 cases because of adverse events. The most common adverse events (37.5%) were dizziness (7 patients) and somnolence (8 patients). Mild hyponatremia was detected in 6 patients.

Conclusion: Oxcarbazepine is an effective therapy for the control of epilepsy in elderly patients at low doses, with good tolerance and a low rate of adverse events.

p556

OXCARBAZEPINE IN PATIENTS WITH BRAIN TUMOURS AND EPILEPSY: IS IT SAFE?

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Purpose: Seizures affect 20-40% of patients with primary brain tumours or brain metastases and significantly alter their quality of life. Furthermore, anticonvulsant treatment is complicated by pharmacological interactions between antiepileptic drugs (AED) and chemotherapeutic agents. Among the newer AEDs, oxcarbazepine (OXC) has a fast and complete absorption and it rarely interferes with other therapies. The aim of this retrospective study was to investigate the safety and efficacy of OXC in monotherapy in a group of patients affected by brain tumour associated epilepsy.

Method: We studied 18 patients affected by brain tumour and epilepsy (11 males, 7 females, mean age 51). Twelve patients underwent radiotherapy and chemotherapy. In 7 patients OXC was the first therapeutic choice, in 7 it substituted the first therapy because of heavy side effects and in 4 it was introduced because of persisting seizures. Follow-up ranged between 2 to 43 months.

Results: Oxcarbazepine did not induce any significant side effect: during the whole period of follow up liver and haematic values were in the normal ranges. OXC induced complete seizure control in 15 patients (83.3% of whole population), a seizure rate reduction higher than 50% in 1 patient, an unmodified seizure rate in 1 patient, and a worsening of seizure rate lower than 50% in 1 patient.

Conclusion: These preliminary data seem to indicate that OXC treatment in patients with brain tumours is quite safe and efficacious. Controlled studies on larger populations are suggested to confirm these open observations.

p557

PLASMA HOMOCYSTEINE LEVELS IN OXCARBAZEPINE TREATED EPILEPSY PATIENTS

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Purpose: It is known that plasma homocysteine (HS), folic acid (FA) and vitamin B12 levels may be affected by antiepileptic drugs (AED) (Tamura T. et al., *Epilepsy Res* 2000;40:7–15). Elevated plasma concentrations of HS are associated with increased risk of coronary artery disease, peripheral vascular disease and thrombosis (Duell PB et al., *The Endocrinol* 1998;8:170–177). The aim of this study was to assess the

effects of oxcarbazepine (OXC) on plasma HS, FA and vitamin B12 levels.

Method: A total of 31 epilepsy outpatients receiving AED therapy were selected. The patients in group1 received OXC for less than 1 year (n = 7), group 2 received OXC for more than 1 year (n = 8), group 3 received OXC with valproate (VPA) for more than 1 year (n = 9), group 4 received VPA monotherapy (n = 7). A control group of 30 healthy subjects without any AED medication was also included. The plasma HS, FA and vitamin B12 levels of the groups were compared with each other using one way ANOVA.

Results: The levels of plasma HS for groups 1, 2, 3 and 4 and the controls were 10.7 ± 4.1 μmol/l, 15.5 ± 10.7 μmol/l, 12.7 ± 4.10 μmol/l, 10.2 ± 2.9 μmol/l, 10.6 ± 4.7 μmol/l respectively. No significant difference could be found between HS, FA and vitamin B12 levels ($p > 0.05$).

Conclusion: According to the findings of our study, it seems that OXC does not have any influence on plasma HS, FA and vitamin B12 levels, but HS levels in patients with nutritional FA supports may not be affected.

p558

RELATIONSHIP BETWEEN THE PLASMA CONCENTRATIONS OF THE MONOHYDROXY DERIVATIVE OF OXCARBAZEPINE AND ITS EFFICACY AND SIDE EFFECTS

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Purpose: To describe the relationship between oxcarbazepine (OXC) plasma concentration and its monohydroxy derivative (MHD) with the therapeutic effect and side effects in epilepsy patients. We pretend to determinate the therapeutic levels of the drug to achieve a seizure-free state without side effects to get a reference in clinical practice.

Method: Data have been obtained from 30 adult and paediatric epilepsy clinic outpatients, 16 adults (10 men, 6 women) with mean 38 ± 16.3 years old and 14 children (8 male, 6 female) with mean 10.6 ± 2.89 years old. All of them suffered from chronic epilepsy with partial or generalised seizures. Measurement of OXC plasma concentrations was made in stable level phase before the first dosage in the morning and OXC + MHD concentrations were obtained by high resolution chromatography (HPLC).

Results: The mean MHD plasma levels in children was 19.03 ± 4.67 mg/l (mean OXC daily dosage of 982.91 ± 364.22 mg). In adults the mean MHD plasma levels was 21.28 ± 4.8 mg/l (mean OXC dosage 1407.7 ± 309.47 mg/d). Global efficacy curve shows that a seizure-free state can be achieved in 84% of patients with plasma concentrations of OXC+MHD between 13.21 and 27.86 mg/l. With regard to side effects, only 9% of the patients had any adverse effects which were mild somnolence. None were related to high OXC plasma concentrations. No haematological or biochemistry anomalies were found in our series.

Conclusion: We consider that OXC metabolite MHD plasma concentrations between 13.21 and 27.86 mg/l are correlated with a good efficacy without significant side effects.

p559

EFFICACY AND TOLERABILITY OF OXCARBAZEPINE DURING ONE-YEAR FOLLOW-UP AS ADD-ON THERAPY IN PATIENTS WITH TREATMENT-RESISTANT EPILEPSY

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Purpose: To investigate the efficacy and tolerability of Oxcarbazepine (OXC) as add-on therapy for Cypriot patients with treatment-resistant seizures.

Method: Twenty patients with partial-onset epilepsy, ages 12–71, were studied retrospectively for 12 months. Patients received OXC as add-on therapy to 1–4 anticonvulsants. We compared mean seizure frequency for a 3-month period prior to and 12 months after introduction of OXC. All subjects had physical and neurological examinations, routine baseline haematological, biochemical, and urinary investigations at entry.

Results: Two patients (10%) became seizure free. Four patients (20%) had a seizure reduction of 75% or greater. Two patients (10%) had a seizure reduction of 50–74% or greater. Seven patients (35%) had no significant change from baseline and 2 patients (10%) worsened. Oxcarbazepine was discontinued in 3 patients (15%) due to side effects. A reduction of 32.4% of concomitant antiepileptics was achieved. Diplopia (15%), dizziness/ataxia (15%), rash (10%), behavioural/psychiatric side effects (10%), cognitive impairment (10%) and numbness (10%) were the most frequently reported side effects.

Conclusion: OXC was effective in focal epilepsy as demonstrated by significant reduction of seizures. A substantial rate of our population became seizure free. 40% of our patients with refractory epilepsy experienced a reduction of 50% or more on their seizure frequency with the addition of OXC. Oxcarbazepine was generally well tolerated by all patients with only 15% discontinuing it due to adverse reactions.

p560

CITALOPRAM DOES NOT CAUSE HYPONATREMIA IN EPILEPSY PATIENTS TREATED WITH CARBAMAZEPINE OR OXCARBAZEPINE

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Purpose: Hyponatremia is a side effect of treatment with carbamazepine (CBZ), oxcabazepine (OXC) or citalopram. Thus the aim of this study was to evaluate the aditional effect of citalopram on sodium blood level in epilepsy patients being already treated with CBZ or OXC.

Method: Epilepsy patients with a stable dose of CBZ or OXC were included. Dosage of CBZ, OXC, citalopram and blood levels of antiepileptics and sodium before and after titration of citalopram were analysed applying a *t*-test for paired samples.

Results: Data of 17 patients (7 male, 10 female, age: 25–76 years) were evaluated. 14 patients received CBZ (800–2100 mg/day), 3 patients were treated with OXC (1200–1800 mg/day). Daily dose of citalopram was 20–40 mg. Average time between titration of citalopram and assesment of sodium levels was 12.75 months. The average CBZ blood level before titration of citalopram was 9.25 μg/ml in contrast to 10.1 μg/ml after titration of citalopram. No significant difference between the CBZ levels before and during treatment with citalopram was found ($p = 0.31$). The average sodium level before titration of citalopram was 135.5 mmol/l in contrast to 135 mmol/l after citalopram titration. No significant difference between the sodium levels before and during treatment with citalopram was found ($p = 0.86$).

Conclusion: No drop of sodium levels could be found in epilepsy patients treated with constant dosages of CBZ or OXC due to additional antidepressant therapy with citalopram. In general citalopram treatment in this group of epilepsy patients can be supposed to be safe with regard to changes in sodium levels.

p561

EVALUATION OF THE EFFECT OF ORAL LACOSAMIDE ON ADJUNCTIVE CONCOMITANT ANTIEPILEPTIC DRUG PLASMA CONCENTRATIONS IN SUBJECTS WITH PARTIAL SEIZURES

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Purpose: Lacosamide (LCM) reduced seizure frequency in a double-blind trial of subjects with uncontrolled partial seizures (SP667). Steady-state plasma concentrations of concomitant antiepileptic drugs (conAEDs) were evaluated for possible pharmacokinetic interactions that could affect seizure frequency.

Method: After an 8-week baseline, subjects (n = 418) taking 1 (16%) or 2 (84%) conAEDs were randomised to placebo, 200, 400, or 600 mg/day LCM (given bid), titrated over 6 weeks by 100 mg/week, and maintained on treatment for 12 weeks. ConAED dose regimens were to

remain constant. Descriptive statistics compared end of baseline and end of maintenance conAED plasma concentrations.

Results: Mean change from baseline (μg/mL) at the end of maintenance was 0.4, 0.6 for CBZ; 1.0, −1.4 for LEV; and 0.4, −0.7 for LTG in placebo and 600 mg/day LCM groups, respectively. LCM also did not affect mean AED concentrations for TPM, OXC (MHD), PHT and VPA. Similar results were observed in the 200 and 400 mg/day LCM groups. LCM (400 and 600 mg/day) produced a statistically significant median percent reduction in seizure frequency from baseline ($p = 0.0023$ and 0.0084, respectively); 200 mg/day exhibited a 26% reduction in seizures ($p = 0.1010$). The most common adverse events ($\geq$ 10% in any LCM group) include dizziness, nausea, fatigue, ataxia, vision abnormal, diplopia, and nystagmus. No clinically relevant LCM influence was observed on ECG, laboratory, vital sign, or body weight variables.

Conclusion: Lacosamide does not affect the mean plasma concentrations of commonly used AEDs. Thus, observed reductions in seizure frequency were not due to increased AED plasma concentrations.

Study supported by: Schwarz Biosciences, Inc.

p562

LACOSAMIDE HAS LOW POTENTIAL FOR DRUG-DRUG INTERACTION

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Purpose: Lacosamide is an investigational drug being developed for the treatment of epilepsy and neuropathic pain. Phase 3 development is currently ongoing for both indications. Information about the pharmacokinetic drug-drug interaction (DDI) potential of lacosamide is an important part of the safety profile.

Method: Regarding DDI potential the results of several preclinical studies, Phase 1 trials (n = 184 subjects) and a Phase 2 trial (n = 91 patients) are presented.

Results: In vitro lacosamide is not substantially metabolised. In vitro results also show no or low potential to inhibit or to induce CYP isoforms. Since lacosamide has low protein binding (<10%), drug displacement interactions are unlikely. In a Phase 1 trial the activity of CYP2C19 had no clinically relevant effect on the metabolic fate of lacosamide. Further phase 1 DDI trials with the antiepileptic drugs carbamazepine and valproic acid showed that lacosamide had no influence on rate or extent of absorption of carbamazepine or valproic acid and vice versa. DDI trials with digoxin and metformin showed no relevant influence of these drugs on lacosamide and vice versa. Lacosamide did not influence the pharmacokinetics and pharmacodynamics of the oral contraceptive Microgynon (containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel). A clinical trial in subjects with epilepsy showed no influence of lacosamide on plasma levels of common antiepileptic drugs including phenytoin.

Conclusion: No relevant DDI have been observed in these studies and therefore the data suggest that lacosamide may have a low potential for DDI in clinical use.

p563

MULTICENTER OPEN-LABEL TRIAL INVESTIGATING SAFETY AND TOLERABILITY OF INTRAVENOUS SPM 927 AS REPLACEMENT FOR ORAL SPM 927 IN SUBJECTS WITH PARTIAL SEIZURES

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Purpose: Lacosamide (LCM) belongs to a novel class of functionalised amino acids specifically synthesised as anticonvulsant drug candidates. LCM has a favourable pharmacokinetic profile and when give orally twice daily (bid) has been shown to reduce seizure frequency in patients with partial seizures. LCM solution for intravenous (iv) infusion is being developed as a short-term replacement for oral LCM. Infusion of 200 mg iv LCM over 30- or 60-minutes has been shown to be bioequivalent ($C_{max,}$ AUC) to 200 mg oral LCM. The objective of SP757 is to investigate whether iv LCM is safe and well tolerated when given bid as short-term adjunctive therapy for partial seizures.

Method: Subjects (n = 40) currently receiving adjunctive, stable, bid dosing (200 to 600 mg/day) were enrolled as Cohort A1. These subjects were administered iv LCM bid as 30-minute infusions for 2 consecutive days. Safety was evaluated through reported adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs and clinical laboratory data.

Results: Forty subjects completed the trial. Seventeen (43%) reported AEs, all of which were mild or moderate in intensity; CNS-related events were most commonly reported. Analysis of ECG and vital signs data showed no issues of clinical concern.

Conclusion: In this trial, administration of 30-minute iv LCM infusions for short-term replacement of oral LCM had a similar AE profile to oral LCM. Funding supported by: Schwarz Biosciences, Inc.

p564

EFFECT OF PHENYTOIN AND PRIMIDONE ON HUMAN SPERM MOTILITY AND CERVICAL MUCUS PENETRATION

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Purpose: Antiepileptic drugs (AEDs) effects on sperm motility have been shown. We previously demonstrated the ability of CBZ and VPA to decrease sperm motility and reduce sperm ability to penetrate cervical mucus (a functional test not studied before in relation to AEDS). In the present study we investigated the effect of phenytoin (PHT) and primidone (PRM) on these parameters.

Method: PHT was dissolved in PBS + ethanol 2% + propylene glycol 8%, PRM in PBS + ethanol 2.5%. Normal semen from healthy human donors (sperm count>20 million/mL, >50% progressively motile) was incubated for 2hr with several dilutions of PHT or PRM. Parameters analysed included sperm motility (%motile cells), EC50, motility quality grade, abnormal motility patterns, ability of spermatozoa to penetrate into bovine cervical mucus after 10 min contact (depth of penetration). Statistical analysis employed the Wilcoxon Signed Ranks Test.

Results: PHT significantly ($p < 0.05$) decreased sperm motility at concentrations $\geq$156 mg/L, with EC50 = 625 mg/L. Motility quality grade was decreased at concentrations $\geq$156 mg/L. Cervical mucus penetration was inhibited at concentrations $\geq$156 mg/L. "Shaking" (abnormal motility pattern) was observed at $\geq$625 mg/L. PRM significantly ($p < 0.05$) decreased sperm motility at concentrations $\geq$150 mg/L; EC50 was not reached with concentrations $\leq$300 mg/L. Motility quality grade was decreased at concentrations $\geq$75 mg/L. Cervical mucus penetration was inhibited at concentrations $\geq$75 mg/L.

Conclusion: PHT and PRM impair sperm motility, quantitatively and qualitatively, at concentrations above the therapeutic range, and also impair the ability of human spermatozoa to penetrate into bovine (with composition and properties similar to human) cervical mucus. This implies impairment of the physiological function of spermatozoa by high concentrations of these AEDs.

p565

CAN THE WIDE-FIELD MULTIFOCAL ELECTRORETINOGRAM DIFFERENTIATE BETWEEN VIGABATRIN-ASSOCIATED RETINAL TOXICITY AND CONVENTIONAL VISUAL FIELD DEFECTS?

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Purpose: This study was designed to differentiate between neuroretinal toxicity associated with vigabatrin (VGB) therapy and nonspecific visual dysfunction in people with epilepsy.

Method: A total of 204 epilepsy patients were grouped according to antiepileptic drug therapy as follows: current VGB treatment (n = 56), previous VGB treatment (n = 49), current GABAergic treatment (no VGB exposure; n = 46) and current non-GABAergic treatment (no VGB exposure; n = 53). Groups were matched for age, sex, seizure-type, and seizure frequency. All patients underwent wide-field multifocal electroretinography (WFmfERG), logMar visual acuity testing, colour vision assessment, static perimetry (Humphrey) and ISCEV standard electroretinography.

Results: When assessed by static perimetry, visual field constriction was observed in 33 current-VGB patients (59%) and 21 of the previous-VGB group (43%). However, significant visual field abnormalities were also demonstrated in 24 patients (24%) with no prior exposure to VGB. Assessment of retinal function by WfmfERG revealed abnormal responses in 27 current-VGB patients (48%), 11 previous-VGB patients (22%), but none (0%) of the patients with no prior exposure to VGB. The incidence of WfmfERG abnormalities was directly related to VGB drug load. There was no difference between groups in terms of visual acuity, colour vision and electroretinography assessments.

Conclusion: Visual field abnormalities are common in the treated epilepsy population. VGB causes peripheral retinal dysfunction that can be manifest as visual field constriction when investigated using perimetry but which is more readily and reliably identified by WfmfERG. Conventional assessments are unlikely to be sufficiently specific to identify VGB-related retinal toxicity. Patients with current or previous exposure to VGB should be considered for WfmfERG.

p566

USE OF ZONISAMIDE IN FOUR PATIENTS WITH LAFORA DISEASE

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Purpose: To evaluate the efficacy of zonisamide (ZSM) in controlling seizures in patients with Lafora disease (LD) with a retrospective observational study performed in 4 adolescents.

Method: Six adolescents with Lafora disease (LD) attending our Department were identified. Four patients were treated with ZSM. We retrospectively reviewed changes in seizure frequency and semiology, EEG findings, alertness and ideomotor slowing, comparing the 3 months preceding the introduction of ZSM with the following 1 month, 3 months and 1 year. Side effects were described when observed.

Results: Four patients affected by LD (1 male: 3 female; median current age: 20 ys 10 mths; range: 19 ys–21 ys 4 mths) were ascertained. All patients were taking 2 or 3 AEDs and Ketogenic diet. The median highest dose was 5.3 mg/Kg/die (range: 3–12 mg/Kg/die). The median period of ZSM administration was 1 y 11 mths (range: 1 y–3 ys 7 mths) and 2 patients are currently taking the drug. In 2 patients (50%) we observed a complete control of generalised tonic–clonic seizures during the first month and at 3 months a reduction > 50% of seizure frequency recorded during the 3 months preceding the ZSM introduction. At 1 year the seizure reduction was unchanged. We did not observe an efficacy in controlling other types of seizures such as absences or myoclonic jerks. In the other 2 girls ZSM was not effective.

Conclusion: ZSM allows a long-lasting reduction of tonic–clonic seizures in some LD patients.

p567

EFFECT OF ESLICARBAZEPINE ACETATE (BIA 2-093) ON THE STEADY-STATE PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN IN HEALTHY SUBJECTS

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Purpose: To investigate the effect of eslicarbazepine acetate (ESL) on the steady-state pharmacokinetics and pharmacodynamics of warfarin in 13 healthy subjects (7 males and 6 females).

Method: Open-label study consisting of three consecutive phases: A: up to 21 day run in phase, for identifying an individualised warfarin dose stabilising INR between 1.3–1.8; B: warfarin pharmacokinetics and INR profiling following a 7 day ESL 1200 mg once daily treatment, concomitantly with the individualised warfarin dose; C: 7 day period with warfarin alone.

Results: Mean S-warfarin C_{max} was respectively 0.375 mg/L and 0.455 mg/L with Test (warfarin plus ESL, day 8 of phase B) and Reference (warfarin alone, day 1 of phase B) treatments; point-estimate (PE) and 90% CI of Test/Reference ratio were 0.81 and 0.76, 0.86. Mean S-warfarin AUC_τ was respectively 5.56 mg.h/L and 7.05 mg.h/L with Test and Reference, and PE and 90%CI of Test/Reference ratio were 0.77 and 0.72, 0.82. Mean R-warfarin C_{max} was respectively 0.556 mg/L and 0.575 mg/L with Test and Reference, and PE and 90%CI of Test/Reference ratio were 0.97 and 0.91, 1.02. Mean R-warfarin AUC_τ was respectively 9.85 mg.h/L and 9.93 mg.h/L with Test and Reference, and PE and 90%CI of Test/Reference ratio were 0.98 and 0.92, 1.04. Mean ± SD INR was 1.45 ± 0.10 following warfarin alone (phase A) and 1.51 ± 0.25 following warfarin combined with ESL (phase B). Following discontinuation of ESL administration (phase C), a slight INR decrease of −5.42% was found (90% CI of −8.85, −1.98).

Conclusion: Following ESL administration, a small although statistically significant decrease in systemic exposure to S-warfarin was found. However, R-warfarin pharmacokinetics and the INR were not affected.

p568

PHARMACOKINETICS OF ESLICARBAZEPINE ACETATE (BIA 2-093) USING A CHIRAL METHOD

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Purpose: Pharmacokinetic studies showed that eslicarbazepine acetate (ESL) is rapidly and extensively metabolised to the active metabolites eslicarbazepine (S-licarbazepine) and R-licarbazepine. However, a non-chiral drug plasma assay method was used in most studies with ESL; the nonchiral method does not distinguish between S-licarbazepine (eslicarbazepine) and R-licarbazepine, and the mixture has been reported as BIA 2-005. In this study, a chiral method for plasma drug assay was used, allowing us to distinguish between eslicarbazepine and R-licarbazepine.

Method: Open-label administration of ESL 900 mg single-dose (n = 12) and 900 mg once-daily for 8 days (n = 11) to healthy volunteers.

Results: Following ESL 900 mg single-dose, plasma eslicarbazepine and R-licarbazepine mean C_{max} was respectively 15.7 ± 3.8 μg/mL and 0.4 ± 0.1 μg/mL and mean $AUC_{0-\infty}$ was respectively 301.7 ± 63.9 μg.h/mL and 16.8 ± 3.6 μg.h/mL. Median t_{max} occurred at 3 h for eslicarbazepine and 15 h for R-licarbazepine. Following the last dose of a 8-day ESL 900 mg once-daily regimen, plasma eslicarbazepine and R-licarbazepine mean C_{max} was respectively 22.2 ± 7.3 μg/mL and 0.7 ± 0.2 μg/mL and mean $AUC_{0-\infty}$ was respectively 389.3 ± 97.3 μg.h/mL and 24.0 ± 24.0 μg.h/mL. Median t_{max} occurred at 3 h for eslicarbazepine and 10 h for R-licarbazepine.

Conclusion: Following single-dose and repeated dose oral administration, ESL was rapidly and extensively metabolised to the active metabolites eslicarbazepine (S-licarbazepine) and R-licarbazepine. Eslicarbazepine was the major metabolite, representing about 95% of drug systemic exposure. Supported by BIAL (Portela & C[a] SA).

p569

TIAGABINE ADMINISTRATION FOR TRIGEMINAL AND GLOSSOPHARYNGEAL NEURALGIA: PRELIMINARY RESULTS

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Purpose: The authors present a group of TN and GPN patients treated with tiagabine. Safety and efficacy of the treatment were evaluated.

Method: Nine neuralgia patients (6 male, 3 female), aged 36–77 (mean 54) were treated with tiagabine. Seven patients had TN and two GPN. All patients had previously been treated with the first choice antiepileptic drugs with no improvement. Tiagabine was administered: 5 mg/d for 7 days and increased to 15 mg/d for 21 days. Dose was then adjusted according to efficacy/tolerability up to a maximum of 30 mg/d. Treatment lasted from 1 to 8 months. The effect was assessed by visual analog scale (VAS).

Results: of the 9 patients enrolled, 4 patients with TN and 2 patients with GPN reported improvement; VAS pain reduction by 5 points or more. Noticeable tiagabine analgesic effect appeared from 2 to 6 weeks of treatment (mean 28 days). Effective daily dosage of tiagabine varied from 15 to 30 mg (mean 20 mg). One patient reported minor improvement by two points in VAS with minor side effect and the treatment was discontinued. Two patients did not report any improvement after 4 weeks and the treatment was discontinued. Tiagabine therapy was well tolerated. Three patients complained of minor sleepiness. One patient complained of nausea.

Conclusion: These preliminary findings suggest that tiagabine treatment of TN and GPN in a selected group of patients is effective and safe.

p570

ESTIMATION OF EFFICACY AND TOLERABILITY OF CARBAMAZEPINE AND VALPROIC ACID IN TREATMENT OF PARTIAL EPILEPSY IN CHILDREN: A PRELIMINARY STUDY

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Purpose: To estimate the efficacy of carbamazepine and valproic acid in the treatment of partial epilepsy in children with seizures of various aetiology (cryptogenic and symptomatic) and different clinical symptomatology. Side effects analysis was also performed.

Method: Fifty-four children aged from 14 months to 17 years with diagnosed (based on clinical and electroencephalographic criteria) focal epilepsy were analysed. For all children the first chosen and used drug was CBZ or VPA. We divided them into two groups: I–initially treated with CBZ and II–initially treated with VPA.

Results: Generally, efficacy of pharmacotherapy in the two analysed groups was similar. Positive results of treatment were observed in 31.5% of patients treated with CBZ and 27.4% treated with VPA. Disturbances in lipid metabolism were noted in some children treated with CBZ. Mild decreasing of red and white blood cells and increasing of transaminase level were found in the VPA group. In a few cases in both investigated groups the disturbances of thyroid gland hormones and concentration of immunoglobulins IgA and IgG were also present.

Conclusion: The efficacy of CBZ and VPA in treatment of partial epilepsy in children is similar. The use of both drugs may cause side effects but their type is different

Tuesday July 4, 2006
13:30–15:00
Poster Session 2
Neuroimaging

p571

REGIONAL DIFFERENCES IN HIPPOCAMPAL (*R*)-[^{11}C]VERAPAMIL DISTRIBUTION IN PATIENTS WITH MEDICALLY REFRACTORY TEMPORAL LOBE EPILEPSY

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Purpose: The radiolabelled P-glycoprotein (P-gp) substrate (*R*)-[^{11}C]verapamil has been developed as a probe for in vivo evaluation of P-gp function at the human blood–brain barrier with positron emission tomography (PET). Since P-gp is discussed as being implicated in pharmacoresistance in epilepsy patients, we studied brain (*R*)-[^{11}C]verapamil distribution in patients ($n = 6$) with medically refractory temporal lobe epilepsy.

Method: After i.v. bolus injection of about 400 MBq of (*R*)-[^{11}C]verapamil (specific activity: >20 GBq/μmol) dynamic brain PET imaging and arterial blood sampling was performed for 60 min. Regions of interest comprising the epileptogenic focus and the contralateral hippocampal area were outlined in MRI-coregistered PET scans. Data were modelled by a standard 1-tissue compartment model using a metabolite-corrected arterial input function.

Results: Focal (*R*)-[^{11}C]verapamil influx and efflux rate constants (K_1 and k_2) were significantly increased compared with control regions ($p < .05$; *t*-test for dependent samples) with differences ranging from $+7\%$ to $+108\%$ and $+6\%$ to $+71\%$ for K_1 and k_2, respectively. No significant differences were observed for focal and non-focal (*R*)-[^{11}C]verapamil distribution volumes.

Conclusion: Our preliminary data point to a locally increased P-gp activity in the epileptogenic area which might lead to increased brain elimination of antiepileptic drugs and thus explain refractoriness to antiepileptic drugs. Our method could allow non-invasive in vivo assessment of the mechanisms underlying medically refractory epilepsy.

p572

POSTSURGICAL fMRI ASSESSMENT OF TEMPORAL LOBE EPILEPSY (TLE): A CASE STUDY

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Purpose: We used fMRI to investigate temporal lobe activation in a TLE patient after temporal lobe resection where the anterior part of the left temporal lobe was removed, including most of hippocampus. Preoperative IAT indicated intact bilateral memory functions, and neuropsychological assessment showed that figurative memory functions were intact. We were interested in functional activation after resection; in particular if any correlates corresponding to processing of novel pictures (as compared to learned pictures) were evident in the left temporal lobe

Method: Preoperative neuropsychological results were compared with postoperative results, in order to evaluate changes in figurative memory function. fMRI activation was analysed with focus on ROIs within the temporal lobe. We anatomically defined ROIs including anterior hippocampus, posterior hippocampus, amygdala and parahippocampal gyrus and looked for differential activation between novel and repeated pictures. Novel pictures (50%) and repeated (and prelearned) pictures were presented in a variable block length design (180 pictures in total). Imaging was performed with a 1.5 Tesla scanner, and data were analysed using SPM2.

Results: An area close to the anterior left hippocampus showed higher activation ($p = 0.01$) for novel than repeated pictures. This activation was located just outside the surgical area. No other ROIs (left or right) showed significant activation at the $p = 0.001$ level.

Conclusion: Higher activation in the left area (close to the surgical area) than in the right area, raise the possibility that some functional ability, i.e., processing novel pictures, is overtaken by surrounding areas after resection, and perhaps the peak is amplified since the functionality is confined to a smaller area in the left temporal lobe due to surgery.

p573

PROEPILEPTOGENIC EFFECTS OF HUMAN BLOOD–BRAIN BARRIER DISRUPTION

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Purpose: The cerebral vasculature is functionally impaired in an epileptic brain. Defects in glucose and drug transport, hypoperfusion and blood–brain barrier (BBB) leakage have all been described in the epileptic brain. We tested the possibility that acute cerebrovascular events could trigger motor seizures. We monitored the onset of behavioural seizures in a population of patients undergoing osmotic BBB disruption (BBBD) to treat primary CNS lymphoma.

Method: The procedure consists of the following steps: 1) Selective catheterisation of the carotid or vertebral artery. 2) Osmotic disruption of the BBB by infusing 25% mannitol in the previously catheterised artery. 3) Intrarterial infusion of antineoplastics in the disrupted circulation. 4) Termination of procedure and documentation of the degree of disruption by CT scan or serum S100B.

Results: Failure of the endothelial protection of the CNS lead to acute seizures occurring controlateral to the hemisphere where the blood-brain barrier was disrupted. Seizures occurred immediately after BBBD in 25% of procedures in spite of premedication with anaesthetic dosages of thiopental. There was no significant correlation of seizure occurrence with age, gender or tumour size/length of previous BBBD treatment. The only predictors of focal motor seizures were positive indices of blood-brain barrier disruption, namely radiological evaluation by contrast-enhanced CT scans or serum S100B.

Conclusion: The most parsimonious explanation of our findings is that BBBD leads to motor seizures even in absence of obvious predisposing serum factors, such as drugs (e.g., penicillin) or unbalanced electrolytes. This may be a mechanism of ictal-to-ictal transition or a trigger for post-traumatic seizures.

p574

STRUCTURAL MRI ANALYSIS OF PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY USING OPTIMISED VOXEL-BASED MORPHOMETRY

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Purpose: MRI scans of patients with idiopathic generalised epilepsy (IGE) are normal on visual inspection. Previous studies have shown large cerebral structure changes in patients with juvenile myoclonic epilepsy (JME). The purpose of this study was to analyse the MRI scans of patients with JME with a group of healthy controls with the optimised voxel-based morphometry (VBM) using the SPM2 software.

Method: We compared the MRI scans (1.5 Tesla, MP-RAGE) of 18 patients with JME with the scans of 31 healthy controls. The groups were matched for age, sex and education and the healthy subjects had no history of seizures and no history of IGE among first-degree relatives. We compared both groups as well as each patient with the group of healthy subjects using optimised VBM both with and without modulation.

Results: The VBM did not show any significant changes in grey matter between the group of patients and the healthy controls or between any single patient and the group of healthy controls.

Conclusion: Optimised VBM was unable to find significant grey matter abnormalities in patients with JME. This contradicts the results of previous studies using a different approach for grey/white matter segmentation, which had shown large mediofrontal grey matter abnormalities in patients with JME.

p575

DIFFUSE LANGUAGE PATHWAY ABNORMALITIES IN TEMPORAL LOBE EPILEPSY

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Purpose: Temporal lobe epilepsy (TLE) is associated with disrupted lateralisation of language function. Functional imaging studies have shown that there is increased atypical language dominance in left TLE patients. The structural abnormalities underlying this have not been demonstrated previously but may be important when planning anterior temporal lobe resection (ATLR).

Method: We performed language fMRI and MR tractography on 14 patients with unilateral TLE (7 left and 7 right) and 10 controls. Verb generation and reading comprehension paradigms were used to define functional regions which were then used to generate starting regions for tractography. MR-tractography was used to trace the white matter pathways underlying the language functions in both controls and patients.

Results: Controls and right TLE patients both had a left-lateralised pattern of language connections. Left TLE patients had reduced fronto-temporal connections in the left hemisphere and increased connections on the right, in comparison with both controls and right TLE patients. Significant interactions between group and hemisphere were observed between controls and left TLE, and between left and right TLE patients, characterised by reduced left-sided and increased right-sided connections in left TLE patients.

Conclusion: We have demonstrated widespread structural changes in language pathways in patients with unilateral TLE. The pattern of structural connections seen reflects the pattern of functional activation with less lateralised, more symmetrical connections in left TLE patients. This method, combining fMRI and tractography, offers a promising tool for studying the relationship between brain structure and function and may prove useful in predicting language deficits following ATLR.

p576

ICTAL SPECT USING ATTACHABLE AUTOMATIC RADIONUCLIDE INJECTING TECHNIQUE

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Purpose: Ictal SPECT is a valuable method in localising the ictal onset zone in presurgical candidates. Conventionally, radionuclide, such as ^{99m}Tc-HMPAO, is injected by medical personnel, which often results in a considerable time lag for many reasons. We developed an automatic device for radionuclide injection for reducing the interval between seizure onset and injection. Comparing the automatic injection method with the conventional method, we could evaluate the clinical usefulness of this device.

Method: The authors compared ictal SPECT patterns by an automatic injection technique with that by a conventional method in 95 patients who were admitted in our epilepsy monitoring unit from 1 January 2003. In 39 patients, the automatic injection technique was performed, and in 56 patients, the conventional technique was performed. First, we evaluated the time lag between seizure onset and injection. Second, we evaluated ictal SPECT patterns. If increased perfusion was limited to one hemisphere, we regarded it as a lateralised pattern. If increased perfusion was observed at one specific lobe, it was regarded as a localised pattern.

Results: The mean delay time was 13.1 ± 14.2 seconds in the automatic injection method, and 42.5 ± 25.4 seconds in the conventional way, respectively. A localised pattern was observed in 16 out of 39 patients in the automatic injection group, and 12 out of 56 patients in the conventional injection group ($p < 0.05$). In patients with extratemporal epilepsy, a localised pattern was observed in 7 out of 20 patients who were treated with the automatic injection device, and 2 out of 21 patients treated by the conventional method ($p < 0.05$). In the patients whose injection time was less than 10 seconds or duration of seizure was less than 20 seconds, the outcomes were not good.s

Conclusion: The attachable automatic radionuclide injection method is superior to the conventional way in reducing the time delay at radionuclide injection, and also, more helpful in localising the ictal onset area in partial epilepsy, especially in extratemporal epilepsy. However, an injection too early could result in poor lateralisation and localisation.

p577
TEMPORAL LOBE EPILEPSY, CORRELATION ANALYSIS OF MRI VOLUMETRY, 1H MRS AND PET
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Purpose: To discuss the aetiology of temporal lobe epilepsy (TLE) and the mechanism of ^{1}H MRS and PET abnormality by correlation analysis of MRI volumetry, ^{1}H MRS and PET results of 20 patients.

Method: 20 patients with intractable TLE (hippocampal sclerosis) verified by operation and pathology were studied. MRI volumetry, ^{1}H MRS and PET were performed before operating. The asymmetry index (AI) of hippocampal volume of both sides, AI of NAA/(Cr+Cho) ratio and AI of glucose metabolism of both temporal lobes were calculated. Correlation analysis was made respectively.

Results: The AI of hippocampal volume of 20 patients was $-27.14\% \pm 24\%$ (7.73% -71.81%). The AI of NAA/(Cr+Cho) ratio was $-19.45\% \pm 10.37\%$ (3.08% -41.86%). The AI of glucose metabolism of the medial temporal region was volume, respectively ($r = 0.50$, $p = 0.029$; $r = 0.56$, $p = 0.011$).

Conclusion: MRI volumetry, ^{1}H MRS and PET are different methods to evaluate TLE. They reflect the structural abnormality, pathophysiology and metabolic changes of the brain, respectively. The correlation of them helps to understand the aetiology of TLE and the mechanism of ^{1}H MRS and PET abnormality.

p578
PRESENTATION OF A NEW METHOD FOR AUTOMATIC CURVILINEAR REFORMATTING OF 3D MRI
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Purpose: Curvilinear reformatting of three-dimensional MRI data (i.e., creating serial convex planes parallel to the cortical surface; Bastos et al., Ann Neurol. 1999;46:88–94) is a well-established tool which improves the display of the gyral structure, permits a precise localisation of lesions, and helps to identify subtle abnormalities difficult to detect in planar slices due to the brain's complex convolutional pattern. However, the method is time-consuming because it requires interactive manual delineation of the brain surface contour. We present a novel technique for automatic curvilinear reformatting.

Method: A T_1-weighted MRI volume data set is normalised using SPM2. Due to the normalisation to a common stereotactic space, predefined masks can be applied to cover skull and outer brain regions in different depths from the brain surface. Thereby, the outer brain regions are subsequently removed in 2 mm slices parallel to the brain surface like onion skins. The serial convex planes enclosing the residual inner part of the brain are presented 3-dimensionally using the "Volume Rendering Tool"' of MRIcro software. If necessary (e.g., for intraoperative navigation), the normalised data can be easily transferred to the original stereotactic space.

Results: Compared to cross-sectional images, curvilinear reformatting offers a markedly superior visualisation of topographic relations between lesions and cortical structures and helps to assess the lesions' extent. In addition, the possibility of different view angles improves planning of operations.

Conclusion: We present a new method for curvilinear reformatting which is automated by a batch script, requires no manual input and is based on freely available software.

p579
TRACTOGRAPHY OF OPTIC RADIATION AFTER TEMPORAL LOBE RESECTION
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Purpose: To investigate whether damage to optic radiation, as studied by diffusion tensor imaging and tractography, correlates with visual field defects after temporal lobe resection.

Method: Two patients with temporal lobe resections for temporal lobe epilepsy with normal preoperative perimetry were included. Patient A had an anterolateral temporal lobe resection and patient B had a posterior temporal lobe resection. Postoperative diffusion-tensor imaging (DTI) data was acquired using a Philips Intera 1.5T MR system (Release 9, HARDI, singleshot EPI, TE 76 ms, nearly isotropic 2mm voxels, 15 diffusion-sensitising gradient directions, b-factor 900 s/mm^2, Philips, The Netherlands). Fibre tracking was performed using the DTI tool in the PRIDE research software (Philips, The Netherlands). Regions of interest were set anterior to the lateral geniculate body. Damage to the tracked fibres was compared to postoperative perimetry results.

Results: Both patients developed a partial contralateral upper quadrantanopia. Damage to the optic radiation, affecting Meyer's loop, could be clearly demonstrated in patient A. In patient B tractography showed only minor damage to the anterior part of the optic radiation, whereas the posterior part of the optic radiation was affected.

Conclusion: Diffusion tensor imaging and fibre tracking can be used to show damage to optic radiation after temporal lobe resection. The correlation of visual field defects and damage to tractography-demonstrated fibres needs to be further evaluated.

p580
SLOW-WAVE DIPOLE DENSITY LOCALISATIONS IN MAGNETOENCEPHALOGRAPHY (MEG) ARE NEARBY MEG-SPIKE LOCALISATIONS IN PATIENTS WITH FOCAL EPILEPSY
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Purpose: Magnetoencephalographic localisation of interictal epileptiform activity is clinically used to search for epileptogenic focus. In epilepsy diagnostic routine it is known that the occurrence of slow wave activity can be an indicator for local functional disturbance or a lesion (Binnie CD, Stefan H, *Clin Neurophysiology* 1999;110(10):1671–97). The aim of the study is to examine whether in patients with monofocal epilepsy, localisation results based on slow wave (2 to 6 Hz) dipole density calculations are spatially correlated to spike localisation results.

Method: Spontaneous MEG was recorded in 11 patients with focal epilepsy and 5 healthy subjects. Spike source localisation was performed in accordance to the protocol of our lab. Analysis of slow-wave activity consisted of filtering, principal component analysis, single dipole fit and dipole density calculation. Voxels of 1 millilitre with clearly increased number of dipoles were displayed on MR-images together with spike localisations.

Results: In all patients, a local increase of slow wave dipole density was obtained. Spike area and regions of increased slow wave dipole density showed a small partial overlap and were close to each other. The distances between the centre of mass of spike activity and dipole density maxima were in the range from 0.8 to 3.8 cm. Five healthy subjects didn't show a significant increase in slow wave dipole density. Cutoff criteria to separate patient's data from those of healthy subjects was discussed.

Conclusion: This study indicates that evaluation of slow wave dipole density might be helpful to provide additional information leading to the epileptogenic zone in patients with focal epilepsy.

p581
CORRELATION BETWEEN INTERICTAL ACTIVITY IN EEG, SEIZURES AND METABOLIC ALTERATIONS IN 1H-MR SPECTROSCOPY
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Purpose: In our study the degree of hippocampal metabolite alterations in ^{1}H-MR Spectroscopy (^{1}H-MRS) was correlated to findings

of intensive video-EEG monitoring and duration of clinical features in patients with temporal lobe epilepsy (TLE).

Method: Hippocampal structures of 14 patients diagnosed with mesial TLE by clinical patterns and intensive video EEG monitoring were investigated by ^{1}H-MRS at 1.5 T. Post processing was carried out using the LCModel. Seizures were analysed by number of clinical seizures, duration of clinical symptoms, frequency of interictal epileptiform discharges (IEDs) and ictal activity, duration of ictal activity and IEDs occurring within 24h EEG monitoring. Results were correlated to metabolite alterations in ^{1}H-MRS.

Results: Negative correlation was found between tNAA values and degree of IEDs ($p = 0.048$). Duration of clinical features registered by video monitoring correlated to increased Cr levels ($p = 0.013$). Neither degree of ictal discharges in EEG nor duration of ictal patterns in EEG monitoring correlated to metabolite alterations. No correlation was found between metabolite alterations and average number of seizures/24h, duration since last seizure, and seizure frequency under antiepileptic therapy before admission to hospital.

Conclusion: Our study supports that ^{1}H-MRS is able to refer severity of TLE in which tNAA reduction, indicating neuronal dysfunction, is correlated with degree of interictal spiking in EEG. Correlation between duration of clinical symptoms and increased Cr levels are probably based on increased energy turnover during seizure activity in which Cr plays an important role in transfer of the phosphate group. The question of how epileptic activity in EEG is related to metabolic dysfunction remains still unclear.

p582

USEFULNESS OF MEG IN EPILEPSY PATIENTS

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Purpose: Evaluate the usefulness of magnetoencephalography (MEG) in epilepsy patients (EP) beyond surgical candidates.

Method: 79 MEG have been carried out on EP assigning them to different groups: Group 1: 12 patients with generalised epilepsy (GE), normal EEG and without seizures that show EEG anomalies and seizures once treatment is withdrawn. Group 2: 9 patients without diagnosis with some GE not close in time and normal EEG. Group 3: 23 neocortical drug resistant patients with a difficult to detect focus. Group 4: 35 temporal lobe EP in whom it was necessary to determine lateralisation using language and memory tasks.

Results: 58.3% of patients of Group 1 showed some generalised spike-waves for which medication was not withdrawn. In 77.7% of patients of Group 2 MEG showed epileptiform activity not present in the EEG. In 43.47% of Group 3 MEG localised a congruent focus that made intervention possible, and the other 56.52% were controlled with medication. In Group 4, MEG gave results about lateralisation and 54.29% were successfully operated.

Conclusion: MEG is new technique that in epilepsy has been used specially for presurgical studies. Nevertheless its contribution is still major, since: a) it contributes to the clinical decision whether or not to withdraw medication in EP with a normal EEG and without seizures; b) facilitates diagnosis and treatment of those patients with seizures and normal EEG; c) it is more sensitive for detecting extratemporal epilepsy focus; d) using neuropsychological tasks MEG determines lateralisation on temporal lobe EP. For these reasons we think MEG should be part of the normal protocol to study EP.

p583

WHITE MATTER ABNORMALITIES IN SCLEROSIS TUBEROUS COMPLEX: AN UNDERDIAGNOSED "MINOR" CRITERION?

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Purpose: Neuroimaging studies of tuberous sclerosis complex (TSC) have previously focused mainly on tubers or subependymal nodules. Subtle pathological changes occur as white matter abnormalities in the structure of the brain have not been focused. We utilised MRI techniques for a reliable study of brain structure to reach an accurate computation of brain abnormalities in patients with TSC.

Method: Dual-echo, FLAIR and IR MRI data were acquired from 28 TSC patients with a cognitive level ranging from mild to severe. Differences in grey matter and white matter abnormalities were estimated at each intracerebral voxel. FLAIR images were acquired for neuroradiological rating of tuber number.

Results: We also found significant alteration of white matter as stripes and candle guttering excrescences of groups of atypical cells perpendicular to the ventricular wall 21 of 28 TSC affected patients involving major intrahemispheric tracts and a bilateral cerebellar region. Furthermore, the white matter abnormalities are not related to the tubers.

Conclusion: Neuropathological changes of white matter associated with TSC may be more extensive than prior suspected and it could be an underdiagnosed "minor" criteria.

p584

COMBINING ADVANCED NEUROIMAGING TECHNIQUES IN PRESURGICAL WORKUP OF NONLESIONAL INTRACTABLE EPILEPSY

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Purpose: The rationale for this case report is to assess the degree of congruency between the results of several advanced functional, metabolic, and structural neuroimaging techniques used in patients with MRI-negative focal epilepsy.

Method: We investigated the presurgical evaluation and operative outcome of a patient with intractable extratemporal epilepsy. Because of the simple induction of habitual seizures in this patient, six advanced neurodiagnostic techniques were successively applied (SISCOM, ictal FDG-PET, ictal fMRI, postictal diffusion-weighted imaging, voxel-based morphometry, and MRS imaging).

Results: Fairly congruent findings of the investigated neuroimaging methods within the left central region were obtained from our patient. Subsequent invasive EEG recordings revealed a seizure-onset zone at the site where most of the neuroimaging had shown abnormal findings. Surgical removal of the epileptogenic zone, as defined by concordant neuroimaging and SEEG data, resulted in a seizure-free postoperative outcome. Histopathological findings revealed mild focal cortical dysplasia.

Conclusion: Great efforts should be made to combine most of the advanced neuroimaging methods in the preoperative assessment of nonlesional epilepsy surgery candidates.

p585

VISUALISATION OF SEIZURE SPREAD INCLUDING ACTIVATION AND DEACTIVATION BY ICTAL FMRI

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Purpose: The aim of the study was to visualise the spread of activation and deactivation in the whole brain during epileptic seizures by means of functional MRI.

Method: An optimised EPI based 2D sequence was applied to yield functional MR images during a clonic seizure of a 19-year-old woman suffering from intractable localisation related epilepsy. Temporal resolution (repetition time) was 2.5 seconds and spatial resolution (voxel size) was $3 \times 3 \times 5$mm. The whole brain was divided into 16 slices and cross correlation function was used to compare the MR signal alterations in each voxel.

Results: The seizure onset appeared to be in the left insular region 40 seconds before the first ictal clinical signs. The activation showed regional spread, then involved the whole ipsilateral hemisphere and propagated to the contralateral frontal and temporal lobes as well as to the cerebellum. Clinical signs of seizure consisting of right-sided facial cloni appeared at the time of the ipsilateral spread. Perifocal and contralateral deactivation were also observed.

Conclusion: To our knowledge this is the first study that describes a whole brain activity during epileptic seizures under acceptable temporal and good spatial resolution. Our observations can help understand the pathophysiology of the seizure-activity and antiseizure inhibition process. Moreover, the identification of the seizure-onset area can be crucial for presurgical evaluation of epilepsy.

p586

EPIGAUSS: ANALYSING SPATIOTEMPORAL PATTERNS IN OCCIPITAL EPILEPSY

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Purpose: EpiGauss is a method to characterise active brain generators in space and time through single dipole model analysis over EEG events. We applied it to study epileptogenic activity in 6 patients with early onset childhood occipital lobe epilepsy, an epileptic syndrome where children have a consistent clinical picture but multifocal and variable spike activity and for which no clearly defined common epileptogenic brain area has been established.

Method: EEG was acquired (10–20 with occipital coverage) and spikes manually identified. For each spike, single moving dipoles were fitted using a standard headmodel during an interval enclosing the spike onset phase to the highest EEG power latency nearer the spike peak. Resulting dipoles were analysed through dipole density distributions and analysis of dipole agglomerations using a cluster analysis method based on Gaussian Mixture Model (Harris et al., *J Neurophysiol* 2000,84:401-14) where dipole time related information was discarded. Stable sources and inter cluster propagation patterns were identified through the analysis of both cluster time structure and their spatial relation. The findings were coregistered with standard MRI and compared with an expert EEG visual analysis.

Results: Three patients exhibited clear focal activity in EEG while others were multifocal. EpiGauss demonstrated different clusters of dipoles, with a common area in the most posterior occipital lobes suggesting that epileptic activity originates in this region and then spreads to other areas (parietal and temporal).

Conclusion: EpiGauss identified consistent sources on the posterior occipital lobes not clear in EEG visual inspection. The method is automatic needing minor user intervention and no technical expertise.

p587

USING INDEPENDENT COMPONENT ANALYSIS IN SIMULTANEOUS EEG/fMRI FOR IDENTIFICATION AND LOCALISATION OF INTERICTAL SLOW BRAIN ACTIVITY

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Purpose: The different methods for examination of functional brain activity provide several advantages and disadvantages. The most outstanding feature of EEG is its excellent temporal resolution while fMRI offers a high spatial resolution. The combination of these aspects promises an improved measurement of ongoing brain activity. Since the first combination of EEG and fMRI in 1993 several aspects of the EEG like frequency-ranges, sleep stages or epileptic spikes have been shown to elicit a corresponding BOLD-response. For epilepsy patients the examination of epileptic activity was mainly focused on spike like activity (ictal and interictal). Interictal epileptic activity also comprises slow potentials like delta and theta activity. The purpose of the present study is to identify and locate interictal slow brain activity in epilepsy patients by an ICA based approach to EEG data in combination with fMRI.

Method: A 62 channel EEG was recorded simultaneously with the functional MR (3 T). Patients were instructed to open and to close their eyes every 30 seconds. The gradient related artefacts and the ballistocardiogram were removed offline. An extended ICA was applied to the EEG data to extract the components rendering the slow brain activity. The components carrying the slow brain activity were then used as a regressor for fMRI-activation.

Results and Conclusion: One advantage of ICA is that it uses the whole EEG-topography and delivers the time-course of activity of independent sources. Results show that it is possible to show brain activation associated with interictal slow brain activity.

p588

MULTIPLE INTRACRANIAL RING ENHANCING CT LESIONS IN PATIENTS WITH NEW-ONSET SEIZURES

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Purpose: Single enhancing CT lesions are the commonest imaging finding in children and young Indian patients with new-onset seizures. In the majority these spontaneously disappearing lesions are cysticercal granuloma. The precise causes of multiple intracranial ring enhancing CT lesions are not known. In this study an effort was made to determine the aetiology with the help of a battery of investigations.

Method: Sixty patients with multiple ring enhancing lesions on CT scan were included. Routine blood biochemical parameters, ELISA for HIV, tuberculosis, and cysticercosis, and chest x-ray were performed. In addition, magnetic resonance imaging, MR spectroscopy, lumbar puncture, abdominal ultrasonography was carried out. Treatment was initiated based on the provisional diagnosis. Patients were followed for six months. Repeat neuroimaging study was done after 6 months.

Results: Among 60 patients, diagnosis was established in 55 while in 5 patients no conclusion could be made regarding final diagnosis. Tuberculoma was the leading cause of multiple ring enhancing lesions in 27 patients followed by neurocysticercosis in 15 patients and metastatic lesions in 9 patients. Of the remaining 4 patients pyogenic brain abscess, fungal granuloma, multiple infarcts and primary brain tumour were the causes. In the children and adolescent age group (<18 years), tuberculoma and neurocysticercosis had an equal incidence. In the adult age group (18–45 years), tuberculoma was the most common cause while in the older age group (>45 years) metastasis was the leading cause.

Conclusion: In contrast to single enhancing CT lesions, tuberculoma is the leading cause of multiple intracranial ring enhancing lesions followed by neurocysticercosis. Metastatic lesions predominate among elderly individuals.

p589

SINGLE SMALL ENHANCING CT BRAIN LESION IN MIDDLE AGED AND ELDERLY PATIENTS WITH NEW-ONSET SEIZURES

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Purpose: Single enhancing CT lesions are the commonest imaging finding in children and young Indian patients with new-onset seizures. In the majority these lesions are cysticercal granuloma and in a few they are caused by tuberculoma. In middle-aged and elderly the causes of single enhancing CT lesions are not known. In this study an effort was made to determine the aetiology of these lesions with the help of a battery of investigations.

Method: Nineteen patients age 45 years or more with a single enhancing CT lesion of size less than or equal to 20 mm were included. The battery of tests employed included routine blood biochemical and haematological parameters along with CSF examination, serum ELISA for HIV, neurocysticercosis and tuberculosis, chest x-ray and ultrasound abdomen. Antiepileptic drugs were administered. Treatment was also given according to the provisional diagnosis. Each patient was followed for 6 months. A repeat CT brain was done after 6-months.

Results: The mean age of patients was 53.4 years (range 45–78). There were 7 female patients in the series. Fifteen patients were diagnosed with neurocysticercosis; in all these patients lesions had spontaneously disappeared. Two patients had tuberculoma of brain and 1 had secondaries in the brain. In 1 patient a diagnosis could not be reached.

Conclusion: Like in younger patients, in most of the older and elderly patients single enhancing CT lesions are caused by neurocysticercosis. Occasionally there may be tuberculoma and metastasis of the brain as well.

p590

AUTOMATIC IMAGE PROCESSING SYSTEM FOR QUANTIFYING DIFFERENCES BETWEEN ICTAL/INTERICTAL BRAIN SPET SCANS AND REGISTRATION WITH MRI

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Purpose: Cerebral ictal/interictal single photon emission tomography (SPET), in patients with partial epilepsy refractory to medical therapy, constitutes an important aid in the localisation of the epileptogenic focus. This analysis can be improved calculating the statistically significant differences obtained by regression analysis (SSDORA) between the ictal/interictal SPET scans and visualising these results overlapped on the magnetic resonance (MRI). The aim of this work was the implementation of an automatic image processing system that calculates the SSDORA 3D map and aligns SPET datasets with MRI.

Method: This system was implemented on Linux, using bash scripts. The following software packages were used: MedCon (http://xmedcon.sourceforge.net), ImageJ (http://rsb.info.nih.gov/ij/), DCMTK (http://dicom.offis.de/dcmtk.php.en), AIR (http://bishopw.loni.ucla.edu/AIR5/) and CISG (http://www.ipg.umds.ac.uk/cisg/); all with free access and with open source; some of these packages were slightly modified. The methodology can be summarised in the following steps: 1) SPET's acquisition in 128 × 128 matrix, with 2mm pixel size; 2) SPET's reconstruction by iterative OSEM, without attenuation correction, with 3D Butterworth postfilter; 3) coregistration (AIR) between ictal/interictal SPET scans; 4) datasets obtained in last step are processed using a new Image plugin (SSDORA); 5) interictal/MRI registration (AIR/CISG); the same transformation matrix is applied to ictal and SSDORA 3D map.

Results: After this automatic processing the 3D map and the ictal/interictal SPET are aligned with MRI. All datasets are ready for visualisation in image processing stations of the nuclear medicine and/or neurology departments.

Conclusion: An automatic image processing system was implemented that allows getting the statistically significant differences between the ictal/interictal SPET aligned with MRI.

p591

DIAGNOSTIC USEFULNESS OF A QUANTIFICATION METHOD TO ASSESS DIFFERENCES IN ICTAL-INTERICTAL BRAIN SPET: COMPARISON TO SIDE-BY-SIDE VISUAL EVALUATION, MRI AND VIDEO-EEG

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Purpose: To compare results of an ictal/interictal SPET (single photon emission tomography) image difference method with side-by-side visual SPET analysis, MRI (magnetic resonance imaging) and video-EEG (video-electroencephalogram), for localisation of an epileptogenic focus in patients with partial epilepsy refractory to medical therapy.

Method: Ictal and interictal SPET of 41 patients, mean age 30 years, were retrospectively reconstructed. A new software, SSDORA (statistically significant differences obtained by regression analysis), was developed for SPET comparison. SSDORA images were blindly reviewed and results compared to SPET, video-EEG and MRI. Coregistration of SSDORA to MRI was performed.

Results: The mean latency period of the injection after seizure onset was 44.1s (7-75s). From the total, 66% of SPET results were concordant for localisation of an epileptogenic area, relative to other techniques. SSDORA was concordant to other diagnostic modalities in 83%. 50% of not concordant SPET were not localising / lateralising and SSDORA was localising and concordant in 57% of negative SPET. MRI and video-EEG were concordant in 63% between themselves and SPET was concordant with 81% of them. Of this group, SSDORA was concordant with 88%. In the group where MRI and video-EEG were not concordant (37%), SPET was concordant with one of the techniques in 40% and SSDORA was concordant in 73%.

Conclusion: SSDORA was concordant with other techniques in a higher proportion of cases then SPET visual analysis and was localising in some negative/not concordant SPET cases. Coregistration of SSDORA results with MRI was always useful in anatomic localisation of the epileptogenic focus.

p592

ICTAL HAEMODYNAMIC CHANGES DURING ABSENCE SEIZURES IN IDIOPATHIC GENERALISED EPILEPSY

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Purpose: Recently EEG/fMRI has been proposed in the field of epilepsy research to detect brain regions activated during EEG epileptiform abnormalities. In recent years some studies have documented cortical and subcortical haemodynamic involvement during interictal and ictal generalised spike-and-wave discharges (GSWDs) confirming the significant role of thalamocortical interactions in the pathophysiology of idiopathic generalised epilepsy (IGE). By using EEG/fMRI we investigated the BOLD responses in the thalamus and cerebral cortex during absence seizures in patients with IGE.

Method: Using EEG/fMRI, we studied haemodynamic changes associated with spontaneous ictal GSWDs in 5 patients (2 M, 3 F) affected by IGE (childhood or juvenile absences epilepsy). fMRI images were acquired using a clinical 1.5 T magnet (Philips Gyroscan). The EEG signal was recorded using an MR-compatible system (Micromed, Italy). Absence seizures were retrospectively recognised on the EEG, and the number of the dynamic scan corresponding to each GSWD was recorded. fMRI data were preprocessed and analysed using SPM99.

Results: In all patients EEG/fMRI data analysis revealed a thalamic symmetrical positive BOLD response related to ictal generalised spike-and-wave discharges whereas no activation was found in cortical regions; concomitant deactivation areas were found in diffuse cortical regions (2 patients), in symmetrical frontal regions (2 cases) and in bilateral parietal-occipital regions (1 case).

Conclusion: Our fMRI findings confirm the role of the thalamus and its relationship with the cortex in absence seizures and offer a contribution to a better understanding of the mechanisms underlying epileptic phenomena.

p593

VOXEL-BASED MORPHOMETRY (VBM) IN UNILATERAL TEMPORAL LOBE EPILEPSY: NEURODEGENERATION BEYOND THE SEIZURE ONSET ZONE

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Purpose: Voxel-based morphometry (VBM) is an indirect volumetric tool which allows one to investigate the entire brain. Recent VBM studies were able to show hippocampal degeneration in TLE patients, however, there was also a marked extrahippocampal loss of brain volume.

Method: We applied an optimised VBM protocol on high resolution T_1 weighted MR-images of 47 patients (m:w = 22:25; mean age = 41 ± 13yrs) with unilateral temporal lobe epilepsy (TLE) in comparison to 94 age and gender matched healthy controls. 27 patients had left and 20 had right sided TLE. Age at onset was 14 ± 12 yrs. Diagnosis for unilateral TLE was confirmed by video-EEG-monitoring, MRI, interictal FDG-PET, and neuropsychology.

Results: VBM revealed a marked volume loss in the tail of the hippocampus at the site of seizure onset. Furthermore, left TLE patients showed marked volume loss ipsilateral in the gyrus parahippocampus, thalamus and prefrontal cortex; ipsi- and contralateral in the cingulum and cerebellar hemispheres. Right TLE patients had additional volume loss in the ipsilateral gyrus parahippocampus and bilateral volume loss in the prefrontal cortex, thalamus, as well as in the cerebellar hemispheres.

Conclusion: Our study confirms a widespread structural change in unilateral TLE ipsilateral to the side of seizure onset, which is far beyond the primary lesion and may probably reflect acquired neuronal damage due to repetitive seizure activity.

p594

MULTIFOCAL PERFUSION ABNORMALITY IN A PATIENT WITH MALIGNANT MIGRATING PARTIAL SEIZURES IN INFANCY

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Purpose: Malignant migrating partial seizures in infancy is a rare epileptic syndrome, described in 1995. It begins during early infancy and is characterised by very frequent, commonly continuous partial seizures of varying semiology. EEG is highly characteristic: ictal activity of high amplitude repetitive rhythmic discharges, jumping randomly from one cerebral region to the other during consecutive seizures, can be seen. Arrest of psychomotor development is the rule. Traditional antiepileptic drugs or steroids can hardly ever control the seizures, which is crucial for favourable further development of the infant. The cause is unknown; brain malformation, metabolic disorder, or an acquired cerebral insult could not be shown. In view of its strict age dependency, malignant migrating partial seizures in infancy are dependent on the special maturation of the infantile brain. Functional neuroimaging can be expected to shed some light on the pathomechanism of the unique electroclinical features of this epileptic syndrome.

Method: An ictal and a periictal brain perfusion investigation were performed by means of Tc99m-HMPAO SPECT in a patient with a typical course of malignant migrating partial seizures in infancy.

Results: The ictal study revealed hyperperfusion over the right frontal, and the periictal one a similar change over the right central and left frontal cerebral regions. These changes corresponded with the location of ictal discharges on scalp EEG.

Conclusion: These results argue against a possible deeply located single irritative focus spreading ictal discharges to brain surfaces at randomly migrating locations.

p595

COMPARISON OF BOLD SIGNAL CHANGES IN THE FRONTAL CORTEX AND THE HIPPOCAMPUS IN PATIENTS WITH MEDIAL TEMPORAL LOBE EPILEPSY

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Purpose: The goal of the present study is to compare the lateralisation of activation patterns within frontal language areas to those within the hippocampi (HC) during a verbal episodic memory task using fMRI.

Method: Twenty-five patients with symptomatic temporal lobe epilepsy and hippocampal sclerosis (HS) performed a verbal episodic memory task including encoding and recognition of word-pairs (12 HS left, M_{age} = 37 yrs, 14 males) within the scanner (1.5T). Data were analysed with SPM2, using 2 different regions of interest (ROI): (1) anterior language area defined as BA 44 and 45, and (2) a medial temporal ROI including the hippocampus. For individual activation patterns within the ROIs lateralisation indices [LI = R−L/R+L)] were calculated for the contrast "encoding vs control condition" using a number of suprathreshold voxels. The LI for the different anatomical areas were compared between the two groups (Mann-Whitney U Test).

Results: The lateralisation of frontal activation patterns showed an LI of −0.52 (SEM = 0.28) for the patients with left-sided and −0.63 (SEM = 0.15) for right-sided HS patients respectively (not significant), whereas the lateralisation indices within the hippocampus differed significantly between the groups (LI HS left = −0.14 (SEM = 0.20), LI HS right = −0.69 (SEM = 0.18), $p < .05$).

Conclusion: The deviating lateralisation of activation patterns within the hippocampus could be explained by a decrease of ipsilesional or increase of contralesional activations; the latter reflecting a shift of verbal memory functions to the contralesional hippocampus, whereas basic language functions are not reorganised.

p596

Z-SCORE TRANSFORMATION OF INDIVIDUAL VOXEL-INTENSITY-DISTRIBUTIONS IMPROVES DETECTION OF STRUCTURAL ABNORMALITIES IN MR-IMAGES

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Purpose: An important issue in epileptology is the detection of structural lesions in MRI images. In recent years automated, voxel-based techniques have been utilised to detect structural abnormalities in different MR sequences. These techniques usually rely on the comparison of individual patients with a healthy control group. The high variability between individual subjects greatly compromises the ability of such methods to detect subtle structural differences between patients and controls. In this study we use a renormalisation of individual distributions of voxel intensities by means of z-score transformation to improve the effectiveness of a voxel-based approach to detect hippocampal sclerosis with T2-Relaxation-Maps.

Method: We performed the acquisition of T2-Relaxation-Maps with a resolution of 1.5 × 1.5 × 5 mm in up to now 30 healthy subjects and 2 patients with hippocampal sclerosis. Images were segmented into gray and white matter. Voxelwise mean and standard-deviation (SD) was calculated from the original T2 values of 30 healthy subjects and were used to define thresholds to detect structural abnormalities. To improve this method, an additional processing step was introduced by renormalising all segmented images using z-score transformation prior to further processing.

Results: Final SD-images showed a much higher spatial variance if no z-score transformation was used, causing a substantial bias in the detection of exemplary patients with hippocampal sclerosis. Use of z-score transformation on the other hand improved detection of aberrant T2-Values.

Conclusion: Findings indicate that voxel-based techniques for an automated detection of individual abnormalities can be improved by renormalising individual distributions of signal-intensities.

Tuesday July 4, 2006
13:30–15:00
Poster Session 2
Neuropsychology

p597

TEMPORAL LOBE SURGERY AND SUSTAINED ATTENTION

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Purpose: Growing evidence suggests that the cerebral hemispheres are asymmetric in the role they play in sustained attention. Studies have suggested that parietal, temporal and prefrontal regions may be involved in the maintenance of a state of vigilance. The present study investigates the effect of left (LTL) vs. right temporal lobectomy (RTL) on a computerised vigilance task (part of the FePsy battery).

Method: The 188 subjects (86 LTL, 102 RTL) were tested before and 6 months after epilepsy surgery. They were presented with 450 stimuli in a signal detection paradigm, equally divided into "signal" (XXXXXXX) or "noise" (XXXAXXX). Duration of the stimuli was 100 msecs, Inter Stimulus Interval 4 secs. The task lasted for 30 minutes. Dependent variables were d' (perceptual sensitivity) as a measure of vigilance and ß (response bias, employing a lax or a conservative criterion).

Results: The LTL group showed a gain in d': before surgery of 2.05 (SD 0.94), and after of 2.17 (SD 1.15) whereas the RTL group showed a decline: 2.23 (SD 1.01) before and 2.03 (SD 0.98) after surgery. This interaction effect is significant, $p = .016$. No difference was found in betas in either group: LTL group 0.60 (SD .40) pre surgery vs. 0.69 (SD 0.49) post and the RTL group 0.63 (SD .54) pre vs. 0.66 (SD .54) post.

Conclusion: The RTL group cannot profit from a retest effect. These results suggest a strong involvement of the right temporal lobe in vigilance, i.e., sustained attention and the disruption of this mechanism after RTL.

p598

MESIAL TEMPORAL LOBE EPILEPSY IMPAIRS ADVANCED SOCIAL COGNITION

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Purpose: While memory, language and executive functions have been extensively studied in patients with mesial temporal lobe epilepsy (MTLE), investigations into advanced social cognitive abilities have been neglected. In the present study we investigated the ability to detect social faux pas and studied possible mediating clinical and demographic variables in patients with MTLE compared to patients with an epilepsy not originating within the MTLE and healthy controls.

Method: 27 MTLE patients (16 were investigated pre- and 11 postoperatively), 27 patients with an extra-mesiotemporal epilepsy (excluding frontal lobe epilepsy) and 8 healthy controls performed a shortened version of the Recognition of Faux Pas Test. Standardised tests to measure intelligence were administered. Only patients with intact reading comprehension abilities were included in the study.

Results: MTLE patients, both pre and postoperative, performed significantly worse in the faux pas test than patients with extra-mesiotemporal lobe epilepsy ($p < .001$) and healthy controls ($p < .001$). The latter two groups showed comparable performance. No statistical association was found between the MTLE patients' deficit in recognising a faux pas and the variables IQ, age, age at seizure onset, and duration of epilepsy. Although no sex differences in recognising a faux pas were found, an interaction effect between side of MTLE and sex was observed, favouring females with right-sided MTLE and males with left-sided MTLE ($p < 0.5$).

Conclusion: We report for the first time that patients with MTLE are specifically impaired in recognising faux pas, suggesting that MTLE as such is a specific aetiology of deficits in higher-order social cognition.

p599

LATERALISING ABILITY OF THE WECHSLER MEMORY SCALE-III IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY

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Purpose: The Wechsler Memory Scale-III (WMS-III) including new visual memory tests was developed to overcome the limitation of WMS-Revised (WMS-R). We examined the usefulness of the WMS-III in predicting laterality of memory impairment in patients with mesial temporal lobe epilepsy.

Method: We included 49 consecutive patients with unilateral mesial temporal lobe epilepsy who had left hemisphere dominance for language by WADA test and underwent temporal lobectomy. Methods of analysis included evaluation of group means on the various indices and subtest scores of WMS-III, the use of ROC curves, an examination of Auditory-Visual Index (AVI) discrepancy scores and correlation analysis between AVI discrepancy scores and age, and age of onset in patients.

Results: 1) Patients with left mesial temporal lobe epilepsy had significantly lower scores on several scores and indices compared to those with right mesial temporal lobe epilepsy. 2) Analysis of ROC curves showed the area under the curve and the suggested cutting score were 0.696 and 4 (a sensitivity 0.704, a specificity 0.727) for immediate AVI discrepancy score and 0.702 and 5 (a sensitivity 0.556, a specificity 0.773) for delayed one, respectively. 3) In the right lesion, there was a tendency for linear correlation between AVI discrepancy scores and age, onset age.

Conclusion: Overall, WMS-III has limited value in identifying particular memory deficits associated with either left or right temporal lobe dysfunction. AVI discrepancy scores may be more useful in predicting right hemispheric dysfunction rather than left hemispheric dysfunction.

p600

NONCONVULSIVE STATUS EPILEPTICUS: FRONTAL ASSESSMENT BATTERY DURING EEG AND IN FOLLOW-UP

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Purpose: The absence variant of nonconvulsive status epilepticus (NCSE) has been reported as the initial form of epilepsy in the elderly and it is mandatory to consider NCSE in the differential diagnosis for patients presenting an altered mental status or behavioural changes from baseline, even when there is no history of seizures. Cognitive impairment may be subtle, mild or severe. We report on 5 elderly patients with a neupsychological evaluation during critical EEG and in follow-up.

Method: Five consecutive elderly patients (mean $\pm$ SD; age 75 ± 13.6 years) meeting the criteria for NCSE with acute onset of subtle or mild cognitive deficits were studied with a brief mental status examination: Mini-Mental State Examination (MMSE), TIB, an Italian version of National Adult Reading Test (NART), Digit Span, Frontal Assessment Battery (FAB) during EEG showing prolonged spike and wave diffuse discharges and at follow-up. Neuroimaging excluded focal lesion.

Results: Evidence of acute, transient impairment of cognitive functions was found in all patients: in particular frontal system functions appeared impaired. The mean FAB score significantly differed between examination during NCSE and in follow-up (3.8 vs. 12.2).

Conclusion: Thomas et al. (*Neurology* 1999) stressed that NCSE of frontal origin is a heterogeneous syndrome and emphasised the similarities between NCSE of frontal origin and absence variants of NCSE. Our results with FAB in patients with generalised NCSE support the influence of EEG discharges on frontal cognitive functions and the difficulty of a close and sure topographic electroclinical correlation.

p601

THE IMPACT OF IN UTERO EXPOSURE TO ANTIEPILEPTIC DRUGS ON NEUROPSYCHOLOGICAL DEVELOPMENT: THE FIRST THREE YEARS

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Purpose: This study informs the debate on the impact of anti epileptic drugs (AEDs) in utero, specifically on neuropsychological development,

where previous research has been conflicting. The results of a follow up assessment at age 3 are reported for a prospective cohort of children.

Method: Interim analyses of 57 children (19 exposed and 38 age and gender matched controls) were blindly assessed using the Reynell Language Test and the Griffiths Developmental Scales. Each mother completed the National Adult Reading Test (NART) to measure intellectual functioning and the Vinelands Adaptive Behaviour Scales to document a subjective view of their child's development.

Results: Using an independent samples *t*-test analysis children exposed to AEDs yielded significantly lower scores on both language comprehension (m = exp 41.28 vs 50.63, p = 0.0195) and expression (m = exp 36.65 vs 46.61, p = 0.012). Exposed children also yielded a significantly lower performance across motor (m = exp 82.73 vs 108.76, p = <0.001), personal and social (m = exp 106.06 vs 121.97, p = 0.003), language (m = exp 97.00 vs 127.68, p = <0.001), hand and eye coordination (m = exp 86.63 vs 103.05, p = 0.001), performance (m = exp 94.35 vs 107.87, p = 0.001) and practical reasoning (m = exp 95.50 vs 115.05, p = 0.007) skills. No maternal IQ classification differences were found. No significant differences for reported developmental progress on the Vinelands were found with the exception of the motor domain.

Conclusion: The results suggest that prenatal exposure to AED's may be associated with developmental delay at 3 years of age. Further analysis at 6 years will identify the existence of specific drug effects for neurodevelopment.

p602

NATURAL HISTORY OF COGNITIVE IMPAIRMENT IN EPILEPSY: THE IMMEDIATE IMPACT OF TREATMENT

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Purpose: The neuropsychology arm of the SANAD trial provides a unique opportunity to assess: 1) The natural history of cognitive impairment in people with newly diagnosed epilepsy, prior to AED treatment; 2) The differing profiles of cognitive side effects with novel and standard AED treatment.

Method: In a prospective, randomised controlled trial, 257 newly diagnosed patients with epilepsy were assessed at baseline on an extensive battery of neuropsychological tests. Of those 204 were re-assessed after 3 months using the same measures.

Results: Interim analyses have shown that performance on a nondominant tapping task deteriorated after three months (50.58 ± 8.94 vs 49.56 ± 8.97, p = 0.047). Fewer words were recalled on the fifth trial and on both the immediate and delayed aspects of a verbal learning test (44.59 ± 9.37 vs 42.99 ± 10.25, p = 0.006; 8.51 ± 3.30 vs 7.87 ± 3.30, p = 0.002; 10.82 ± 2.35 vs 10.46 ± 2.62, p = 0.021). Motor speed decreased at three month follow up (44.60 ± 10.63 vs 43.20 ± 10.53, p = 0.015; 46.41 ± 11.12 vs 45.20 ± 10.85, p = 0.037). However, ratings of tension improved on the Profile of Mood Scale (44.84 ± 9.46 vs 42.82 ± 9.98, p = 0.004).

Conclusion: Preliminary analyses have revealed that patients with newly diagnosed epilepsy show reduced functioning in psychomotor speed and some aspects of memory and learning in the three months following diagnosis. This study provides a unique opportunity to understand the natural history of cognitive impairment and the impact of seizures and treatment.

p603

EFFECT OF OXCARBAMAZEPINE AND TOPIRAMATE ON COGNITIVE PERFORMANCE IN NEWLY DIAGNOSED EPILEPSY PATIENTS

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Purpose: To valuate possible changes in cognitive functioning in adults who take oxcarbamazepine (OXC) and topiramate (TPM) as monotherapy after 6 months of treatment.

Method: We evaluated 51 patients, 26 took TPM, 25 OXC and 1 received both. Each subject has a measure in our cognitive battery before and 6 months after starting their treatment. We assessed learning and memory (Test de Aprendizaje Verbal España-Complutense and delayed recall of Rey-Osterrieth Complex Figure Test (ROCFT)), executive function (direct digits, backwards digits, fluency tasks of animals and words beginning with F and trail making test), visuoconstruction (copy of ROCFT), naming (Aphasia Diagnostic Boston Test) and depression (Beck Depression Scale). Our hypothesis is that after 6 months there will be no important changes in cognitive performance in either group.

Results: In OXC group, 25 of 26 patients (1 had an allergic reaction) were finally evaluated and in TPM group 22 of 25 (3 washed out because of psychophysics alterations). We found after 6 months of OXC treatment a statistically important improvement in learning and verbal memory items (p < 0.05 in Mann-Whitney), more speed of processing (p = 0.014) and better naming (p = 0.004). In TPM group, we found there was better verbal recall but more perseverance (p = 0.032) and worse execution in executive test (direct digits (p = 0.05) and fluency tasks (p = 0.025) in words starting with F and p = 0.009 in animals)).

Conclusion: There was a soft worsening only in the TPM group in executive function but it didn't indicate a wash out of treatment or any impairment in the patient's life.

p604

IS THERE A COGNITIVE DECLINE IN PATIENTS WITH FOCAL EPILEPSY? A LONGITUDINAL STUDY

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Purpose: The aim of this study is to assess the possible cognitive alterations in epilepsy patients compared with controls over five years, and to investigate the clinical variables mainly implied in mental impairment.

Method: In our longitudinal single-centre study, 50 patients with focal epilepsy and 50 controls were administered the same battery of comprehensive neuropsychological tests at baseline and after five years.

Results: Epilepsy patients showed a significant impairment in attention compared with controls after five years, while the other cognitive domains did not exhibit any important changes. The worsening of attention was mainly related to the duration of epilepsy, the age at onset, a history of tonic-clonic seizures and a low educational level.

Conclusion: Our results could have important implications, considering the influence of attention on other cognitive functions, its impact on the quality of life and one's work status.

p605

TOPIRAMATE AND DEPAKINE EFFECTS ON COGNITIVE FUNCTIONS IN PATIENTS WITH FRONTAL LOBE EPILEPSY

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Purpose: The study was aimed to analyse the cognitive effects of the new antiepileptic drug topamax (TPM) in patients with symptomatic frontal lobe epilepsy (left and right-sided epileptic foci) manifested by focal seizures with secondary generalisation as compared with depakine (VPA) effect and control group.

Method: Three groups of epilepsy patients and a control group (healthy subjects of the same age) were administered neuropsychological and cognitive tests for attention, psychomotor speed, language, memory, and frontal lobe functions (Wisconsin Card Sorting Test), emotion conceptualization task (ECT), and others. The 1-d and 2-d groups included patients with symptomatic frontal lobe epilepsy with focal secondarily generalised seizures (left and right-sided foci, 79 and 74 subjects, respectively, mean age 24 years, S.D. 4.5). All patients had a medication change from DPA to TPM 1.5 ± 0.5 years ago, on average. They were free from seizures and had a medium TPM dosage of 200 mg/day. The patients of 3-d group had the same form of epilepsy and had long-term VPA therapy without withdrawal, mean DPA dosage of 400 mg/day (162 subjects, mean age 32.5 years, S.D. 6.5). The statistical intergroup comparisons were analysed (WinStat-7.0) for all tests in double-blind study.

Results: The statistically significant differences on measures of attention, digits backwards, speed performance, and frontal lobe associated

functions (WCST and ECT tests, etc.) were obtained for groups of patients and control. Higher scores in cognitive performance and tests for frontal lobe associated functions were obtained in 1 and 2 TPM groups as compared with the VPA group. Results demonstrate also the more distinct improvement ($p < 0.01$) in patients of the TPM-1 group with left-sided foci in frontal areas as compared the TPM-2 and DPA groups: in scores for temporal ordering, sorting of cards, synthesis, depression, estimation of emotions presented, planning and control functions, etc.

Conclusion: In symptomatic partial epilepsy with secondarily generalised seizures, VPA therapy displayed slight adverse cognitive effects in the majority of cognitive tests; 1 and 2 groups showed only mild negative effects in psychomotor speed (compared with the control group). Data obtained in the TPM-1 group demonstrated the positive alterations in the left frontal lobe associated functions (this may be explained by anticonvulsive, cerebroprotective, and activating psychotropic effects of TPM). The results help to elucidate the contradictory data concerning the cognitive effects of topamax.

p606

EXPERIENCE ABOUT COGNITIVE FUNCTIONING IN 161 EPILEPSY PATIENTS

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Purpose: To evaluate the number of epilepsy patients with cognitive difficulties and analyse the correspondence relating to the patients perception.

Method: 161 epilepsy patients were assessed with a neuropsychological battery including executive function skills, memory, attention and language tasks. All of them were asked before the examination about their difficulty with perception in daily life. We used these results as a measure of patient's consciousness of deficit. We also took into consideration other variables such as age of onset, frequency and treatment.

Results: The most frequent age of evaluation was between 18 and 50 years. Age of onset was early: 41.61% between 0–15 years, and 32.92% between 16–25 years. 68.94% have a frequency higher than one or more seizures a year, and 61.49% are on monotherapy. Although 90.68% show some kind of cognitive deficit, the personal perception is only 46.58%, specially referred to memory, denomination and concentration difficulties. Therefore, only 53.42% have a clear consciousness of deficit. However, these difficulties do not prevent a normal labouring life because 79.50% are working and only 4.35% receive any help for this handicap.

Conclusion: Although the percentage of epilepsy patients with cognitive dysfunction is high (90.68%), these difficulties are hardly seen, because 79.50% are capable of preserving a normal working life, in spite of recurrent seizures and antiepileptic drugs. This and the low percentage of patients with an adequate consciousness of deficit, justifies the relevance of neuropsychological assessments that detect possible deterioration produced by seizures and provide the patients with strategies to minimize the impact on daily life.

p607

EFFECTS OF LAMOTRIGINE AND OXCARBAZEPINE ON SEIZURES, COGNITION, MOOD AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH UNTREATED EPILEPSY

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Purpose: To compare the two novel antiepileptic drugs (AED) lamotrigine (LTG) and oxcarbazepine (OXC) as monotherapy in patients with untreated epilepsy regarding cognition, mood and health-related quality of life (HRQL).

Method: The prospective, open-label study comprised 48 untreated patients with epilepsy (26 men; 22 women, aged 15–61), who were randomly assigned to LTG ($N = 21$) or OXC ($N = 27$). Neuropsychological examination took place before titration and 6 months later and included tests on attention, word fluency, language comprehension, confrontational naming, short term and working memory as well as episodic memory. Questionnaires addressed depression and HRQL.

Results: Intention-to-treat analysis showed seizure freedom in 42.5% of the patients (8 LTG; 12 OXC); a further 10.6% had a significant seizure reduction (greater than 50% or only simple seizures remaining) (2 LTG; 3 OXC). Twenty five patients (52.1%) completed follow-up (10 LTG; 15 OXC). Both groups showed improvement in verbal learning and in one out of four measures of attention. In addition, patients under OXC improved in word fluency. Improved mood was reported with OXC only.

Conclusion: Seizure reduction was seen in 53.2% of the patients with comparable outcomes for both groups. Consistent with previous findings, the results indicate unchanged if not improved neuropsychological performance (LTG 2/16, OXC 3/16 parameters improved). Under OXC additionally improved mood was noted. Yet, the inclusion of further patients and long-term follow up still have to confirm these preliminary findings. This study was supported by funds from Novartis.

p608

SHORT-TERM EFFECTS OF COGNITIVE REHABILITATION ON MEMORY OUTCOME AFTER TEMPORAL LOBE SURGERY

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Purpose: To study the short term effects of cognitive rehabilitation on memory outcome after temporal lobe surgery.

Method: Two groups of patients, one with ($n = 55$) and one without postoperative rehabilitation ($n = 57$) were evaluated with respect to memory and attention before and three months after temporal lobe surgery. The groups stemmed from different epilepsy centres but were matched with regard to age, sex, type of surgery, and seizure outcome.

Results: After surgery, 78% of the patients were seizure free. MANOVA revealed a significant "side X surgery" effect on verbal recognition and a "rehabilitation X surgery" effect on verbal learning and recognition. There were no effects for loss in verbal delayed recall or figural memory. Detailed analyses indicated gains due to rehabilitation particularly after right surgery. Attention generally improved.

Conclusion: The results indicate major effects of rehabilitation on short term aspects rather than long term aspects of verbal learning and memory. Figural memory was not affected at all, and attention also improved without rehabilitation. Finally, left resected patients who mostly needed rehabilitation showed less profit than right resected patients. Thus although rehabilitation had some positive effect on memory outcome its usefulness for risk groups is debatable.

p609

PRE- AND POSTOPERATIVE MEMORY PERFORMANCE IN MESIAL TEMPORAL LOBE EPILEPSY AS A FUNCTION OF HIPPOCAMPAL PATHOLOGY

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Purpose: We investigated the influence of hippocampal morphological integrity (as measured by neuron cell density) on preoperative verbal memory and postoperative memory change in 67 patients with mesial temporal lobe epilepsy (mTLE) and unilateral hippocampal sclerosis (HS, 31 right-, 36 left-sided).

Method: Pre- and postoperative performance on verbal learning and memory were correlated to cell counts (neurons per mm^2) within different subregions of the resected hippocampus [i.e. external and internal dentate gyrus (GDE/GDI), CA1-4].

Results: Preoperatively, verbal learning was correlated ($r = .39–.41$, $p = .01–.02$) with cell densities in GDE and CA3/CA4 regions, respectively, and this was seen only in patients with left mTLE. In contrast, preoperative memory recall and recognition were correlated with cell

densities in CA2–4 regions in patients with both right and left mTLE ($r = 0.32–0.48$, $p = 0.01–0.05$). For patients with left-sided mTLE, cell densities in GDE and CA3/CA4 regions predicted outcome in verbal learning ($r = 0.49–0.53$, $p = 0.001–0.004$), whereas no relation was found for loss in verbal memory.

Conclusion: The data indicate a differential role of the left and right hippocampus and its subfields for verbal learning and memory in unilateral mTLE. While verbal memory (long term consolidation retrieval) appears to be subserved bilaterally, verbal learning (or short-term memory) appears rather lateralised to the left hippocampus, whose integrity is also predictive for losses in this function. As for hippocampal subfields the left dentate gyrus was differentially associated to verbal learning but not memory.

p610
A STUDY OF FACTORS RELATED TO COGNITIVE FUNCTION IN EPILEPSY PATIENTS
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Purpose: To investigate the factors related to cognitive function in epilepsy patients.

Method: We evaluated 166 epilepsy patients (65 newly diagnosed) using neuropsychological tests. The battery of neuropsychological tests included auditory verbal learning (AVL), logical memory (LM), digital symbol (DS), Stroop colour word (SCW), trail making (TM), verbal fluency (VF), Rey-Osterrieth complex figure (ROCF) and Boston Naming (BN). We used multivariate progressive regression analysis to determine the relation between the scores of neuropsychological tests and the factors.

Results: Seizure onset age was inversely related to the scores of delayed recall, cued recall, recognition task of the AVL, immediately and delayed recall of LM, SCW-A and TM. Epilepsy duration was inversely related to the scores of immediate recall of AVL and VF. The decreased score of semantic clustering of the AVL and VF was associated with primary of secondary GTCS. The decreased score of delayed recall, cued recall, and semantic clustering of the AVL and remind naming score of BN was associated with CPS. The account of antiepileptic drugs was inversely related to the scores of the immediate and delayed recall, cued recall, and recognition task of the AVL, immediate and delayed recall of ROCF, VF, DS, TM and SCW.

Conclusion: Besides sex, age and evaluation degree, the cognitive function of epilepsy patients is related to seizure onset age, epilepsy duration, seizure severity, seizure type and the account of antiepileptic drugs.

p611
PRE- AND POSTSURGICAL FIGURAL MEMORY SCORES AMONG LEFT AND RIGHT TLE PATIENTS IN A RECURRING FIGURES TEST (RFT)
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Purpose: Material-specific memory deficits are well established for left TLE and the verbal domain. The complementary deficit for the figural domain in right TLE patients is still under debate. We analysed the figural memory data of TLE patients for effects of the side of seizure origin and sex before surgical treatment and 12 months postoperatively.

Method: 54 female and 58 male TLE-patients passed two parallel forms of a RFT in which a sequence of 120 curved (C) and geometric (G) abstract figures were presented. Within the presented sequence some C and G figures recur 5 times. The subjects have to recognise these recurring figures. For the factors sex and side of seizure origin an ANOVA with repeated measurements for figure type (C vs G) was computed. Handedness and speech lateralisation were controlled.

Results: Pre- and postoperatively the recognition of the curved figures were substantially more difficult ($p < 0.000001$) for men and women. There was a main effect on the operation side. Right TLE patients performed worse than patients with left TLE ($p = 0.04$). In respect to the figure type, there was a tendency ($p = 0.09$) for only the male subgroup to perform pre-operatively specifically worse on the recognition of the curved figures.

Conclusion: Effects of the side of the seizure onset on a RFT were relatively marginal. The tendency for the interaction of side of seizure origin and gender is probably due to item difficulty. Women may find it easier to verbalise even curved figures and hence do not show specific deficits in a RFT even in the case of right TLE.

p612
EMOTIONAL VULNERABILITY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: EVIDENCE FROM A STUDY OF ATTENTIONAL BIASES
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Purpose: Some studies have suggested a higher prevalence of anxiety and depression in temporal lobe epilepsy (TLE). Moreover, cognitive studies provided evidence that anxiety and depression are associated with selective attentional biases that could favour the processing of negative emotional information. In this study, we investigated: i) the prevalence of anxiety and depression in TLE patients, ii) the related attentional biases for negative emotional information, iii) the incidence of patients in whom seizures were triggered by emotional factors.

Method: TLE patients were compared with normal controls and patients with other types of epilepsy. Attentional biases were investigated using an emotional Stroop task, in which participants were instructed to give the colour of words, with negative or neutral emotional valence. Anxiety and depression were assessed by Spielberger anxiety scales and Beck depression inventory. Finally, patients were asked to report if seizures were elicited by specific emotional factors.

Results: There was no effect of groups on the levels of anxiety and depression. No effect was found for reaction times during the emotional Stroop task (to name the colour of negative emotional words compared to neutral emotional words). Furthermore, 45% of TLE patients reported to have emotional factors favouring seizures. In this subpopulation, we found significant attentional biases toward negative words compared to neutral words.

Conclusion: In our TLE patient population, we identified a subgroup of patients who disclose an emotional vulnerability. These patients have emotional factors which favoured seizures, accompanied by selective attention toward negative information.

p613
UNILATERAL HEMISPHERE INVOLVEMENT ASSOCIATED PREDOMINANTLY WITH VIQ>PIQ DISCREPANCIES IN CHILDREN WITH REFRACTORY EPILEPSY
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Purpose: Although verbal (VIQ) versus performance IQ (PIQ) discrepancies in intelligence tests are thought to be equally distributed in both directions (VIQ>PIQ, VIQ<PIQ) on psychometric and on empirical bases, in children with developmental disorders discrepancies are often skewed; in adults they reflect brain pathology imperfectly. We studied the relation between hemisphere involvement and verbal-performance discrepancies in childhood epilepsy.

Method: The Wechsler test scores of 102 children with epilepsy, mean age = 10 years (5−19), mean IQ = 84 (60−120), mean age epilepsy onset = 7 years (0−16), 61% male, 81% right-handed, were collected. Classification was based on EEG/MRI information on brain involvement: partial left (LH, $n = 23$), right (RH, $n = 24$) or bilateral (bi, $n = 24$); generalised ($n = 15$), and uncertain ($n = 16$) onset. Rates of occurrence of large VIQ-PIQ discrepancies were contrasted to those normally expected using chi-square statistics.

Results: Group means (2-sided-*t*-test) did not differ for age of seizure onset, age of testing, IQ-scales or VIQ-PIQ differences. Children with partial seizures present more often with large discrepancies than "expected"; surprisingly, irrespective of side of hemisphere involvement, they relate predominantly to large VIQ>PIQ discrepancies (VIQ>PIQ:

significant values for LH, RH and bi against "expected"; VIQ<PIQ: significant value for RH). Results are most pronounced in LH involvement; right-handed boys; IQs<90. The "generalized" and the "uncertain" group do not show these results ("expected" versus VIQ>PIQ or VIQ<PIQ n.s.).

Conclusion: Counterintuitive, unilateral hemisphere involvement appears not to be mirrored in its IQ-scale; rather, both left and right unilateral involvement is associated with higher rates of unusually large VIQ–PIQ discrepancies, suggesting that PIQ-task solving also recruits abilities dependent on an intact left hemisphere.

Studying frequencies discloses valuable information on discrepancies.

p614

CORRELATION BETWEEN DENSITY OF NEUROPEPTIDE Y-POSITIVE NEURONS IN DIFFERENT NUCLEI OF THE AMYGDALA AND SELF-REPORTED ANXIETY AND DEPRESSION IN EPILEPSY PATIENTS

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Purpose: Amygdaloid neuropeptide Y (NPY) has been implicated in depression, anxiety and memory. In the rat, the number of NPY-positive neurons in the amygdala correlates with anxiety related behaviour. Furthermore, increased NPY expression in the epileptic rat brain is supposed to represent an adaptive mechanism counteracting epilepsy-related hyperexcitability. We attempted to investigate whether NPY in the human brain is also involved in these processes.

Method: In 37 adult epilepsy patients, who underwent temporal lobe surgery for seizure control, the density of NPY-positive neurons was assessed in basal, lateral and accessory-basal amygdala nuclei. In 11 to 26 patients cell counts were related to self reported depression, anxiety, and personality, to measures of verbal/figural memory, to clinical parameters (onset/duration of epilepsy, seizure frequency), and to amygdala and hippocampal MRI volumetric measures.

Results: Cell counts of NPY-positive basolateral amygdala neurons showed significant positive correlations to self-reported depression ($r = 0.53/n = 26$) anxiety ($r = 0.85/n = 11$), drive impairment ($r = 0.53/n = 25$), and compulsivity ($r = 0.58/n = 25$). Furthermore, correlation baso-dorsal cell counts with verbal memory recall could be obtained ($r = 0.475/n = 22$). NPY cell counts showed no relation to epilepsy related factors ($n = 26$–37) or to amygdala and hippocampal volumes ($n = 19$).

Conclusion: The results point to a role of the human amygdaloid NPY in negative emotion, and might reflect both state- and trait-related processes at least in patients with temporal lobe epilepsy. Furthermore, a role of NPY in human memory was indicated. However, no relation to common clinical parameters of epilepsy was found. This study is funded by DFG SFB/TR3 TP C3 to D.Y.-H. and TP A1 to C.H. and J.S.

p615

MEMORY FUNCTION DURING WADA TESTING USING SODIUM AMYTAL VERSUS BREVITAL IN EPILEPSY SURGERY PATIENTS

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Purpose: The intracarotid amobarbital procedure (IAP) is the standard method for lateralisation of memory function, used to predict the risk of postoperative amnesia in epilepsy surgery patients (Milner et al, 1962). Because of recent shortage of amobarbital supply sodium methohexital, or brevital, has been used in some centres as an anesthetic agent (Buchtel et al 2002; Grote and Meador, 2005). The purpose of this study was to compare the neuropsychological effects of Wada testing using IAP versus intracarotid brevital procedure (IBP).

Method: 32 patients who underwent the IAP were compared with 20 patients who underwent IBP at the Tel-Aviv Sourasky Medical Center. The IBP procedure was based partially on the protocol developed at the University of Florida (Buchtel et al, 2002). Results of the Wada ipsilateral and contralateral memory scores in these patients were analysed and compared, as well as differences in neurological status during the action of the drugs.

Results: There were no patients with significant memory decline after surgery. No significant difference was found between Wada contralateral memory scores (first injection) using the IAP ($M = 81.17\%$) or IBP ($M = 84.91\%$). However, significant differences in memory scores of the hemisphere ipsilateral to the epileptogenic focus (second injection) were observed between IAP ($M = 30.74\%$) versus IBP ($M = 55.26\%$) ($p = 0.01$).

Conclusion: These results suggest that the Wada procedure performed by the use of Brevital provides information on prediction of postsurgical amnesia in epilepsy patients. However, they raise the question of the ability of IBP to adequately assess the ipsilateral memory reserve of the epileptogenic hemisphere.

p616

EFFECT OF TIME ON VISUOSPATIAL WORKING MEMORY PERFORMANCE

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Purpose: Knowing the variables that can affect neuropsychological performance and test reliability is crucial to plan assessments and cognitive rehabilitation. Individuals with epilepsy usually complain about attention and memory deficits which may reflect seizure frequency and anti-epileptic drug (AED) side effects. The aim of the present study was to analyse the effect of time on the performance of individuals with focal epilepsy on the Corsi Test, a widely used visuospatial test exploring attention and working memory.

Method: A sample of $N = 30$ individuals with mild severity focal epilepsy (50% female; Mean age = 37.23, DP = 11.88, 17–61 yrs; mean education = 9.27, DP = 4.84, 3–18 yrs) was assessed, and re-assessed, about 6 months later, with the Corsi Test.

Results: There was a considerable variability on performance: in the fist assessment, scores varied from 3 ($n = 1$) to 7 ($n = 2$); on the second from 3 ($n = 2$) to 8 ($n = 1$). There were no statistically significant differences between the first and second assessments on the Corsi Test (mean score 1 = 4.87, SD = 0.86; mean score 2 = 4.80, SD = 1.09).

Conclusion: These results suggest there are no practice/learning effects on the Corsi Test that can be detected about 6 months after the first assessment. Given the multiple determinants of cognitive impairment in epilepsy patients, these findings support the inclusion of the Corsi Test in neuropsychological protocols assessing AED or rehabilitation treatments.

p617

DIFFERENTIAL EFFECTS OF TEMPORAL POLE RESECTION WITH AMYGDALOHIPPOCAMPECTOMY VERSUS SELECTIVE AMYGDALOHIPPOCAMPECTOMY ON MATERIAL SPECIFIC MEMORY IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY

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Purpose: To compare the effect of different surgical approaches to mesial TLE on memory outcome one year after surgery.

Method: Cognitive outcome was evaluated in 97 patients with MTLE and hippocampal sclerosis, who were postoperatively seizure free, and who received temporal pole resection with amygdalohippocampectomy (TPR, N = 33, 48% left) or selective transsylvian amygdalohippocampectomy (SAH N = 64, 56% left). The project was part of a multicentre study (SFB/TR3) where patients with TPR and SAH underwent surgery at different epilepsy centres, which otherwise followed the same presurgical protocol. Neuropsychology included psychomotor speed, attention, language function, and verbal/figural memory.

Results: Except for worse verbal memory performance in SAH patients, surgical groups did not differ in clinical or demographic variables at baseline. MANOVA with "pre-post" cognitive tests as within and "side" and "type" of surgery as between group factors, revealed a "test X side" interaction for verbal learning, recognition, and naming, an effect of "test" on psychomotor speed, and "test X side" and "test X type" interactions for figural memory. Post hoc *t*-tests showed generally improved attention and speed, and improved verbal functions after right SAH. Mild versus severe decrease in figural memory was observed in right SAH and TPR respectively. Verbal learning and recognition deteriorated significantly after left SAH.

Conclusion: On the basis of the neuropsychological tests used in this study, different surgical approaches are suggested in left and right mesial TLE. While transsylvian SAH appears to be favourable in right MTLE, TPR appears safer in left MTLE. Supported by DFG (SFB/TR3).

p618

AFFECT AND SPIRITUALITY PREDICT QUALITY OF LIFE IN EPILEPSY

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Purpose: Individuals with comparable severity of epilepsy may differ widely in perceived quality of life (QOL). Studies of disease-related and psychological determinants have in part explained the variability of QOL, suggesting a role for unexplored personal facets. This study evaluated spirituality in patients with focal epilepsy and healthy subjects aiming to assess its contribution to QOL.

Method: Thirty-six adult patients with partial epilepsy and 45 healthy subjects compiled the WHO QOL-100 and Spiritual, Religious and Personal Beliefs (SRPB) scales, Beck Depression Inventory, State-Trait Anxiety Inventory, and Multiple Ability Self-Report Questionnaire for QOL, spirituality, mood, and cognitive self-efficacy, and underwent neuropsychological tests.

Results: T statistics comparing the two groups showed significant differences in the total WHO QOL-100 score, spirituality, mood, cognitive self-efficacy, and neuropsychological performances with lower scores in epileptics. Of these, the WHO QOL-100 total score significantly correlated with SRPB dimensions (meaning and purpose in life, wholeness and integration, inner peace, spiritual strength, hope and optimism, acceptation, inner independence), and the levels of anxiety and depression. Spiritual strength and mood were significant predictors of overall QOL. No relationship was found for disease-related variables. In the controls, the WHO QOL-100 total score significantly correlated with different SRPB dimensions, anxiety, depression, and cognitive self-efficacy.

Conclusion: These findings suggest that, although QOL is worse in people with epilepsy than in those without epilepsy, for both groups spirituality has an important role in QOL, paralleling the influence of mood. Spirituality may be a missing element in the understanding of the QOL of these patients, explaining differences between individuals with the same clinical severity.

p619

NEUROPSYCHOLOGICAL PERFORMANCE IN PATIENTS WITH TEMPORAL LOBE EPILEPSY AND INTERICTAL (SCHIZOPHRENIA-LIKE) PSYCHOSIS: CORRELATION WITH MAGNETIZATION TRANSFER IMAGING

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Purpose: Cognitive deficits in patients with temporal lobe epilepsy (TLE) and interictal (schizophrenia-like) psychosis were compared to a matched group with TLE without psychosis and their relationship with magnetization transfer imaging was examined.

Method: 20 patients with TLE and interictal psychosis were compared to 20 nonpsychotic TLE patients. Patients were matched with respect to previous IQ, age and conventional MRI findings. A battery of neuropsychological tests assessing intellectual level, memory and executive function was administered. The neuropsychological tests which showed significant group differences were used for correlational analysis with magnetization transfer ratio (MTR) which provides a quantitative measure of macromolecular structural integrity.

Results: Patients with interictal psychosis were significantly more impaired on executive (spatial working memory, spatial span, arithmetic) and semantic memory tasks (verbal fluency, vocabulary) than the non psychotic control group. Vocabulary test scores correlated significantly with MTR reduction in the left fusiform gyrus in the psychotic but not the non psychotic group.

Conclusion: Patients with TLE and interictal psychosis were more cognitively impaired resembling the pattern of patients with schizophrenia. In contrast to schizophrenia where neuropsychological deficits tend to remain stable, cognitive deterioration in patients with interictal psychosis may occur as the illness progresses. MTR may be useful in investigating structural correlates of cognitive impairment.

p621

NEUROPSYCHOLOGICAL OUTCOME FOR THREE PATIENTS WITH EPILEPTIC STATUS INDUCED BY EYE CLOSURE

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Purpose: To detect the presence of transient or stable cognitive impairment (TCI/SCI) in 3 patients with photosensitive epilepsy showing continuous epileptic activity during eye closure.

Method: Three children with electric status induced by eye closure underwent periodical clinical evaluations and EEG investigations during a mean follow-up period of 10 years (range: 8–14 yrs). A complete neuropsychological assessment was carried out at first evaluation (T0) and at the end of the follow-up (T1) to detect SCI. Some tasks were performed during video-EEG monitoring either with eyes closed or with eyes open, to evaluate possible TCI related to ongoing epileptic activity.

Results: The results of neuropsychological assessment during eyes closed as compared to performances with eyes open did not show significant differences at T0 as well as at T1. In all the patients the Wechsler Intelligence Scale documented deterioration of performances at T1 respect to T0. Moreover, we observed at T1 impairment in facial recognition and block design.

Conclusion: Deterioration of IQ in the follow up period could be due to disruption of cognitive processes possibly related to the continuous epileptic activity during eye closure over the years. A dysfunction of visual processing in posterior cortical areas could be involved in impairment in face recognition and block design tests as well as in eye closure sensitivity.

p622

DYSLEXIA IN THE FAMILY OF WOMEN WITH EPILEPSY

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Purpose: The aim of the study is the analysis of symptoms of developmental dyslexia in mothers with epilepsy and their offspring.

Method: The study group consisted of 40 women with idiopathic/cryptogenic epilepsy and their offspring who were born in 1990–92 in our hospital and were prospectively evaluated neuropsychologically. Raven, Benton tests were used as well as 15 words Rey memorising test and lateralisation test. Dyslectic symptoms questionnaire was administered and statistic analysis and Fisher exact test were performed.

Results: 16 children were diagnosed as dyslectic and 24 without developmental dyslexia (40%). 12 mothers of dyslectic children had symptoms of developmental dyslexia and only 2 mothers of nondyslectic children ($p < 0.01$)

Conclusion: Developmental dyslexia occurred in a considerable percentage of women whose idiopathic/cryptogenic epilepsy was more frequent in women whose children have developmental dyslexia. Further evaluations concerning the occurrence of dyslexia in women with epilepsy are needed.

p623

DIFFERENT PATTERNS OF HIPPOCAMPAL PATHOLOGY IN TEMPORAL LOBE EPILEPSY ARE ASSOCIATED WITH DIFFERENT SEVERITY OF MEMORY DEFICITS

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Purpose: Hippocampal sclerosis (HS) and associated memory decline is a common finding in refractory temporal lobe epilepsies (TLE). Cluster analysis was used to identify distinct homogeneous subgroups in hippocampal sclerosis and their relation to memory dysfunction.

Method: Cluster analysis in a large sample of hippocampal neuronal cell counts, obtained from surgically en bloc resected specimens, revealed 4 distinct subgroups of hippocampal sclerosis beside normal findings (Hildebrandt et al. 2006). We investigated 42 surgically treated TLE patients who had Intracarotid-Amytal-Test (IAT) for memory as part of presurgical evaluation. The hippocampal specimens were analysed neuropathologically by counting neuronal cell density within hippocampal subfields CA1-CA4 and internal/external limb of dentate gyrus. The resulting patterns of neuronal cell loss were classified to distinct clusters: healthy hippocampus ($n = 12$), CA1 sclerosis ($n = 4$), classic ($n = 9$) and severe hippocampus sclerosis ($n = 16$). No patients were found with end folium sclerosis. IAT memory scores of the awake ipsilateral hemisphere were transformed into z-scores according to normative values (Pauli et al., 2006).

Results: The different subgroups of hippocampal sclerosis were accompanied by different degrees of memory loss. Most interestingly, patients with neuronal cell loss restricted to CA1 showed no memory deficits, and memory performance corresponded to those observed in healthy individuals. In contrast, classic and severe hippocampal sclerosis was associated with significant memory deficits.

Conclusion: Although a complex interplay between hippocampal sectors is likely to be involved in memory formation and recall, selective loss of CA1 pyramidal neurons appears not to be associated with significant memory deficit in patients with refractory TLE.

p624

EXECUTIVE FUNCTIONS OF CHILDREN AND ADOLESCENTS WITH TEMPORAL LOBE EPILEPSY

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Purpose: Executive functions are cognitive processes like problem solving, mental planning, the selection of action goals as well as the control and regulation of action. According to actual knowledge of the science the frontal lobe takes an authoritative part in these processes. Deficits in executive functions are clear hints of damage of the prefrontal cortex and subcortical structures, like the thalamus and the basal ganglion (McPherson & Cummings, 1998). A frequent form of focal epilepsy is epilepsy of the temporal lobe. Aetiopathogenetic dysontogenetic neoplasms, dysplasia, as well as mesial temporal sclerosis, play an important role. Because of the important aspect of the attack manifestation within the bounds of brain development, it might be possible that not only are functions disturbed in the area of lesion but also in the areas which are connected to this lesion (Huttenlocher, 1977). Although research is on-going, knowledge of function and performance of the brain of children with epileptic attacks is limited. The cognitive stage of development at the point of manifestation as well as the duration of epilepsy is very important. If the epileptic excitement has got a harmful effect on cell metabolism, an impairment of executive function is possible even the structural damage lies in the frontal lobe. Therefore the present study should make a contribution.

Method: Executive functions were examined postoperatively for 25 children age 10 to 18 with epilepsy because of a neoplasm, dysplasia or hippocampal sclerosis, and for a control group of healthy children, paralleled on age, gender and IQ. The registration of executive functions took place with a neuropsychological test battery, consisting of 9 special tests. Information about the personality of the children was established with CBCL/ 4- 18 (Achenbach, 1991).

Results: First outcomes show significantly worse results concerning attention and planning of actions of patients with epilepsy.

Conclusion: Based on these results, the fundamental importance of a differentiated neuropsychological examination of children with temporal lobe epilepsy, also when examining executive functions, becomes clear.

p625

EXECUTIVE FUNCTIONS IN LEFT AND RIGHT FRONTAL LOBE EPILEPSY: AN EXPLORATORY ANALYSIS

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Purpose: To describe the frontal-executive functioning in frontal lobe epilepsy (FLE), as well as to evaluate the lateralisation value of different frontal executive measures in this sort of epilepsy.

Method: Participants in this investigation were 18 patients with unilateral FLE (10 left and 8 right) and 18 controls. Both groups were assessed with a broad neuropsychological battery made up of 26 different frontal-executive measures.

Results: As a group, FLE patients showed a significant ($p < .05$) impairment in almost 70% (18/26) of the executive measures. However, a more detailed analysis confirmed that it was actually the left FLE group which showed a wider executive impairment (left: 73% of the measures vs right: 42%). Thus, the left FLE group performance was specially impaired on verbal and design fluency, inhibition processes (Stroop test, Go-Nogo task) and set-shifting abilities (Trail Making Test). On the other hand, different regression analyses showed that epilepsy related variables, such as age of seizure onset and duration of epilepsy, have a significant effect over the executive performance of both FLE groups.

Conclusion: FLE shows a clear dysexecutive syndrome, more significant when the focus is lateralised to the left hemisphere and when the epilepsy has an early age of onset and a longer duration. Finally, as well as in temporal lobe epilepsy, current neuropsychological assessment procedures are able to characterise this lateralised profile, proving its utility in the presurgical context.

p626

EFFICACY AND TOLERABILITY OF OXCARBAZEPINE IN PARTIAL EPILEPSY: RESULTS OF THE GERMAN LEUKOTRIAL FOCUSSING ON QUALITY OF LIFE AND COGNITION

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Purpose: Exposure response analysis of oxcarbazepine (OXC) in patients with partial epilepsy (PE) depending on application time and pretreatment.

Method: Prospective observational study on efficacy and tolerability of OXC [special focus on quality of life (QoL) and cognition] as first line or supplementary treatment in PE.

Results: One hundred and fifty-two patients participated (48.7% female, age: 16.0 ± 11.9 yrs.). OXC-related seizure free rates were 43.4% in newly diagnosed patients (n = 53) vs 32.1/21.7% in those who received OXC after one or two (n = 53/46) other AEDs. Overall, QoL, assessed with the side effects and life satisfaction and the quality of life in epilepsy scale improved in 77.4/79.2/78.3% (SEALS) and in 64.2/79.2/82.6% (QOLIE) respectively. Cognitive functioning (assessed with a trail-making test, TMT) improved in 54.7% of patients who received OXC as first line AED and in 79.2/67.4% after one/two prior AEDs. Non-responders to carbamazepine (CBZ) vs other AEDs became seizure free in 29.6 vs 21.4%, showed higher QoL-improvement rates (SEALS/QUOLIE) than those changed to OXC from other AEDs (83.1/85.9% vs 67.9/67.9%) and comparable cognitive improvement rates: 73.2 vs 75.0%.

Conclusion: OXC is not only a highly efficacious 1st line AED for PE, but also the drug of choice for AED non-responders (even to CBZ). Its use was, irrespective from AED pre-treatment and application time, followed by significant improvements in QoL and cognition.

p627

COGNITIVE FUNCTIONING IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Purpose: In this follow-up study we decided to evaluate cognitive functions in patients with drug-resistant and newly diagnosed temporal lobe epilepsy (TLE) before and after six months of treatment.

Method: 154 patients with resistance and 97 patients with newly diagnosed TLE underwent extensive neuropsychological interviews which included measures of attention, memory, initiation, perseveration, word fluency and mood before and after six months of treatment.

Results: Comparative analysis of cognitive functioning before treatment showed that patients with drug–resistant TLE performed more poorly in neurocognitive tests and exhibited higher scores of depression than patients with newly diagnosed TLE. Patients taking antiepileptic drug (AED) polytherapy showed more distinct cognitive dysfunctions than patients taking AED monotherapy. 49 (31.8%) patients with drug resistant TLE became seizure free after correcting the AED therapy. After six months treatment 47 (30.5%) patients with resistant TLE showed a reduction of cognitive disadvantage and 35 (22.7%) patients showed an improvement of cognitive abilities. In the group with newly diagnosed TLE 41 (42.2%) patients were seizure free, 40 (41.2%) showed a reduction of cognitive dysfunction, 18 (18.5%) an improvement of cognitive abilities.

Conclusion: Drug resistance and AED polytherapy negatively affect the extent of cognitive dysfunction.

p628

AFFECTIVE AND BEHAVIOURAL PROBLEMS IN PATIENTS WITH EPILEPSY AND SLEEP DISORDERS

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Purpose: Epilepsy is a factor influencing the sleep and it is defined as an important risk factor in disturbing emotional functioning and behaviour in patients. Data analysis shows a two-way dependence between sleep disorders and disturbances of behaviour and emotions. The aim of the study was to state the prevalence of behavioural problems in patients with epilepsy and sleep disorders and its correlated disturbances in emotional functioning.

Method: 40 patients aged 14–18 years with epilepsy participated in the study. The median of age was 16.2 yrs with normal intelligence quotient. The median time of epilepsy treatment was 2.4 yrs. The patients underwent pharmacological treatment in monotherapy mode with conventional antiepileptic drugs. The reference group was a group of healthy teenagers with sleep disorders (40 pts) and a group of healthy persons (40) without any disorders. They were matched according to age, sex and level of intelligence. A questionnaire of sleep disorders and TRF and YSR scales was used in the study.

Results: The data shows the prevalence of sleep disorders in the examined epilepsy group. The prevalence of behavioural problems in a group of epilepsy patients is estimated as 50%; emotional disturbances, aggression, lack of emotional control, impulsivity estimates are over 40%. The average of these disorders grows in a group of epilepsy patients with sleep disorders to 60% in behaviour and 50% of emotional disturbances as well. There is an important correlation between sleep disturbances and behavioural problems and emotions in the reference group. However, the average appearance of the disorders in patients with sleep disturbances 50% and 40% are lower.

Conclusion: Sleep disorders and epilepsy correlate and are the reason for important behavioural problems and emotional dysfunction including aggression.

p629

SUBJECTIVE COMPLAINTS, NEUROPSYCHOLOGICAL FUNCTIONING AND DEPRESSION IN PATIENTS WITH EPILEPSY

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Purpose: The aim of the study was to investigate subjective complaints of epilepsy patients, to compare self-reported complaints with objective neuropsychological functioning and to assess the influence of possible depression on self-reported cognitive problems.

Method: Forty-eight patients with epilepsy were included to the study. The patients had to have a definite diagnosis of epilepsy, have no other neurological diseases, be aged between 18–65 years, and be native Estonian speaking. Patients with symptomatic epilepsy and patients incapable of filling out the questionnaires were not included in the study. There were 31 female and 17 male patients, and the mean age of the study sample was 35.3 (13.3) years. The majority of patients had focal epilepsy, mainly temporal lobe epilepsy. The subjective complaints questionnaire, Beck Depression Inventory (BDI) and a series of neuropsychological tests were carried out. Data was analysed using Pearson correlation (r); the level of significance was set at 0.05.

Results: There were no statistically significant correlations between the self-reported complaints assessed by the score of subjective complaints questionnaire and objective neuropsychological test measures. There were strong correlations between subjective complaints and severity of depression assessed by the score on BDI ($r = 0.68$, $p < 0.05$). BDI score did not correlate to the results of neuropsychological tests.

Conclusion: The results indicate that subjective and objective cognitive functioning are not necessarily associated, not only in case of memory but in a wide range of different cognitive domains. Depression is strongly related to the number of subjective problems reported by the patients.

p630

SPEECH DEVELOPMENT AFTER REMOVAL OF FOCAL CORTICAL DYSPLASIA

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Purpose: Cortical dysplasia is a known cause of epilepsy, often drug-resistant and associated with additional neurodevelopmental

disturbances. Neurosurgical treatment has been proved to be effective in certain cases of cortical dysplasias.

We would like to present a patient whose neurosurgical treatment not only improved seizure control but also released suppressed speech development.

Method: A 4-year-old boy was admitted to the neurosurgical department for assessment and qualification for surgical treatment of drug resistant epilepsy. He had had a history of GTCS and left-sided seizures since 3rd month of age.

Results: On neurological examination left spastic hemiparesis was found. Psychological evaluation revealed lateralisation to the right side and intellectual functioning at the level of mild delay (Psyche-Cattel scale II58). The boy understood even complex commands, however, word expression remained severely delayed (hardly spoke single words). On MR examination a large focal cortical dysplasia in the right frontocentroparietal area was found. Interictal EEG revealed high amplitude theta activity over the affected area, spreading to the left frontal area during seizures. The boy was operated on at 5 years of age (right hemispherectomy), the surgery complicated by massive bleeding, cardiac arrest and purulence requiring partial cranium removal.

Conclusion: After the surgery the boy remains almost seizure free. Additionally, shortly after the surgery an explosion of speech development could be observed. He is 15 years old now and his intellectual functioning remains at the level of mild to moderate delay with verbal capabilities masking worse results of performance tests.

p631

NEUROCOGNITIVE FUNCTIONING OF PRESCHOOL CHILDREN WITH "EPILEPSY ONLY"

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Purpose: The aim was to investigate neurocognitive functioning of 3–6 year old children with "epilepsy only," i.e., seemingly age appropriate neurological and social development. They were compared with matched healthy controls, and the neurocognitive impairments of epilepsy only children in this age range were described.

Method: The neurocognitive functioning of the children with "epilepsy only" ($n = 13$) was compared with matched controls ($n = 13$). Wechslers Primary and Preschool Scale of Intelligence-Revised (WPPSI-R) and the Developmental Neuropsychological Assessment (NEPSY) were administered. Functions of attention, language, sensorimotor, visuospatial and memory were included in the assessment.

Results: Preliminary results indicated that verbal IQ and full scale IQ differed significantly between the study and control groups, but no differences between the two groups was found in performance IQ. VIQ of children with "epilepsy only" also differed statistically significantly from WPPSI-R normative data, but no differences between PIQ or FIQ and normative data were found. Children with epilepsy had significant difficulties in verbal short-term memory ($p < .01$) and attention ($p < .05$).

Conclusion: Children with early onset (i.e., before or during preschool age) "epilepsy only" seem to have difficulties, especially in short-term memory and attention skills compared to healthy preschool children.

p632

EPILEPSY AND MEMORY: LEARNING PROCESSING AND WORKING MEMORY COMPROMISE IN FRONTAL LOBE EPILEPSY

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Purpose: It is conceptualised that temporal lobes are critical in episodic memory while frontal regions are dominant in semantic and working memory. Localised epilepsies are a good study model of focal cognitive defects, and in a previous work we demonstrated that performance in frontal lobe epilepsy (FLE) was poorer in the Trail Making Test, which evaluates working memory processing. To further investigate the intervention of frontal lobe in memory processes and to evaluate the relevance of working memory compromise in epilepsy we compared learning primacy and recency effects in frontal and mesial temporal lobe epilepsy patients.

Method: We studied 15 patients with FLE and 51 patients with medial temporal lobe epilepsy (mTLE). Primacy and recency effects were evaluated in the first learning trial of California Verbal Learning Test (CVLT). Primacy (recall of the first four items) indicates storage in a more long-term memory while recency (recall of the last four items) indicates storage in short-term memory (working memory).

Results: Mean and standard deviation (SD) of primacy effect score (total) for the FLE and mTLE were 1.5 (SD0.8) and 2.1 (SD0.9) ($p < .05$). For the same groups and parameters recency effects were 1.2 (SD0.7) and 2.0 (SD1.2) ($p < .05$) indicating that FLE patients were poorer in both effects. Meanwhile, the evaluation of the relative scores of the same indexes demonstrated that only the recency effect was significant: FLE 20.9 ± 12.2 and mTLE 31.4 ± 18.7 ($p < .05$).

Conclusion: These results indicate that 1) frontal lobe has a crucial role in encoding processes of memory, 2) in FLE patients, learning defects seem to be conditioned mainly by a compromise of working memory processing.

p633

PROSPECTIVE FIVE-YEAR FOLLOW-UP OF COGNITIVE FUNCTION IN ADULTS WITH NEWLY DIAGNOSED FOCAL EPILEPSY

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Purpose: To evaluate cognitive performance of newly diagnosed adult patients with focal epilepsy before antiepileptic drug treatment and after five years of treatment.

Method: Altogether 122 patients had comprehensive neuropsychological evaluation at the time of the diagnosis and after five years of follow-up. The test battery measured intellectual ability, verbal ability, verbal memory, attention and flexible mental processing, and psychomotor speed.

Results: At five-year evaluation cognitive performance was significantly better in the majority of tests (15/22, 68%), losses were shown in only one task (Letter Cancellation). Patients with complete seizure control showed improvement in 63% of the tests and patients with seizures in 18%. When the patients were classified according to age at baseline, younger patients (<55 yrs) had better scores at five years in 77% of the tests and older patients (≥55 yrs) in 5% of the tests. In the group of older patients 4 tests (18%) showed significant slowing of psychomotor speed.

Conclusion: Cognitive performance of adult patients with focal epilepsy and complete seizure control remains the same or improves due to practice effects during the five-year time period. Patients with seizures show practice effects less consistently in repeated testing suggesting mild adverse cognitive changes. Patients who are older at the time of the diagnosis show a slowing of psychomotor speed, possibly because of a combination of adverse cognitive changes and aging effects.

p634

NEUROPSYCHOLOGICAL FINDINGS IN PATIENTS WITH HIPPOCAMPAL SCLEROSIS: INFLUENCE OF ASSOCIATED MALFORMATION OF CORTICAL DEVELOPMENT IN TEMPORAL POLE

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Purpose: Presence of temporal pole pathology, mainly malformation of cortical development (MCD) in addition to hippocampal sclerosis (HS) might correspond to a different aetiology of mesial temporal lobe epilepsy (MTLE). The aim was to compare neuropsychological findings in groups of MTLE/HS patients with and without associated microscopic MCD.

Method: Thirty-four patients with a diagnosis of refractory MTLE were included–mean age 31.8 years, range 21–58. No overt pathology except HS was revealed by MRI examination. Following anteromedial temporal lobe resection hippocampus and part of temporal pole were histopathologically examined. HS was confirmed in all cases and pathological changes in the temporal pole classified. Patients with atypical language lateralisation were excluded ($n = 7$). Of the remaining, 16 patients had left-sided surgery; on histopathological examination MCD was present in 10 (left HS+) and was absent in 6 patients (left HS). Right-sided surgery was performed in 11 patients; MCD was found in 3 (right HS+) and absent in 8 (right HS). Results of presurgical neuropsychological assessment were compared in distinct groups of patients.

Results: In comparison with left-sided groups: HS patients scored worse in general intellectual performance and verbal learning; HS+ patients showed lower performance in delayed verbal recall and had lower scores on contralateral application in intracarotid metohexital procedure (IMP). In comparison with groups with isolated HS (left vs right), right-sided patients had lower performance in delayed visual recall and on contralateral application in IMP; they also scored lower for depression and neuroticism.

Conclusion: The neuropsychological finding in MTLE/HS patients may be influenced by the presence of associated microscopic MCD in the temporal pole.

p635

EPILEPTIC DEVELOPMENTAL RIGHT-HEMISPHERE SYNDROME

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Purpose: In a class of epileptic encephalopathies, neuropsychological frontal lobe, agnosia, apraxia and speech dyspraxia epileptic syndromes are described. We present an epileptic developmental right-hemisphere syndrome, caused by continuous epileptiform discharges in right hemisphere in a girl not having actual epileptic seizures.

Method: An 8-year-old girl with educational problems was submitted for neurological, neuropsychological and EEG studies.

Results: In early childhood the girl had slight left leg pyramidal insufficiency and one generalised epileptic seizure. At the present time she presents dyslexia, marked slowness of performance, inability to join social group activities, marked deficit of orienting in nearest environment and interpersonal and emotional problems. A neuropsychological study reveals a decrease of visual memory, deficit of attention, dyscalculia, and a visuospatial cognitive deficit. In EEG continuous slow-spike-and-slow-wave discharges in right occipital, posterior temporal and parietal area are present combining with intermittent bilateral slow-spike-and-slow-wave discharges with larger amplitude right. Treatment with valproate suppressed epileptiform activity and improved cognitive functions. So the girl presents all the criteria of nonverbal learning disability developmental right-hemisphere syndrome described by V.Gross-Tsur et al. (1995) in non epileptic disorders: 1) emotional and interpersonal difficulties, 2) paralinguistic communication problems, 3) impaired visuospatial skills, 4) dyscalculia, 5) neurological signs on the left side of the body. Close correspondence of the localisation of epileptiform discharges to functional localisation of impaired function and effectiveness of antiepileptic treatment suppressing epileptiform activity in EEG supports interpretation of the epileptic discharges as a casual factor of the disorder.

Conclusion: Epileptic discharges in posterior regions of the right hemisphere may cause epileptic encephalopathy presenting as nonverbal learning disability developmental right-hemisphere syndrome. Valproate treatment improves cognitive development in this case.

p636

IMPACT OF A SINGLE EPISODE OF STATUS EPILEPTICUS ON THE COGNITIVE DEVELOPMENT OF YOUNG CHILDREN

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Purpose: Status epilepticus (SE) is a serious, potentially life-threatening neurological condition. Although better medical management has improved the clinical outcome, the impact on cognitive development remains uncertain. The aim of the present study was to assess the effect of SE on cognitive functioning and self-regulation of behaviour.

Method: In the first experiment, 20 infants (mean age: 12.9 mo.) treated for a single episode of SE and a comparison group consisting of 9 children having experienced a first febrile seizure (FS) were assessed on the Griffith Developmental Scales 4 months after the episode. The two groups were further compared to 34 healthy age-matched controls. In the second experiment, 12 SE children (mean age: 24.11 mo.), 7 FS children and 12 healthy controls were submitted to 3 measures of self-regulation of behaviour 9 months after the first and only seizure.

Results: The SE children scored significantly lower than the control group in the social, language and performance domains of the Griffiths. The FS children differed neither from the SE children nor the controls. Compared to healthy subjects, the SE group also had significantly more difficulties on 2 tasks assessing self-regulation of behaviour but they were inferior to the CF group on only one of these tasks.

Conclusion: It seems that a single prolonged seizure suffices to interfere with the normal development of higher mental functions. Although the effect may be global, it is reasonable to assume that the functions that are emerging at the time of impact are most vulnerable to such interference.

p637

LEXICAL AMBIGUITY AND SEMANTIC KNOWLEDGE IN EPILEPSY

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Purpose: A limited number of previous studies suggested that the ability to interpret lexical ambiguity is impaired in patients with partial and to a lesser extent generalised epilepsy. It is currently unclear whether this deficit occurs as an isolated phenomenon or in the context of a wider semantic deficit in the "mental lexicon" of these patients. Accordingly, the present study was designed in order to investigate lexical ambiguity in relation to the status of conceptual knowledge in epilepsy.

Method: Thirty-five patients with partial (20) and generalised (15) epilepsies and 39 matched controls entered the study. Two separate experiments were designed. All subjects were given the Ambiguous-Words-Test (AWT) and three subtests of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA).

Results: Total scores for the AWT were found to differ significantly between the patient and the control groups (one-way ANOVA, $p < 0.05$). In patients with partial epilepsy, a significantly disturbed conceptual knowledge was found which resulted in the production of semantic errors during performance (Mann–Whitney Test, $p < 0.05$). In patients with generalised epilepsy, a more restricted deficit was found that is difficulty in processing specific kinds of words, particularly verbs and words with low image ability (Mann–Whitney Test, $p < 0.05$).

Conclusion: The present results suggest that impairment in lexical ambiguity interpretation occurs within the context of a wider semantic deficit in epilepsy. In patients with generalised epilepsy this latter deficit is characterised by difficulties in interpreting words with complex representations in the "mental lexicon." In contrast, patients with partial epilepsy have difficulty in processing all kinds of administered lexical items.

p638

SWITCHING FROM AN OLD TO A NEW ANTIEPILEPTIC DRUG: ASSESSMENT OF SLEEP, QUALITY OF LIFE AND NEUROPSYCHOLOGICAL EVALUATION

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Purpose: To analyse the perception of quality of life (QoL), the cognitive abilities and the quality of sleep in 9 patients switched from carbamazepine (CBZ) to oxcarbazepine (OXC), and to evaluate whether performances improved with the new antiepileptic drug (AED).

Method: We investigated 9 patients (7 M, 2 F; 49.5 yrs ± SD 13.6) all with complex partial seizures, 5 with secondary generalisation. The neurological examination was normal. All were under treatment with CBZ, 2 of them were under polytherapy, 1 with lamotrigine, the other with phenobarbital. All underwent, at baseline and 6 months after switching from CBZ to OXC, the QOLIE-89 to assess the QoL; a neuropsychological evaluation for intelligence, attention, memory, language and a nocturnal sleep recording to evaluate the quality of their sleep. A comparison was made between the data collected at baseline and that collected after 6 months.

Results: The patients under OXC had a better score in the QOLIE-89 in: health perception, social function, energy/fatigue, social support, overall QoL, medication effects. They reported better performances also in neuropsychological evaluations such as verbal and nonverbal memory. Concerning sleep we found no differences between the 2 groups.

Conclusion: The patients under treatment with OXC showed a subjective improvement concerning QoL and an objective ameliorating with regard to the neuropsychological evaluation. Seizure worry was not taken into account from our population.

p639

SUBCLINICAL EPILEPTIFORM ABNORMALITIES AND COGNITIVE FUNCTION: DATA FROM DEVELOPMENTAL ATTENTION AND LEARNING DISORDERS

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Purpose: Recently, we have reported EEG abnormalities in 39% of 98 children diagnosed as Attention Deficit Hyperactivity Disorder (ADHD) and/or Learning Disorder (LD) based on strict criteria (Zaimoglu S, Turkdogan D. When EEG is indicated in attention deficit and learning disorders? *Eur J Paed Neurol* 2005;9:286). In the present research, we aimed to study the effects of subclinical epileptiform potentials on cognitive functions in children with ADHD and/or LD.

Method: Thirty-three children with subclinical epileptiform activity and 33 children with normal EEG matched for age (mean: 8.8 ± 1.7), sex (5 female), grade (mean: 3.5 ± 1.8) and diagnosis (2 with LD, 19 with ADHD and 12 with LD+ADHD) were assessed neuropsychologically. Epileptiform discharges were classified based on the following features: frequency (rare-moderate: 54%, frequent: 46%), location (generalised: 17%, frontal: 37%, extrafrontal: 46%), relation with vigilance (sleep: 6%, sleep and wakefulness: 85%, wakefulness: 9%) and relation with activation (9%).

Results: The presence of epileptic discharges was significantly associated with a worse performance on California Verbal Learning and Memory Test. Higher free-recall intrusions ($p = 0.015$) and false-positive responses on recognition ($p = 0.006$), and lower recognition discriminability index ($p = 0.017$) were found in children with epileptiform activity compared to children with normal EEG. On the other hand, the percentage of primacy score was higher in children with epileptiform activity ($p = 0.034$). The scores of Stroop Task, Wisconsin Card Sorting Test, Category Naming and Visual Memory Span, which assess attention and executive functions, were not significantly different.

Conclusion: Our results clearly indicate that subclinical epileptiform discharges have been associated with source memory deficit.

p640

SHORT-TERM MEMORY IN PATIENTS WITH FOCAL AND PRIMARY GENERALISED EPILEPTIC SEIZURES

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Purpose: Short-term memory characteristics are known to be vulnerable in epilepsy, although the findings are controversial in verbal and non-verbal short-term memory.

The goal of the study was the investigation of disease variable effects on the short-term verbal and visual memory indicators in patients with epilepsy.

Method: One hundred forty-five consecutive patients (74 women, 71 men) were studied by Benton Visual Retention Test (BVRT) and short-term verbal memory test (STVT); clinical and EEG parameters were considered. One hundred six had focal seizures (35 without and 75 with secondary generalisation), 25 had primary generalised seizures and 14 had unclassified epilepsy. Effects of localisation, type of seizures, side of foci, sex, seizure frequency, and disease duration were taken into account. Results were analysed by SPSS-12.

Results: Effects of seizure type were revealed in both tests; especially, significantly lower total scores had patients with secondary generalised seizures and with unclassified epilepsy ($p < .001$). In BVRT these groups had higher distortion, metric and omission-adding errors ($p < .001$). Effect of localisation was significant only in BVRT; namely, misplacement and metrical errors were significantly higher in temporooccipital localisation; reversion errors were significantly higher in fronto-temporal localisation. In BVRT, when seizure type was controlled, women had significantly lower total score ($p < 0.02$) and higher errors (omission, reversion).

Conclusion: Significant effects of seizure type, localisation of foci, gender were revealed in BVRT. Higher BVRT errors occurred in cases where temporal epileptic activity was involved.

Wednesday July 5, 2006
13:30–15:00
Poster Session 3
Epilepsy Syndromes

p641

CASE REPORT: STATUS EPILEPTICUS AND STURGE-WEBER

A. Arsovska and A. Popovski (Clinic of Neurology, Skopje, Macedonia)

Purpose: Sturge-Weber syndrome (SWS) is a neurocutaneous disorder with angiomas on the leptomeninges and the face. Neurologic symptoms include seizures, focal deficits, and developmental disorders. A case of a 28-year-old male patient with SWS is reported. He was admitted to hospital due to status epilepticus (SE) with generalised tonic–clonic seizures (GTCS).

Method: The patient had epilepsy from his earliest childhood with rare GTCS. They became more frequent in adolescence and were provoked by infections. The patient regularly took antiepileptic therapy (AET). One month before hospitalisation, he had 2–3 GTCS everyday. Then, he suffered from acute gastroenterocolitis and cholecystopancreatitis. AET was completely abolished and the patient had no AET for 5 days. On the 5th day, he fell into SE with GTCS for a duration of 8 hours and was admitted to hospital, where therapy for SE was applied. At admission the patient was in a soporous condition, febrile, with port wine stain hemangioma, glaucoma, mental retardation and spastic right hemiparesis.

Results: Blood analysis: increased levels of leucocytes, fibrinogen, alpha amylase, lipids; other parameters were normal. Brain CT: Massive calcified arteriovenous malformation in the left parietal and occipital lobe. EEG: slow wave background activity, with epileptogenic activity consisting of single and multiple sharp waves. Chest x-ray: massive

bilateral bronchopneumonia. During the stay in hospital, the first day, the patient had another 2 GTCS in the afternoon. The next day he had 1 more GTCS. Afterwards, no seizures were registered until he was released from hospital. Also, his physical condition improved, he became conscious and afebrile. The patient was released after 2 weeks with recommended AET.

Conclusion: Physicians should be very careful when treating patients with SWS because episodes of SE can worsen the neurologic symptoms secondary to metabolic disturbances.

p642
COELIAC DISEASE, EPILEPSY, CEREBRAL CALCIFICATIONS: INCOMPLETE FORMS
P. Benna, R. Colonna, and E. Montalenti (Dipartimento Di Neuroscienze, Università Di Torino, Torino, Italy)

Purpose: The syndrome "coeliac disease, epilepsy, occipital calcifications" (CEC) is a rare condition characterised by bilateral serpiginous shaped occipital calcifications, epilepsy with onset in the first decade and coeliac disease, often latent at the time of diagnosis. Seizure semiology initially suggests a posterior onset, but may evolve towards an epileptic encephalopathy, with progressive cognitive deterioration. EEGs may show occipital spike and wave discharges stopped by eyes opening. Incomplete forms of CEC syndrome, because of clinically silent celiac disease or absence of epilepsy, are described. We describe two case reports of patients with incomplete CEC.

Method: The two cases have been extracted from a 2500 patient database of our Centre. The patients had been followed with periodic clinical and instrumental check.

Results: Two male adult patients suffered from incomplete CEC syndrome, both presenting typical clinical and EEG features: seizure onset in the first decade of life with occipital semiology, good response to therapy followed by worsening of seizure frequency, drug resistance and evolution to an epileptic encephalopathy. EEG of both patients showed sub-continuous diffuse paroxysmal anomalies with a posterior prevalence and fixation-off sensitivity. One of the two patients had no occipital calcification; the other did not show clinical or laboratory findings of celiac disease but underwent in infancy radio and chemotherapy for acute lymphatic leukaemia.

Conclusion: The CEC syndrome can appear as an incomplete form in which only two elements of the triad are evident; particularly, in the presence of typical epileptic syndrome and cerebral occipital calcifications, the possibility of other uncommon aetiologies must be considered.

p643
INTERICTAL HAIR PHENOMENA IN EPILEPSY
A. Boika (5th City Clinic, Minsk, Belarus)

Purpose: To study interictal changes of hair patterns on the body of patients with epilepsy.

Method: Face, neck, torso and extremities of 120 patients with different types of epilepsy were examined twice by us for hair patterns to exclude casual results. Hair patterns and their localisation, described by Straubesand J (*Sobotta atlas of human anatomy*. 11th English ed. Munich: Urban & Schwarzenberg 1989; Vol.1.P.382-383), serve as a standard. Changes were recorded by digital camera.

Results: Seventy-three patients had changes. They were: (a) deformation of normal patterns (30 cases); (b) additional pattern on the body (36 cases); (c) combined–deformation and additional patterns (7 cases).

Conclusion: Autonomic epileptic phenomena may not characterise only piloerection as example of ictal changes of hair (Scoppetta C. et al. Funct Neurol 1989;4:283-286) but also deformation and additional hair patterns on the body of patients with epilepsy which are examples of interictal changes of hair.

p644
TONIC ABSENCES: 3 CASE REPORTS
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Purpose: To characterise and discuss an unusual type of seizure, the tonic absence, in the evolution of drug-resistant idiopathic generalised epilepsies (IGE).

Method: We undertook a retrospective case study of 3 epilepsy patients with absences and rare tonic–clonic seizures since the age of 3 to 9 years. The patients are now 45 to 59 years old. We reviewed the clinical and video-electroencephalographic (EEG) data from the beginning of the disease.

Results: Typical absences were recorded in all 3 patients during childhood. They all had absence status epilepticus as well. After several years of inappropriate treatment, and as the patients reached adult age, two new types of seizures were recorded recurrently on video-EEG: atypical absences and tonic absences. The latter were previously described in symptomatic generalised epilepsies (SGE) and have a particular EEG pattern with fast generalised discharges of spikes (10-20 Hz, 0.5 to 7 s) followed or preceded by slow and irregular spike and polyspike and wave complexes. There is no considerable clinical tonic component. They persist with an adapted drug regimen. The patients still have many features of IGE: normal background activity; unremarkable history; normal psychomotor childhood development, neurological examination and socio-professional insertion; unremarkable cerebral magnetic resonance imagery.

Conclusion: The tonic absences were described in SGE. However they can occur in apparently typical IGE on inappropriate treatment and maybe because of an individual predisposition. A tonic generalised discharge of spikes is not necessarily synonymous of a SGE but it is likely a drug-resistance marker. These data suggest an SGE-IGE continuum, with intermediate evolution and prognosis.

p645
HOT WATER EPILEPSY: CLINICAL AND ELECTROENCEPHALOGRAPHIC FEATURES
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Purpose: Our purpose is to analyse the clinical and electroencephalographic findings of 25 patients with hot water epilepsy.

Method: The personal and family history, neurological state, age of onset and types of seizures, provoking factors, bathing habits, EEGs and neuroimages were all reviewed. The follow-up period for 18 patients with regular visits every 3 months and many EEG recordings ranged between 1–6 years. Seven patients could not be reached at the address or phone number noted at their first visit.

Results: The age of onset of seizure ranged from 6 months to 37 years. Twenty patients had complex partial seizures. Eight patients had spontaneous seizures as well, 1 of them was typical for idiopathic photosensitive occipital lobe epilepsy. One patient described an episode interpreted as nonconvulsive status. In our study group, pouring the water over the head and the temperature of the water were the most common triggering factors. A special kind of soap and entry of water into the mouth were determined as unusual triggering factors. Interictal EEGs revealed epileptogenic abnormalities located over the temporal regions in 9 patients. Seventeen patients had neuroimaging mostly cranial magnetic resonance imaging. One had right mesial temporal sclerosis and 1 had cortical atrophy, others had normal findings. Sixteen patients received antiepileptic drugs, mainly carbamazepine, and stayed seizure free.

Conclusion: The high rate of epileptogenic abnormalities localised in the temporal region and the complex partial seizures observed in most of our patients indicate the considerable role of temporal lobe in hot water epilepsy.

p646
WHEN VALPROATE DOES NOT CONTROL CHILDHOOD ABSENCE EPILEPSY

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Purpose: In our department, valproate is the first line treatment for childhood absence epilepsy. We noticed some patients respond only partially and need combination or replacement for complete control of seizures. The aim of this study is to find predictive factors for this therapeutic response.

Method: We retrospectively evaluated all case records of patients diagnosed in our department with childhood absence epilepsy between January 2002 and December 2005. Considering responses to valproate, patients were classified as responsive if seizures were controlled completely on monotherapy, and nonresponsive if replacement or combined therapy was needed. The differences and common features between the two forms were outlined.

Results: We retrospectively evaluated all case records of patients diagnosed in our department with childhood absence epilepsy between January 2002 and December 2005. Considering responses to valproate, patients were classified as responsive if the seizures were controlled completely on monotherapy, and nonresponsive if replacement or combined therapy was needed. The differences and common features between the two forms were outlined.

Conclusion: It is known that absences are very sensitive to valproate, and monotherapy controls childhood absence epilepsy in 60% of patients. A clinical difference has been found on the age of debut, which was for a nonresponsive form, and EEG differences on the appearance of specific complexes predominantly in hyperventilation for nonresponsive patients. To confirm those hypotheses, larger comparative studies are necessary.

p647

CLINICAL EXPERIENCE WITH ZONISAMID (ZNS) IN PATIENTS WITH SEVERE DRUG RESISTANT EPILEPSIES

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Purpose: Zonisamid (ZNS) is a well established antiepileptic drug in the treatment of focal and generalised epilepsies. This drug was recently licensed in Germany in June 2005. We now report our first clinical experience with the drug in the treatment of patients with severe, so far drug resistant, epilepsies.

Method: This is a retrospective observational study. The data was collected from patient records and diaries. We report on 40 patients with a median observational period of 10 weeks. The median age was 36.8 years. The median duration of epilepsy was 20.5 years. The number of previous prescribed antiepileptic drugs was 8. The median steady state dosage of the drug was 300 mg.

Results: 35% of the patients responded with 8% seizure free. 22% patients suffered from adverse events with predominantly widespread unspecific somatic disturbances. Only 3 of the patients suffered from sedation.

Conclusion: We report on a group of patients with severe highly drug resistant epilepsies. Nevertheless, we have excellent efficacy in this group of patients. We have to keep in mind that the average number of previously prescribed antiepileptic drugs was 8. Also this difficult to treat group has high tolerability to the drug. These preliminary results indicate that ZNS is a helpful treatment option in this difficult to treat patient group.

p648

FOUR YEARS OF REMISSION IN THE FIRST UNVERRICHT-LUNDBORG CASE IN THE BALKAN REGION

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Purpose: Progressive myoclonic epilepsies (PME) are a heterogeneous group of rare inherited disorders. Unverricht-Lundborg disease (ULD) is the most common, prevalent around the Baltic Sea and in the western Mediterranean region.

Method: A 30-year-old male patient had the first symptoms of PME at the age of 15, with stimulus sensitive myoclonus and slowly progressive cerebella symptoms, rare GTC and low concentration. He was treated with mono- and polytherapy (carbamazepine, phenytoin, phenobarbital, valproic acid), inadequately responding to any. At age 26 he was hospitalised with myoclonic epileptic status. He responded to new therapy (carbamazepine excluded, dosage of valproic acid increased, piracetam slowly introduced) and after two months became self-functional. During hospitalisation all laboratory tests were normal, evoked potentials showed giant SEP, with normal EEG, CT and MRI findings. Neuropsychological examination showed minor reduction of attention, without cognitive deterioration. Molecular diagnostics (PCR based Southern blot hybridisation) confirmed ULD, which is the first case of this form of PME in this region.

Results: Today, our patient is age 30, has rare stimulus sensitive myoclonic seizures after emotional stress, but is still self-functional after 4 years. Improvement in general condition and life expectancy in ULD patients nowadays is due to the increase in social contacts, intensive rehabilitation, treatment of infections, and avoidance of phenytoin, carbamazepine and barbiturates in medication, in contrast to 1960s and early 1970s when the mean survival period was about 14 years, the patients were often confined to bed and died of infections or other incidental causes.

Conclusion: This case report is followed by video sequences at the time of hospitalisation and after four years of remission.

p649

IDIOPATHIC GENERALISED EPILEPSY: NONPHARMACOLOGICAL FACTORS INFLUENCE ON JUVENILE MYOCLONIC EPILEPSY

T. Mazurczak, I. Terczynska, D. Antczak-Marach, A. Jeziorek, K. Szymanska, J. Tryfon, D. Hoffman-Zacharska, and E. Szczepanik (Clinic of Neurology, Epileptology and Sleep Disorders in Children and Adolescents, Institute of Mother and Child, Warsaw, Poland)

Purpose: Although antiepileptic drug therapy offers complete seizure control for the majority of patients with juvenile myoclonic epilepsy (JME), relapses occur in about 10–50% of patients due to the fact that nonpharmacological factors have a great impact on the progression of the condition. The purpose of this survey was to determine the frequency of relapses in patients with juvenile myoclonic epilepsy (JME) and to determine causes of treatment failure.

Method: The records of clinical and EEG data from 36 patients (31 female and 4 male) with JME, treated between 1990–2004 with follow-up lasting at least one year, were studied retrospectively. Clinical picture, seizure types, relapse rates, seizure precipitating factors were analysed.

Results: In the study group 14 patients had myoclonic and generalised tonic-clonic seizures (GTCS), 5 patients had absence and myoclonic seizures, 16 patients had three types of seizures and one patient had only myoclonic seizures. A photoparoxysmal response in EEG tracing was present in 28 of 32 patients. All but 1 patient received valproic acid (VPA) in the average dosage of 1000 ± 380 mg (as monotherapy or in bitherapy). The average period of treatment was 5 years (range 1–5). During follow-up, 12 of 36 patients had relapses of GTCS. Among them in 4 seizure-free patients >3 years dosages of VPA were reduced by doctors to 300–400 mg per day, but this resulted in relapses of GTCS (group of "relapses due to doctor's fault").The remaining 8 patients relapsed because of non-compliance (group of "relapses due to patient's fault"). Relapses were precipitated by sleep deprivation (6 patients), failure to keep to drug dosing regimen (3), flashing light stimuli (3) and fatigue (1). Three patents had more than one seizure.

Conclusion: The important cause of relapses in patients with JME is poor drug compliance with abnormal life style, so education of a treated patient about nonpharmacological factors as seizure precipitants should be considered.

p650
EYELID MYOCLONIA WITH ABSENCES (JEAVON'S SYNDROME)
D. Domanska-Pakiela, M. Bachanski, J. Kasprzyk-Obara, D. Chmielewski, and S. Jozwiak (The Childrens' Memorial Health Institute, Warsaw, Poland)

Purpose: This syndrome is a form of epilepsy manifested by myoclonic jerks of the eyelids and brief absences. Most authors support the view that it is an idiopathic epileptic syndrome, genetically determined, age related and affects normal children with a female preponderance.

Method: An 11-year-old girl was admitted to our hospital because of episodes of squinting and upward deviation of the eyes, which occurred many times a day. She was born as a third child; pregnancy and delivery were without complications. She attended elementary school, with average results due to dyslexia, dysgraphia.

Results: Routine awake EEG showed generalised discharges of multiple spikes and polyspikes–slow waves 3-6HZ lasting 0.5-1 sek with preponderance of the left side. Therapy with valproic acid was launched, with fast cessation of seizures. Control EEG after 10 months of therapy revealed many generalised discharges as above, active for closing eyes and hyperventilation. The patient and her mother continued to deny any epileptic episodes. Full Video EEG (awake, sleep, awaking) was performed to confirm or exclude any epileptic presentations and showed many eyelid myoclonias and short absences correlating well with generalised discharges of polyspikes-slow wave complexes 2-3-4HZ, lasting 0.5–several sek, mostly observed after waking.

Conclusion: Video EEG figured out to be the only diagnostic tool in recognising full symptomatic Jeavon's syndrome.

p651
CLINICAL REVIEW OF PATIENTS WITH UNVERRICT-LUNDBORG DISEASE IN SLOVENIA
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Purpose: To assess the epidemiology of Unverricht-Lundborg disease (ULD) in Slovenia, and to review its clinical evolution.

Method: Phone questionnaire by the Centre for Epilepsy–Children and Adolescents (CfECA)–the only one in the country, addressed to regional neurological/neuropaediatric wards to exclude patients with progressive myoclonus epilepsy (PME) that might have ULD. Retrospective review of medical records for the last 25 years to study the clinical evolution of the disease and its management.

Results: A similar study 20 years ago detected no ULD patients in addition to patient 1. Between the years 1980 and 2005 2 more patients were diagnosed with ULD at the CfECA. Rare older incompletely diagnosed patients with PME having not been notified to the CfECA may still be reported in future. Patient 1 is now 40 years old; diagnosis of ULD was made on clinical and EEG grounds. Valproate enabled the wheel-chair bound adolescent to independently walk for 3 more years. Patient 2 and patient 3 are siblings, 21 and 16 years old; clinical suspicion of the diagnosis in both, was genetically confirmed in one. Beside a typical clinical picture of ULD, all patients developed arterial hypertension. Suspicion of extrapyramidal signs was not confirmed in patient 2, cognitive deterioration was mild in all, psychiatric disorder severe in patient 3.

Conclusion: In Slovenia (2 million) 3 patients have ULD. Clinical course has been typical; open questions remain. How to reach diagnosis earlier? Is arterial hypertension coincidental or part of the syndrome? Best psychiatric management?

p652
VERBAL ABILITIES IN PATIENTS WITH NOONAN SYNDROME
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Purpose: Noonan syndrome was described for the first time in 1963, as the pseudo Turner's syndrome, XX or XY Turner phenotype with the normal cariotype XY. It falls into genopathies and the last time it was described by us (The Clinics for Cerebral Paralysis and Developmental Neurology in Belgrade) in 1999, 2001 and 2002.

Method: A boy, born in 2002, with the normal male cariotype 46, XY, weighing 3700 gr., body length 52 cm, chest circumference 36 cm, AS 9; mother 24, father 33 years old. After birth, he had a prolonged physiological jaundice, slept long, woke up infrequently in comparison with other babies, did not open one eye, occasionally as if he was suffocating, stopped breathing and sucked weakly. Hydrocephalus, strabismus, epicanthus, a minor ptosis of the left eyelid, antimongoloid position of the eyes, IQ 75-80 (RPM), dysphagia, compromising logomotorics, drawn in tongue, tongue dyspraxia, high palate, head big and wide in the frontal part EEG, the left findings temporally irritable (sparse single sharp waves on the left side, with partial phase changes during sleeping), due to possible EPI fits, the therapy was introduced. The hearing, both peripheral and central, was in order. He had poor vision with ptosis of the eyelids.

Results: The logopedic findings (speech and language pathologist): there was not the prelingual period at the projected age, as with children with typical development. When he utters, he speaks loudly, laughs and cries loudly, while playing, he pronounces onomatopoeic sounds on his own initiative. He grimaces on his own initiative or as a belated reaction. He is inclined to imitate gestures of the mimic musculature in front of a mirror, together with the model and the logopedist's stimulation. We stimulate the uttering by following the phonological developmental scale; the vowel-plosive, sound games and the frequent occurrence of sound clusters or typical words or syllables typical of commencing speech.

Conclusion: After three months logopedic treatment, the patient names an idea with a single sound, a sign of approval, while more familiar ideas with a single sound, a sing of approval, while more familiar ideas with an onomatopoeia or with a part of the word. He understands the words MAMA (mummy), BABA (granny), and connects them with the idea; occasionally he pronounces them as whole words and in syllables on request.

p653
EPILEPTIC MIGRAINE IN A RASMUSSEN'S ENCEPHALITIS PATIENT
L. Fusco, N. Specchio, and F. Vigevano (Neuroscience Department, Division of Neurology, Bambino Gesù Children's Hospital, Italy)

Purpose: To report the documentation of epileptic migraine attacks in a patient with Rasmussen encephalitis developed some years after a hemispherotomy.

Method: A 14-year-old boy had a diagnosis of right side Rasmussen encephalitis at the age of 6 and a half years, one month after the onset of seizure. The illness had a typical and quick course, and the child was operated on one year later. In the following two years he had a striking recovery, except for the onset of sporadic migraine attacks of brief duration. After discontinuation of therapy, migraine attacks increased in frequency and duration and the child was readmitted for further study.

Results: A video/EEG recording was performed during a migraine attack and showed subcontinuous ictal discharges over the disconnected hemisphere, mainly over the central regions. The administration of 10 mg of diazepam i.v. caused the disappearance of epileptic discharges and simultaneously the disappearance of migraine. MR image failed to show any surgery complication and a video/EEG performed out of migraine returned to basal value. Antiepileptic and analgesic drugs were ineffective, while high dosages of corticosteroids were able to stop EEG seizures and migraine.

Conclusion: The present case illustrates a late and very rare complication of Rasmussen encephalitis, and demonstrates how migraine attacks can be not only triggered by epileptic discharges but also remitted with their remission.

p654
COMPARATIVE EVOLUTION OF THE CLASSIFICATIONS OF EPILEPSIES AND HEADACHES

J. Gomez Alonso, B. Giraldez, M. Rodriguez, and P. Bellas (Servicio de Neurologia, Hospital Universitario Xeral-Cies. Vigo, Spain)

Purpose: To compare the results of the efforts made by the International Headache Society (IHS) and the International League Against Epilepsy (ILAE) to improve the Classifications of Headaches and Epilepsies.

Method: Comparative clinical applicability of the classifications launched by the IHS and the ILAE.

Results: Both the 1988-IHS and the 1989-ILAE Classifications had worldwide acceptance. The 1988 Classification of Headaches is a 90-page document that includes definitions and descriptions of the disorders, operational diagnostic criteria, and rules to classify difficult cases, as well as 373 selected references. The 1989 Classification of Epilepsies appeared in an 11-page paper which included 6 references, and provided a brief description of the syndromes, although lacked operational diagnostic criteria. Moreover, some fundamental criteria were imprecisely defined, and irregularly used along with the classification. Finally, some proposed subgroups were not mutually exclusive. After meticulous work by several subcommittees and open discussions in international meetings, the IHS published an improved version of the Classification of Headaches in 2004. Meanwhile, the ILAE has not been able to revise the imperfect and outdated 1989 Classification. In 2001, an ILAE document (8 pages, 5 references) considered that the 1989 Classification could not be replaced by a similar one, and proposed a diagnostic scheme which would permit a variety of approaches to classification.

Conclusion: The IHS has been more successful than the ILAE in developing an updated and useful classification in their respective fields. The different methods used by both Societies might have had some influence on the divergent results.

p655

EFFECTS OF SUBCLINICAL EEG DISCHARGES ON BEHAVIOUR IN CHILDREN

N. Ismail and Y. Yýlmaz (Marmara University, Istanbul, Turkey)

Purpose: To investigate the effects of subclinical EEG discharges on behaviour in children.

Method: Children under 10 years of age attending the outpatient clinic with behavioural problems whose EEG examination showed epileptiform discharges were included in the study. Patients with neurological, neuroradiological findings, epileptic seizures, medical or familial problems, and mental retardation which might effect the behaviour pattern were excluded. Behaviour was assessed with the Conners rating scales for parents and teachers. Valproic acid 20 mg/kg/day was started. EEG examination and Conners rating scales for parents and teachers were repeated again after 4 weeks and the results compared.

Results: Preliminary results of 6 patients assessed are included and the study is still continuing. Those patients started on valproic acid showed a significant improvement in behaviour on the Conners rating scales.

Conclusion: Our data suggests that suppressing subclinical discharges can improve behaviour in children. With an increase in the number of patients assessed at the end of the study a more detailed result will be discussed.

Wednesday July 5, 2006
13:30–15:00
Poster Session 3
Paediatric Epileptology

p656

CHANGING INCIDENCE OF EPILEPSY IN FINLAND

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Purpose: To study possible changes in the incidence of epilepsy in Finland.

Method: Secular trends in the incidence of epilepsy are poorly known. All residents with epilepsy have been granted full-refundable antiepileptic drugs since 1967, and the patients are centrally registered by the Social Insurance Institution. We analysed these data from the years 1986–2002.

Results: There was a marked decreasing trend in the incidence of epilepsy, from 72 in 1986 to 53/100,000 in 2002. The incidence was throughout all age groups, and was higher in men than in women during the whole observation period. The incidence significantly decreased in children (0.77; 0.71–0.84, $p < .0001$) and middle-aged (0.83; 0.77–0.89, $p < .0001$), but increased in the elderly (1.18; 1.10-1.26, $p < .0001$). In children, the decrease was least in the age group 0–4 years, more considerable in 5–9 year olds and most marked in 10–14 year olds. Among the elderly, the trend was an increasing one in all subgroups. The trend varied nonsignificantly between the five-year age groups in men, but invariably increased from the age of 70 years in women.

Conclusion: The incidence of epilepsy has consistently decreased in the 1980s and 1990s in Finland. The decrease is in children and adults of working age, while a distinct increase in the elderly has taken place.

p657

CORTICOSTEROID EFFICACY IN EPILEPTIC SYNDROMES WITH CONTINUOUS SPIKES AND WAVES DURING SLOW SLEEP

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Purpose: To report our experience in treating patients with continuous spikes and waves during slow sleep (CSWS) with corticosteroids.

Method: Children who received corticosteroid therapy for behavioural and/or cognitive deterioration associated with the CSWS pattern were retrospectively reviewed. In all cases, awake and sleep EEG records, clinical examinations and neuropsychological assessments were available before and after corticosteroid therapy. Eleven patients received hydrocortisone, 5 mg/kg/day for 1 month, and the other 2 patients received prednisolone, 2 mg/kg/day for 1 month. In children with clinical and EEG improvement, the treatment was continued at a low dose until 21 months.

Results: Thirteen patients, aged 3–12 years, were included. Eleven cases were cryptogenic and 2 cases were related to perisylvian polymicrogyria. All but 1 patient (a child with Landau-Kleffner syndrome) were refractory. The antiepileptic drugs (AEDs) which had failed were valproate (12 cases), clobazam (12 cases), lamotrigine (9 cases), topiramate (7 cases), and levetiracetam (3 cases). Ten patients (77%), including the symptomatic cases, showed disappearance of the CSWS pattern with normal EEG in 5 cases. This evolution was associated with cognitive and behavioural improvement. Only in 1 case was the treatment stopped because of side effects. In 3 patients, corticosteroid discontinuation was followed by relapse of the CSWS pattern.

Conclusion: This study suggests that children with CSWS show better response to corticosteroid therapy than to classical AEDs.

p658

COMPARING THE EFFECT OF INTERMITTENT CLONAZEPAM WITH DIAZEPAM IN PROPHYLAXY OF FEBRILE CONVULSIONS IN CHILDREN

T. Mahmoudian and S. Bajoghli ([1]Pediatric Neurology Department, Medical University of Isfahan, Iran)

Purpose: Febrile convulsion (FC) is one of the most common neurological disorders in children. There are many different studies about FC treatment and many different drugs have been used for it, but since there is not any proved document about the prophylactic effect of clonazepam for FC, this study wants to compare the effect of intermittent clonazepam with diazepam in prophylaxy of FC.

Method: This is an experimental study and was done with two groups using a randomised trial control method. For the first group, clonazepam 0.05 mg/kg/day was administered during the fever period and for the second group diazepam 1 mg/kg/day was administered. The occurrence of FC was compared between the two groups.

Results: In our study there was no significant difference in age, sex, type of seizure and family history of FC between the two groups. Thus each group had a similar risk for recurrence of FC. In the first group (clonazepam) 30 patients were selected and 6 patients were exited from the group. 162 febrile episodes occurred in 24 patients and none of them had a convulsion during episodes of fever (this means clonazepam was 100% effective). In the second group (diazepam) 30 patients were selected and 7 patients were exited from the group. 100 febrile episodes occurred in 23 patients in this group and 2 cases had a convulsion with fever with consumption of diazepam (this means that diazepam was 98% effective). Statistically the p value between the two groups was 0.14 which means there is a difference between the two groups but this difference isn't meaningful statistically.

Conclusion: An important result of this study is that clonazepam is as effective as diazepam for FC prophylaxis. In our study clonazepam was 100% effective. There are mild complications such as ataxia, restlessness and somnolence but these complications were not severe enough to discontinue the drug. With respect to similar effectiveness of clonazepam and diazepam in our study and absence of significant complications, this study is an introduction for more extensive studies of the effect of clonazepam on FC prophylaxis.

p659

LEVETIRACETAM INFLUENCE ON CONTINUOUS SPIKES AND WAVES DURING SLOW SLEEP

M. Nikanorova and J. Alving (Danish Epilepsy Centre, Dianalund, Denmark)

Purpose: To assess levetiracetam (LEV) effect on continuous spikes and waves during slow sleep (CSWS).

Method: 10 children (6 boys, 4 girls), aged between 6 and 14 years, with CSWS have been treated with LEV for 3–6 months. In all cases CSWS was refractory to conventional AEDs and corticosteroids. LEV was used as an add-on drug at the doses 25–45 mg/kg/day. LEV efficacy was assessed with 24-hour EEG monitoring after 2, 4 and 6 months of therapy initiation.

Results: After 2 months of LEV treatment awake EEG became normal in 3 patients, in 2 a marked decrease of multifocal activity was observed; CSWS disappeared in 7 children, one case showed moderate reduction of CSWS (from 85 to 53% during whole night recording), in 2 cases there was no effect. In those 7 responders CSWS did not recur after 6 months of LEV therapy. LEV was well tolerated by all patients.

Conclusion: LEV can be considered as an additional therapeutic option in children with CSWS, especially in cases refractory to conventional antiepileptic drugs and corticosteroids.

p660

SYMPTOMATIC EPILEPSY IN SHAKEN-IMPACT SYNDROME

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Purpose: To evaluate the influence of different treatment methods on Shaken-Impact Syndrome (SIS) outcome.

Method: Twenty-one patients with SIS, aged 2 to 9 months, were observed and treated in the acute and residual period. The following clinical investigations were performed on all patients: fundoscopy, roentgenography, lumbar puncture, CT, EEG.

Results: The diagnosis of SIS was established in the acute period according to the criteria of Pediatric Community on Child Abuse and Neglect (American Academy). Severity of clinical state, neurological symptoms and CT data (zones of brain ischemia) in the acute phase were comparable in all patients. Symptomatic epilepsy developed in 11 cases. All patients were divided into 3 groups, according to the therapeutic approach in the acute phase and outcome. In groups 1 and 2 management in the acute period corresponded to conventional recommendations (symptomatic in general). In group 1 (8 patients) symptomatic epilepsy developed in 6 cases (none drug-controlled), motor deficit remained severe in 8 and development was ceased also in 8 cases (outcome was poor in all cases). In group 2 (7 patients) symptomatic epilepsy developed in 5 cases (drug controlled in 3), motor deficit remained significant in 5 and development delay was expressed in all. None had even a satisfactory outcome. In group 3 (6 patients) our original treatment was conducted immediately after registration of retinal haemorrhages. None of the patients developed symptomatic epilepsy, neither motor nor sensory deficit; development was not delayed in anyone (good outcome).

Conclusion: Outcome in SIS (symptomatic epilepsy, motor and sensory deficit development, mental retardation) depends upon management in the acute stage.

p661

CHILDHOOD AND JUVENILE ABSENCE EPILEPSY

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Purpose: To analyse types and dynamics of seizures in childhood and juvenile absence epilepsy. Anamnesis, clinical-instrumental investigation findings were taken into account.

Method: 16 patients with childhood absence epilepsy, aged from 4 to 9 years 3 months and 4 patients with juvenile absence epilepsy, aged from 10 years 2 month to 14 years, were examined. All children were studied with a full clinical assessment including CT, MRI and EEG.

Results: Among all 16 patients with childhood absence epilepsy the condition manifested from complex absence seizures, which were the leading seizures type. Absence seizures were characterised by the sudden suppression of mental functioning of brief duration (5–15 sec). Absence frequency was from dozens to hundreds per day. In 12 patients more then one motor component was observed during an absence attack. In 4 patients tonic–clonic seizures appeared later during the course of disease. All children with childhood absence epilepsy (16 patients) had a normal intelligence level before and after seizure manifestation. EEG features of typical absence attacks consists of generalised, symmetrical, and synchronous spike-wave complexes with frequency of 3–3.5 Hz. Hyperventilation provoked these EEG patterns in all patients. CT and MRI examinations did not reveal any abnormalities. Sodium valproate monotherapy showed a good final seizure response in 80% of patients. Among the examined 4 patients with juvenile absence epilepsy the condition manifested from tonic–clonic seizures; in 3 cases simple absence attacks and in one case complex absence seizures with motor components appeared later. Nonpyknoleptic seizures were characterised by the sudden suppression of mental functioning of brief duration (5–10 sec), non-pyknoleptic seizure frequency was lower: 3–4 per week. All children with juvenile absence epilepsy (4 patients) had normal intelligence level before and after seizure manifestation. EEG features of non-pyknoleptic absence attacks consisted of generalised, symmetrical, and synchronous spike-wave complexes with frequency of 3.5–4 Hz. Hyperventilation provoked these EEG patterns in 3 patients. In juvenile absences consciousness loss was superficial and difficult to register. CT and MRI examinations did not reveal any abnormalities. Sodium valproate monotherapy showed a good final seizure response in 75% of patients with juvenile absences.

Conclusion: Childhood absence epilepsy prevails among epileptic syndromes of childhood with typical absence seizures. It is important to follow-up patients with childhood absence epilepsy until adolescence, because sodium valproate dosage decrease at this age might result in the development of generalised tonic–clonic attacks. Juvenile absence epilepsy manifests with tonic-clonic seizures with absences developing later during the disease course. Sodium valproate monotherapy ensures seizure control in 75% of patients.

p662

COMPARISON OF TOPIRAMATE AND GABAPENTIN IN REFRACTORY EPILEPSY IN CHILDREN

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Purpose: Childhood epilepsy represents a significant clinical challenge. Since it is a chronic disorder the long term effectiveness and tolerability of the medications are very important. Topiramate (TPM) and gabapentin (GBP) are two new antiepileptic drugs (AEDs) used in patients refractory to conventional drugs. The aim of the study is to investigate the efficacy, safety and adverse event profile of these two agents used as add-on therapy in children with refractory epilepsy.

Method: Sixty-five patients (38 males, 27 females) suffering from epilepsy were enrolled consecutively from September 2002 to September 2003 and evaluated in January 2005. All patients underwent haematologic, biochemical investigations and all had EEG and cranial MRI at enrollment. In group I, TPM was started with 0.6–1.1 mg/kg/day and was titrated to a target dose of 6 mg/kg/day. In group II, GBP was administered with a dose of 30–40 mg/kg/day. The efficacy, safety and adverse event profile of these two agents used in children with refractory epilepsy were studied allowing at least one year follow-up. Data were calculated on the SPSS 11.0 Windows programme and Pearson correlation test, Mann-Whitney U test, Willcoxon test and Fisher's exact test.

Results: The mean age was 9.5 ± 2.8 with a range of 4.1 and 13.8 years old. The median frequency of seizure at baseline was 4 and 4.5 monthly in group I and II respectively. In group I, seizure control was seen in 78.3% of the patients at the end of one year with the avarage dose of 6.3 ± 1.8 mg/kg/day. The final seizure control rate for the second group was 60.7% with the avarage dose 50 ± 4.5 mg/kg/day. Seizure frequency decreased significantly after one year of add-on therapy to I and II. Side effects were reported in 14 patients in group I (37.8%) and 6 patients in group II (21.4%). Most common adverse effects in both groups were nervousness and headache.

Conclusion: The two drugs decreased the seizure frequency but no difference in efficacy of seizure types was observed; so they were effective, safe and well tolerated but none was prior to the other.

p663

WEIGHT CHANGE BY OXCARBAZEPINE MONOTHERAPY IN CHILDHOOD EPILEPSY

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Purpose: To evaluate the changes of body weight associated with oxcarbazepine monotherapy in children with epilepsy.

Method: We conducted a retrospective review of 71 childhood epilepsy patients (40 boys, and 31 girls) attending Pusan National University Hospital on oxcarbazepine monotherapy for at least 3 months. We evaluated the changes of standard deviation scores (SDS) between the baseline body weight and the posttreatment body weight.

Results: The mean age of the patients at diagnosis was 7.3 years old and the mean body weight SDS at diagnosis was 0.389 ± 1.560. After the administration of oxcarbazepine, the mean body weight SDS increased substantially to 0.577 ± 1.795 ($p < 0.05$). A significant increase of the body weight SDS were observed especially in boys, children under 7 years old, patients with partial seizures, patients with idiopathic epilepsies, and patients with negative body weight SDS at diagnosis.

Conclusion: Oxcarbazepine monotherapy was associated with significant weight gain in children with epilepsy. It is necessary to warn patients starting oxcarbazepine medication of the possible body weight gain and to advise them to start a diet and routine exercise.

p664

EARLY EFFECT OF CARBAMAZEPINE MONOTHERAPY ON HOMOCYSTEINE METABOLISM IN CHILDREN WITH EPILEPSY

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Purpose: Hyperhomocysteinemia is an independent risk factor for cardiovascular disease and thrombosis. Prolonged treatment with some antiepileptic drugs, including carbamazepine, may cause hyperhomocysteinemia. The aim of this study was to investigate whether a short-term period of carbamazepine monotherapy may have an effect on homocysteine metabolism.

Method: Fasting plasma total homocysteine, serum folate, serum vitamin B12 and plasma pyridoxal-5′-phosphate was measured in 20 children (aged 4–14 years, mean age $\pm$ SD: 9.2 ± 3.2 years) before and after a 20-week period of carbamazepine monotherapy.

Results: The mean fasting plasma total homocysteine value significantly increased in the 20-week period of carbamazepine treatment (6.8 ± 1.5 vs 7.7 ± 1.7 μmol/l, $p \sim 0.009$). The mean values of serum folate and plasma pyridoxal-5′-phosphate significantly decreased (7.9 ± 3.2 vs 6.2 ± 1.9 nmol/l, $p \sim 0.033$ and 48.4 ± 11.3 vs 42.1 ± 8.7 nmol/l, $p \sim 0.001$, respectively), while the mean concentration of serum vitamin B12 did not significantly change during therapy. Serum levels of carbamazepine were within the therapeutic range during the period of the study. There was no correlation between the above parameters and the serum carbamazepine levels at 20 weeks of therapy.

Conclusion: Carbamazepine monotherapy may increase fasting plasma total homocysteine early in the course of treatment in children with epilepsy. This increase seems to be associated with low concentrations of serum folate and plasma pyridoxal-5′-phosphate.

p665

PSEUDOGENERALISED SEIZURES CAUSED BY SECONDARY BILATERAL SYNCHRONY PHENOMENON IN SYMPTOMATIC FRONTAL LOBE EPILEPSY

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Purpose: To investigate the electroclinical correlates of seizures caused by secondary bilateral synchrony phenomenon (SBS) among patients with symptomatic frontal lobe epilepsy (SFE).

Method: We observed 14 patients (8 men and 6 women) aged 2–20 years (medium 10.4 years) with the established diagnosis of SFE with SBS on the EEG. Detailed anamnestic data, neurological investigation, video-EEG monitoring (VEM) (Biola, Medicom, Russia), MRI, antiepileptic drug levels in blood were detected.

Results: According to anamnestic data, and at the moment of examination, focal seizures were observed in 57% of patients. Synchronously with SBS phenomenon, the following seizure types were clinically marked: atypical absences 57% cases, short tonic spasms with asymmetric motor phenomena 36%, eyelid myoclonia with absences 29%, myoclonic seizures 14%, myoclonic absences 7%, atonic, including atonic-astatic seizures 7%. Atypical absences had video-EEG correlation with diffuse bilateral-synchronous spike-and-wave discharges; myoclonic absences with diffuse bilateral-synchronous polyspike-waves; eyelid myoclonia with absences, with diffuse asynchronous discharges of polyspike-wave complexes; and myoclonic seizures with diffuse asynchronous discharges of polyspike-waves (or) diffuse polyspikes; short tonic spasms with diffuse fast activity with the frequency about 30 Hz ("recruiting rhythm"). In all cases the beginning of diffuse discharges of SBS phenomenon was preceded by regional epileptiform activity. In all patients the deficit of cognitive functions was observed. Seizures were resistant to antiepileptic drugs in all patients. Valproic acid was the drug of first choice as monotherapy. For the cases resistant to valproates, we combined it with levetiracetam, ethosuximide or topiramate.

Conclusion: Registered seizures during VEM had clinical and EEG features of generalised seizures, but their origin was focal due to SBS phenomenon. For such seizures we offer the term "pseudogeneralised seizures."

p666

CLINICAL CHARACTERISTICS AND TREATMENT OF EPILEPSY IN CHILDREN WITH CHROMOSOMAL DISEASE

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Purpose: The aim of this study is to estimate the outcome of epileptic seizures in children with chromosomal disease.

Method: We included in the study 21 children (9 girls and 12 boys) diagnosed with genetic syndromes and epilepsy (14.28% Angelman syndrome, 9.52% Klinefelter syndrome, 33.36 Down syndrome, 14.28% trisomy 18, 9.52% trisomy 13, 19.04% X-fragile).

Results: The age of onset of epilepsy was 2 months–8 years. At the beginning seizures were: febrile (19.04%), partial complex (23.80%), partial (4.76%), generalised (42.36%), and infantile spasms (14.28%). Nine patients have a family history of epilepsy. The evolution of seizures was heterogenic: 38.09% generalised epilepsy, 61.91% partial epilepsy. The EEG was abnormal for all children; the epileptiform discharges were multifocal or focal in 6 cases, hypsarrhythmia in 3, generalised spike-wave discharges in 8 and attenuation of background activity with bilateral or generalised spikes discharges in 4 patients. The children were treated employing ACTH, sodium valproate, lamotrigine, clonazepam single or add-on. Therapeutic efficacy was estimated by the percentage of patients who had achieved a significant clinical response. Seizure control was achieved in 61.9% patients.

Conclusion: Epilepsy is particularly common with chromosomal disease and the risk for seizures varies in different types of this disorder. Our data suggest that a family history of seizures and association with mental retardation increased the risk for epilepsy in children with chromosomal disease. Therapeutically efficacy was variable depending on type of seizures or antiepileptic drugs used.

p667

CHARACTERISTIC AND PROGNOSIS OF SEIZURES FOR CHILDREN WITH CEREBRAL PALSY

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Purpose: To reveal the clinical types and prognosis of seizures for children with cerebral palsy (CP)

Method: We used a group of 117 children (aged 4.5–17 years) diagnosed with different types of CP (spastic tetraplegia-43, spastic diplegia-35, hemiplegia-29, mixture-10). A family history of epilepsy or febrile seizures was present in 16.24% of patients. 79.48% of children had associated mental retardation.

Results: All types of seizures were present (generalised tonic–clonic 44.44%, simple or complex partial seizures 38.46%, atypical absence 17.09%, tonic 6.83%, myoclonic-astatic 14.53% and atonic 18.08%). The age of onset was correlated with type of CP. 18 patients had a history of infantile spasms and in evolution 8 have the diagnosis of Lennox-Gastaut syndrome (LGS). 67 patients have a history of status epilepticus. A correlation between the distribution of seizures and different forms of CP was observed. Partial seizures were more frequent in patients with hemiplegia (79.31%) and generalised tonic–clonic was more common in diplegia and tetraplegia (55.13%). Children with tetraplegia revealed a high incidence of LGS (18.60%) and epilepsy with myoclonic-ataxic seizures (27.90%). 37.60% of children received monotherapy and 62.40% polytherapy with different antiepileptic drugs. Patients with tetraplegia and hemiplegia more often needed polytherapy (48.83% and 37.93%). A significant seizure reduction (50%) was observed in 29.05% of patients, 52.13% had seizure refractory to treatment and 18.82% were seizure-free for 36 months.

Conclusion: All types of seizures can be present in children with CP. Associated CP and mental retardation increase the risk of epilepsy. Antiepileptic therapy raised important problems to those children because the type of CP represents an aggravating factor.

p668

AGE- AND DOSE-RELATED HYPONATREMIA DURING CARBAMAZEPINE AND OXCARBAZEPINE THERAPY IN CHILDREN WITH EPILEPSY

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Purpose: To assess the prevalence of biochemical hyponatremia (BH) and the clinically relevant hyponatremia (CRH) in children with epilepsy who are receiving carbamazepine (CBZ) or oxcarbazepine (OXC), retrospectively.

Method: We reviewed the clinical data of 197 patients, who were divided into 67 CBZ-treated, 75 OXC-treated and 55 patients CBZ or OXC with add-on treated as group I, II and III. S- Na^+ levels (mEq/L) before treatment were used as controls. We defined hyponatremia as S-$Na^+ < 135$. Predictive factors for occurrence of hyponatremia according to age, serum CBZ(S-CBZ) levels, and daily OXC dose were examined.

Results: Mean S-Na^+ level was 140.8 ± 3.8 before treatment. The overall prevalence of hyponatremia was 20.8%, and this was significantly lower in groups II and III compared with controls ($p < 0.05$). Serum Na^+ levels relation to S-CBZ levels: those with levels >10ug/ml were significantly lower than those with <10 ug/ml), and to daily OXC dose: those with >30mg/kg/day were significantly lower than those 20–30 mg/kg/day ($p < 0.05$), but, not in age-related: patients less than 10 years compared with patients over 10 years old. Out of 41 patients having BH, 7 had CRH (3.7%) (5 patients: $120 \leq Na^+ < 125$, 2 patients: $Na^+ < 120$). There were clinical symptoms in each 0.5–2.0%: nausea and vomiting, headache, seizure, mental confusion, anxiety, and delusion.

Conclusion: The prevalence of BH and CRH were 20.8% and 3.7%, respectively. Hyponatremia occurred more often in the OXC and/or add-on treated group. There were significant differences with high S-CBZ and high daily OXC dose for occurrence of hyponatremia, but not in age related.

p669

EPILEPSY IN CHILDREN WITH CEREBRAL PALSY MIGHT BE REVEALED DURING THE SECOND DECADE OF LIFE

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Purpose: The majority of studies concerning the occurrence of epilepsy with cerebral palsy (CP) points out the particular frequency of epilepsy occurrence in the first years of life, and the severity of its course. The aim of this study was to establish the onset and the course of epilepsy during the period from 1 to 20 years.

Method: The clinical records of 106 children with epilepsy and CP were retrospectively evaluated from the first seizures to 20 years of life.

Results: The occurrence of the first seizures was most frequent at age 4 (63% in hemiparetic cp, 87% in quadriparetic CP form). In 28% of cases epilepsy revealed after age 10; most frequently in diparetic and hemiparetic cp. In 21% of patients the treatment was finished before age 20. 75% of cases were on monotherapy. In the 10th and 14th year of life the frequency of epileptic attacks decreased respectively in 27% and 14% and at the same time increased in 14th to 18th year of life in 18% and 10% of the group.

Conclusion: 1. The first epileptic attack might occur in CP patients during their second decade 2. The majority of epilepsy patients with CP are well controlled on monotherapy 3. During the second decade of life the course of epilepsy in CP improved in almost one third of patients, but frequency of the attacks might also increase in the teen years and in early adulthood.

p670

EFFECT OF ANTICONVULSANTS ON SERUM COPPER AND ZINC CONCENTRATION

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Purpose: Anticonvulsants have a number of side effects and some of them may be attributable to a disturbance of serum trace metal homeostasis. Although there are minor components in tissues, they play important functional roles in the peripheral and central nervous system. We measured serum copper and zinc levels in children with epilepsy who were

treated with anticonvulsants to find the effects of the anticonvulsant on serum copper and zinc levels.

Method: Serum copper and zinc levels were determined in 64 epilepsy patients receiving anticonvulsant therapy for more than 6 months in Chungnam National University Hospital, and in 20 normal controls. Sixty-four epilepsy patients were divided into three groups: 16 patients treated with valproic acid monotherapy; 26 patients treated with valproic acid in addition to another anticonvulsant; and 22 patients treated with an anticonvulsant other than valproic acid.

Results: All patients receiving anticonvulsants had significantly lower serum copper levels (80.21 ± 19.42 □/dL) in comparison to the normal controls (102.12 ± 32.8 □/dL). Serum zinc levels in patients receiving anticonvulsants (79.78 ± 21.88 □/dL) were not statistically different from those of controls (85.26 ± 29.81 □/dL). There were no significant differences of serum copper and zinc levels among the three groups.

Conclusion: In this study, we clearly showed that anticonvulsants decreased serum copper levels. Although we did not observe any clinical findings related to copper deficiency, we should pay attention to copper deficiency in patients with anticonvulsants.

p671

STUDY OF THE NEUROPROTECTIVE EFFECT OF THE L-TYPE CALCIUM CHANNEL BLOCKER FLUNARIZINE ON THE DEVELOPMENTAL OUTCOME OF INFANTS WITH WEST SYNDROME

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Purpose: West syndrome is considered to be one of the "catastrophic" childhood epilepsies and is associated with arrest or regression of cognitive development. Only 15 to 20% of the children develop normally. Evidence from animal studies and clinical research suggests that the L-type calcium blocker flunarizine (nimodipine) possesses neuroprotective properties against seizure-induced brain damage. In the pilot study reported here we intended to test the effect of flunarizine on cognitive outcome in infants afflicted with West syndrome.

Method: Flunarizine or a placebo was administered as an add-on drug to standard treatment (vigabatrin) to 11 infants, aged 4 to 17 months, with new onset of infantile spasms in a double-blind, randomised paradigm. The patients were assessed on the Griffiths Mental Developmental Scales at diagnosis (baseline) and 6 and 12 months after initiation of treatment.

Results: The infants in the active treatment group showed substantial improvement of their global developmental quotient (mean gain of 7.8 points) with normalisation of the psychomotor status in 2 patients. The children in the placebo group failed to show any notable improvement (mean loss of 4.7 points: 15 points in 1 and no changes in 2 others), except for a patient with tuberous sclerosis who improved on vigabatrin alone. Significant differences between the two groups were observed in object manipulation (performance), hearing and speech and eye-hand coordination ($p < 0.05$).

Conclusion: Flunarizine may have the potential to arrest, and possibly reverse cognitive deterioration in infants with West syndrome. A Canada-wide, multicentre study is presently underway to further explore this hypothesis.

p672

COMBINATION OF DEPAKIN AND MEXIDOL IN TREATMENT OF CHILDREN WITH PRIMARY GENERALISED EPILEPSY AND MONOTHERAPY WITH MEXIDOL FOR FEBRILE SEIZURES

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Purpose: The aim of our study was to estimate the role of a combination of depakin and mexidol (antioxidant) in stopping epileptic fits and improving electroencephalographic (EEG) pathological patterns in children.

Method: 180 patients with generalised epilepsy (from 4 to 16 years old) were investigated. All patients were treated by depakin chrono–30 mg/kg. Children were divided into 2 groups. The study group consisted of 90 children with a combined treatment of depakin and mexidol (5mg/kg). In the control group (90 children) only depakin was administered. 140 children with the first episode of febrile seizures (from 6 month to 4 years old) were investigated. 70 children comprised the study group treated by mexidol and 70 patients the control group without any treatment.

Results: Using depakin in combination with mexidol in the study group of patients with generalised epilepsy has revealed improvement of the clinical picture of disease and normalisation of EEG patterns in 93% of cases. In the study group of patients with febrile seizures, normalisation of EEG pathological patterns and its improvement was seen in 82% and 18% of cases, relatively. The relapse of febrile seizures was observed in 3 cases. In the control group EEG patterns were improved only in 20% and in 41% its worsening was seen. The relapse of febrile seizures was observed in 26 cases.

Conclusion: Mexidol titrated to the target doze of 5mg/kg may be effective in combination with depakin for treatment of patients with generalised epilepsy and as a monotherapy in patients with a first episode of febrile seizures.

p673

TREATMENT RESULTS IN EPILEPSY CAUSED BY CYTOMEGALOVIRUS INFECTION

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Purpose: Symptomatic epilepsy can be caused by viral infections, including cytomegalovirus infection, which is the most frequent congenital viral infection. Seizures occur in the neonatal period, during the 1st year of life or later in early childhood. We therefore investigated the evaluation of treatment results in infants with different types of epilepsy in congenital/perinatal human cytomegalovirus infection categories.

Method: We reviewed 84 infants (47 female, 37 male) treated in The Children's Memorial Health Institute in Warsaw from 1 January 1995 to 31 December 2005 with epilepsy and confirmed cytomegalovirus infection established as the aetiological factor of the seizures. DNA HCMV was found by PCR method in cerebrospinal fluid, blood leukocytes and urine. Infants were treated with different AEDs and followed up from neonatal period on.

Results: In 10 infants, tonic–clonic seizures started during the 1st month of life. In 2 infants with cytomegalovirus infection diagnosed in the 2nd month of life, partial onset seizure began in the 3rd year of life. Onset of infantile spasms, partial onset seizures with and without generalisation and myoclonic seizures, in the vast majority of infants occurred during the 1st year of life. Nine featured very severe, drug resistant epilepsy. One infant died. Vigabatrin, phenobarbital, lamotrigine and carbamazepine monotherapy were effective in 26 cases. In 11 treated alongside antiviral with ganciclovir, after more than 2 years seizure-free period antiepileptic drugs were withdrawn.

Conclusion: 1) Early treatment of epilepsy caused by HCMV infection can result in long term cassation of seizures. 2) Antiviral treatment should be considered.

p674

ANTIEPILEPTIC EFFECT OF ZONISAMIDE IN PAEDIATRIC INTRACTABLE EPILEPSY

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Purpose: To confirm the effectiveness and safety of zonisamide in paediatric intractable epilepsy.

Method: We retrospectively reviewed the medical records of 41 children with intractable epilepsy, who had taken zonisamide and had been followed up for more than 6 months at the Division of Paediatric Neurology, Asan Medical Center.

Results: The study cohort included 41 patients with intractable epilepsy, some of whom had more than one antiepileptic drug but whose seizures were medically intractable. There was a male predominance (24/17). Zonisamide starting age was 7.7 ± 5.3 years. Seizure reduction

rate of more than 50% was 43.9% (18/45). According to seizure types, results were as follows: 1) generalised seizures (n = 25), {Lennox-Gastaut syndrome (n = 15), infantile spasm (n = 2), myoclonic seizures (n = 2), and generalised tonic–clonic seizures (n = 3)} was 52% (13/25); 2) secondarily generalised tonic–clonic seizure (n = 9) was 22.2% (2/9); 3) complex partial seizure (n = 1) was 100% (1/1); 4) mixed seizure (n = 6) was 33.3% (2/6). Mean effective dose was 10.4 ± 3.9mg/kg/day. Major side-effects were not detected.

Conclusion: Zonisamide is effective and safe as an adjunctive antiepileptic drug for paediatric intractable epilepsy.

p675

HIGH NEONATAL MORTALITY RATE IN PRETERM NEWBORNS WITH NEONATAL SEIZURES AND THE ASSOCIATION WITH VIDEO-ELECTROENCEPHALOGRAPHY

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Purpose: The aim of the study was to examine the neonatal mortality rate of preterm infants with seizures and the association with the first video-electroencephalography.

Method: We analysed all preterm infants consecutively admitted to the neonatal intensive care unit of the University Hospital of Parma, from January 1999 to June 2003. 34 newborns were selected according to the following criteria: gestational age below 37 weeks, repeated neonatal video-EEG confirmed seizures, need of chronic anticonvulsant therapy, neurological follow-up up to 24 months of corrected gestational age.

Results: An abnormal video-EEG recording is significantly associated with mortality rate ($p < 0.001$). Normal EEG activity or activity with mild alteration were found in 10 newborns in our study group and their mortality rate was 10% (1/10); moderate abnormality in EEG activity was found in 13 newborns and their mortality was 23.1% (3/13); finally severe abnormality in EEG activity was found in 11 infants, with a mortality rate of 81.8% (9/11). In a comparison between 21 preterm infants in our study group (with seizures and with gestational age below 34 weeks), and a control group of 217 preterm infants with the same gestational age and without seizures, the mortality of our study-group was 39%, while the control-group reports a mortality of 14.7% ($p = 0.002$).

Conclusion: In our study the first EEG, performed during the neonatal period, appears to be a strong predictor of mortality rate in preterm infants with seizures, and among these the percentage of mortality is significantly higher than that of newborns without seizures and with the same gestational age.

p676

NONEPILEPTIC SEIZURES IN CHILDREN AND YOUNG PEOPLE WITH COMPLEX EPILEPSY AND LEARNING DISABILITY

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Purpose: To describe the clinical features of nonepileptic seizures (NES) and to review management strategies and outcomes in children and young people with complex epilepsy and learning disability.

Method: Retrospective review of case notes of patients attending a specialist epilepsy centre in the UK from 2001–2005. Further information was obtained by interviewing carers. EEG/video telemetry reports were reviewed for detail of the attacks and to confirm the diagnosis.

Results: Fifteen patients with NES (7 males, 8 females) aged 12–21 years were included. All patients have coexisting epilepsy, 14 cases have learning disability, and 7 cases have psychiatric conditions. The most frequent manifestations of NES were convulsive-like (46.6%) and with motor symptoms (33.3%), similar to previous reports. Common characteristics observed were: maintenance of responsiveness, awareness of events, absence of seizure-related injuries, and presence of witnesses. NES were confirmed by EEG/telemetry in 14/15 patients; this led to medication reduction or change in emergency treatment in 4 cases. 12 patients received psychological treatment: cognitive behaviour therapy, behavioural management, relaxation training, or supportive counselling. 7 patients (58%) showed a reduction or elimination of NES, which is less than the outcomes in previous studies in populations with no associated co-morbidities.

Conclusion: Despite various presentations, NES episodes share common characteristics that may distinguish them from epileptic seizures. The high percentage of coexisting epilepsy and learning disability in this study group, may contribute to the differences noted in the clinical manifestations and treatment outcomes when compared to previous studies.

p677

SOME RISK FACTORS FOR CHILDHOOD EPILEPSY: A CASE-CONTROL STUDY

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Purpose: The goal of this case-control study was to identify the significance of certain risk factors for epilepsy in Turkey.

Method: A total of 805 cases aged 1–16 years, followed-up for epilepsy at the Pediatric Neurology Departments of Gazi University Medical Faculty and Dr. Sami Ulus Pediatric Diseases Training and Research Hospital, and a control group consisting of 846 age matched cases without epilepsy, followed-up at the Gazi University Medical Faculty General Pediatric Outpatient Department, were included in the study. The data on the patients and control subjects were obtained through a questionnaire via personal interviews. The medical records were then reviewed and were analysed.

Results: Univariate analysis showed an increased risk for epilepsy with male sex (1.38-fold), abnormal neurological signs (5.92-fold), history of febrile seizure (9.29-fold), severe and moderate head injury (27.76- and 7.09-fold respectively), CNS infection (4.76-fold), history of epilepsy in first-, second- or third-degree relatives (6.42-, 3.09- and 2.66-fold respectively), presence of maternal hypertension (4.31-fold), an apgar score ≤ 6 at any time (7.78-fold) and neonatal jaundice (3.12-fold). Possible significant variables from the univariate analysis were grouped to observe the total number of variables present in a single child from the case and control groups.

Conclusion: The most important risk factors for epilepsy in this study were neurological impairment and severe head trauma. Other important risk factors were history of febrile seizures, a history of epilepsy in the family and a low apgar score.

p678

IMPORTANCE OF PATIENT HISTORY AND SEIZURE CHARACTERISTICS IN DISCRIMINATION OF EPILEPTIC AND NONEPILEPTIC SEIZURES IN CHILDREN

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Purpose: The aim of this study was to compare some ictal and postictal seizure characteristics, history of febrile seizures and cranial magnetic resonance images for nonepileptic seizures (NES) and epileptic seizures (ES) and to determine the differences.

Method: A total of 43 nonepileptic and 104 epileptic patients with generalised tonic–clonic seizures (GTCS) were included in the study. Following a literature search, we specified 5 items that could be used to differentiate nonepileptic and epileptic seizures. These items were evaluated as present or absent in every patient with ES and NES, and the results were compared statistically.

Results: There was a statistically significant difference between the two groups for the presence of ictal and postictal altered consciousness ($p < 0.0001$), a seizure duration of more than 2minutes ($p < 0.001$), the presence of febrile seizures ($p < 0.008$) and the presence of pathological findings in cranial magnetic resonance images ($p = 0.002$).

Conclusion: Patients who experience tonic–clonic seizures should be evaluated for ictal and postictal altered consciousness as it plays a key role in differentiating ES from NES. Seizure duration, history of febrile seizures and cranial MRI findings may help in making the differential diagnosis.

p679

POSTSURGICAL SEIZURE OUTCOME IN CHILDREN WITH REFRACTORY LOCALISATION-RELATED EPILEPSY AND NORMAL OR NONSPECIFIC MRI FINDINGS

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Purpose: To identify the predictors of postsurgical seizure freedom in children with refractory epilepsy and normal or nonlateralised MRI findings.

Method: We analysed 22 children (M10:F12) under 18 years with normal, subtle or nonlateralised MRI findings, who underwent surgery for intractable epilepsy following intracranial EEG. Clinical profiles, neurophysiological data (VEEG, magnetoencephalography and intracranial EEG) and surgical data (type, location and completeness) were compared to post-operative seizure outcome (good seizure outcome = >90% seizure control).

Results: We performed combined lobectomy and corticectomy (10), corticectomy (9), lobectomy (2) and multiple subpial transections (1). Seventeen children (77%) had good seizure outcome; 8 (36%) seizure free and additional 9 (41%) with >90% seizure control. Ictal onset confined to <5 adjacent intracranial electrodes (5/5) predicted seizure freedom p = 002). Children with more than one type of seizure (5/5) (p = 0.07) and children with both generalised spike and wave and extra-resection site epileptic discharge (4/4) did not become seizure free. Age of onset, duration of epilepsy, presence of developmental delay, number of lobes involved in resection, completeness of the resection or pathology (cortical dysplasia-9, dysembryoplastic neuroepithelial tumour-1, mesial temporal sclerosis-1, non-specific gliosis-6, no pathological lesion-4) did not correlate with seizure freedom.

Conclusion: Surgery for intractable partial epilepsy in children with normal MRI findings can provide good seizure outcome in the majority of children. Restricted localised ictal onset zone predicted postoperative seizure freedom. Seizure freedom less likely occurred in multiple seizure types and incomplete resection of the proposed epileptogenic zone.

p680

ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS AND THEIR IMPACT ON QUALITY OF LIFE IN CHILDREN WITH EPILEPSY

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Purpose: Epilepsy is a major cause of childhood disability. Additionally AED through their potential to evoke side effects can potentiate this disability. Both efficacy and safety of treatment are important parameters in assessing quality of life as an outcome measure. In order to assess the impact of side effects of antiepileptic drugs (AED) on quality of life in children with epilepsy following study was performed.

Method: Two hundred fifty children with epilepsy (aged 3–13 years) and their caregivers participated in the study. The quality of life questionnaire specially developed in our department for parents of children with epilepsy was applied. Additionally, 5 questions especially designed to describe side effects were asked. Comparisons between parents and medical staff opinions were made.

Results: The most frequent side effects observed in 70% of patients were tiredness, poor concentration, nervousness, headache, vertigo, weight loss or gain, rush and other skin problems, abdominal pain and others. Occurrence and number of side effects as well as the efficacy of treatment significantly correlated with quality of life. It also correlated with the caregiver's opinion about the disease and their fear about its influence on the children. Interestingly parents reported their worries about the effects of drugs on cognition much stronger than effects of epilepsy itself.

Conclusion: Not only epilepsy by itself but also the side effects of AED have an important impact on quality of life in children with epilepsy.

p681

PAEDIATRIC EPILEPSY: LOWER COSTS OF ADVERSE EVENTS WITH LEVETIRACETAM ADD-ON FOR PARTIAL ONSET SEIZURES

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Purpose: To estimate and compare the costs of adverse events (AE) leading to medication and hospitalisation in a paediatric epilepsy trial comparing levetiracetam (LEV) and placebo (PBO) as add-on therapy.

Method: Data from a double-blind-randomised controlled trial (LEV, N = 101; PBO, N = 97) were analysed. Unit costs were assigned to medications and hospitalisations related to AE using average wholesale prices and diagnosis-related groups respectively (2003 values), from a US third-party payer perspective. Comparisons of the mean medication costs were conducted using t-bootstrap at baseline and over the 20 week treatment period which included titration, evaluation and withdrawal periods.

Results: The frequency and cost of medications due to AE were comparable between the 2 groups at baseline. The mean cost of medications per patient was significantly lower in the LEV group vs PBO during the treatment ($56.9 vs $120.8, p = 0.032), evaluation ($38.3 vs $88.5, p = 0.022) and withdrawal periods ($1.9 vs $19.8, p = 0.046). Over the titration period, a nonsignificant higher mean cost in the LEV group vs PBO was observed ($16.7 vs $12.5, p = 0.520). Mean cost of hospitalisations and per hospitalised patient were lower in LEV vs PBO during the treatment period ($189.4 vs $452.8 and $3188.5 vs $4880.1 respectively).

Conclusion: Lower costs of medications and hospitalisations due to AE were demonstrated with LEV add-on in paediatric epilepsy vs PBO. Both of these cost components are considered important medical cost drivers of epilepsy disease management. (Work supported by UCB).

p682

TRANSIENT COGNITIVE DETERIORATION ASSOCIATED WITH VALPROATE: A CASE STUDY

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Purpose: Few reports are available on cognitive deterioration associated with valproate in children.

Method: A previously healthy boy with no family history of epilepsy started having daily seizures with brief arrest of activity at 12 months. EEG at 2.3 years showed generalised spike-wave discharges. Valproate was started at 35 mg/kg/day at 2.4 years; seizures disappeared within two weeks. Generalised spike-waves persisted until age nine years. Valproate was continued until age seven (from age five on at 600 mg/day). As interictal EEG continued to show epileptiform abnormalities, valproate 300 mg/day was restarted at age eight and continued for a year.

Results: The boy was considered normally developed at two years. Marked developmental delay was observed by a neuropsychologist at age five and confirmed at six. The boy started special education for the mentally retarded. Two months after discontinuing valproate teachers reported that he was much too bright for his class. When reassessed, he performed within low average range. He was placed in a mainstream class, where he did well except for some attentional difficulties. While back on a lower dose of valproate, the cognitive test scores were slightly lower again, but the boy was doing well enough at school. His school career has since been uneventful.

Conclusion: The patient probably had idiopathic absence epilepsy although with unusually early onset. Cognitive decline after commencing valproate and rapid improvement after its discontinuation after a long seizure-free period suggest that valproate was the cause of the deterioration. The importance of cognitive monitoring in epilepsy is emphasised.

p683
EFFICACY OF ACTH IN INTRACTABLE FRONTAL LOBE EPILEPSY
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Purpose: We analysed the short- and long-term efficacy of brief administration of adrenocorticotropic hormone (ACTH) in 2 patients affected by intractable frontal lobe epilepsy.

Method: The subjects were 2 children, 1 boy and 1 girl, characterised by daily high frequency of seizures of frontal lobe onset. They had received a high dosage of carbamazepine, sodium valproate and a combination of these drugs. We performed a clinical examination on both patients, including MRI and EEG during sleep before and after ACTH treatment.

Results: The clinical examination and MRI were normal. Both patients showed remarkable secondary frontal bisynchronism on the EEG and they did not respond to the above mentioned drugs before ACTH treatment. After a low dose of ACTH (0.010 mg/kg/dose), administered for 2 weeks, the patients showed significant reduction in frequency of seizures, disappearance of secondary frontal bisynchronism on the EEG and a good response to carbamazepine. The follow-up of our patients is 12 months and, at the moment, they continue to present a good response to carbamazepine.

Conclusion: We believe that our results suggest a good efficacy and tolerability of a low dose of ACTH in drug-resistant frontal lobe epilepsy. Moreover, we could explain these results with a possible mechanism of action of ACTH on the secondary frontal bisynchronism by decreasing CRH release and by direct, steroid-independent, action on melanocortin receptors, according to data existing in the literature.

p684
EEG IN CHILDREN SUSTAINED ON THE KETOGENIC DIET: DO RESULTS CORRELATE WITH SEIZURE OUTCOME?
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Purpose: To determine if the routine electroencephalogram (EEG) is a useful indicator of response to the ketogenic diet in the treatment of epilepsy.

Method: As part of a randomised controlled trial of the use of the ketogenic diet in the treatment of drug resistant epilepsy, children underwent an EEG recording at baseline, after 3 months on the diet, after 6 months and after 12 months. For inclusion in the study children had been tried on at least 2 anticonvulsant medications and had at least 7 seizures/week. EEGs were visually scored for background and paroxysmal/epileptiform activities by an experienced clinical physiologist and compared with clinical response.

Results: EEG data were reviewed in 48 children (29 males) with age range 19 months to 15.2 years, at baseline and after 3 months, 36 children after 6 months and 24 children after 12 months on the diet. In the 24 who had completed the 12 months study period, the background EEG remained similar in 16, worse (∼50%) in 5 and significant improvement (∼50%) in 3. A significant reduction in paroxysmal activity/discharges (up to 50%) was seen in 6 children; 14 had no change and 4 worsened. No correlation was seen between seizure control and degree of change in EEG. 22 children were able to reduce medication with no decline in seizure control.

Conclusion: In this cohort of patients treated with the ketogenic diet for varied seizure disorders, the EEG does not appear to be a good indicator of seizure response.

p685
HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH EPILEPSY AND CEREBRAL PALSY: PRELIMINARY RESULTS
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Purpose: The aim of this study was to compare health related quality of life (HRQL) of children with cerebral palsy (CP) with and without epilepsy.

Method: Eleven children suffering from CP and epilepsy and 11 children suffering from CP without epilepsy (aged between 5 and 18 year) participated in a comparative study. The two groups were comparable for type and severity of CP. For all children we evaluated the type of epilepsy, and any other disorder in comorbidity and social status of family. Parents of children rated their child's quality of life with the Impact of Childhood Neurological Disability Scale (ICND). The severity of a child's motor disability was assessed using a paediatric functional measure, the Wee-Functional Independence Measure (WeeFIM).

Results: Parents reported significantly reduced HRQOL ($p < 0.01$) in the group of children with CP and epilepsy compared to the group of children with CP without epilepsy.

Conclusion: Children with CP and epilepsy have reduced HRQOL and the degree to which it is reduced is related to the severity of their CP. In our study there is a clear relationship between seizure frequency and health related quality of life and other clinical variables (overall sensorial disorder and mild–severe mental retardation).

p686
KETOGENIC DIET FOR INFANTS IS POSSIBLE WITH KETOCAL
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Purpose: A formula for a ketogenic diet has been marketed for children above 1 year of age (Ketocal SHS). Infants with medical intractable catastrophic epilepsy are in desperate need for an alternative treatment. We describe the use of Ketocal for 5 infants.

Method: Five infants treated with Ketocal were reviewed. All had medical intractable epilepsy. The ages of the children at the start of the diet were: 3, 7, 7, 8 and 11 months. Ketocal contains a higher load of lipids including transfatty acids and sodium than recommended. Kidney, liver function and sodium were closely monitored. Ketocal was gradually introduced over 3 days without fasting. Caloric intakes were set to 85% of recommended requirements and regulated depending on ketosis and weight increase.

Results: All infants tolerated the formula and were able to develop moderate or large ketonuria within 2 weeks. Four of the 5 infants had marked seizure reduction including 2 temporarily seizure free children. One child was seizure free for 12 months followed by epilepsy surgery after seizure recurrence. The child started on Ketocal at age 3 months and has only been followed for 1 month. Introduction and short term observations revealed no complications including normal blood sample results.

Conclusion: Ketogenic diet is possible to introduce and seems to be effective in some infants under 12 months of age. Longer follow-up on Ketocal in small infants is necessary to evaluate the sufficiency of the formula.

p687
PREVALENCE OF ATTENTION DEFICIT DISORDER IN PAEDIATRIC EPILEPSY PATIENTS IN MEXICO
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Purpose: To evaluate the prevalence of attention deficit disorders in the paediatric epilepsy population in Mexico. It is an important issue to try to differentiate the attention problems secondary to epilepsy and treatment and the attention deficit disorder itself, because the treatment for these two conditions is independently suggested.

Method: We evaluated all patients with epilepsy, 6 and 12 years old, in the neurology department of Hospital Infantil de Mexico between January and December 2005. The patients were evaluated with clinical history, neurological examination, WISC-R, Conner's scales, ADHD-RS, CGI and DSM-IV-TR, independently of type of seizure, number of antiepileptic drugs or aetiology.

Results: We analysed data from 450 patients, both genders, between 6 and 12 years old. 234 patients had one of the symptoms of ADHD (inattention, hyperactivity or impulsivity). Of these (178 males and 56 females) only 89 patients met all the criteria for the disorder. The most frequent subtype of ADHD in males was the combined type, in females the inattentive subtype. Only 23 of these patients had received treatment support with medications specific for the disorder. The prevalence of ADHD in our population was 19%; very similar to that in the normal population.

Conclusion: ADHD is a biologic-genetic condition that affects the normal population, and we find the same prevalence in the paediatric epilepsy population. It is important to differentiate the symptoms of this disorder from epilepsy symptoms, because the therapeutic approach is different for each group, and the impact and prognosis is better for ADHD patients.

p688

RISK FACTORS OF UNPROVOKED SEIZURES AFTER ACUTE SYMPTOMATIC SEIZURES IN CHILDREN

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Purpose: Some patients with acute symptomatic seizures (ASS) have related unprovoked seizures during follow-up. So we were going to evaluate the risk factors of unprovoked seizures after ASS in children.

Method: We retrospectively reviewed the medical records of 167 children with ASS admitted to Chungbuk National University Hospital between January 1998 and December 2003, and the patients were followed up for 2 years.

Results: Acute symptomatic seizures were most common in younger children aged 13 to 24 months, and sexual distribution did not differ. Most of the children had generalised seizures (73.6%). Acute gastroenteritis (32%) was main cause. Minor infections (22%) involving urinary tract or upper respiratory infections were noted. During follow-up, 52 children (31%) had unprovoked seizures after ASS. The mean age at the onset of first seizures was 40 months. Causes in order of frequency were minor infection (24%), CNS infection (9%) and acute gastroenteritis (9%). Partial seizures were more common than generalised seizures. The risks of unprovoked seizures were greater for those with ASS with status epilepticus (SE) (56.3%) than without SE (25%). The risks of unprovoked seizures were also high in preterm babies, postictal lethargic states and delayed development.

Conclusion: Based on this retrospective study, the risks of unprovoked seizures after acute symptomatic seizures were high in partial seizures with status epilepticus, developmental delay, and perinatal problems. The risks of subsequent unprovoked seizures are determined by underlying precipitation factors, so children with acute symptomatic seizures with SE should be followed up carefully.

p689

EFFICACY OF LEVETIRACETAM AS ADD-ON THERAPY IN 10 CHILDREN WITH AUTISTIC REGRESSION AND EPILEPSY

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Purpose: To evaluate the clinical usefulness and safety of levetiracetam (LEV) as add-on therapy in children with autistic regression and epilepsy.

Method: We introduced LEV as add-on therapy in 10 children age 22 months to 14 years affected by autistic regression and epilepsy. Eight patients had partial-onset seizures and 6 had generalised seizures including 5 children with myoclonic epilepsy. Efficacy was assessed by measuring changes in seizure frequency per month and achievement of seizure freedom. Patients were analysed for possible improvement in attention and behaviour using CAVE scale for quality of life in children with epilepsy, Conners test for parents and teachers, Ladd child behaviour scale for parents and teachers, autism behaviour checklist scale (ABC) and Kauffman brief intelligence test (K-BIT). Safety was assessed by evaluating LEV-related adverse events.

Results: Eight of 10 patients (80%) showed a seizure frequency reduction of more than 50% including 4 children (40%) who became seizure-free. In 5 of 10 patients (50%) there was a significant improvement in behaviour, alertness and attention. Only 2 patients (20%) showed additional improvement in verbal responses and cognition. Adverse events were reported in 4 patients (40%) and were mild and transient. Somnolence (30% of children) was the most common referred adverse event.

Conclusion: LEV is an effective and safe alternative as add-on therapy in children with autistic regression and epilepsy. LEV has a positive neuropsychological effect not directly related to seizure control.

p690

CONVULSION AS THE MOST COMMON PRESENTING SIGN OF ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) IN CHILDREN

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Acute disseminated encephalomyelitis is an uncommon inflammatory demyelinating disease of the central nervous system. Approximately 70% of patients report a precipitating event, e.g., viral or bacterial infection or vaccination. The true incidence of the disease in Iran is undetermined; exanthematous fevers and other viral infections, which predispose to ADEM, are still prevalent.

A 2-year descriptive, retrospective chart review of children with a diagnosis of ADEM is presented. Fifteen cases 53% male; 47% female, age: 1–12 years (33%), 9–12 years (36%), 6–8 years (26%), 1–2 years (25%), no cases aged between 2–5 years. 88% presented in either winter or spring. 46.4% had a recent upper respiratory tract illness. A previous vaccination was administered to 13.6%; 40% had no URI or vaccination. VZV infection was present in 1; UTI in 2. Mycoplasma pneumonia was present in 1 case. Presentation signs were: ataxia 60%; altered consciousness 60%; fever+nausea and vomiting 46%; cranial nerve involvement 33%; dysarthric speech 26%; convulsions 20%; hemiparesis 20%; paresthesia 13%; meninsismus 13%; headache 6%. Twelve patients were treated with corticosteroids, and 3 with intravenous immunoglobulins. Only 1 death was recorded. Three patients (20%) had long-term neurologic sequelae. Probably, with advances in disease control, ADEM in our country, as in other developing countries, there could be a change from traditional exanthematous diseases to nonspecific respiratory infections. Here, only one case of VZV infection developed ADEM. The prognosis for survival and outcome was excellent.

p691

EPILEPSIES IN CHILDREN DURING ONE YEAR IN OUR CLINIC

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Purpose: Studying of new cases presented at our clinic during the year 2002.

Method: Our study is a prospective one. We have studied all new cases presented in our clinic and out patients. Every child has gone under neurological examination, EEG, ophthalmic examination. In children under one year old we have performed also transfontanelar ultrasound; for children with neurological impairments we have performed CT scan of the head. The study is based on ILAE 1985, 1989 classifications.

Results: We studied 511 children with seizures, of which 278 were female (45.4%) and 279 male (54.5%). The study included children from 1 month to 14 years old: 1–12 months 73 children, 13 months–4 years 165 children, 5–10 years 179 children, 11–15 years 94 children. We have reported: with partial epilepsy 298 children. 15.2% with benign centrotemporal spikes, 8% with temporal spikes, 23.2% with occipital spikes and 11.7% with plurifocal spikes. Twelve cases are symptomatic with anomalies at CT scan of the head. With partial secondary generalised epilepsy 103 children; 29 of them are evolving from simple partial seizures and 74 from complex partial seizures. With generalised epilepsy 67 children: 16 atonic seizures, 23 tonic–clonic, 3 clonic, 11 tonic, and 4 myoclonic seizures. 5 children presented with absence, 4 children with West syndrome and one child with epileptic encephalopathy. 40 children presented with febrile convulsions and 3 children were unclassified.

Conclusion: From 511 children with epilepsy during the year 2002 most of them, 53.3%, presented with partial epilepsy and 20.2% with partial secondary generalised. We noticed a predominance in males (54.5%). Most of the cases (35%) were 5–10 years old. 7.8% of cases had febrile convulsions. The most common forms of epilepsy are idiopathic (partial 86.26% and generalised 76.71%).

p692

AUTISM SPECTRUM DISORDERS AND TEMPORAL LOBE EPILEPSY: REPORT OF 30 PAEDIATRIC PATIENTS

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Purpose: To describe the natural outcome of 30 paediatric patients with autism spectrum disorders, temporal lobe epilepsy and temporal lobe lesions.

Method: This was a retrospective chart review of 30 consecutive paediatric patients aged 36 months to 18 years who were diagnosed with symptomatic temporal lobe epilepsy and fulfilled clinical criteria of autism spectrum disorders according to DSM-IV. In all patients, we analysed age at onset, sex, type of seizure, psychopathological disorders, evidence of paroxysmal activity on EEG and neuroimaging findings.

Results: All patients had normal psychomotor development prior to seizure onset. Epileptic seizures were the first neurologic sign and appeared between 6 and 24 months of age. Convulsive status epilepticus was the first ictal manifestation in 15 patients. Autistic regression was well-defined in all patients between 24 and 36 months of age. Eight children had temporal lobe sclerosis, 7 had cortical dysplasias, 5 had tuberous sclerosis complex, 6 had arachnoid cysts and 4 had gangliogliomas. Temporal lobe lesions were on the left-side in 13 patients, on the right-side in 12 and were described as bilateral in 5.

Conclusion: Early onset seizures (<2 years) with temporal lobe epileptiform activity on the EEG are associated with pervasive developmental disorders and mainly with autistic regression syndrome. It is difficult to know if patients became autistic because of repetitive epileptic seizures and/or persistent paroxysmal activity on the EEG, or because of the epileptogenic and psychopathologic effect of temporal lobe lesions during infancy and early childhood.

p693

SUBCLINICAL HYPOTHYROIDISM AND EPILEPSY IN CHILDREN

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Purpose: To analyse the correlation between epilepsy and subclinical hypothyroidism in children.

Method: During two years (2001–2003) I measured the levels in serum triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) in 132 children with epilepsy. They were receiving VPA (32 children), CBZ (12 children), LTG (11 children), TPX (16 children) in monotherapy and add-on therapy of two drugs: VPA+CBZ (10 children), VPA+LTG (27 children), VPA+TPX (17 children) and LTG+TPX (7 children). The results of T3, T4, TSH levels were compared with a control group of 121 healthy children. Children were 5–16 years old and had different kinds of epilepsy. All the results were assessed by statistical methods.

Results: In all treated groups the mean of T3, T4 levels in serum was statistically lower than in the control healthy group ($p < 0.05$) and the TSH level was significantly higher ($p < 0.05$) in patients with epilepsy (especially in the group receiving VPA or CBZ in mono and add-on therapy).

Conclusion: The epilepsy treatment with antiepileptic drugs (especially VPA and CBZ) induces subclinical hypothyroidism.

p694

SYMPTOMATIC EPILEPSY IN CHILDREN WITH HEMIPLEGIC CEREBRAL PALSY

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Purpose: The aim of this study was to investigate clinical and electroencephalographic (EEG) features of symptomatic epilepsy in children with hemiplegic cerebral palsy.

Method: The population based study group comprised 70 children with hemiplegic cerebral palsy (41 (58%) with right-sided hemiparesis, 30 (42%) with left-sided hemiparesis), 5–15 years of age. All were assessed by case history, neurological, EEG, CT/MRI brain imaging and psychological examination.

Results: Epileptic seizures developed in 40% children with hemiplegic cerebral palsy. Epilepsy was as common in boys as in girls (56% boys and 44% girls respectively). The median age of onset of epilepsy in children with right-sided hemiparesis was 2.5 years, in children with left-sided hemiparesis the median age of onset of epilepsy was 5.5 years. Among the patients with right-sided hemiparesis 35% had their first seizure during the first year of life. Among the patients with left-sided hemiparesis the first seizure appeared after 3 years in 50%. 61% children with right-sided hemiparesis and 80% children with left-sided hemiparesis had abnormal brain CT or MRI findings (unilateral ventricular dilatation, cortical and/or subcortical atrophy). Epileptic abnormalities on EEG were observed in 35% children with right-sided hemiparesis and 58% children with left-sided hemiparesis. Lower IQ was found in 58% children with right-sided hemiparesis and 62% children with left-sided hemiparesis.

Conclusion: The onset of epileptic seizures was previous in children with right-sided hemiparesis and developed with equal frequency on right-sided hemiparesis and left-sided hemiparesis. In children with left-sided hemiparesis epilepsy was more severe with focal epileptic abnormalities on EEG.

p695

ELECTROENCEPHALOGRAPHY IN CHILD EPILEPTOLOGY

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Purpose: Electroencephalography is the most commonly used diagnostic method in children's neurology. Electroencephalography is a standard diagnostic method of assessment used after any disorders of consciousness with children but is not of primary importance in making a diagnosis. The aim of this study was to show that the EEG has been applied too often in the process of getting information it cannot obtain.

Method: The study was conducted in the period from 1993 to 2003 in the Institute for Child and Youth Health Care in Novi Sad in 2000 for first time hospitalised children after any consciousness disorder.

Results: Starting from the fact that an EEG checkup is expected to confirm the presence of a change, and having in mind that the absence of the latter does not necessarily mean excluding epileptic activity, it has been found that 75% of EEG findings do not meet expectations.

Conclusion: The dominance of normal EEG findings compared to those changed due to epilepsy, is the result of the fact that a large number of EEG checkups are being done in order to "exclude epilepsy." The EEG has been applied too often in the process of getting information it cannot obtain. The EEG checkup only, without precise anamnestic data and

clinical observations, is not enough, neither to diagnose epilepsy nor to deny its existence.

p696

LEVETIRACETAM IN CHILDREN AND ADOLESCENTS WITH REFRACTORY EPILEPSY: A CLINICAL EXPERIENCE

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Purpose: Levetiracetam (LEV) is a new antiepileptic drug (AED) with proven efficacy in partial and generalised seizures in adults and children. This study evaluated the effect of LEV on 86 children and adolescents with refractory epilepsy.

Method: Patients aged 2–20 years with refractory epilepsy (based on ILAE classification and EEG), not adequately controlled with existing AEDs or with adverse events (AEs) were included. LEV, as monotherapy or add-on therapy, was commenced (at 20 mg/kg/day for most patients), and uptitrated individually according to efficacy and tolerability. Patients were followed for 3–48 months.

Results: Eighty-six patients (54 males [62.8%], aged 2–20 [mean 8.8] years) were enrolled. Eight patients (9.3%) received LEV monotherapy; 78 (88.7%) received LEV as add-on therapy: 8 (9.3%) patients valproate (VPA) + oxcarbazepine (OXC); 5 (5.8%) topiramate (TPM) + OXC; 5 (5.8%) TPM+VPA; 31 (36%) VPA; 25 (29.1%) OXC; 18 (20.9%) TPM; 11 (12.8%) phenytoin (PHT). Mean final LEV dose was 40.8 (maximum 62) mg/kg/day), reached in a mean of 3 weeks. Mean treatment duration was 14.3 months. 19 (22.1%) patients became seizure-free; 63 (73.3%) patients had ≥50% reduction in seizure frequency. LEV was withdrawn due to lack of efficacy in 16 patients. AEs were reported in 13 (15.1%) patients; transient somnolence in 4 (4.7%), irritability in 3 (3.5%). Positive effects were reported in 23 (26.7%) patients, 10 of whom reported improved cognition.

Conclusion: LEV is effective and well tolerated in children and adolescents with refractory epilepsy and has a positive effect on cognition.

p697

LEVETIRACETAM IN CHILDREN AND ADOLESCENTS: NO TRADE-OFF BETWEEN SAFETY AND EFFICACY

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Purpose: To assess the safety, efficacy and impact on EEG-specific epileptic abnormalities of levetiracetam (LEV) treatment in children with uncontrolled partial seizures.

Method: Clinical audit of children treated with LEV add-on treatment for partial onset seizures since 2002. LEV was up-titrated to achieve seizure control and maintain tolerability. Safety and efficacy were compared before, and 1 and 3 months after LEV initiation. The main outcome parameters were retention rate, reduction in seizure frequency/month, changes in EEG-specific abnormalities (rated 1 [improved], 2 [no change], 3 [worsened]), and adverse events (AEs).

Results: 74 patients were included. Mean age was 11.1 ± 3.9 (range 4–19) years; mean duration of epilepsy was 5.8 ± 3.4 years; median number of concomitant AEDs was 1; aetiology was lesional in 64.9% (48/74) patients. Mean LEV dose was 27.1 ± 10.1 (median 27.0; range 8-54) mg/kg/day. Responder rate (≥50% seizure frequency reduction) was 41.9% after 1 month and 39.2% after 3 months. Seizure freedom rate (100% seizure frequency reduction) was 22.9% after 1 month and 16.2% after 3 months. EEG recordings significantly improved in responders compared with nonresponders ($p = 0.019$ after 1 month and $p < 0.001$ after 3 months). AEs were reported in 9.5% (7/74) patients; majority were of mild-to-moderate severity (somnolence n = 2, asthenia n = 1, fatigue n = 1, slight worsening of aggressiveness n = 1, abdominal pain n = 1, worsening of behaviour n = 1). LEV was discontinued in 17.6% (13/74) patients (lack of efficacy n = 12, AE n = 1).

Conclusion: LEV add-on treatment was efficacious and well tolerated in children with refractory focal epilepsy, and significantly improved EEG abnormalities.

p698

EFFECTIVENESS AND SAFETY OF LEVETIRACETAM IN TREATMENT OF THERAPEUTICALLY RESISTANT EPILEPSIES IN CHILDHOOD

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Purpose: To prospectively assess the effectiveness and safety of levetiracetam (LEV) add-on therapy in children and adolescents with therapeutically resistant epilepsy.

Method: LEV was administered to patients refractory to all conventional and new antiepileptic drugs registered in Bulgaria at a mean dose of 40 mg/kg. Follow-up was 4-24 months. Efficacy was assessed as responder rate (≥50% seizure frequency reduction) and seizure freedom rate (100% seizure frequency reduction); safety, by evaluating LEV-related adverse events (AEs).

Results: Forty-nine children, mean age 12.4 years, were included; 67.3% (33/49) had focal epilepsy, 22.4% (11/49) had generalised epilepsy (idiopathic, n = 9 [myoclonic-astatic, n = 4; generalised tonic-clonic seizures, n = 4; absences, n = 1]; symptomatic, n = 2), and 10.2% (5/49) had epileptic encephalopathies (Dravet's syndrome, n = 3; Lennox-Gastaut syndrome, n = 2). Mean epilepsy duration was 7.7 years. Seizures occurred daily in 59.2% (29/49) patients and weekly in 40.8% (20/49). Overall responder and seizure freedom rates were 85.7% (42/49) and 16.3% (8/49), respectively. LEV was effective in all types of epilepsy syndromes: responder and seizure freedom rates were, respectively: 93.9% (31/33) and 24.2% (8/33) for focal epilepsy patients; 72.7% (8/11) and 9.1% (1/11) for generalised epilepsy patients; and 60% (3/5; Dravet's, n = 2; Lennox-Gastaut, n = 1) and 0% for patients with encephalopathies. LEV was effective for all seizure types. In 78.6% (33/42) patients showing clinical improvement, EEG abnormalities also reduced. 8.2% (4/49) patients experienced AEs (irritation, n = 3; headache, n = 1); none experienced aggravation of epileptic syndrome.

Conclusion: LEV is highly effective in children and adolescents with long-lasting therapeutically refractory epilepsies, with a good safety profile.

p699

LEVETIRACETAM OR OXCARBAZEPINE AS MONOTHERAPY IN NEWLY DIAGNOSED BENIGN ROLANDIC SEIZURES IN CHILDREN: AN OPEN-LABEL, PARALLEL GROUP STUDY

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Purpose: To evaluate the efficacy and tolerability of levetiracetam (LEV) or oxcarbazepine (OXC) as monotherapy in children with newly diagnosed benign epilepsy with centrotemporal spikes (BECTS).

Method: Children with BECTS were randomised to receive monotherapy with either LEV or OXC. LEV was titrated up to 20–30 mg/kg QD or BID, and OXC up to 20–35 mg/kg QD or BID. Efficacy was assessed by evaluating seizure frequency reduction and tolerability by evaluating treatment-related adverse events (AEs).

Results: Thirty-nine consecutive patients (21M/18F), age 3.3–14 (mean 10.7) years, were recruited into the study. 21 received LEV (11M/10F; mean age 10.5 years), and 18 received OXC (10M/8F; mean age 8.4 years). After a mean follow-up of 18.5 (range 12–24) months, 90.5% (19/21) LEV patients and 72.2% (13/18) OXC patients achieved seizure freedom. Mean serum levels were 4.1 (range 1.3-9.0) mcg/mL for LEV and 15.2 (range 4.2-27.5) mcg/mL for mono-hydroxy-derivative of OXC. Mild and transient AEs were reported in 14.3% (3/21) LEV patients (decreased appetite n = 2 and cephalalgia n = 1) and in 11.1% (2/18) OXC patients (headache n = 1 and sedation n = 1).

Conclusion: These preliminary data from an open, parallel group study suggest that LEV and OXC as monotherapy may potentially be effective and well tolerated in the treatment of children with BECTS.

p700
LEVETIRACETAM IN EPILEPSIES WITH CONTINUOUS SPIKES AND WAVES DURING SLOW SLEEP
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Purpose: A prospective study on 6 children to evaluate the efficacy of levetiracetam (LEV) add-on therapy in children with continuous spikes and waves during slow sleep (CSWS), in terms of EEG, seizures and neuropsychological functioning.

Method: LEV add-on therapy was initiated at a dose of 40–60 mg/kg/day and uptitrated weekly by approximately 10 mg/kg to a maintenance dose of 40–60 mg/kg/day. Patients' medical charts and EEGs were reviewed to analyse LEV's effects on seizures, paroxysmal EEG activity, and cognitive functions and behaviour. Awake and sleep EEGs, as well as neuropsychological tests, were performed at baseline and 1 month after LEV treatment initiation. In children with clinical and/or electrophysiological improvement after 1 month, LEV was continued with regular evaluations after 3 and 6 months.

Results: Six children, aged 6–12 years, with CSWS in the course of their idiopathic (n = 3) or symptomatic (n = 3) epilepsy were included. After 1 month of LEV treatment, 50% (3/6) patients showed CSWS cessation and full seizure control; 33.3% (2/6) demonstrated EEG improvement and >50% seizure frequency reduction; 1 child (16.7%) showed no improvements and LEV was discontinued. In 83.3% (5/6) patients, neuropsychological functioning improved in parallel with clinical and EEG improvement. In 1 child, despite excellent efficacy, aggression was noted during the second month and LEV was discontinued. 66.7% (4/6) patients continued LEV after 3 and 6 months because of maintained clinical, EEG and neuropsychological efficacy.

Conclusion: Although small, this prospective study suggests that LEV has an overall positive effect on the seizures, EEG, and neuropsychological functions of children with CSWS in epilepsies with different aetiologies.

p701
LEVETIRACETAM TREATMENT IN RARE EPILEPTIC SYNDROMES OF EARLY CHILDHOOD: A CASE SERIES
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Purpose: To assess the efficacy of levetiracetam (LEV) in the treatment of rare epileptic syndromes of early childhood.

Method: LEV was administered to children previously unsuccessfully treated for 3–8 months with combined antiepileptic drug (AED) and hormone therapy.

Results: LEV was administrated to 15 children, age 4–18 months with different childhood syndromes: 1) West syndrome, aged 8–18 months (n = 5): LEV (50 mg/kg/day) + topiramate (TPM) (n = 3) or LEV monotherapy (50–80 mg/kg/day) (n = 2). 2 children (LEV monotherapy) achieved seizure freedom and improved cognitive function, 3 children (add-on LEV) a marked seizure frequency reduction, up to 83%. 2) Otahara syndrome (n = 1): LEV (50 mg/kg/day) + valproate (VPA) + clobazam (CLB) resulted in marked seizure frequency reduction, 60–70%. 3) Focal epilepsy from birth (n = 5): LEV monotherapy (60–90 mg/kg/day) (n = 3) resulted in seizure freedom; LEV (30–40 mg/kg/day) + TPM + CLB (n = 2) produced 80% seizure frequency reduction. 4) Lennox-Gastaut syndrome (n = 4): LEV monotherapy (40–80 mg/kg/day) produced seizure freedom in 2 patients, but was ineffective in 2 patients. 5) Neuronal ceroid lipofuscinosis (n = 1): LEV (60–70 mg/kg/day) + ethosuximide resulted in marked seizure frequency reduction of ≥50%. 6) Unspecified infant myoclonic epilepsy with encephalopathy (catamnesis 2 month) (n = 1): LEV (40 mg/kg/day) + TPM resulted in myoclonic status reduction, 70–80% seizure frequency reduction and marked psychomotor development improvement.

LEV was well tolerated in all patients with no adverse events.

Conclusion: Our results demonstrate LEV's efficacy in rare, refractory, progressive childhood epilepsy syndromes. Over 3–14 months follow-up there was a marked reduction in seizure frequency and some cognitive improvement.

p702
EFFICACY AND SAFETY OF LEVETIRACETAM AS ADJUNCTIVE TREATMENT IN ADULT AND PAEDIATRIC PATIENTS SUFFERING FROM IDIOPATHIC GENERALISED EPILEPSY WITH PRIMARY GENERALISED TONIC–CLONIC SEIZURES
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Purpose: To assess the efficacy and safety of adjunctive levetiracetam (LEV) in children and adults with idiopathic generalised epilepsy with primary generalised tonic–clonic seizures (PGTCS).

Method: A multicentre, double-blind, randomised, placebo-controlled parallel-group study of adjunctive LEV in patients 4 to 65 years old with PGTC seizures uncontrolled on 1–2 AEDs. Eligible patients with ≥3 PGTCS during 8 weeks baseline (4 week historical, 4 week prospective) randomly received LEV (target dose 3000 mg/day adults, 60 mg/kg/day paediatric) or placebo. Four weeks titration was followed by 20 weeks at stable dose. Efficacy, adverse events (AEs), neurological, physical status and ECGs were assessed.

Results: Two hundred twenty-nine patients were screened, 164 randomised; 140 completed treatment (titration and stable dose period); primary efficacy analysis based on 163 (ITT population). PGTCS weekly frequency reduction of LEV over placebo during treatment (primary endpoint) was 28.3% (p = .004). Patients with ≥50% reduction of PGTCS frequency was 72.2% (57/79 patients) for LEV patients, 45.2% (38/84 patients) for placebo (p = .0005). 24.1% (19/79) LEV patients were seizure-free throughout the entire stable dose period compared with 8.3% (7/84) on placebo (p = .009), and 34.2% (27/79) receiving LEV were PGTCS seizure-free, compared to 10.7% (9/84) on placebo (p = .0003). During the double-blind period, 1.3% (1/80) LEV patients vs 4.8% (4/84) placebo withdrew with AEs.

Conclusion: Levetiracetam proved to be effective in reducing PGTCS frequency in patients with IGE and the known tolerability profile of LEV was confirmed. This study further demonstrates the broad spectrum antiepileptic activity of LEV.

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p703
SEIZURE FREEDOM RATES IN DIFFERENT EPILEPSY POPULATIONS TREATED WITH LEVETIRACETAM
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Purpose: Seizure freedom reduces mortality, morbidity and improves quality of life. This review assessed seizure freedom rates in adults, adolescents and children with refractory epilepsy treated with add-on LEV for partial onset seizures (POS), idiopathic generalised epilepsy (IGE) with myoclonic seizures and IGE with primary generalised tonic-clonic seizures (PGCTS).

Method: All studies were double-blind, placebo-controlled with 4 weeks uptitration and 10–20 weeks evaluation. Adult POS patient data were pooled from 2 Phase III studies of add-on LEV 3000 mg/day, and paediatric (3–17 years) POS data from a study of LEV 60 mg/kg/day. Adolescents and adults (12–65 years) with IGE and myoclonic seizures received LEV 3000 mg/day and adults and children (4–65 years) with PGTCS LEV 3000 mg/day adults, 60 mg/kg/day paediatric. Patients were considered seizure-free if achieving freedom from all seizure types throughout the entire evaluation (dropouts not considered seizure-free).

Seizure freedom rates are expressed as percentages of all patients randomised, taking at least one dose of study drug (ITT population).

Results: For each epilepsy population LEV-treated patients achieved higher seizure freedom rates than did placebo-treated: POS adults, LEV 7.8% (22/282), placebo 0.5% (1/200) ($p < .001$); POS paediatric patients LEV 8.9% (9/101), placebo 3.1% (3/97) ($p = 0.135$); IGE with myoclonic seizures LEV 21.7% (13/60), placebo 1.7% (1/60) ($p = 0.001$); IGE with PGTCS LEV 24.1% (19/79), placebo 8.3% (7/84) ($p = 0.009$).

Conclusion: LEV add-on therapy was associated with high seizure freedom in different epilepsy patient populations confirming its efficacy across a large spectrum of seizure types in patients with IGE and focal epileptic seizures.

p704

LEVETIRACETAM: TWO YEARS EXPERIENCE WITH CHILDREN

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Purpose: Levetiracetam (LEV) was recently licensed for paediatric use. We evaluated its efficacy and tolerability in our paediatric population.

Method: Forty-eight patients with refractory epilepsy were included; 3 were later excluded with <1 month follow-up. LEV's efficacy was assessed by seizure frequency reduction and tolerability by adverse event (AE) reporting.

Results: Forty-five (31 male, 14 female) patients, mean age 11 years 4 months were analysed. 32 (66.7%) had partial epilepsy with secondary generalisation; 5 (11.1%) simple partial, 4 (8.9%) complex partial, 6 (13.3%) generalised seizures from birth; of these 2 patients had more than one seizure type. 6/45 (13.3%) patients received LEV monotherapy, 2 with primary generalised seizures. In 18 (39.6%) children seizure frequency decreased by ≥25%, 11/45 (24.5%) achieving seizure freedom. 29/48 (60.4%) patients experienced no seizure reduction, 4/48 (13.8%) showed initial improvement. 6/48 (12.5%) patients experienced seizure worsening. In 4 children aged <4 years, LEV was discontinued for lack of efficacy or seizure worsening. LEV appeared less effective when combined with topiramate. Responders received lower mean doses (33.9 mg/kg/day) than nonresponders (49.5 mg/kg/day). Mean doses were 25.7 mg/kg/day in seizure-free; 36.5 mg/kg/day in ≥50% responders; 45.7 mg/kg/day in ≥25% responders; 40.4 mg/kg/day in non-responders. Patients with seizure worsening received 64.5 mg/kg/day. Moderate AEs were reported in 15 (31.2%) patients, not requiring LEV discontinuation.

Conclusion: Our study showed LEV as effective and well tolerated in nearly 40% of our patients and supports widespread evidence of LEV's broad spectrum of activity and good safety profile.

p705

EFFICACY AND SAFETY OF LEVETIRACETAM IN JUVENILE MYOCLONIC EPILEPSY (JME)

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Purpose: To evaluate the efficacy and safety of levetiracetam (LEV) in patients with JME.

Method: Twenty-one patients with JME (5 male, 16 female) aged 12–54 (mean 26.4) years, (SD ± 11.2) were retrospectively evaluated. All had previously been treated with one or more antiepileptic drugs (AEDs) (mostly valproate). 15/21 (71.4%) patients had received LEV as monotherapy and 6/21 (28.6%) LEV as add-on therapy. Follow-up was from 6–48 (mean 21.7) months. Efficacy was evaluated using the following parameters: number of patients achieving seizure freedom, seizure frequency reduction and EEG improvements. Safety was evaluated by recording the intensity and duration of adverse events (AEs).

Results: 85.7% (18/21) patients achieved seizure freedom of between 6–48 (mean 23.3) months duration. One patient achieved a seizure frequency reduction of 33% and in 2/21 (10.5%) patients, no change in seizure frequency was observed. Of the 18 patients achieving seizure freedom, 13/15 (86.7%) were receiving LEV monotherapy and 5/6 (83%) were receiving LEV as add-on. The mean dose of LEV used was 2810 mg/day. EEG improvement was seen in 7/21 (33.3%) patients, with no change observed in 12/21 (57.2%); in 2/21 (9.5%) patients the EEG worsened. Minor, transient AEs were reported; drowsiness (n = 2), asthenia (n = 1), diarrhoea (n = 1) and irritability (n = 1).

Conclusion: The results of this study demonstrated LEV to be both effective and well tolerated in patients with JME.

p706

EPIDEMIOLOGICAL ANALYSIS OF CHILDHOOD EPILEPSY FOR THE POPULATION OF LATVIA

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Purpose: To analyse the incidence of epilepsy in a Latvian child population according to gender, seizure type, and aetiology.

Method: This retrospective study includes analysis of 868 hospital medical records in the period from 2001 to 2004. Provoked and repeatedly treated cases were not included. Diagnosis was classified according to International Classification of Epilepsy of the International League Against Epilepsy. For statistical analysis, Windows SPSS version 11.0 was used.

Results: The mean annual incidence rates vary from 24.3 to 36.8 cases per 100,000 population. The incidence rate was significantly higher in males compared to females: 32/100,000 versus 25/100,000, respectively ($p = 0.031$). The mean age (±SD) of the study population was 9.54 (±5.1) years. Generalised seizures (58%) were diagnosed more frequently than partial seizures (40%) and unclassified seizures (2%). Symptomatic epilepsy was diagnosed in 50%, and idiopathic epilepsy in 42% of cases. Aetiology of epilepsy was recognised as unclear in 8% of cases. In 4% of patients, a family history of epilepsy was confirmed.

Conclusion: The observed incidence rates of childhood epilepsy in Latvia are relatively consistent with data reported from other Baltic countries and Scandinavia. Generalised seizures were noticed more frequently than partial seizures. Epilepsy was diagnosed more frequently in the male population.

p707

NEUROPHYSIOLOGICAL BACKGROUND OF THE CLINICAL SPECTRUM OF LANDAU-KLEFFNER SYNDROME

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Purpose: The clinical course and outcome of the Landau-Kleffner syndrome (LKS) can vary significantly in different children. The purpose of this study was to clarify the impact of the electrophysiological characteristics in the course and the outcome of the disease.

Method: Clinical and EEG data were analysed in the cases of 7 children with typical LKS. The following data were observed and considered: age of children at the onset of epilepsy, of aphasia, of treatment with antiepileptics, with ACTH/steroids. The pattern of the awaking EEG and sleep EEG at the time of the onset of epilepsy, of aphasia, during aphasia, during severe behavioural disturbances, during antiepileptic, ACTH/steroid treatment, and after remission of aphasia, or after the cure. Event related potential (ERG), source-localisation and PET study were performed on 1 of the children during the course.

Results: Better outcome, and slighter clinical course in linguistic and cognitive respect were related to the later onset, earlier treatment, more anterior (central) or predominantly right sided SW activity in awakeness, less bilateral ESES during sleep, quicker and more pronounced normalisation of the sleep EEG pattern on the ACTH/steroid treatment.

Conclusion: The language and cognitive course and outcome of LKS seems to be related to the spreading tendency of the partial, "benign" SW activity of the dominant hemisphere to the whole hemisphere during awakeness, and to the contralateral hemisphere during sleep in the "critical" period of language development. Early ACTH/steroid treatment of

this spreading seems by this time to be the best prevention of the fixation of linguistic and cognitive defect.

p708

REFRACTORY EPILEPSY AND DEVELOPMENTAL BRAIN DEFECT

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Purpose: The problem of diagnosis and treatment of most severe refractory epilepsy in childhood is the main problem in epileptology. This disease may be established after retrospective observation for two or more years.

Method: We studied 1957 patients with different forms of epileptic syndromes, aged 0–16 years from St. Petersburg during 2000–2005. Children aged 0–3 years, 1070; 4–10 years, 493, 10–16 years, 394. Neurological examination, MRI scans, CSF study, EEG and EEG-video, immunological and virological tests were done in all.

Results: Idiopathic forms had 750 patients (38.4%), cryptogenic 286 (14.6%), symptomatic 921 (47%). Refractory epilepsy was diagnosed in 235 patients (25.5% of symptomatic forms). Developmental brain defects were detected in 169 children (71.9%): microcephalia in 61, Dandy-Walker syndrome in 17, Aicardi syndrome in 31, lissencephaly in 12, pachygyria in 24, double cortex and other cortical disgenesies in 24 patients. Metabolic disturbances were confirmed in 36 children and mitochondrial diseases in 15. Other factors causing refractory epileptic seizures were diagnosed in 10 patients (cerebral tumour, Rasmussen syndrome). West syndrome was established in 151 causes (64.3% of refractory epilepsies). Aetiological factors of West syndrome: developmental defect in 78 patients, perinatal hypoxia in 39, TORCH-infection in 14, tuberous sclerosis in 17, neuroinfection in 3. After 2 years of onset of refractory West syndrome in more cases (118) with established partial symptomatic epilepsy: Lennox-Gestalt syndrome was diagnosed in 25 patients (10.6%); partial symptomatic epilepsy as primary diagnosis in 59 (25.1%). All patients with refractory epilepsy showed neurological signs: developmental retardation, speech and behavioural problems, and motor defects. Diagnosis of refractory forms was detected after two years non effective treatment with high doses of 4 (or more) antiepileptic drugs. Neurosurgical correction was provided for 12 patients in this group.

Conclusion: Developmental brain defects are a main cause of refractory epilepsy (71.9%). The most common form of refractory symptomatic generalised epilepsy in children aged 0–3 years is West syndrome. After long term observation of this group more cases established the transformation of seizures in partial (partial symptomatic epilepsy).

p709

BENIGN CHILDHOOD OCCIPITAL EPILEPSY WITH LESIONS IN CRANIAL MRI INVESTIGATION

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Purpose: Our purpose is to describe the clinical and electroencephalographic features of 7 patients diagnosed with benign childhood occipital epilepsy (BCOE) with different lesions detected in cranial MRI.

Method: Our study was based on patients seen in our Epilepsy Outpatient Department where we initiated a prospective study of BCOE in 1995. Our records revealed 30 patients with Panayiotopoulos syndrome (PS) and 50 patients with Gastaut syndrome (GS); among them 7 with cranial lesions in their MRI.

Results: The onset was between 5 and 13 years. According to ictal symptomatology 3 patients were classified with PS and four with GS. The seizures of patients with PS included mainly autonomic symptoms such as pallor, mydriasis, urinary and faecal incontinence. The seizures of the other 4 patients always started with visual symptoms such as multicolored, bright, moving lights or blindness. All patients had occipital spike-wave complexes in their EEG blocked by eye opening. In the cranial MRI, 1 patient had bilateral and another had unilateral occipital encephalomalacic lesions, 2 had mild hippocampal atrophy and high signal intensity on Flair images in the described region, 1 had a neuroepithelial cyst whereas another 1 had an arachnoid cyst and colpocephaly in lateral ventricles. The last patient had millimetric focal focuses in the subcortical regions as well as in the superior and inferior temporal gyri. All patients, except for 1, received carbamazepine treatment 450–600 mg/day. None of our patients had a seizure under antiepileptic treatment.

Conclusion: We concluded that different lesions can be detected in patients with BCOE.

p710

NEUROLOGICAL CHARACTERISTICS OF CHILDREN WITH CRYPTOGENIC LOCALISATION–RELATED EPILEPSY CORRELATED WITH ACADEMIC DELAY

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Purpose: The prognosis of cryptogenic localisation–related epilepsy (CLRE) with childhood onset is difficult to study: due to the definition the population constantly changes. Epilepsy can influence academic achievement. In a multidisciplinary programme data were collected regarding school-aged children with epilepsy, to correlate clinical, neuropsychological, neurophysiological and academic variables and obtain an overview of a CLRE cohort.

Method: Seventy children with CLRE were assessed, mean age 10.2 years (6.1–15.11). A standardised program was administered to all children. Using SPSS, correlations between clinical neurological variables and academic achievement were computed.

Results: For 60 children the onset of epilepsy could be determined; mean age at onset was 6.4 years. Seizure types varied considerably, nevertheless 44 children experienced absence-like complex partial seizures. Thirteen children had been seizure free for at least one year, 36 experienced at least one seizure per week. Nine children did not use antiepileptic drugs, 46 were on monotherapy. EEG abnormalities were absent in one-third of the children, and present in less than 1% of the time in another third. Mean IQ was 88 (70–127). Mean delay in school (two subsets of language, and arithmetic) was almost one year (6.59, 8.44, 9.95 months; ten months equivalent to one year). Only age at onset was positively and significantly correlated with academic delay, not with IQ. This was not explained by duration of the epilepsy.

Conclusion: Age at onset is the main characteristic defining academic delay in children with CLRE.

p711

CYTOCHROME P450 CYP2C9 AND CYP2C19 GENETIC POLYMORPHISMS IN CROATIAN CHILDREN WITH EPILEPSY

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Purpose: The aim of this study was to clarify the effects of CYP2C9 and CYP2C19 genotyping on ongoing antiepileptic drug (AED) treatment and on AED choice. The correlation of efficacy or adverse events of each AED with the CYP2C9 and CYP2C19 polymorphisms was carried out.

Method: Croatian children with epilepsy, treated with different AEDs ($n = 68$) and before the introduction of therapy ($n = 20$) were genotyped for CYP2C9 and CYP2C19 alleles (*1, *2 or *3). Children were divided

into three subgroups: A (n = 19) received AED inducers of CYP isoforms (CBZ, PH); B (n = 49) AEDs noninducers of CYP metabolism (VPA, LTG, TPM, GBP, CLB, ESM, CZP, LEV) and C (n = 20) before AED treatment.

Results: There were 44 girls and 44 boys, average 6.5 yrs. CYP2C9 genotyping results revealed: 47 extensive metabolisers (EM)–*1/*1 and 8 poor metabolisers (PM)–*2/*2 (n = 3), *2/*3 (n = 3) and *3/*3 (n = 2). There were also 33 heterozygous patients for CYP2C9 (intermediate metabolisers (IM)–*1/*2 (n = 22) and *1/*3 (n = 11). Genotyping of CYP2C19 revealed: 71 homozygous patients for *1/*1 (EM) and only 17 heterozygous (IM) for *1/*2. Following these results 13 patients in group A were substituted by noninducing AEDs. In 13 patients in group B, VPA (substrate and inhibitor of CYP2C9) was substituted with LTG/TPM because of poor seizure control. In 7 patients in group C genotyping guided a first-choice AED.

Conclusion: For the better management of childhood epilepsy we should put greater emphasis on the influence of CYP2C9 and CYP2C19 genotyping on the optimal choice of AEDs.

p712

EPILEPSY AND EPILEPTIFORM EEG: ASSOCIATION WITH AUTISM SPECTRUM DISORDERS

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Purpose: To assess, retrospectively, the prevalence of EEG abnormalities and/or seizures in a sample of autistic children and to describe EEG and epileptic features.

Method: Eighty-six children with primary autism (CARS score $\geq$30) were investigated regarding age of onset and severity of autism, IQ, main characteristics of seizures and EEG abnormalities. The prevalence and the relationship among the examined features were determined.

Results: Twenty-one percent showed epilepsy and/or epileptiform EEG; only 14% suffered from epilepsy. Forty-two percent of epileptiform abnormalities were focal. The totality of focal abnormalities was temporal, left-sided in 80% of the recordings. Higher frequencies of EEG abnormalities were associated with more severe autistic symptoms. Language was most severely compromised when EEG abnormalities were located in the left temporal lobe. Sixty-six percent of seizures were generalised, 17% were focal, 17% were secondarily generalised. Children presenting with epilepsy and/or epileptiform abnormalities showed a lower IQ and the trend to a later onset of autistic symptoms.

Conclusion: Our results are in accordance with literature data (Tuchman R. et al. Epilepsy in autism, *Lancet Neurology* 2002,1:352–8) showing that in autism the risk of EEG abnormalities and/or epilepsy is higher compared to the general population. Our data support the hypothesis that epileptiform abnormalities and epilepsy could interfere with the presentation and the course of autism. It would be interesting to test whether antiepileptic treatment is also relevant for autism.

p713

REFRACTORY GENERALISED CONVULSIVE STATUS EPILEPTICUS IN CHILDREN: A LOCAL EXPERIENCE

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Purpose: To describe clinical characteristics of children with refractory generalised convulsive status epilepticus (RGCSE) in the local setting and analyse factors affecting outcome.

Method: A prospective cohort study of all patients <19 years old with RGCSE in Philippine General Hospital over a 7 month period was conducted. Demographic data, seizure characteristics, therapeutics, complications of seizure and hospitalisation were determined. Factors affecting outcome were analysed independently.

Results: Eight Filipinos (mean age 6.28 $\pm$ 7.35 years) were included. Acute symptomatic RGCSE occurred in 5 patients who were neurologically normal prior to seizure onset. Three with epilepsy-related RSE had developmental delay. Six patients received treatment within 1 hour from seizure onset. All received at least 1 dose of diazepam and a therapeutic dose of a second line anticonvulsant. In addition, midazolam infusion was administered to 2 patients. Mean treatment duration before seizure control was 7.49 $\pm$ 5.17 hours. Outcome was poor for all. Of 4 deaths, 3 patients had acute symptomatic RGCSE. Death occurred in 60% of patients who had normal baseline neurodevelopmental status and in 57% whose seizures were controlled >2 hours from treatment initiation. However, there seemed to be no association between age, time before treatment initiation and outcome. Survivors developed neurologic deficits.

Conclusion: Occurrence of RGCSE is associated with poor outcome and an increasing trend to mortality in patients with acute symptomatic RGCSE, normal baseline neurodevelopmental status and seizures lasting >2 hours before control. These data emphasise the need for aggressive management of an underlying cause and termination of seizures.

p714

ELECTROCLINICAL FEATURES OF INFANTILE SPASMS ASSOCIATED WITH ASYMMETRIC MRI FINDINGS

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Purpose: Pathophysiology and underlying epileptogenesis of infantile spasms (IS) have not been fully understood. The aim of this study was to investigate the clinical and EEG features of IS associated with asymmetric lesions on brain MRI.

Method: Twelve IS patients (male 5, female 7) who had asymmetric MRI findings were reviewed. Brain MRI findings were as follows: focal cortical dysplasia in 6, asymmetric periventricular leukomalacia with unilateral porencephalic cyst in 2, asymmetric hydrocephalus in 2, tuberous sclerosis in 1 and Sturge-Weber syndrome in 1. We analysed the ictal semiology and EEG by long-term video-EEG monitoring (VEM) and compared them with interictal EEG.

Results: Interictal EEG showed symmetric hypsarrhythmia in 6 patients and asymmetric hypsarrhythmia in 6 patients. During the VEM symmetric spasms were noted in 5 patients, while 4 patients had asymmetric spasms and 3 patients showed symmetric as well as asymmetric spasms. Ictal EEG revealed an asymmetric ictal pattern in 10 patients, however, 2 patients showed symmetric ictal EEG features. Among the 6 patients who had symmetric hypsarrhythmia on interictal EEG, all showed asymmetric ictal EEG patterns. Asymmetric delta bursts were found in 5 patients, and in a patient who showed symmetric delta bursts, concurrent focal rhythmic sharp wave discharges were also noted.

Conclusion: Interictal EEG may not reflect asymmetric features of structural imaging, but may imply cortical phenomenon according to the propagation of epileptiform activity. Ictal EEG was more helpful in determining the contribution of focal structural abnormality for developing infantile spasms.

p715

EVOLUTION OF SEIZURE TYPE AND EEG PATTERN IN A PATIENT WITH VERY EARLY ONSET OF HUNTINGTON DISEASE

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Purpose: Huntington's Disease (HD) is an autosomal dominant, neurodegenerative disorder caused by dynamic mutation in the *IT15* gene. The onset of disease is usually in the 4th/5th decade of life but under the age of 20 in about 10% of patients. This Juvenile Huntington's Disease (J-HD) is clinically distinct from the adult-onset form. One of the J-HD

characteristics features epilepsy and occurs in 90% of patients with onset in the first five years of life. Although it is so common in J-HD, the type of seizures, and the main EEG data are still poorly described. We report the case of a patient with an evolution of seizures in the context of data referring to epilepsy in patients with J-HD.

Method: The patient was a boy with J-HD of very early onset (died at the age of 11). The clinical diagnosis was confirmed by DNA analysis [$(CAG)_{95}/(CAG)_{17}$]. The first symptoms were observed at the age of 3 as a worsening of speech and episodes of absence (controlled with valproate). At the age of 8 EEG showed sharp waves, polyspike and spike-and-wave discharges with right side predominance. At the age of 9 intractable tonic–clonic and myoclonic seizures were noticed. At the age of 11 the patient suffered from intractable epilepsy and EEG showed reduction of background activity without any epileptiform discharges.

Results: In the case of the presented patient the noncharacteristic symptoms started at the age of 3, but J-HD was suspected when he was 9, showing cognitive and psychomotor decline, rigidity and involuntary movements (there was no HD in his family). The seizure evolution started very unusually, from absences, when the most common seizure types in HD are GTC and myoclonic seizures. Knowing the molecular data we can say now that clinical presentation was not very unusual for such an early form of J-HD, but without the family history of disease the differential diagnosis was not so obvious.

Conclusion: Our data, as well as that published elsewhere, shows that J-HD is not self-evident from a clinical point of view and should be considered in children with intractable epilepsy and signs of progressive encephalopathy even without a family history of the disease.

p716

PARTNERS IN EPILEPSY (PIE): EPILEPSY MANAGEMENT WITH INTERNATIONAL ELECTRONIC RECORDS REGISTRY SYSTEM: ANALYSIS UPDATE IN PAEDIATRICS

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Purpose: To study current practices and clinical outcomes based on a large naturalistic data cohort, and to identify needs in paediatric epilepsy management.

Method: Electronic records management in daily clinical practice (demographics, aetiology, syndrome and treatment) in epilepsy centres in Belgium, France, Portugal, Spain, Switzerland, and United Kingdom.

Results: Data was analysed from 1420 children (M/F = 54.4%/45.6%), mean age at first attack: 5.6. Follow-up was available for 1359 children, [mean = 227 days, median = 320, sd = 403 (range 1 day–12.4 yrs.)] Aetiology reported for 37% of total children. Of these, the most frequent cause was cortical/developmental disorders/malformations (11.7%). In 39% of the cohort, epilepsy syndrome was defined: 49% diagnosed with partial epilepsy, 36% with generalised epilepsy, 10% with undetermined epilepsy, and in 5% special epilepsy syndromes were described. 52% were seizure-free at last follow-up visit. Among children still experiencing seizures, the most frequent seizure type was partial seizures, 55% (median: 3/month; range: 0–600/month). Of those using AEDs at the last follow-up visit, 72% were on monotherapy: valproic acid (36%), carbamazepine (17%), lamotrigine (6.4%), and topiramate (43.6%). 18% were on two, 8% on three, and 2% on four AEDs. The most common AED combinations were: lamotrigine/valproate (2.7%), carbamazepine/valproate (2.3%), topiramate/valproate 1.7% and carbamazepine/lamotrigine (1.1%).

Conclusion: Registry analyses provide valuable naturalistic information on epilepsy characteristics, outcome and AED treatment patterns in children. Partial epilepsy was the most common type identified. In the majority, however, the epileptic syndrome was not recorded. Five out of 10 were seizure-free at the last consultation. The majority received monotherapy. Side effects were not often reported. (PIE is supported by Janssen-Cilag)

p717

FAST TITRATION OF ADJUNCTIVE TOPIRAMATE IN PAEDIATRIC PATIENTS WITH DIFFICULT-TO-TREAT EPILEPSY

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Purpose: To evaluate efficacy and tolerability of adjunctive topiramate (Topamax, TPM) using fast titration in children with difficult to treat epilepsy and frequent seizures.

Method: A 12 week single centre prospective noninterventional study in topiramate-naive hospitalised patients age 2 to 12 years. If clinically indicated, TPM was started at the discretion of the investigator at approximately 1mg/kg/day bodyweight with dose increments of 1mg/kg every 3 days and a target dose up to 8mg/kg/day. Seizure frequency and adverse events were documented at each visit.

Results: Nineteen children (64% male, mean age 4.4 $\pm$ 3.5 years, median epilepsy duration 1.6 years) were enrolled. Difficult to treat epilepsy was characterised by frequent seizures (84% of patients), and unsuccessful use of other antiepileptic drugs (AEDs) (mean 5.2). All patients had $\geq$1 concomitant AEDs at baseline, (valproic acid (59%), clobazam (47%) or oxcarbazepine (22%)). Mean TPM starting dose was 1.1 $\pm$ 0.5mg/kg/day and 3.3 $\pm$ 2.0mg/kg/day at endpoint (range 0.5–6.7mg/kg). Median seizure frequency was approx. 182 in the 4 week retrospective baseline. 47% of patients were TPM responders with a $\square$50% seizure reduction, 1 patient was seizure free at time of study conclusion. TPM efficacy was rated very good or good in 42% of patients, tolerability in 37%. No serious adverse events occurred. Adverse events $\geq$5% were somnolence (21%), psychiatric symptoms (14%), decreased appetite (10%) and nervousness (7%).

Conclusion: In children with difficult to treat epilepsy, a fast titration of TPM appears to be effective, and given the difficult situation, well tolerated. Interestingly, relatively low doses of adjunctive TPM provided significant improvement in seizure frequency.

p718

THALAMIC LESION AND EPILEPSY WITH ELECTRICAL STATUS EPILEPTICUS IN SLOW WAVE SLEEP AND/OR GENERALISED SPIKE-WAVE PATTERN

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Purpose: To report on 4 patients, who have unilateral thalamic lesion and epilepsy with clinical and electrical features of generalised epilepsy.

Method: Clinical, MRI and awake and sleep EEG data were evaluated.

Results: The first 3 patients have unilateral perinatal lesion, 1 with generalised tonic–clonic seizures (GTCS) on awakening and later nonconvulsive status epilepticus with 2.5 Hz SW pattern, 1 with Landau-Kleffner-like syndrome, and the 3rd with mainly atonic seizures. During the course of the disease all children developed electrical status epilepticus in slow wave sleep (ESES). The 4th patient has a dominantly unilateral thalamic tumour and epilepsy that mimics juvenile myoclonic epilepsy. All the patients have a lesion located in the postero-inferior medial part of the thalamus. The role of some thalamic nuclei in the generalised spike-wave (GSW) electrical pattern pathophysiology is discussed, with emphasis on the possible role of dorsal intralaminar nuclei and zona incerta.

Conclusion: A unilateral thalamic lesion located in the postero- inferior medial part of the thalamus may facilitate ESES.

p719

SPECTRUM OF SYNDROMES WITH MYOCLONIC SEIZURES IN DIFFERENT PAEDIATRIC AGE GROUPS

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Purpose: Myoclonic seizures are frequent seizure types in the paediatric age group. They appear as different syndromes at different ages and are frequently associated with difficulties in classification and managing. The aim of the study was the identification of frequency of different syndromes with myoclonias for classification according to age groups.

Method: During 2001–2002 we examined 397 patients with myoclonic seizures. Ages varied from neonatal to 18. All patients underwent long term EEG, MRI, neuropsychological testing. Clinical data was analysed prospectively with reevaluation in 2005. Distribution of patients according to age groups was as follows: neonates 51, infants 126, children (2–11) 152, adolescents 66. Reevaluation was carried out on 385 patients. 12 patients were missed during follow up.

Results: Patients were divided according to syndromes and age groups. For 10.5% classification was impossible. Problems were minimal in adolescence: 3%.

Classification difficulties most frequently occurred in infancy, 14.8%; in childhood in 10.1%. Distribution of syndromes was: neonatal seizures 13.2%, benign myoclonic epilepsy 1.3%, severe myoclonic epilepsy (SME) 2.3%, early myoclonic encephalopathy 1.3%, epilepsy with myoclonic astatic seizures 6.49%, childhood absence epilepsy 11.7%, juvenile absence epilepsy 10.1%, epilepsia with myoclonic absences 4.4%, LGS 2.9%, infantile spasms 23.9% and juvenile myoclonic epilepsy 13.2%. Unclassifiable cases were difficult for treatment. In 35 such cases, full seizure control was not achieved, reduction of seizure frequency occurred only in 3 cases, while even in severe epilepsy syndromes such as SME, LGS and IS seizure control was significantly ($p < .001$) better.

Conclusion: Myoclonic seizures are frequent in all age groups. Difficulties in classification and treatment are more prominent in infancy. Resistance to treatment is higher in unclassifiable cases.

p720

EARLY ONSET EPILEPSY: AETIOLOGICAL STUDY AND FOLLOW-UP ON 59 PATIENTS

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Purpose: We reviewed data of 59 patients admitted to the Division of Neuropsychiatry of "Regina Margherita" Hospital in their first year of life in order to evaluate peculiar aspects of clinical features and follow-up between subjects with infantile spasm and early onset epilepsies without spasms.

Method: We analysed demographic features, clinical aspects, aetiology, neuroimaging studies, neurophysiological recordings, therapy and psychomotor development of 27 subjects with infantile spasms (Group I) and 32 subjects with other types of epilepsy without spasms (Group II) in a 5 year period (2000–2005).

Results: Age at onset of seizures ranged from 1 to 9 months, mean age 4.7 months (SD $\pm$ 2.6) in group I, and ranged from 1 to 12 months, mean age 5.9 months (SD $\pm$ 2.8) in group II. Prevalent aetiology was prenatal injury (group I: 27%, group II: 16%), cerebral malformation (I: 26%; II: 28%), idiopathic (I: 11%, II: 31%), and others: vascular, genetic, metabolic disorders, neurocutaneous syndromes (I: 36%, II: 25%). Neuroimaging studies showed a normal brain (I: 19%, II: 38%), brain abnormalities (I: 69%, II: 59%), cerebrospinal fluid abnormalities (I: 12%, II: 3%).

Seizure free patients were 52% in group I and 62% in group II after onset of drug therapy. Psychomotor development was delayed in 40% of subjects in group I and 20% in group II.

Conclusion: Our data show worse prognosis in terms of cognitive and psychomotor development, than in terms of poor seizure control, in those patients whose epilepsy started with infantile spasms.

p721

MALIGNANT MIGRATING PARTIAL SEIZURES OF INFANCY: ANALYSIS OF ICTAL VIDEO-EEG

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Purpose: Malignant migrating partial seizures of early infancy (MMPSI) is a rare and age-specific epileptic condition characterised by onset within the first 6 months of life in which nearly continuous intractable partial seizures involve multiple independent areas of both hemispheres with progressive severe psychomotor retardation. Few authors who reported this epileptic encephalopathy have attempted to recognise the aetiology but there are no identifiable causes.

Method: We retrospectively reviewed 4 patients who arrived in our institution over the last 3 years, and who fulfilled the diagnostic criteria for MMPSI. Electroclinical characteristics by video-EEG were recorded and therapeutic options were evaluated.

Results: All patients have early seizures with motor and autonomic components, consisting of apnea, cyanosis, and flushing, lasting a few minutes. Many of these seizures were clinically mild and easily overlooked without video-EEG recording. Later, seizures were more polymorphic, arising independently from multiple regions of both hemispheres, lasting a few to many weeks. Extensive investigations failed to identify an underlying cause. There was no response to antiepileptic drug therapy and no developmental progress. Two infants have been implanted with vagus nerve stimulation (VNS). No patients became seizure-free but a reduction in seizure frequency and severity was observed mainly in VNS implanted patients.

Conclusion: Our patient data confirm the peculiar clinico-EEG pattern of the syndrome, the lack of evidence for an underlying disorder, the severity of prognosis despite multiple therapies and also suggest that the syndrome could be overlooked in absence of serial VEEG recordings.

p722

EPILEPTIC SEIZURES IN CHILDREN WITH SUBACUTE SCLEROSING PANENCEPHALITIS

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Purpose: This is a retrospective analysis of epileptic seizures occurring in SSPE (subacute sclerosing panencephalitis), either as a first sign or in evolution of the disease. Prognostic correlations relating to different aspects of seizures were made.

Method: Ninety-one SSPE cases admitted in our clinic during a 16 yr period (1990–2005) were analysed. Data was extracted from medical records and directly from families (telephone calls). CSF evaluation for measles virus antibodies was performed in all patients except 4, but all cases had clinical and EEG features for SSPE. Thirty-eight cases had imagistic evaluation (CT, MRI). Extensive clinical, electrical data will be presented.

Results: The group included 63 males and 28 females. Seventy-one patients had measles (37 < 2yr of age) and 10 were vaccinated. In our group, 1 patient presented seizures, 9 as a first sign and 8 during the course of SSPE. Six patients presented focal seizures at onset, compared with 3 patients with generalised seizures, and generalised seizures in the course of the disease (11 patients from 17), developed mainly in stage II (15 patients) or III (2 patients), raising the idea of a widespread pathological process as SSPE progresses. Two patients had atypical absences documented by clinical and electroencephalographic findings. AEDs had a good effect on seizures, but not on the overall prognosis. No correlation between duration, frequency, age of onset, type of seizures and prognosis was established. Resistance to AEDs (3 cases) was correlated with poor prognosis (exitus in 2 at 5 months after onset).

Conclusion: SSPE diagnosis was delayed by 1 to 7 months in cases with epileptic seizure onset compared with cases with typical onset that were diagnosed immediately. 1) Seizures resistant to AEDs were correlated with a poor prognosis. 2) There is a high percent (11%) of SSPE patients who developed the disease after declared immunisation, raising problems concerning correct and careful vaccination of all children.

p723
IDENTIFICATION OF BRAIN ABNORMALITY IN CHILDREN WITH INTRACTABLE FOCAL EPILEPSY AND NORMAL IMAGING USING VOXEL BASED MORPHOMETRY
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Purpose: Children with intractable focal epilepsy and normal imaging pose a difficult management problem. Seizure remission rates with medical therapy are low and the option of surgery is limited by the absence of visible abnormality on MR. Cortical dysplasia has been reported in operative specimens from this patient group. MRI is a noninvasive tool and development of MR techniques might allow detection of such "occult" pathology. We propose that voxel-based morphometric (VBM) analysis of diffusion tensor (DTI) and 3D structural images may allow detection of focal brain abnormality, not seen on conventional imaging.

Method: Patients were recruited from the Epilepsy clinics at Great Ormond Street Hospital, London. All patients underwent full presurgical evaluation including ictal EEG. 3D structural datasets and DTI were acquired preoperatively. VBM was performed using SPM2 (Wellcome Department of Imaging Neuroscience, London).

Results: VBM identified abnormality concordant with the seizure focus (determined by ictal EEG) in 2/7 of the 3D structural images and in 1/5 fractional anisotropy (FA) maps. Other areas of abnormality were also noted outside the seizure focus in 4/7 3D structural images and 1/5 FA maps. These may represent separate areas of developmental or acquired pathology, and are not visible on conventional imaging.

Conclusion: Initial results suggest that VBM may demonstrate focal abnormality in children with intractable focal epilepsy and negative conventional imaging. Correlation of these areas of abnormality with operative pathology may provide support for the use of VBM in the pre-surgical evaluation of this patient group.

p724
SLEEP DISTURBANCES IN CHILDREN WITH EPILEPSY
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Purpose: Children with epilepsy often have cognitive deficits that affect their quality of life. Some of them experience daytime somnolence and poor attention during daytime school activities, which may be related to the concomitant sleep disorders. The aim of the present study was to investigate the incidence and type of sleep disorders among children with epilepsy.

Method: Parents of 80 children with epilepsy were asked to fill out the questionnaire screening for the sleep disturbances, SDSC (Bruni et al, 1996).

Results: Twenty-one children (36%) had total SDSC scores indicating the presence of sleep disturbances. The most prevalent were sleep wake transition disorders (SWTD 37.46%), followed by disorders of excessive somnolence (DOES 21.26%) and disorders of arousal and nightmares (DA 20.25%), disorders of initiating and maintaining sleep (DIMS19.22%). Two other groups of sleeping disturbance, sleep breathing disorders (SBD 8.10%) and sleep hyperhidrosis (6.7%), seldom occurred. Seven children had a high T-score value (>70) on ≥ 4 subscales, showing a distributed pattern of sleep disturbances. The age of children ranged from 5 yr 6 mo to 17 yr 9 mo (11.9 ± 3.33) and age had a significant effect on the DA scores. The type of sleep disturbance was related to the type of epilepsy: SBD ocurred significantly more often among children with rolandic epilepsy, and DIMS among children with temporal epilepsy. DA and SWDT scores were significantly higher in children with night seizures ($p = 0.01$).

Conclusion: Children with epilepsy have a high frequency of sleep disorders. Their timely management may improve the quality of daily activities.

p725
DECREASE OF ARTIFACTS OF EEG ELECTRODE METALLIC PARTS WITH ELECTROLESS NICKEL-PHOSPHOROUS COATINGS
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Purpose: In this research, the contacting of EEG electrode metallic parts to head scalps was studied. If the electrode to scalp contact is not proper, the EEG signal shows artifact. To avoid this, ensure that all electrodes are securely placed. This check is very critical for the reference electrode. If the contact of the reference electrode is poor, all the channels get artifact. One of the EEG artifacts is electrode pop and its poor impedance (lack of conductivity). This artifact is related to some impurity and oxide and corrosion products in the metallic portion of the electrode due to the chemical reactions between corrosive materials as sweating water of patient, gel, paste or NaCl dionised water with metallic portions of electrodes. Already the coatings of metallic portions of electrodes are nickel coatings, but these coatings have not the corrosion resistance and so after using for many patients cause artifact. In this study, with the aim of increasing corrosion resistance of electrode metallic portions, plated electroless nickel-phosphorous (Ni-P) coatings were used. Electroless Ni-P coatings are widely used because of their good resistance to corrosion and wear. The corrosion resistance is a result of the amorphous nature and passivity of Ni-P deposit.

Method: The Ni-P coatings on electrode metallic parts were deposited in a commercially available bath that contained nickel sulfate and sodium hypophosphite. Temperature of 90°C and pH 4.6 were employed. The thickness of coatings was about 60 micron. Then, the corrosion resistance of electroless Ni-P coated metallic parts of the electrode was compared with common Ni coatings after EEG tests of 1000 paediatric patients in 6 months.

Results: The results show that the life of electrode metallic parts with Ni-P electroless coatings had 10 times of Ni coatings and the electroless Ni-P coatings had not any artifacts on EEG comparing with Ni coating.

Conclusion: Using the electroless Ni-P coatings on electrode metallic parts can reduce major parts of instrumental artifact due to elimination of electrode pop, oxide and corrosion products and this may be suggested to EEG machine manufacturing companies.

p726
CEREBRAL PALSY AND EPILEPSY: FACTORS ASSOCIATED WITH UNSATISFACTORY SEIZURE CONTROL
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Purpose: To analyse factors associated with incomplete seizure control in children and adolescents with cerebral palsy (CP).

Method: The group of 59 patients with CP and epilepsy with a mean age of 8 years (range, 2 to 27 years) was studied retrospectively. The criteria for inclusion included the follow-up period for at least 1 year. Distribution of clinical forms disclosed 46 patients with spastic CP, 2 patients with a dyskinetic form and 11 patients with a mixed form. Other factors associated with CP and epilepsy such as mental retardation, age of seizure onset and types of seizures were also analysed.

Results: All patients were treated with 1, 2 or 3 AEDs. More than one half of our patients (56%) were treated with AED polytherapy. Forty patients in our group (68%) became seizure-free. Complete seizure control was mainly achieved in children with spastic hemiplegia (16/40) and diplegia (15/40) while patients with mixed form and spastic quadriplegia belonged to the subgroup with incomplete seizure control (8/18 each). Early seizure onset (in the first 2 years of life) occurred in 52% of children with complete seizure control as compared to 79% of children without well-controlled seizures. Partial seizures with secondary generalisation occurred more frequently in the subgroup with seizure reduction of $>50\%$ (9/19) than in the subgroup with complete control of seizures (7/40). Associated mental retardation was seen in 52% of seizure-free patients and in 78% of patients with unsatisfactory seizure control.

Conclusion: Severe neurological condition, mental retardation, earlier age of seizure onset and focal seizures with secondary generalisation are factors mainly associated with unsatisfactory seizure control.

p727

NONCONVULSIVE STATUS EPILEPTICUS AND NEURODEVELOPMENTAL DELAY

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Purpose: Nonconvulsive status epilepticus is characterised with continuous or near continuous epileptiform discharges on electroencephalography without overt motor or sensory phenomena. It is a symptomatic condition related to a disease such as epileptic encephalopathy or a metabolic disorder. It consists of very different syndromes and it is divided into typical absence status epilepticus, complex partial status epilepticus, and nonconvulsive status epilepticus in patients with learning difficulties (including electrical status epilepticus during sleep, atypical absence status epilepticus and tonic status epilepticus).

Method: The diagnoses are dependent on EEG and have different prognoses and treatments (Walker MC. *CNS Drugs* 2001;15(12):931–939). Children with isolated nonconvulsive status epilepticus rarely present with global neurodevelopmental delay (Shinawi M. J *Child Neurol* 2001;16:215–217). We report an 18-month boy who presented with global neurodevelopmental delay and decreased alertness in whom electrical status epilepticus during sleep, which is a form of nonconvulsive status epilepticus, was determined.

Results: Metabolic investigations and cranial magnetic resonance imaging were normal. He began to achieve developmental milestones following treatment with valproic acid.

Conclusion: We consider that, although rare, paediatric neurologists and paediatricians must be aware of this condition in making the differential diagnosis of global neurodevelopmental delay and decreased alertness.

p728

PROGRESS OF TREATMENT FOR SUBACUTE SCLEROSING PANENCEPHALITIS WITH MYOCLONIC JERKS

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Purpose: Subacute sclerosing panencephalitis (SSPE) is a progressive neurologic disorder of childhood and early adolescence by persistent latent measles virus infection. We have diagnosed and experienced a case of SSPE in an 11-year-old child with the chief complaint of myoclonic jerks, progressive deterioration in scholastic performance and cognitive function.

Method: We checked a brain MRI, and electroencephalogram. We measured the measles IgG and IgM level, oligoclonal band, PCR in serum and cerebrospinal fluid.

Results: We treat an intrathecal interferon-alpha and oral inosiplex. On the 5th day of admission, inosplex (100 mg/kg/day, per oral) treatment was initiated. On the 18th hospital day, interferon-alpha (450,000U/m^2/three times a week, intrathecal) treatment began. Cerebrospinal fluid protein, sugar, cell count were within the reference values. Measles IgG antibody in the CSF and serum were checked at 38,508mIU/ml and 17,293mIU/ml by ELISA. Measles virus RNA can be detected by PCR, but the oligoclonal band was not detected. There were no abnormal findings in brain MRI. The EEG showed periodic complexes consisting of bilaterally symmetrical, synchronous, high voltage bursts of polyphasic, stereotyped delta waves. These periodic complexes repeat at fairly regular 4–10 second intervals and have a 1:1 relationship with myoclonic jerks.

Conclusion: This patient was diagnosed with a subacute sclerosing panencephalitis by measles virus PCR and IgG level in the CSF. We are treating this patient for 4 months. Myoclonic jerks are improving, but still remain. Cognitive function and scholastic performance is improving.

p729

EPILEPSY IN CHILDREN WITH BILATERAL CEREBRAL PALSY (CP): CORRELATION WITH MAGNETIC RESONANCE IMAGING (MRI) FINDINGS

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Purpose: CP refers to a group of disorders characterised by abnormal movement and posture due to nonprogressive insult to the brain. Seizures are often present. The purpose of this study was to determine the relationship between epilepsy and MRI findings in patients with tetraparetic forms of CP.

Method: We studied 101 children with tetraparetic forms of CP. All of them had perinatal asphyxia. Epilepsy was found in 18 of the 101 patients. The types of seizures were focal in 16 children, generalised in 1 child and polymorphic in 1. In 15/18 hypoxic-ischaemic encephalopathy was diagnosed. The first epileptic seizure appeared at the median age of 2.5 years. Paediatric neurologist, neurophysiologist, psychologist, speech therapist and physiotherapist examined all children. MRIs were performed on 1.5 Tesla Siemens (Magnetom) scanner using a 256×256 matrix. MRI findings were divided into the following categories: (a) central atrophy and periventricular (PV) white matter lesions; (b) diffuse white matter lesions; (c) cortical atrophy and/or basal ganglia lesions; (d) normal.

Results: Normal MRI was found in 1 child with generalised epilepsy. In 17 patients pathology in MRI was diagnosed. In 6 patients, central atrophy and PV white matter lesions, in 6 diffuse white matter lesions and in 5 cortical atrophy and/or basal ganglia lesions were found.

Conclusion: Ventricular dilatation and PV white matter lesions were related to motor development and well treatable epilepsy ($p < 0.05$). Significant correlations between problems of mental development, intractable epilepsy and diffuse white matter lesions and cortical atrophy and/or basal ganglia lesions were found ($p < 0.05$).

p730

HOMOCYSTEINE LEVELS IN CHILDREN RECEIVING ANTIEPILEPTIC DRUGS

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Purpose: Hyperhomocysteinemia is a risk factor for atherosclerotic vascular disease. In adults, it has been reported that some antiepileptic drugs cause elevated homocysteine levels due to reduced folic acid concentrations. We aimed to investigate the serum homocysteine, folic acid and vitamin B12 levels in children with epilepsy receiving antiepileptic drugs.

Method: Twenty five children with idiopathic epilepsy (13F, 12M) were included in the study. Of them 8 were receiving valproate, 11 were receiving carbamazepine and 6 were receiving oxcarbazepine monotherapy. Ten healthy children (6F, 4M) served as the control group. Serum homocysteine, folic acid and vitamin B12 levels were measured and were compared between the two groups.

Results: The mean age of the study patients was 11.44 ± 3.33 and the mean age of the control subjects was 12.00 ± 3.94 ($p = 0.595$). The mean plasma homocysteine, folic acid and vitamin B12 levels in the study group were 7.57 ± 3.78 μmol/L (normal: 5–15 μmol/L), 10.19 ± 4.05 ng/mL (normal: 3.0–17 ng/mL) and 428.20 ± 256.12 pg/mL (normal: 193–983 pg/mL), respectively. In the control group, the mean plasma homocysteine, folic acid and vitamin B12 levels were 7.66 ± 2.34 μmol/L, 9.76 ± 3.57 ng/mL and 406.80 ± 172.18 pg/mL, respectively. The differences between the two groups were not significant ($p = 0.522$; $p = 0.855$; $p = 0.798$). There was also no significant difference between the valproate, carbamazepine and oxcarbazepine groups in respect to homocysteine, folic acid and vitamin B12 levels ($p = 0.794$; $p = 0.183$; $p = 0.165$).

Conclusion: Although the number of our study patients was limited, we thought that hyperhomocysteinemia is not a serious problem in children with epilepsy receiving valproate, carbamazepine or oxcarbazepine.

p731
ATROPHY IN CHILDREN WITH PRIMARY IDIOPATHIC EPILEPSY
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Purpose: Some studies have indicated a high incidence of allergic illness in adult patients with epilepsy, but few studies provide adequate clinical and laboratory data to document the higher incidence of allergy in children with epilepsy. The aim of this study was to evaluate the relationship between atrophy and epilepsy in children with idiopathic epilepsy and compare the results with those of healthy children.

Method: Thirty-nine children with idiopathic epilepsy were included in the study. They were grouped according to the type of epilepsy and antiepileptic drug regimen. Allergic complaints and family history of allergy were investigated. Plasma IgE levels and total eosinophil content was measured and epidermal pinprick was applied. The results were compared with those of a group of healthy children.

Results: Twenty-one patients (54%) had primary generalised and 18 patients (46%) had partial epilepsy. Twenty-one patients (54%) were treated with valproic acid and 18 patients (46%) were treated with oxcarbazepine. Regarding the allergic complaints, family history of allergy, plasma IgE levels, eosinophil counts and pinprick test results, no significant differences were found between the generalised and partial epilepsy group. Again, there were no significant differences between the valproic acid and oxcarbazepine group. Positive pinprick results were significantly higher in epilepsy patients when compared with healthy control subjects ($p = 0.001$, $p < 0.05$).

Conclusion: The significantly higher positive pinprick results in children with epilepsy suggest a role of atopy as a possible predisposing factor in the development of epilepsy.

p732
CANTAB NEUROPSYCHOLOGICAL PROFILES OF PAEDIATRIC PATIENTS: A COMPARATIVE STUDY
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Purpose: The neuropsychological profiles of paediatric populations are still unclear, and the impact of early neural damage remains largely undefined, maybe due to the fact that, during development, reduction in learning potential and greater functional plasticity are both at work, in opposite directions. Our study aimed to circumscribe specific neuropsychological profiles of paediatric patients (8–12 years of age) compared to their normal counterparts.

Method: Five categories of neurological and psychiatric populations were compared to normal children: a) children with craniocerebral traumatic injuries; b) children with temporal epilepsy; c) children with extratemporal epilepsy (benign rolandic, frontal or generalised); d) children with other neurologic disorders (Wilson disease, neurofibromatosis type II, cerebellar ataxia); e) children with psychiatric disorders (affective or somatoform disorders). All subjects were tested with the Cambridge Neuropsychological Testing Automated Battery (CANTAB), a computerised battery valid for the assessment of frontal, temporal, and striatal functions.

Results: Although temporal lobe memory functions, measured via CANTAB subtests like Delayed Matching to Sample or Paired Associates Learning, were shown to reach mature stable levels by the age of 8 (e.g., Luciana et al. *Developmental Neuropsychology* 2002;22:595–624), our results indicate significant impairments in paediatric patients versus normal children, the most severely affected being, somehow paradoxically, children with extratemporal epilepsy. Tests sensitive to frontal lobe functions indicated most acute deficits in children with craniocerebral traumatic injuries (e.g., Spatial Working Memory), or psychiatric patients (e.g., Spatial Recognition Memory).

Conclusion: Specific neuropsychological impairments individualised categories of paediatric patients. Such information remains largely undetected during routine neurological assessment.

p733
ERRATIC MYOCLONIA AND DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY (DPD)
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Purpose: To present the case of an infant diagnosed with dihydropyrimidine dehydrogenase deficiency (DPD).

Method: Case report.

Results: AK is a male infant, who presented at age 3 months with erratic myoclonia, poor weight gain, arching, and abnormal movements. He had no reciprocal smile and poor visual interaction. Examination was significant for irritability, hypertonicity, and opisthotonus. EEG was diffusely slow, disorganised with shifting delta and multifocal spikes similar to that in B-6 dependency. There was no response to IV pyridoxine 100-mg. Urine had increased uracil, thymine, and pyrimidine. Urine Pipecolic acid was 18.9 Umole/G Cr (2.3–62.0) and carnosine was not detected. MRI was normal. Enzyme analysis showed a complete deficiency of dihydropyrimidine dehydrogenase.

Treatment with vigabatrin led to better-organised bilateral myoclonic seizures and extreme irritability and no change in EEG. Levetiracetam decreased myoclonia, as did the addition of zonisamide. Clonazepam showed modest improvement of seizures and no change in arching. L-carnosine 500-mg/day increasing to 1000-mg resulted in improved alertness with increases in urine carnosine and alanine. EEG continued to show slowing and poor organisation. Pyridoxal-5-phosphate 80-mg/day was added.

Conclusion: DPD is an autosomal recessive disease is linked to chromosome 1p22 and is associated with a variable clinical phenotype including severe epilepsy, mental retardation, and hypertonia. Dihydropyrimidine dehydrogenase is the initial and rate-limiting enzyme in the pathway leading to the formation of beta-alanine. L-carnosine was supplemented in order to increase brain beta-alanine. Furthermore, reasoning that there may be a secondary deficiency of pyridoxine as is postulated in pyridoxine dependent epilepsy (PDE) and given the similarity in the EEG to that seen in untreated PDE, pyridoxal-5-phospahate was also supplemented.

p734
RELATIONSHIP BETWEEN THE AGE AT DISEASE ONSET AND VERBAL DISTURBANCES IN PATIENTS WITH ROLANDIC EPILEPSY
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Purpose: To evaluate the relationship between the age at onset of rolandic epilepsy (RE) and the results of speech evaluation tests.

Method: We studied verbal functioning in patients with RE ($n = 64$) and in healthy controls ($n = 35$) by using sub-tests of the Neuropsychological Development Study (NEPSY).

Results: Relationship between the age of RE patients at the onset of the disease and the results of the speech evaluation tests were as follows: (1) verbal fluency $r = 0.66$ ($p < 0.001$); (2) speed naming: time of task accomplishment $r = -0.60$ ($p < 0.001$), number of errors $r = -0.21$ ($p = 0.09$); (3) comprehension of instructions: number of errors in the first part $r = -0.33$ ($p = 0.01$), number of errors in the second part $r = -0.49$ ($p < 0.001$).

Conclusion: Relationship was established between the age of epilepsy onset and the results of the speech and attention evaluation tests: the younger the age of epilepsy onset, the worse were the results of the evaluation tests ($p < 0.05$).

p735

EPILEPSY IN CHILDREN WITH PERIVENTRICULAR LEUKOMALACIA: OUTCOME IS RELATED TO LESION PATTERN AND TYPE OF EPILEPTIFORM ACTIVITY IN THE EEG

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Purpose: Periventricular leukomalacia (PVL) occurs in children as a consequence of cerebral ischemia or haemorrhage in the immature brain. Since pathogenesis and timing of the lesion are homogeneous, this could serve as a model to study the impact of brain lesions on manifestation and outcome of epilepsy. Therefore, we investigated the relation between lesion patterns, epilepsy and EEG findings in children with PVL.

Method: Twenty-four children (mean age 6:3 years, range 3:2–10:10 years) with bilateral periventricular lesions and a follow-up of more than three years were included in the study. MRI, clinical data and EEG were systematically reviewed by patient-blinded evaluators.

Results: From the children with mild lesions, i.e. <50% reduction of the periventricular white matter ($n = 14$) only 2 had epilepsy. From the children with severe lesions ($n = 10$) 7 had epilepsy ($p < 0.01$). Five children initially had West syndrome with a favourable course. In only 1 child was the epilepsy considered severe. Fifteen children (62%) had benign focal spikes in the EEG; in 10 this constituted the only type of epileptiform activity. Of these children, only 3 had epilepsy.

Conclusion: In children with PVL outcome of epilepsy, this is closely related to (1) the extent of the periventricular lesion and (2) the type of epileptiform activity in the EEG. Benign focal spikes are found much more often than expected indicating that PVL constitutes a trigger mechanism for this genetic trait.

p736

CLINICAL AND ICTAL VIDEO-EEG CHARACTERISTICS OF 28 CASES WITH INFANTILE SPASMS

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Purpose: Infantile spasms (IS) are generally divided into 3 types including flexion, extension or mixed, but nothing more definitive has been stated as to the duration, extent or mode of muscle contraction or associated ictal electroencephalographic changes. The aim of the study is to investigate the clinical interictal and ictal video-EEG characteristics of 28 cases with IS and evaluate clinical significances for early diagnoses and treatment.

Method: Clinical observation and video-EEG monitoring were analysed and followed up in 28 babies with IS.

Results: Twenty-eight babies (19 male) were diagnosed to have IS after clinical spasms and hypsarrhythmia at the onset of initial seizures. The babies ranged in age from $2 \sim 16$ months with an average of 6.5 months. All cases were involved in the axial musculature with three generally divided types including flexion, extension or mixed by 12, 9 and 7 cases respectively. After analysis (64 times) of clinical spasms and video-EEG recordings in all babies, the spasm patterns of this group were clinically classified as follows: symmetric spasms in 14 cases, asymmetric/asynchronous spasms in 8 cases, focal or hemispasms in 6 cases, spasms combined with partial seizures in 8 cases, spasms preceded by brief atonia in 2 cases, subclinical spasms in 5 cases; in addition, subtle spasms were found alone or in coexistence with most cases. Interictal EEG showed the typical and atypical hypsarrhythmia in 8 and 20 cases respectively, focally polyspike/sharp and slow waves or hemihypsarrhythmia in 5 cases; at least three different patterns of ictal-EEG were associated with clinical spasms: fast wave bursts, diffuse polyphasic high slow voltage wave complex and desynchronisation or decremental activity, in which the prominent positivity of the polyphasic high voltage slow wave complex of negative-positive-negative deflection was usually parallel with clinical tonic or tonic spasms. Video-EEG monitoring was more valuable than the routine EEG for the early diagnosis and treatment of IS, particularly in those babies with a history of hypoxic-ischemic encephalopathy and subclinical spasms. Although most of the clinical spasms were usually symmetric, focal lesions could not be excluded. EEGs were not surely synchronous and symmetric.

Conclusion: IS was a special type of epileptic seizure as well as an epileptic syndrome with different patterns and could be associated with partial and other types of seizures; video-EEG was much more valuable for its early diagnosis and treatment.

p737

IDIOPATHIC CHILDHOOD OCCIPITAL EPILEPSIES: AN UNDERDIAGNOSED EPILEPTIC SYNDROME

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Purpose: To identify and characterise the clinical and EEG aspects of idiopathic childhood occipital epilepsies (ICOE) in our epilepsy clinic patients.

Method: We retrospectively reviewed the ictal phenomenology, interictal EEG findings, and prognosis in patients diagnosed with ICOE.

Results: Fifteen patients were identified, 9 with Panayiotopoulos-type, 4 with Gastaut-type, and 2 atypical cases. In the first group, sleep-related seizures, with ictal vomiting and tonic eye deviation were the rule. Secondarily generalised seizures occurred in 3 patients and focal status epilepticus in 1. In Gastaut-type patients, visual phenomena were prominent. The other 2 patients did not fulfil the criteria of any of the two above mentioned, and had a single seizure. Prognosis was very favourable in the first and variable in the second group. Interictal EEG revealed occipital paroxysmal discharges strictly in the occipital regions in only 1 patient of each group. In the remaining cases, they were found also in temporal or parietal regions. Eye closure elicited epileptic discharges in only a few patients.

Conclusion: In most of our patients we could identify two subgroups of ICOE, with different seizure patterns and prognosis. This epileptic syndrome corresponds to about 10% of all focal idiopathic childhood epilepsies in our epilepsy outpatient clinic, maybe because the epileptic nature of these complaints is not often recognised.

p738

INFLUENCE OF ANTIEPILEPTIC THERAPY ON BONE MINERAL DENSITY AND SERUM CALCIUM LEVELS IN ADOLESCENTS WITH EPILEPSY

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Purpose: Antiepileptic therapy (AET) can produce disturbances in bone and calcium metabolism: decrease of bone mineral density (BMD) and hypocalcemia. Risk factors are: drug enzyme induction, usage of multiple AET drugs, duration of therapy and its introduction at early age.

Results: Our results have shown significant BMD differences between AET and control group in boys (0.934 ± 0.15 vs 1.064 ± 0.112; $p < 0.05$) while in girls BMD was not significantly lower in the AET group when compared to controls (1.131 ± 0.135 vs 1.167 ± 0.085; ns). We have not found a significant correlation between age at which AET was introduced and BMD results achieved in both boys' and girls' ATE groups. Duration of AET have shown significant influence on BMD achievements in girls' group ($p < 0.01$). Serum total calcium levels were significantly lower in the boy patients' group ($p<0.05$), while serum ionized calcium levels were not significantly lower in both groups, as compared to controls.

Conclusion: Study results clearly indicate that AET therapy strongly influences BMD and serum total calcium levels, especially in boys at age 13–18 years. Duration of AET is important for bone quality measured by BMD only in girls. An early start of vitamin D and calcium

supplementation could be of great importance for future bone quality in children on long-term antiepileptic therapy.

p739
A REAUDIT OF PAEDIATRIC EEG REQUESTS: 10 YEARS LATER
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Purpose: An audit of EEG requests in this institution in 1995 demonstrated an inadequacy of clinical information and 40% of requests were considered unnecessary (Nicolaides P, Appleton RE, Beirne M. EEG requests in paediatrics: an audit. *Archives of Disease in Childhood* 1995;72:522–523). Guidelines were subsequently published on the role of EEG in the diagnosis/classification of the epilepsies and our institution introduced a computerised request system to guide clinicians when requesting an EEG. The current study has reaudited EEG requests.

Method: All children undergoing an EEG over 6 months were audited. The standardised audit form collected data on the reason for requesting the EEG, the adequacy of clinical information and the result of the EEG. The electro-clinical usefulness of the EEG was classified as being "helpful," "unhelpful" or "potentially misleading" by the paediatric neurologist reporting the EEG.

Results: Four hundred sixty-five EEG's were audited. Adequate clinical information was provided in 371 requests (79.7%). The most common reasons for requesting an EEG included, "syndrome classification," a "clinical suspicion" of epilepsy and to "exclude a diagnosis of epilepsy." The EEG was considered "unhelpful" in 195 (41.9%) and "potentially misleading" in 7 cases. The reduction in inappropriate EEG requests compared with the previous audit (Nicolaides P, Appleton RE, Beirne M. EEG requests in paediatrics: an audit. *Archives of Disease in Childhood* 1995;72:522–523) was statistically significant at $p < 0.05$ (x^2).

Conclusion: This audit has demonstrated that the EEG is still being used inappropriately to diagnose epilepsy. There was a statistically significant reduction in the number of inappropriate EEG requests, which may in part reflect on-going educational activities.

p740
OUTCOME OF INFANTS WITH NEONATAL SEIZURES BY HYPOXIC-ISCHEMIC ENCEPHALOPATHY AETIOLOGY
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Purpose: We followed infants with hypoxic–ischemic encephalopathy (HIE) and seizures in the neonatal period to determine the neurological outcome.

Method: We studied 112 infants admitted to Neonatal Care Unit of Sibiu Maternity between 1995 and 2000. They had neonatal seizures by HIE aetiology and were assessed by neurological evaluation, cranial ultrasound, electroencephalogram (EEG), CT or MRI, and psychological evaluation.

Results: From 112 patients 11 (9.8%) died in the neonatal period and 2 (1.78%) in the follow–up period. 44 infants (39%) had associated intracranial haemorrhage. The mean follow–up period was 2.97 ± 2.37 years (0–9 years). The onset of seizures was in the first 24 hours of life for 56% of cases. The most frequent seizure type was subtle followed by clonic, tonic, myoclonic and generalised tonic–clonic seizure. The patients with hypoxic lesions in 80.8% of cases had one or two types of seizure. The infants with intracranial haemorrhage had 3 or more types of seizure or status epilepticus in 43.2% of cases. The complexity of seizures had a significant correlation with psychomotor retardation ($p < 0.05$), cerebral palsy ($p < 0.01$), hydrocephalus ($p < 0.05$). In the follow–up period 9 cases (8.03%) developed epilepsy, 3 cases (2.67%) febrile seizures, 36 cases (32.14%) psychomotor retardation, 19 cases (16.96%) cerebral palsy, 6 cases (5.35%) hydrocephalus, 2 cases (1.78%) ventriculomegaly, 6 cases (5.35%) sensorial impairments.

Conclusion: The HIE facilitated neonatal seizures but intracranial haemorrhage increased the complexity of the seizures and sequel at long time follow–up.

p741
CSWS AND THALAMIC CYSTS IN CHILDREN
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Purpose: Epilepsy with continuous spike-waves during slow sleep (CSWS) is difficult to treat and leads to disastrous cognitive disturbances, stagnation and behavioural problems. In symptomatic CSWS therapy is even more problematic, especially if thalamic cysts are present. The question is whether there are aetiological coherences between CSWS and thalamic lesions. The long term courses of 12 children with CSWS and thalamic cysts are investigated.

Method: Twelve children (9 girls, 3 boys) aged 7 to 19 years, with thalamic cysts (twice on the right, 7 times on the left, 3 times on both sides) because of perinatal problems and CSWS were treated with several antiepileptic drugs. Epilepsy, EEG and cognitive development were controlled for at least 3 years, mostly much longer.

Results: The seizures were usually easy to control, but the CSWS could not be stopped, not even with corticoids. The cognitive functions deteriorated in 10 cases, 2 children were already severely handicapped at the beginning. After reduction of the spike-wave activity during awake as well as during sleep, especially when CSWS is dissolved, the cognitive situation gets more stabilised and progress is seen, but the patients remain mentally handicapped.

Conclusion: Corresponding to the literature we could prove that children with thalamic cysts and lesions due to perinatal problems develop with great certainty an epilepsy with CSWS. Even with cerebral lesions the epilepsy and the CSWS seem to become better during puberty.

p742
TYPICAL ABSENCE: NOT ALWAYS TYPICAL?
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Purpose: To determine clinically prognostic parameters of absence epilepsy in children.

Method: Diagnostic criteria of typical absence epilepsy: onset of seizures from age 4–10 years, a sudden loss of consciousness lasting over 4 seconds, EEG charges of a 3 Hz spike-wave complex lasting 4–20 seconds. The criteria that exclude typical absence epilepsy: occurrence of other seizures in the active phase of the absence seizures: generalised tonic–clonic (GTCS), myoclonic, stimulus-sensitive absence with eyelid myoclonia, perioral myoclonia and massive myoclonia of extremities, head and trunk. We performed a retrospective analysis of 101 children, aged 1.5–14 years, with absence epilepsy. Seventy-five children (group A) had typical absence seizures, while 26 children (group B) had non-typical absence seizures. All children had normal psychomotor development.

Results: Relation group A/group B: 2-year remission of absences 100%/77%, GTCS seizures 8%/35%, recurrence after cessation of therapy 1.3%/27%, monotherapy 92%/62%, mean therapy duration 3.5 years/4.8 years. Gender, age, family history of epilepsy and EEG findings were not significant prognostic parameters.

Conclusion: In childhood absence epilepsy unfavourable prognostic factors are nontypical absence seizures (eyelid and perioral myoclonia, massive myoclonia of head, shoulders and hands) and the occurrence of GTCS in the active phase and remission of absence seizures.

p743
RELATIONSHIP BETWEEN THE CHARACTERISTICS OF SLOW-WAVE COMPONENTS AND COGNITIVE IMPAIRMENT IN ROLANDIC EPILEPSY
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Purpose: Rolandic epilepsy is a common form of partial and idiopathic epilepsy in childhood. The course is generally benign. However, some children develop neuropsychological regression. The slow-wave component of the spike-and-wave complex represents the excess of inhibition following cortical hyperexcitability. This inhibition could lead to neuronal injuries when repeated. We studied the impact of the slow wave characteristics (duration and amplitude) on the behavioural and developmental prognosis of these children.

Method: Eleven children were analysed retrospectively and divided in two groups. Group one (C) for patients ($n = 6$) without intellectual impairment, developmental regression or school difficulties. Group two (U) ($n = 5$) for those with at least one of these criteria.

Results: No statistical difference was observed between the two groups according to mean amplitude and duration of the slow wave during the first cycle of non-REM sleep. Nevertheless the presence of bilateral foci was correlated with a worse prognosis ($p = 0.066$, IC95% [Fisher' exact test]; $p = 0.0303$, IC 95% [Fisher' exact test two-tailed]). Continuous spike and wave during slow sleep, multiple interictal paroxystique activities, variability of paroxysms, focus laterality, and the age at onset are signs of worsening evolution but did not reach statistical significance.

Conclusion: "Benign" childhood epilepsy with centrotemporal spikes can lead to cognitive impairment when the foci are bilateral. More data are needed to determine the influence of the slow wave component of the spike and wave complex on the clinical evolution.

p744

EARLY-ONSET ABSENCES: STILL UNDERDIAGNOSED EPILEPSY?

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Purpose: The classification of epilepsies and epileptic syndromes recognises many syndromes with typical absences, none of which are characterised by onset in early childhood, and little is known about the nosology and prognosis of early-onset absences.

Method: We describe the clinical and electroencephalographic features of 3 female infants (aged 2–4) diagnosed as early-onset absence seizures (onset of absences as the only seizure type before age 3).

Results: The age at onset of the seizures ranged between 9 and 22 months. Ictal EEG revealed a normal background and generalised spike-and-wave complexes at 3–3.5 Hz accompanied by disruption of ongoing activity in keeping with absence seizures. The duration of seizures ranged from 5 to 20 s. Clinical and electroencephalographic follow-up ranged from 10 months to 3 years. Two children were on treatment with valproate and in 1 case, the rational combination of valproate and ethosuximide with adjunctive clonazepam was necessary. Complete control of absence seizures was achieved in all our cases. The neurological evaluation was normal in all patients. Neuropsychological assessment during clinical follow-up disclosed mild mental retardation in 2 girls, while the remaining patient showed normal intelligence on WISC measurement.

Conclusion: Early onset of absences is uncommon, and multicenter studies are necessary to better define both their nosology and prognosis. A video-electroencephalography is the method of choice in the diagnostic evaluation and syndromic classification of these seizures.

p745

EVALUATION OF NIGHT SLEEP EEG MONITORING TO DIAGNOSE EPILEPSY IN CHILDREN AND ADOLESCENTS

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Purpose: The main aim of this study was to estimate the usefulness of night sleep EEG monitoring (NSEM) to paroxysmal EEG activity detection during sleep in children with the tentative diagnosis of epilepsy.

Method: The analysis was performed on a group of 76 children admitted to the Department of Developmental Neurology from January 2004 to December 2005, to diagnose epilepsy or to estimate the effectiveness of antiepileptic therapy. The average age of the children was 10.4 ± 5.1 years. Fifty children (65.8%) from the group of 76 were admitted for diagnosis of seizures, 26 (34.2%) children were admitted to control treatment efficiency. The AEDs were administered as monotherapy in 17 patients and as polytherapy in 9 children.

Results: Clinical events appeared in 23 (30.3%) patients during EEG recording. The correlation between the clinical event and EEG paroxysmal activity was noticed in only 8 children (10.5%). A nonepileptic seizure took place in 15 patients (19.7%) and it had a form of an awakening, sleep terror, sleepwalking, sleep starts, making tense muscles, swinging and other motor activities. Seizure-like epileptiform EEG changes during wakefulness were found in 17 (41.5%) patients and during sleep in 38 cases (92.7%).

Conclusion: The analysis revealed that NSEM recording was an effective and sensitive method to estimate patients with the tentative diagnosis of epilepsy, particularly with night seizures. The NSEM recording seems to be better for detecting paroxysmal activity than the standard EEG.

p746

LEVETIRACETAM MONO- AND ADD-ON THERAPY IN CHILDREN WITH FOCAL AND GENERALISED EPILEPSY: A RETROSPECTIVE STUDY

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Purpose: Levetiracetam (LEV) is licensed as add on therapy for children older than 4 years. Studies trying to evaluate efficacy of LEV as monotherapy are of interest.

Method: This is a single centre, retrospective study. We investigated 28 paediatric patients with focal and generalised epilepsy between 2002 and 2005. All were treated with levetiracetam as mono- or add-on therapy. We recorded seizure frequency i.e. reduction, tolerability i.e. side effects, and serum concentrations in relation to dosage.

Results: of the patients, 73% had a focal and 27% a generalised epilepsy. Mean age was 10.4 ± 4.6 years (median 10 years, range 3–20 years). Mean given dosage of levetiracetam was 46.5 mg/kg b.w./day. For 48%, we gave levetiracetam as monotherapy. We measured serum concentrations between 3.5 and 34.2 μg/ml (aimed 5-52 μg/ml). Mean observation time was 9.6 months (median 4 months, range 1–34 months). We achieved complete seizure control in 54%; in almost half of these patients (47%) after introduction of levetiracetam as monotherapy. In 1 patient seizures were reduced by 75%. We stopped therapy in 14% due to ineffectiveness after 6-8 weeks. Side effects were observed in 9/28 patients. No patient had to stop therapy due to side effects.

Conclusion: We consider LEV to be a potent new anticonvulsant for treatment of generalised and focal epilepsy in childhood, also as monotherapy. With similar dosage children reach significantly lower serum concentrations than adults. Thus, dosage should be increased until side effects appear. We plan further prospective pharmacokinetic studies for confirmation of our observations.

p747

MULTIMODAL IMAGING FOR FOCUS LOCALISATION IN PAEDIATRIC EPILEPSY

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Purpose: To determine the extent to which combined multimodal imaging techniques contribute to improved focus localisation in paediatric pharmacoresistant epilepsy.

Method: Fifty children and adolescent patients evaluated and operated between 1996 and 2004 and followed up after surgery for a period of at

least 12 months were included in the study. Outcome was measured by postoperative seizure frequency using Engel's classification.

Results: 78% of patients (n = 39) were completely seizure free. All patients operated within two years of epilepsy onset had a favourable outcome (class 1 and 2). No difference was noted in the outcome in children with or without special education needs as well as in younger and older children. PET provided better localising information in patients with extra temporal epilepsy and/or dysplastic lesions, whereas SPECT was superior to PET in temporal lobe epilepsy and/or tumours ($p < 0.05$). The likelihood to benefit from surgical treatment was significantly higher if more examinations were concordant with respect to the resected brain area ($p < 0.001$).

Conclusion: Multimodal imaging techniques improve the yield in epileptogenic focus localisation in paediatric epilepsy, both for extra temporal and temporal lobe epilepsy. Early surgical intervention is worthwhile, given the potential benefit of complete postoperative seizure control, particularly in younger patients.

p748

DAILY CHANGES OF INTERICTAL EEG ABNORMALITIES IN CHILDREN WITH IDIOPATHIC OCCIPITAL LOBE EPILEPSY

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Purpose: To evaluate the changes of epileptic EEG abnormalities in relation to daily activities and to awake/sleep cycle in idiopathic occipital lobe Epilepsy (IOE).

Method: At home 24-h ambulatory EEG was obtained by a 12 channel recording system in 18 patients (11 males, 7 females; age 6–16.7 yrs, mean 10.2 yrs) with IOE. Previous informed consent was obtained and we asked parents to mark on the EEG the start and end of all activities and any clinical events. At least 30 minutes of EEG (including hyperventilation) were recorded in the laboratory. The amount (N) of epileptic abnormalities within each period (T) of activity was used to compute an index of abnormalities (N/T). Wilcoxon test and ANOVA were used for statistical analysis.

Results: The index was higher in sleep than in awake at rest (7.51 ± 17 vs 3.15 ± 11; $p < 0.05$). Significantly higher values were found in the afternoon than in the morning for both awake at rest (3.55 ± 12 vs 2.65 ± 8; $p < 0.035$) and awake during activity (3.79 ± 13 vs 2.01 ± 6; $p < 0.015$). With respect to the rest, abnormalities were increased by hyperventilation (6.34 ± 12.8; $p < 0.005$) and TV watching in the afternoon (5.92 ± 13; $p < 0.008$) but not in the morning. Five patients reported ictal events; 3 seizures in the afternoon (2 while watching TV, 1 at rest), and 2 nonepileptic manifestations during sleep.

Conclusion: Patients with IOE show significant changes in the amount of epileptic EEG abnormalities in everyday life, closely related to the awake/sleep cycle and to activities involving visual function. TV watching seems to be more epileptogenic in the afternoon than in the morning.

p749

EEG FINDINGS IN CHILDREN WITH CEREBRAL PALSY

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Purpose: Epilepsy is common in children with cerebral palsy (CP). 15–60% of children with CP have epilepsy according to population based studies. Children with spastic CP have a higher incidence of epilepsy than patients with other forms of CP. We evaluated EEG findings in children with CP with or without epilepsy in our sample.

Method: We retrospectively analysed clinical and EEG data on 59 children with CP (23 girls and 36 boys) age 12 months to 18 years. Follow up period was 6 months to 2 years.

Results: In the group of 59 children with CP, 50 had spastic CP, 2 dystonic CP, 3 ataxic CP and 4 mixed CP. Thirty-three (55.9%) of the children had epilepsy. Different types of epilepsy occurred, and epileptic encephalopathy (West syndrome) and localisation related seizures were the most common types. Epilepsy most commonly affected children with spastic CP (27 children, 81.8%). In the group of children with CP and epilepsy, 6 (18.2%) had no epileptic discharges on EEG recording. Another 27 children in this group (81.8%) had abnormal EEG findings, mostly focal but also with secondary generalised discharges. In a group of 26 children with CP but no evidence of epilepsy, 13 children (50%) had epileptic discharges on EEG recordings.

Conclusion: CP is associated with a high incidence of epilepsy but also with EEG abnormalities which are not always associated with clinical manifestations of epilepsy.

p750

VERBAL FLUENCY IN CHILDREN WITH FOCAL EPILEPSY

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Purpose: Impaired verbal fluency is associated with frontal lobe damage, particularly the left anterior frontal lobe. Fluency in speech is usually measured by the quantity of words produced, usually within restricted categories and within a time limit.

Method: The results of verbal fluency test (VFT), for both categories: phonological and semantic, of 80 children aged 7–16 years suffering from focal epilepsy were compared with results of 80 healthy age matched controls. We compared the results of VFT between two groups of children: those who have EEG epileptogenic focus in left (L) hemisphere (n = 38), versus right (R) side epileptogenic focus (n = 42). We also compared scores on VFT in a group children with temporal (T) (n = 36) with scores in a group children with extratemporal epileptic focus (ExT) (n = 44). The effects of type of seizures, number of seizures, and age at seizure onset were also examined.

Results: We found significant differences between results in the experimental and control group, for both categories. Group differences were found when we compared results of LT vs RT group, only for the phonological category ($p < 0.05$). Age at seizure onset (under 7 years) was related with low performances on VFT only for semantic category ($p < 0.05$), but the number of seizures was not significant. Complex seizures were a significant predictor for both categories, phonological ($p < 0.02$) and semantic ($p < 0.001$), respectively.

Conclusion: Children with focal epilepsy have impaired verbal fluency, for both categories. Children with EEG focus in left T lobe have low performance, only for the phonological category. Age at seizure onset (for semantic category only) and type of seizure (for both categories) are very important predictive factors for cognitive functioning in children with focal epilepsy, including verbal fluency.

p751

NITRAZEPAM IN REFRACTORY FRONTAL LOBE PAEDIATRIC EPILEPSY

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Purpose: Nitrazepam (NZP) has been found to be of benefit in some epileptic conditions, such as myoclonic seizures and epileptic encephalopathies. Unfortunately, development of tolerance, reported after 1 to 12 months (Allen JW, et al., *BMJ* 1983;286:1246–7), had drastically reduced its use in clinical practice. Up until now, NZP therapy has never been tried taking into account the clinical-EEG focal aspects. On the other hand, more recently, with an understanding of molecular complexities of the GABA receptors and its subtypes (Wafford KA. *Curr Opin Pharmacol* 2005;5:47–52), we clarified that affinity, tolerance, and efficacy of the most clinically used benzodiazepine, critically depend both on the specific subunit composition of the receptor and on its selective topographic brain distribution (Rowlett JK. *CNS Spectr* 2005; 10:40–8).

Method: We retrospectively investigated safety and efficacy of NZP treatment in refractory frontal epilepsy, both as mono- and add-on therapy in 33 children (3 idiopathic) previously treated (all, old and new, AEDs), aged between 2.8 to 18 years (mean = 4.3). Mean follow-up = 2.8 years.

Results: Six children (18.18%) are taking nitrazepam as monotherapy and are seizure-free (mean follow-up: 14 months). Twenty-seven (81.8%) children decreased in seizure frequency (at least 50%) and only in 3 patients (9%) was reappearance and worsening of seizures observed.

Conclusion: Focal electroclinical aspects should be considered in order to choose the best antiepileptic treatment. To assess its safety and long-term efficacy, NZP needs studies in a large cohort of patients, although our preliminary results seem to be promising.

p752

THE PHE365SER MUTATION IN *SCN1A* GENE CAUSES SEVERE MYOCLONIC EPILEPSY OF INFANCY

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Purpose: We present an 11 year old boy with severe myoclonic epilepsy of infancy due to a *SCN1A* mutation (Phe 365 Ser).

Method: Clinical examination, EEG, brain MR scans, laboratory tests for exclusion of inherited metabolic disorders and molecular genetic analysis were performed. The patient was born from a normal pregnancy, parents are nonconsanguineous. He developed the first seizures at the age of 16 months during febrile illness. The seizures included hemiconvulsions with transitory postictal hemiparesis, atypical absences, secondary generalised grand mal seizures and status epilepticus. He developed ataxia and speech regression at the age of 3 years. He was treated unsuccessfully with all combinations of available antiepileptics.

Results: EEG shows slow background activity, with high voltage slow waves, focal and paroxysmal discharges. His brain CT and MR scans are normal. On examination he showed mild mental retardation associated with ataxia, bradykinesia and bradylalia, as well as signs of corticospinal tract involvement. DNA sequencing analysis of the coding exons of *SCN1A* showed nucleotide change c. 1094T > C in exon 8 predicting phenylalanine to serine substitution at codon 365 (Phe 365 Ser). Parents are not carriers of the same mutation. Patient is a heterozygous carrier of a mutation in *SCN1A* which has not yet been described.

Conclusion: Newly discovered Phe 365Ser de novo mutation in *SCN1A* gene is most probably the cause of SMEI in our patient.

p753

ANTIEPILEPTIC TREATMENT FOR CHILDREN WITH LEARNING DISABILITIES WITHOUT EPILEPY BUT WITH EPILEPTIFORM ACTIVITY IN THE ELECTROENCEPHALOGRAM

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Purpose: In clinical practice there is no evidence as yet to justify routine use of antiepileptic drugs to treat children with learning disabilities without epilepsy but with epileptiform discharges in EEG. This study aimed to find whether it is useful to treat these children.

Method: One hundred eleven children with specific learning disabilities without epilepsy were assessed. A randomised, double blind, single crossover trial was carried out with magnesium valproate (20 mg.kg.day), carbamazepine (20 mg.kg.day) or placebo for six months on 18 children who showed epileptiform discharges in EEG. Previously they had performed cognitive testing (BTL, Lecture Disabilities Assessing Battery for Latin-American Children; WISC-RM, Wechsler Intelligence Scale for Children, Mexican Version and DIANA, Neurocognitive Automatized Diagnosis). Children were reevaluated at the end of the treatment.

Results: Children who received magnesium valproate or carbamazepine improved in long term memory, visual perception, word encoding, phonetic analysis, working memory, semantic memory, phonologic knowledge, visual attention and visuospatial organisation, among other cognitive domains. No changes in epileptiform discharges in EEG were observed but in Brain Electrical Source Analysis (BESA) there were positive changes in children who received magnesium valproate or carbamazepine in 3.90, 4.29, 4.68, 5.07, 5.46 y 10.92 Hz for cortex and basal ganglia.

Conclusion: Our data support the idea that magnesium valproate or carbamazepine may be a useful treatment in children with learning disabilities without epilepsy and electrographic epileptiform discharges in EEG.

p754

EPIDEMIOLOGICAL CHARACTERISTICS IN SCHOOL-AGE CHILDREN WITH EPILEPSY IN THE CENTRAL SERBIA REGION (CITY OF KRAGUJEVAC)

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Purpose: Epilepsy represents one of the commonest neurological disorders in childhood. The aim of our research was to determine epidemiological characteristics of epilepsy in school-age children (7–14 years old).

Method: The research was performed as retrospective and longitudinal for a five year period (2001–2005), and the region of investigation was the territory around the city of Kragujevac with 180,000 inhabitants. There were so-called hospital statistics data used in the research.

Results: In the five year period of the research there were 486 children with epilepsy treated; 34.8% of whom had symptomatic or cryptogenic epilepsy and 65.2% had idiopathic epilepsy. There were slightly more male than female patients (52.9%:47.1%), but without statistical significance regarding the type of epilepsy. The prevalence rate has been determined and on 31 December 2005, it was 25.2/1000; the prevalence of symptomatic-cryptogenic epilepsy was 8.8/1000 and of idiopathic epilepsy was 16.5/1000.

Conclusion: The established data point out the scope and the significance of this problem in our surrounding are and also can be used by child health care planners in recognising the need for a type and way of organising health care, as well as the need for outpatient and hospital capacities. These data are valuable for promoting preventive measures and activities of taking care of this category of disability from epilepsy.

p755

EFFECTS OF METABOTROPIC GLUTAMATE ANTAGONIST ON NEURAL STEM CELLS IN FRAGILE X SYNDROME

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Purpose: Fragile X syndrome is a common cause of inherited mental retardation. The majority of affected individuals display EEG abnormalities and about 20% of patients develop childhood seizures. The syndrome is caused by the absence of the FMR1 protein (FMRP) and the *fmr1*-knockout mice (*fmr1-KO* mice) serve as a mouse model for the syndrome. The transgenic mice exhibit elevated susceptibility to audiogenic seizures and treatment with metabotropic glutamate receptor antagonist, MPEP, suppressed epilepsy phenotype. We have previously shown that the differentiation of neural stem cells (NSCs) is altered in fragile X syndrome. An increase in the number of cells with metabotropic glutamate response was a unique feature in the differentiation of FMRP-deficient NSCs.

Method: We investigated the effects of MPEP on growth and differentiation of NSCs in neurosphere cultures generated from brains of *fmr1-KO* mice using the MTT assay and calcium imaging.

Results: Treatment with 1-10 μM MPEP did not affect growth of proliferating wild-type or FMRP-deficient mice NSCs. However, treatment with 100 μM MPEP caused a significant reduction in the cell growth in transgenic but not in wild-type neurosphere cultures suggesting that FMRP-deficient NSCs were more sensitive to the high concentration of MPEP. Calcium imaging studies confirmed the expression of metabotropic glutamate receptors in a subpopulation of differentiated NSCs. Exposure to MPEP significantly increased (4-fold) the number of cells in this subpopulation of NSCs derived from the *fmr1-KO* mice after differentiation for 2–3 days.

Conclusion: These studies provide evidence that antagonism of metabotropic glutamate receptor signalling influences differentiation of FMRP-deficient NSCs.

p756

CLINICAL EXPERIENCE WITH ZONISAMIDE ADJUNCTIVE THERAPY FOR PAEDIATRIC EPILEPSY

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Purpose: To reveal the outcomes from using zonisamide adjunctive therapy for paediatric epilepsy.

Method: A clinical retrospective study was performed for 2 years from September 2003 to August 2005 at a tertiary epilepsy centre. All 75 patients (male 50, female 25) experienced more than four seizures per month. They were not controlled by an initial combination of two or more conventional antiepileptic drugs and could be followed up for at least 6 months after prescribing zonisamide for various epilepsies or epileptic syndromes of childhood. The target dosage of administered drug was decided to be 10mg/kg/day and adjusted depending on each patient's tolerability.

Results: Thirty-five patients (46.6%) out of 75 showed a reduction of seizure frequency of more than 50%, and 12 patients (16.0%) were seizure free. Of 27 patients who mainly manifested myoclonic seizures, 16 (59.2%) showed a seizure reduction of more than 50% and 6 patients (22.2%) had no further seizures. The mean maintenance dosage of drug was 8 mg/kg per day (range 3–15 mg/kg per day). 9 patients (12.0%) showed adverse reactions in the following order of frequency: somnolence 5 patients, rashes and agitation respectively, 1 patient. Zonisamide should be discontinued due to acute pancreatitis in 1 patient, and in an additional patient the dosage should be reduced due to enuresis.

Conclusion: Zonisamide is believed to be an effective, safe anticonvulsant when used as an adjunctive therapy for various refractory childhood epilepsies.

p757

KETOGENIC DIET IN INTRACTABLE CHILDHOOD EPILEPSY WITH MITOCHONDRIAL RESPIRATORY CHAIN ENZYME COMPLEXES (MRC) DEFECT

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Purpose: To reveal the efficacy of ketogenic diet (KD) in patients with intractable childhood epilepsy caused by mitochondrial respiratory chain enzyme complexes (MRC) defect.

Method: We retrospectively analysed 13 children (M/F:5/8) with intractable epilepsy who received KD over 3 months. MRC defects were confirmed by biochemical enzyme analysis from patients; muscle and/or lymphocytes using spectrophotometry.

Results: 1) KD started at the age of 3.7 $\pm$ 3.0 years (8 months–4.8 years), and mean duration between seizure onset and KD was 1.5 $\pm$ 1.3 years. 2) MRC I defect was seen in 8 cases (61.5%), II in 1 case (7.7%), IV in 3 cases (23.1%), and combined I and IV defect in 1 case. 3) Two cases were Leigh's encephalopathy, but 11 other cases were not categorised to any clinical diagnostic classification. 4) Five cases were infantile spasm, 4 cases with Lennox-Gastaut syndrome, 1 case with generalised epilepsy, and 3 cases were partial epilepsy. 5) Seven cases became seizure free after KD, 1 case showed seizure reduction more than 90%, 3 cases between 50 and 90% seizure reduction, and 2 cases showed no benefit in seizure reduction. 6) Hypoglycemia was complicated in 2 cases, which were controlled by additional oral steroids. 7) Global developmental function improved in 8 cases (61.5%) on KD.

Conclusion: KD is effective in treating intractable epilepsy with MRC defect as well as global cerebral function in children.

p758

ELECTRICAL STATUS EPILEPTICUS DURING SLOW SLEEP (ESES): A STUDY ON SPECTRUM OF EPILEPTIC SYNDROMES, CLINICAL AND ELECTROENCEPHALOGRAPHIC FEATURES AND THERAPEUTIC RESPONSE

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Purpose: ESES is a rare but potentially devastating phenomenon that may complicate various epileptic syndromes or present independently. We aimed at revealing pre-ESES epileptic presentation, the features of ESES and its response to treatment.

Method: All epilepsy patients with unexplained neuropsychological and/or motor deterioration underwent prolonged sleep EEG recordings. From a cohort of 600 children with epilepsy in the last 5 yrs ESES was diagnosed in 7 of them. They were neurologically and psychologically evaluated. Therapeutic regimen of ESES started with clonazepam (Czp) and if it failed ACTH or steroids were introduced.

Results: ESES developed in 2 children with an atypical variant of BECTS and initial normal development; in 2 other patients with cryptogenic or symptomatic partial epilepsy and mental retardation (MR), in 1 child with symptomatic Lennox-Gastaut syndrome and severe MR and in another 2 patients with non-classifiable epilepsy and mild MR. When ESES developed motor impairments and/or psychological regression appeared and a new type of seizures occurred or existing focal and generalised seizures got worse. Two of the 7 cases responded to Czp 0.05–0.2 mg/kg with full recovery, but after 2–5 months ESES relapsed. They and 3 of the 5 nonresponders to Czp were successfully treated with ACTH 0.5–1 mg every other day. Three patients relapsed after discontinuation of ACTH and a second course of ACTH or another benzodiazepine were applied. Two of the nonresponders to Czp were lost for further treatment.

Conclusion: ESES appears to be a complication of various epileptic syndromes rather than an independent syndrome. It should be suspected in every child with epilepsy with neuropsychological regression. Benzodiazepines and ACTH are reaffirmed as treatments of choice.

p759

INTRAVENOUS IMMUNOGLOBULINS (IVIG) IN REFRACTORY CHILDHOOD EPILEPSY: PROSPECTIVE STUDY OF EFFECTS ON SEIZURE FREQUENCY, EEG ACTIVITY, AND CEREBROSPINAL FLUID CYTOKINE PROFILE

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Purpose: Several studies have reported a favourable effect of IVIG in refractory epilepsy. Data substantiating an immunomodulatory effect are scarce. We prospectively investigated the effect of IVIG on clinical, EEG and serum/CSF immunological parameters in refractory childhood epilepsy.

Method: Thirteen children (median 6.9 years (range 1.6y–25.8y)) with a median monthly seizure frequency of 152 (range 3–1286) despite 3 or more therapeutic AEDs were given IVIG (Sandoglobulin, ZLB-Behring, add-on, 4 $\times$ 400 mg/kg/3weeks). Before and after completion of the course, seizure frequency, 24h-videoEEG (automatic spike counting), and CSF and serum routine immunological parameters and cytokine profiles (IL-6/IL-8/IL-12/IL-10 (CBA/BD Biosciences) were documented.

Results: Seizure frequency was reduced by $> = 50\%$ in 4, and 25–50% in 3 children. In contrast, spike-counts (1-hour-wake and -sleep) did not decline, but increased significantly in 6 children. Serum and CSF routine immunological parameters were normal, CSF immunoblotting showed transsudate patterns in 6, and oligoclonal bands in 2 patients. IL-6 and IL-8 were detectable in all CSF samples but only in 7 serum samples, with CSF IL-8-levels being significantly higher than

serum-IL-8 levels. Detectable IL-10- and IL-12-levels in CSF and serum were rare. These profiles did not change under IVIG.

Conclusion: In 7 of 13 refractory childhood epilepsy patients, without preexisting immunological disorders, a proinflammatory cytokine profile was documented, with selective intrathecal presence of IL-8, supporting a possible role for inflammatory immune responses in the pathogenesis/potentiation of epilepsy. In contrast to clinical efficacy, EEG and cytokine profiles were not influenced by IVIG treatment and no clear association between these parameters was found.

p760

SIGNIFICANCE AND CUTOFF VALUE OF SERUM GLUCOSE IN DIAGNOSIS OF FEBRILE STATUS EPILEPTICUS IN CHILDHOOD

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Purpose: Status Epilepticus (SE) is a potentially life-threatening and poor prognostic disease. But SE caused by febrile seizure (febrile SE) has an excellent prognosis and very little sequelae. We investigated the significance and cutoff value of serum glucose in diagnosis and prediction of febrile SE in childhood.

Method: We selected 40 children who were admitted to our hospital due to SE from May 2000 to June 2004. Their medical records were reviewed retrospectively. We surveyed clinical features, aetiology and laboratory findings, especially serum glucose. Subjects were classified into febrile SE and nonfebrile SE according to aetiology. For diagnosis and prediction of febrile SE we investigated the statistical significance and predictive cut-off value of serum glucose between febrile SE and nonfebrile SE.

Results: Twenty-three patients (58%) had febrile SE and 17 patients (42%) nonfebrile SE. Aetiology of nonfebrile SE were encephalitis (9 patients), epilepsy (5 patients), head trauma (1 patient), Reye syndrome (1 patient) and near drowning (1 patient). The mean value of serum glucose in febrile SE was 209.6 ± 67.7 mg/dL and nonfebrile SE was 127.8 ± 43.7mg/dL ($p = 0.0021$). The predictive cutoff value of serum glucose in febrile SE was 167mg/dL in confidence of 95 percentile.

Conclusion: The serum glucose level in febrile SE is significantly higher than in nonfebrile SE. The predictive cutoff value is 167mg/dL. Therefore we suggest that SE above 167mg/dL of serum glucose has a high likelihood of febrile SE and it is possible to discriminate the cause of SE by checking serum glucose.

p761

EPILEPSY IN ANGELMAN SYNDROME

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Purpose: The authors present 9 children (5 girls and 4 boys) with Angelman syndrome (AS). The purpose of this study was to analyse the type of epilepsy and EEG pattern.

Method: The diagnosis was based on clinical criteria, EEG and molecular examinations. The patients' age at the time of diagnosis ranged from 12 months to 10 years. Polymorphic epileptic seizures (atypical absence, myoclonic, tonic–clonic, atonic and infantile spasms) were present in 7 children. One child suffered from tonic seizures only. The most frequently used drugs were valproic acid, clobazam, clonazepam, lamotrigine and topiramate.

Results: The children fulfilled the clinical criteria according to Williams et al. EEG showed disturbances in the sleep architecture, general discharges more pronounced in the posterior areas. In 4 patients MRI of the head revealed demyelination, cortical atrophy with ventricular enlargement, thin corpus callosum and perisylvian syndrome. AS was confirmed by deletion of chromosome 15 (UBE3A) or disturbed methylation pattern in 4 children.

Conclusion: Angelman syndrome accounts for 6% of the children presenting with severe mental retardation and epilepsy. Epileptic seizures start between 1 month and 5 years (mean 2–3 years) and they initially present with febrile convulsions in the 1st year of life. The most frequent seizures types in infancy are tonic–clonic, atypical absence, myoclonic and tonic. In that period seizures are difficult to control.

p762

CLINICAL CHARACTERISTICS OF MITOCHONDRIAL RESPIRATORY CHAIN ENZYME COMPLEX DEFECT IN CHILDREN

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Purpose: To characterise clinical and laboratory features for mitochondrial respiratory chain enzyme complex (MRC) defects to provide more precise diagnosis and effective treatments.

Method: We retrospectively reviewed clinical and laboratory features of 28 patients who showed defects in MRC activity, confirmed by biochemical assay from spectrophotometry in muscle and/or lymphocytes.

Results: 1) Mean age was 6.67 ± 4.44 years and sex ratio was 1.15:1. 2) Eighteen (64.3%) were MRC I deficient, 8 (28.5%) of VI deficient, 1 (3.5%) of II deficient, and 1 case of combined deficiency of I and IV. 3) Eight cases (28.5%) were classified as Leigh syndrome, 1 case (3.5%) each as MELAS, Kearns-Sayre syndrome, and Alpers disease, but 17 cases (60.7%) were not clinically categorised for specific disease criteria. 4) Epilepsy was seen in 21 (75.0%) patients, developmental delay in 27 of 28 (96.4%). 5) Clinical symptoms most commonly started before 1 year of age, in 15 (53.6%) patients. 6) Brain MRI showed diffuse cortical atrophy in 18 (64.3%) and basal ganglia signal changes in 12 cases (42.9%). 7) Positive rate for laboratory studies were: 92.9% in lactic acidosis, 62.5% in urine organic acid assay, 26.1% in serum amino acid assay, and 57.9% in MR spectroscopy. 8) Ketogenic diet and mitochondrial cocktail with coenzyme Q_{10} and multivitamin showed clinical improvements in 75% of patients.

Conclusion: MRC defect can be the cause of many unexplained neurological disorders including epilepsy. Treatments with coenzyme, multivitamin and/or ketogenic diet have shown considerable benefits.

p763

DEVELOPMENTAL OUTCOME OF EPILEPSY SURGERY IN INTRACTABLE CHILDHOOD EPILEPSY

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Purpose: We aimed to determine the developmental outcome including cognitive function after various epilepsy surgeries in intractable childhood epilepsy.

Method: We retrospectively analysed clinical features and data of our 66 patients {mean age 7.51 ± 4.98 yrs (ranging from 1.3-19.1 yrs) M:F $= 1.4$:1} who underwent epilepsy surgery between October 1998 and September 2003 due to intractable epilepsy based on their symptoms, imaging study results and electroencephalography. Neuropsychological assessment was done prior to and 1 year after surgery with age matched batteries (Bayley Scales, K-WISC).

Results: 1) 48 cases (72.7%) were retarded with DQ < 70, and 10 cases (15.1%) were within the normal range intelligence level between 85 and 115. 2) Short duration of epilepsy and young age at surgery were significant factors for better developmental quotients. 3) 40 cases (60.6%) became seizure free (Engel class I) during the follow up period, and 21 cases (31.8%) showed a significant reduction of seizures (Engel class II, III). 4) Patients without a seizure-free outcome showed a tendency of developmental decline. 5) 10 cases (15.1%) showed significant developmental gaining with DQ over 10 points in patients with a seizure

free outcome. 52 Cases (78.8%) showed stable developmental progress after surgery. 6) Developmental improvement was significantly higher with partial seizures, infantile spasms and Lennox-Gestalt syndrome in order of improvement. 7) Developmental gain was better in patients with abnormal pathologic findings.

Conclusion: We could conclude that successful epilepsy surgery at an earlier age can provide a better developmental outcome.

p764

RESULTS OF SURGICAL TREATMENTS ON INTRACTABLE EPILEPSY WITH INFANTILE SPASM

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Purpose: To determine the surgical outcome of intractable childhood epilepsy with infantile spasm (IS), Lennox-Gastaut syndrome (LGS), and intractable partial seizure (PS) later evolving from IS.

Method: We retrospectively reviewed 22 cases of intractable childhood epilepsy, who received epilepsy surgery since 1999, 5 cases were IS, 14 cases were LGS, and 3 cases evolved from IS. EEG features, imaging studies including MRI, SPECT and PET, types of surgery, pathologic findings and seizure outcome were reviewed.

Results: Sex ratio of 22 cases was 1:1.4 (M:F). The mean duration from diagnosing epilepsy until the operation was 6–10 years in 8 (36%) cases, 1–2 years in 7 (32%). In preoperative EEG, abnormalities implying possible focal lesion were seen in all 22 patients. Seven (32%) out of 22 cases showed focal lesions in MRI while 12 (92%) out of 13 cases in ictal SPECT, 8 (62%) out of 13 cases in interictal SPECT, and 11 (61%) out of 18 cases of PET showed abnormal findings. Single lobectomy was most commonly performed, in 13 (59%) cases, among whom a frontal lobectomy was performed in 11 cases. Also, multilobar resection was performed in 6 (27%) cases and hemispherotomy in 2 (9%). During the pathological examination, cortical dysplasia was most commonly observed, in 11 (50%) cases, microdysgenesis in 3 (14%), gliosis in 2 (9%) and tuberous sclerosis in 2 (9%) as well. Nineteen (86%) patients were classified as Engel class I after surgery.

Conclusion: In cases of children with IS not controlled by medical treatment, epilepsy surgery should be strongly considered when cortical pathology can be identified from various studies.

p765

POSSIBILITY OF MAKING PAEDIATRIC SOFTWARE TO DIAGNOSE NEUROLOGICAL DISEASES

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Purpose: Expert system is a computer program that simulates the thought process of a human expert to solve complex decision problems in a specific domain. Human experts have limited resources. They get tired, forget crucial details of a problem and are not available anytime and everywhere. Human expert knowledge is a composition of rational knowledge and heuristic knowledge. It is easy for an expert system to have rational knowledge and hard for it to have heuristic knowledge. Software engineers therefore like to define problems which need rational knowledge more than heuristic knowledge for their expert systems. They are able to build an expert system that is capable of diagnosing by asking the patient or patient's parents a number of questions.

Method: In this study the knowledge engineer works in close cooperation with the paediatric neurologist. Symptoms and types of epilepsy, tools and methods of diagnosis and paths of reasoning were described. The knowledge engineer tries to find the best possible solutions to describe symptoms for software and to make software able to reason based on these inputs.

Results: Computers do not need to rest. They do have a truly accurate and permanent memory so they do not forget crucial details of a problem. When software engineers work on a medical expert system they don't try to make it work as well as a physician. Physicians have a lot of abilities that an expert system can never reach. Software and hardware limits make software engineers define simple problems for an expert system to solve. Paediatric neurologists are able to diagnose and treat a number of diseases such as epilepsy, floppy infants, microcephaly and macrocephaly. An expert system may not be able to diagnose and treat all these diseases but it is possible for a software engineer to define simpler problems for the expert system to solve. Questioning is easy for personal computers, because they do not need any extra hardware to perform this operation. But physical examination as an important part of diagnosing is not easy and in most cases is not possible for a personal computer.

Conclusion: Expert systems can greatly help physicians in diagnosis and treatment of childhood neurological diseases but they are not yet able to act alone.

p766

TREATMENT WITH OXCARBAZEPINE IN CHILDHOOD: HIGH EFFICACY WITH LOW RISK OF AGGRAVATION

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Purpose: To determine the efficacy of OCBZ in paediatric patients with special attention to its insufficiently known seizure aggravation profile.

Method: A retrospective observational study of 136 children aged 1–18 yrs was conducted; 42.7% with idiopathic, 34.3% with symptomatic and 23.1% with cryptogenic epilepsy. The percentages of partial, generalised and undetermined epilepsies were accordingly 88, 5.6 and 5.6%. OCBZ treatment duration varied from 1mo to 5 yrs (mean 1.6) at daily doses from 10 to 40 mg/kg (mean 22.5). Aggravation was defined as increase in frequency and severity of seizures or appearance of new seizure types after introduction of OCBZ.

Results: In 49 patients (36.0%) OCBZ abolished seizures. In 52 (38.2%) the seizure reduction was higher than 50%. In 27 children (19.9%) OCBZ was ineffective. Aggravation was observed in 8 patients (5.9%; CI 0.5–11.3%). It was noticed in the first month after introduction of OCBZ (mean 8 days) at a relatively low daily dose (mean 13.9 mg/kg) and always ceased after OCBZ discontinuation. OCBZ induced absences in 4 patients (2 with continuous spike-wave during slow sleep, 1 with Lennox-Gastaut syndrome, 1 with idiopathic partial epilepsy). Myoclonic seizures worsened in 1 patient with juvenile myoclonic and 1 with myoclonic-astatic epilepsy. Partial epilepsy was aggravated in other 2 patients.

Conclusion: OCBZ has high efficacy (74.3% responders) when used for mainly partial epilepsy in paediatrics. The risk of aggravation is this setting is low (5.9%) and mostly in cases with generalised epilepsy. OCBZ may induce or worsen absences, myoclonic or partial seizures.

p767

WHEN CHILDREN WITH EPILEPSY AND MENTAL RETARDATION BECOME SEIZURE-FREE, DISCONTINUATION OF AEDs IS OFTEN SUCCESSFUL: A POPULATION-BASED STUDY

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Purpose: Children with epilepsy and mental retardation (MR) have a poor prognosis for seizure control. We report the success rate of discontinuing AED treatment when children with MR become seizure-free.

Method: The Nova Scotia population-based epilepsy cohort has followed 693 children with all types of epilepsy beginning 1977–85. We focused on those with documented mental retardation.

Results: of 693 total epilepsy patients, 138 (20%) had mental retardation. 27 died, 1 was untreated, leaving 110 for study with average follow-up 20.6 $\pm$ 5.3 years (range 1.5–28). 58% became seizure-free and attempted discontinuation of AEDs, 74% with mild MR, 62% with moderate, 43% with severe/profound. Overall 44% stopped AEDs for a first time successfully and remained seizure-free for 13.2 $\pm$ 7 years of further follow-up. Some who failed the first discontinuation, tried again

successfully. Overall 54% discontinued AEDs at least once and were eventually successful.

The 51% with symptomatic partial epilepsies were more likely to attempt discontinuation of AEDs ($p = 0.006$) compared with the 49% with secondary generalised epilepsies but the success rate was the same ($p = 0.8$). Of the 395 children with normal intelligence and epilepsies characterised by convulsive and partial seizures, 294 (74%) discontinued medication at least once and on the first discontinuation 73% were successful; a higher rate than those with MR ($p < 0.0001$).

Conclusion: The challenge for children with epilepsy and mental retardation is to become seizure-free. Once they do so, their rate of successfully stopping AED treatment was 44–54%, less than those with normal intelligence but still worth the attempt.

p768

EMOTIONAL DISTURBANCES IN CHILDREN AND ADOLESCENTS WITH SLEEP DISORDERS AND EPILEPSY

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Purpose: The prevalence of sleep disorders (SD) estimates as 30% in a healthy population; in a population with epilepsy it is higher, even 50–60%. The classification of disorders based on ICSD 2005 criteria, includes eight main groups. They appear in children and adolescents as well. The aim of the study was the estimation of the level of anxiety understood as trait and state in children and adolescents with SD.

Method: Sixty school boys and girls aged 7–18 yrs of age participated in the study. They were treated with antiepileptic drugs, because of epilepsy, in monotherapy mode. The time of duration of epilepsy was 1.5 yrs. They underwent a two step examination. First, they completed a questionnaire of the SD. In the second part, 30 patients with diagnosed sleep disorders chosen from the examined group participated in psychological and neurological examinations. The STAI and STAIC scale, Bender Gestalt test, d-2 test were used in the psychological examination. They underwent an intelligence examination as well.

Results: Statistical analysis (analysis of variance) shows the significance at $p < 0.05$ level correlation between SD and the prevalence of emotional disorders; anxiety as a state, impulsivity in patients with epilepsy. There was no correlation between the duration of the SD and the results of psychological tests. The median IQ was 98.4. There was a significant correlation between high level of anxiety and sleep disturbances in a subgroup with intelligence quotient lower than 90.

Conclusion: The conclusion is that the relationship between SD and anxiety in epilepsy is close and may have a two-way phenomenon. Emotions and its disturbances, which are very strong in the epilepsy group, can be a reason or a consequence for the SD prevalence. The diagnosis of it is important data for planning therapy for the patients with SD and epilepsy as well.

p769

INFLUENCE OF ANALYSIS TOOL SETTINGS ON RESULTS OF COMPUTERISED INVESTIGATION IN EPILEPSY

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Purpose: All analysis methods (AMs) developed for investigation of brain dynamic have their intrinsic parameters. Evaluation features of the AM's are affected and preset by these parameters. Answers on given investigation problems could also be influenced by (in-) appropriate selection (setting) of time sections from analysed EEG recordings that are usually associated with specific patient clinical statuses. Both settings can have influence upon results from AMs. The aim of this presentation is an indication of influences (effects) upon obtained results in our 2 studies when 1) different settings of AM-tools are applied and when 2) various time sections of EEG recordings are chosen.

Method: Our 2 studies were: 1) sensitivity of AM-tools in seizure prediction, 2) effect of therapy detected by AM-tools. Two basic intrinsic parameters of AM's are "window length" (WL) and "window overlap" (WO). We used 4 combinations of WL/WO (chosen within mathematical and practical boundaries). Different wakeful states and sleep stages were used as appropriate sections compared with inappropriate (random) sections. All these pre-settings were applied with 31 available AM-tools on groups of 16 and 12 patients for investigation of results consistency.

Results: In both studies we found similar effects: different WL/WO settings influenced analysis results only in some types of AM's, mostly they had no effect. Selection of (in-) appropriate sections produced distinct results in all AM's.

Conclusion: Different settings of AM-tools produced notable variations in comparable analysis results. Next studies should be based on database of "AM's-references." Presentation of data on used settings is a necessary rule in publications dealing with EEG analysis.

p770

COGNITIVE OUTCOME IN WEST SYNDROME

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Purpose: To find out the spectrum of cognitive deficits in children after West syndrome.

Method: A retrospective analysis of medical records provided data about the age of IS onset, psychomotor development before IS, aetiology and treatment schedules. The hypsarrhythmia duration in weeks was estimated from data on age of onset of spasms, the first EEG pattern and from consecutive EEGs. At follow up study children were psychologically examined according to the child's age and mental level, by standardised psychometric tests; the minimum follow-up time was 3 years after the IS onset.

Results: Normal mental development was established in 14 children (29%) out of 48, mild mental retardation was found in 6 children, moderate in 10 and severe mental retardation in 14 children (29%); 4 children died. The outcome was statistically significantly related to aetiology ($p = 0.001$); only 6 out of 30 children with a symptomatic aetiology had a favourable outcome in comparison with 13 out of 18 children from the cryptogenic and idiopathic groups. Specific cognitive tests showed the following deficits: in visual functions in 11 out of 42 children capable of testing, language in 15/30, graphomotor field 25/30, autistic features in 7/37 and behaviour disturbances in 8 out of 30 children.

Conclusion: The presence of hypsarrhythmia during the period of rapid development of the brain may cause damage to cognitive abilities. The duration of hypsarrhythmia is of major importance as short term disturbances are believed to be not harmful to the brain cortex.

p771

UTILITY OF CONVENTIONAL ELECTROENCEPHALOGRAM IN THE MANAGEMENT OF NEONATAL SEIZURES

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Purpose: To evaluate the effectiveness of limited use of electroencephalographic investigation for neonates with clinically registered seizures

Method: Medical records and EEG files of all neonates treated in Neonatal Unit and Intensive Care Unit with registered seizures (Volpe's classification) from January 2003 to December 2005 were surveyed for aetiology of seizures, type of attack, need for mechanical ventilation and type of EEG abnormalities. Severity of EEG changes was opposed to the clinical presentation of 3 categories of patients: a) with 1 to 5 seizures, b) with many seizures but no vital signs compromised, c) with seizures and mechanical ventilation.

Results: There were 101 neonates with seizures who had 148 EEGs done during hospital stay with only 6 ictal tracing. First EEG was normal in 14 and abnormal in 87 neonates. Basic activity was abnormal (low voltage, rhythmic or discontinuous) in 26 and Rolandic sharp waves were detected in 12 records. In the group with seizures and mechanical ventilation (32), 16 had significant EEG abnormalities (depressed basic rhythm, inactive or discontinuous EEG). None had normal EEG. In the

group with less than 5 seizures, 8 had depressed basic activity, discontinuous EEG or rolandic sharp waves, but none inactive EEG. Seven had normal EEG. The EEG abnormalities correlated significantly with the gravity of the basic condition in the neonates with seizures.

Conclusion: Conventional EEG is a powerful tool of managing neonates with seizures, which gives insight to the extent of brain compromise.

p772

EPILEPSY IN THE COURSE OF FAMILIAR LEUKOENCEPHALOPATHY WITH D-BIFUNCTIONAL PROTEIN DEFICIENCY

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Purpose: The authors present siblings (girl 11 months, boy 6 months) with polymorphic seizures in the course of familiar leukoencephalopathy. In a younger brother peroxisomal disorder, namely D-bifunctional protein deficiency was confirmed. The sister died at the age of 14 months, before a diagnosis was possible.

Method: The pregnancy period of the sibling was uneventful. At birth, a profound hypotonia with a reflexia and a reactivity, myoclonic seizures and breathing difficulties were noticed. Antiepileptic therapy with phenobarbital, valproic acid, carbamazepine and benzodiazepines was introduced. In physical examination craniofacial dysmorphia and failure to thrive, large frontal fontanelle, severe axial hypotonia and hypertonia of the limbs were found.

Results: MRI of the head showed demyelination in both patients and ventricular enlargement in the girl. EEG disclosed paroxysmal changes with right temporal lobe predominance. Neurophysiological study detected peripheral neuropathy in a brother. In a boy increased level of very long chain fatty acids (VLCL) serum and fibroblasts, decreased phytanic acid oxidation, normal level of phytanic acid and a decreased number of peroxisomes pointed to deficiency of a single enzyme, deficiency of D-bifunctional protein.

Conclusion: 7-αbeta-hydroxysteroid dehydrogenase IV is involved in the degradation of VLCL, as well as of the branched-chained fatty acids, pirystanic acid, and the bile–acid intermediates: di-, trihydroxycholestanoic acid. To data, D-bifunctional protein deficiency constitutes one of the most frequently occurring single-peroxisomal-enzyme-deficiency disorders. Among the inborn errors of metabolism epilepsy is relatively frequent in peroxisomal disorders.

p773

ESTIMATION OF THE INFLUENCE OF VALPROATES ON PSYCHOMOTOR DEVELOPMENT IN CHILDREN WITH INFANTILE SPASMS BY USING COHERENCE ANALYSIS OF ELECTROENCEPHALOGRAM

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Purpose: To study the influence of valproates on psychomotor development in children with infantile spasms and alterations of the exponents by using coherence analysis of electroencephalogram (EEG).

Method: Twenty-four children with infantile spasms (23-symptomatic and 1-cryptogenic) aged from 3 months to 3 years were examined. The estimation of psychomotor development was conducted using the L.T. Jurba, E.M. Mastyukova scale, the G.V. Pantyukhina, K.L. Pechora, E.L. Frukht scale. All children were studied and clinically assessed including CT, MRI and EEG with its coherence analysis.

Results: The estimation of coherence analysis of EEG, when patients entered hospital, revealed that in all the children the coherence was reduced in intra- and between-pairs ($p < .001$; $p < .05$) to compare to norm. With valproate treatment in average dose of $59 \pm 5{,}6$ mg/kg/day and synacten-depo in average dose 0.04 mg/kg/day convulsions ceased in 12 cases; the frequency of seizures was reduced in 8 and there was no effect in 4 cases. After treatment the coherence analysis of EEG revealed an increase in exponents of intracerebral coherence ($p < .001$; $p < .01$). The improvement of coherence combined with improvement of psychomotor development ($p < .05$). In catamnesis over 2 years the stable anticonvulsant effect was reached in 7 cases (29%), revival of seizures occurred in 5 cases (40%). Transformation in partial epilepsy was in 16 (66.6%) cases; in Lennox-Gastaut syndrome in 1 case (4.2%). In patients with stable anticonvulsant effect the coherence was stable or had a tendency to increase. But in the children with revival seizures the intracerebral coherence (in frontal and temporal parts) decreased below norm side by side with worsening of the exponents of psychomotor development.

Conclusion: Valproates don't negatively influence psychomotor development and vice versa by suppression of epileptic activity, standardise functional activity of the brain, which can be seen by using coherence analysis of EEG and improved psychomotor development.

p774

NEW-ONSET NARCOLEPSY IN A PATIENT SURGICALLY TREATED FOR RASMUSSEN'S ENCEPHALITIS

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Purpose: To describe the onset of narcolepsy in a patient with Rasmussen encephalitis (RE), four years after left hemispherotomy.

Method: Case report

Results: A 23-year-old female patient, affected from the age of 11 by left sided RE, underwent hemispherotomy at the age of 19. Surgery stopped seizures and progressions of right hemiparesis and aphasia. At the age of 23 the patient began to experience fatigue, excessive daytime sleepiness, and the need for daytime naps. The symptoms progressively worsened in a few months. At clinical examination the patient was drowsy, frequently yawning, postural control was impaired. Neither spontaneous nor provoked cataplectic phenomena were observed. The excessive daytime sleepiness was assessed by polysomnography (PSG) and multiple sleep latency test (MSLT). PSG showed a normal sleep organisation with the exception of a REM sleep onset period (SOREMP) with a latency of 2′, and excluded other sleep related disturbances. MSLT showed a mean sleep latency of 4′05" with 1 SOREMP. The search for HLA DQB1* 0602 was negative. The MRI showed the expected disconnection of the left hemisphere; but also signal abnormality and stretching of the left postero-lateral aspect of the hypothalamus. The endocrinologic assessment was normal.

Conclusion: The clinical, PSG and MSLT picture is consistent with the diagnosis of probable narcolepsy. This is the second reported case of the association between RE and narcolepsy. Our findings lend support to the hypothesis that these two conditions may share common immunologic pathogenetic mechanisms. Alternatively, postsurgical hypothalamic dysfunction cannot be excluded.

p775

MENKES DISEASE: A RARE DIFFERENTIAL DIAGNOSIS OF EARLY-ONSET PROGRESSIVE ENCEPHALOPATHY

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Case Report: Menkes disease (MD) is a rare X-linked multisystemic lethal disorder of copper transport metabolism due to a defect of a transmembrane P-type ATPase. We report a case of MD with proven ATP7A gene mutation and rapidly progressive phenotype. The boy was born as the first child of healthy nonconsanguineous parents. After an uneventful delivery a cephalic haematoma was present. At age of 11 wks the child was presented for treatment of pharmaco-refractory seizures. Clinical examination showed severe generalised muscular hypotonia and nystagmus. No dysmorphic features or hair abnormalities were noted. Intractable multifocal seizures and progressive loss of sensor-motor functions complicated the clinical course. EEG showed severe abnormalities

with multifocal irregular slow-wave activity. Repeated CSF analysis revealed elevated lactate (3.1–4.9 mmol/l) and alanine concentrations (79 μmol/l). Mitochondrial encephalopathy was excluded by analysis of respiratory chain enzymes in muscle tissue. Initially, brain MRIs showed no abnormalities except mild bifrontal atrophy. At the age of 16 wks, neuroimaging revealed diffuse demyelination, severe brain atrophy, and subdural effusions/haematomas. By MR-angiography tortuosity of intracranial vessels was demonstrated representing a typical radiological sign of MD. Diagnosis was confirmed by low serum ceruloplasmin level (0.06 g/l) and detection of a deletion in the ATP7A gene (exons 18/19).

Conclusion: Characteristic MRI changes together with clinical features of a rapidly progressive neurodegenerative disorder led to the diagnosis of MD. MD should be included in the differential diagnosis of early-onset progressive encephalopathy and unexplained subdural haematomas in infants.

p776

EPILEPSY IN IFAP SYNDROME (ICHTHYOSIS FOLLICULARIS, CONGENITAL ALOPECIA, PHOTOPHOBIA)

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Purpose: Better information on seizure (sz) types in a rare syndrome.

Method: Heteroanamnestic description of seizures in a 6 year old boy.

Results: Developmental delay, skin abnormalities, inguinal hernia, urinary tract stenosis, hypoplasia of corpus callosum and localised left temporoparietooccipital hemimegalencephaly in favour of sporadic IFAP syndrome. Epilepsy onset 1.3 yr: tonic–clonic generalised (G) febrile. Age 3–4.6 yr: G to-clo, head to left/unstable gait, G limb jerks, 2 hrs postictal rigidity right/G to-clo 10 minutes, followed by increased muscle tone 30 minutes, whole-day persisting jerking. Sz change at 4.5 yr: G less, focal (F) more articulated: as if fighting against it (aura?). Stares, drops down slowly, floppy, or falls suddenly. Stiffens as if pulled down, cries, vomits, bothered by light. Vomits 10 min, sleeps whole day. Age 5 yr: long stare, lacrimation, head pulled backwards, eyes right, eyebrows upward, floppy body, falls backwards. Postictal stiffness of the right side of the body described twice: valproate: partial mprovement (sz shorter).

Conclusion: The syndrome includes a variety of epileptic F and G seizures: initial G, then F with or without secondary generalisation become more prominent. Unusual features: photophobia as a part of ictal episode, but no photosensitivity. Ictal and postictal increase of muscle tone. More detailed electroclinical analysis to follow.

p777

ASPECTS OF EPILEPTIC SEIZURES IN CHILDREN WITH PRETERM BIRTH

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Purpose: The aim of this paper is to present the results of a retrospective study regarding particular aspects of epilepsy in children born preterm.

Method: The study included all children with epilepsy admitted in our hospital from 1 January 2000 to 30 December 2005. From these patients we selected the cases with a personal history of preterm birth. The children were evaluated in the clinic and paraclinically. We noted the age of seizure onset, seizure type, epileptic syndrome, neurologic and neuroimagistic features, outcome, antiepileptic treatment.

Results: of the 1255 children with epilepsy admitted in our hospital over this period, 80 children had a preterm birth: 49 boys, 31 girls. In 50 children, seizure onset was in the first 3 years of life. The most frequent type of seizure was focal (41 cases), and the most frequent type of epileptic syndrome was focal symptomatic epilepsy with partial secondary generalised seizures (27 children). Forty-three children presented a neurologic syndrome. The most frequent neuroimagistic feature was leukomalacia, which was present in 23 cases. In all symptomatic epilepsy more than one antiepileptic drug was necessary, with poor outcome.

Conclusion: In our study, preterm birth was associated with epilepsy in a small number of cases. In children with abnormal neurologic and neuroimagistic features, the seizure onset was early, with focal seizures and poor outcome, with more than one antiepileptic drug being necessary for seizure control. The relationship between preterm birth and seizures with late onset or occasional/rare seizures in normal children will be discussed.

p778

EEG-VIDEOTELEMETRY OF PAEDIATRIC ONSET EPILEPSY PATIENTS IN SLOVENIA IN 2004 AND 2005

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Purpose: EEG-videotelemetry (VTM) was used in differential diagnosis of paroxysmal disorders, classification of seizures and localisation of the epileptic focus. In Slovenia VTM was inaugurated in paediatrics in 1996, but has been in continuous use just the last 1.5 years.

Method: Retrospective analysis of recordings performed in 47 patients in 2004 and 2005 using the Grass-Telefactor Millennium system.

Results: VTM was used 127 recording days (from 2 to 166 h; mean 48 h/patient; 82 full 24 h cycles). Seizures were recorded in 30 patients (64%). In 8 patients therapy was changed during VTM. Three peaks of maximum seizure frequency were identified: 5 a.m., 1 to 3 p.m. and 8 to 11 p.m. In 35 (74%) patients VTM showed relevant new information regarding diagnosis and treatment. Paroxysmal disorder differentiation was done in 12 patients (epilepsy confirmed in 3), seizure type evaluation in 21 (seizures recorded in 15) and in 15 possible surgery candidates (seizures recorded in 12). We identified 12 surgery candidates for further evaluation. In 11 patients neuropsychological evaluation was done in parallel with VTM recordings.

Conclusion: Only one-third of recorded seizures occurred during regular office hours (8 a.m. to 4 p.m.) allotted for intensive monitoring. The rest (2/3) were recorded with the help of accompanying parents or relatives, since the continuous presence of dedicated personnel is not covered by health insurance. Professional monitoring during nonoffice hours and weekends would significantly increase diagnostic yield. Equipment proved to be stable, needing only modest maintenance: 1× camera failure, 2× DVD-writer problems not compromising the recording goals.

p779

CLINICAL AND NEUROINSTRUMENTAL CORRELATION OF SYMPTOMATIC EPILEPTIC SEIZURES IN CHILDREN

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Purpose: The work is aimed at a rectification of the role of impairments of main cerebral metabolites in a locally selected region of the brain in children with symptomatic epileptic seizures.

Method: Ninety-eight children from 2 months to 9 years of age with different forms of epilepsy underwent the following investigations: clinical monitoring, neurosonography, EEG, MRI and MRS of the brain. Neurochemical processes of the main metabolites in the brain were studied by using a noninvasive method of magnetic resonance spectroscopy (H^1MRS).

Results: A comparative analysis of the clinical picture, EEG and MRI and MRS of the brain made it possible to diagnose symptomatic epilepsy in 83.7% of children involved in the study (in 57.1% of such children, structural changes in the brain were detected by MRI). Epileptic foci were detected by EEG and in such locally selected regions, impairments of neurochemical processes involving main cerebral metabolites were found in 72.4% of the studied children by using MRS. An increase in Cho concentration ($p < 0.01$) and in Cho/Cr ratio ($p < 0.01$) and reduction of

NAA in the studied regions of the brain suggested metabolic impairments in such regions showing no structural changes.

Conclusion: Monitoring study of the concentration of main cerebral metabolites in the brain of children with symptomatic epilepsy has been employed by us for the purposes of an objective evaluation of the efficacy of different anticonvulsant therapies.

p780

OUTCOME OF VAGUS NERVE STIMULATION (VNS) FOR DIFFICULT TO TREAT EPILEPSY IN CHILDHOOD 5–10 YEARS AFTER IMPLANTATION

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Purpose: To determine the long-term outcome for seizure frequency and patient/parent satisfaction following implantation of a vagus nerve stimulator.

Method: Twenty-three children were identified from theatre records, implanted between 1995 and 2000. A retrospective case-note review was carried out followed by a parent/patient telephone interview in November 2005, using a structured proforma. Average number of seizures per month for the year prior to VNS implantation was calculated and compared with current seizure records.

Results: Mean age at implantation was 11.9 years. Information was available for 21/23 patients, with mean duration of follow-up of 8.4 years. All children had refractory epilepsy. 10 had a symptomatic or probably symptomatic epilepsy. Six patients were considered to have Lennox-Gastaut syndrome, 2 Dravet's syndrome and 3, a symptomatic partial epilepsy. The majority (18/21), had moderate to severe learning difficulties and 8 reported significant problems with behaviour preimplantation. Nine patients (43%) reported a greater than 50% reduction in seizures. Syndrome classification did not predict response. Seven patients reported significant benefit for behaviour. In no child did behaviour worsen following implantation. Sustained benefit is supported by the retention rates with 9/21 having their battery replaced and a further 3/21 awaiting replacement. Nine have had the device switched off because of inefficacy. There were no significant side effects.

Conclusion: This is the first paediatric VNS study demonstrating long term and sustained benefit for over 40% of children with medically refractory epilepsy. The response is highly favourable when compared to medical treatments in this group of patients.

p781

FEBRILE CONVULSIONS: PARENTS ATTITUDE AND BEHAVIOUR

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Purpose: Febrile convulsions (FK) are a clinical entity known for over 2000 years, but parents still panic and think that their child is dying.

Method: There were 200 patients over a period of 12 months. We collected data by means of a questionnaire, filled in by parents. The sample was divided into two groups: 1) children with first febrile convulsions (FK I), and 2) children with recurrent convulsions (FK II).

Results: First FK the age 1–2 yrs. (41.67%), recurrent FK at the age of 3–4 yrs (40.91%). Most often occur in male children in 1) and 2) FK (54.55%). Occur most frequently in winter and autumn. One parent was present for 37.5% episodes, both parents for 50%, some other member of the family for 12.5%, or in 2) FK 18.19%.

50% of the parents reacted with panic, 13.04% gave the antipyretic or diazepam microclysm. 18.19% of the parents gave antipyretic and microclysm. 52.17% of the parents thought that the child was dying and there was a small difference between the two groups.

Conclusion: Mothers are the most frightened. More than half of the parents panic, thinking that the child is dying. Parents are not sufficiently prepared and are insecure about the procedure when the next episode of FK occurs. Actions should be taken to educate parents; composure and knowledge should take place of fear and shock.

This work was not sponsored by anybody; it was done solely by the doctors, themselves, working at the ward.

p782

SYNDROMIC CLASSIFICATION IN CHILDHOOD-ONSET EPILEPSY

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Purpose: The response of seizure types to antiepileptic treatment and prognosis for remission differs among epileptic syndromes. Their precise classification is essential to both patient care and the scientific studies. Most of the known epileptic syndromes occur in children and adolescents. The purpose of our study was to estimate: 1) the possibilities of syndromic classification of epilepsy by means of mostly conventional methods of diagnosis, 2) the distribution of epileptic syndrome types in a group of patients with childhood-onset epilepsy.

Method: Data from 600 (318 male, 282 female) patients with epilepsy onset at age 2 months to 15 years (mean 3.3 years) were analysed retrospectively. They were examined at the in- and outclinic between 1987 and 2000, and were followed-up for mean 4.5 years (range 1–14). The schemes of diagnostic criteria (inclusion to an epileptic syndrome and criteria of exclusion from one) were worked up according to ILAE (1989) and Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy (2001), and other published data.

Results: Thirty-four epileptic syndromes were recognised. Syndromic classification was possible in 476 (79%) patients. Among them classification according to ILAE (1989) was made in 451 (74%) children, and in 25 (4%) according to the new diagnostic proposal of ILAE (2001). Generalised epilepsies were recognised in 234 (39%), partial ones in 346 (57.7%) patients, and underdetermined epilepsies in 20 (3.3%) children. According to aetiologic classification idiopathic epilepsies were recognised in 225 (37.5%), cryptogenic in 189 (31.5%), and symptomatic in 186 (31%).

Conclusion: 1) Most childhood epilepsies could be classify by means of conventional methods of diagnosis; 2) long follow-up period is often useful for syndromic recognition; 3) in some cases accurate syndrome classification is not possible due to lack of universally accepted diagnostic criteria.

p783

REFERRALS ABROAD FOR EPILEPSY SURGERY: EXPERIENCE IN NEUROPSYCHOLOGICAL ASSESSMENT GATHERED BY THE CENTER FOR CHILD & ADOLESCENT EPILEPSY AT THE CHILDREN'S UNIVERSITY HOSPITAL IN LJUBLJANA

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Purpose: When considering paediatric patients with intractable epilepsy for epilepsy surgery, neuropsychological assessment contributes vital information on the developmental level of a child pre-and postsurgery. Data collected for these purposes was examined in the current retrospective study to examine the neuropsychological outcome of patients with intractable epilepsy who underwent surgery at epilepsy centres abroad.

Method: The children, adolescents and young adults included in the study had frontal lobe ($n = 7$), as well as left ($n = 5$) and right temporal lobe epilepsy ($n = 5$). Their median age at the time of surgery was 14 (range 6–25), with a median confirmed age at epilepsy onset of 3.8 years. Presurgical neuropsychological assessment was conducted six months prior to surgery. In investigating the neuropsychological outcome we included data gathered at the last completed neuropsychological assessment, which was on average 24 months after surgery (range 12–128 months).

Results: At the last neuropsychological follow-up patients who underwent surgery showed no significant reduction in neuropsychological scores, even showing a trend towards improvement in performance IQ as measured by the Wechsler intelligence scales ($p = 0.051$). The effect

was of medium size (Cohen d = 0.61). Of possible factors influencing neuropsychological outcome only preoperative global (r = 0.40) and performance IQ (r = 0.42) approached significance, higher presurgical scores being associated with better neuropsychological outcome.

Conclusion: Although the neuropsychological data presented show no signs of a cognitive decline, neuropsychological assessment at various points after surgery proved to be of great value for patients in their postsurgical adjustment to the school and work environment.

p784
PREVALENCE OF ANTIPHOSPHOLIPID AND ANTINUCLEAR ANTIBODIES IN CHILDREN WITH EPILEPSY

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Purpose: An increased prevalence of antiphospholipid autoantibodies (aPL) has been described in clinical studies among patients with epilepsy. On the other hand seizures are also reported causing immunological alterations, even drug induced lupus.

Method: The presence of antinuclear, antiphospholipid antibodies, serum levels of immunoglobulins and complement factors were also investigated in 65 randomly selected children with epilepsy. We analysed the following clinical data: time of follow-up; type and duration of epilepsy; frequency of seizures; time from last seizure; results of neuroimaging and EEG data; antiepileptic medication.

Results: The mean duration of disease was 4.8 years. The mean time between the last convulsion and the laboratory analysis was 1.9 years. Most patients achieved good disease control and have 1–2 convulsion(s)/year. Partial immunoglobulin deficiency was detected in 14/65 patients. Hypocomplementaemia was detected in 4 children. One of them showed concurrent ANA and lupus anticoagulant (LA) positivity. Although the diagnostic criteria for SLE are not fulfilled, the patient is being regularly followed up. Twenty-eight of our patients were ANA positive. Anti-C1q antibody was positive in 2 cases; none of them have renal manifestation of lupus. Only 1 child had anticardiolipin (aCL) antibody, while 6/39 patients were LA positive. Anti-β2-glycoprotein-I-antibody positivity was not observed. None of the patients have aDNA antibodies.

Conclusion: In our study lower total prevalence of aPLs was observed in children with epilepsy than in previous reports (20–30%). The cause of it can be a higher percentage of well controlled epilepsy patients in our cohort.

p785
NEUROCOGNITIVE FUNCTIONING IN CHILDREN WITH COMPLICATIONS, NEUROINFECTIONS AND CONVULSIVE SYNDROME

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Purpose: Hard neuroinfections in children may lead to a convulsive syndrome that increases a level of invalidisation of them. The aim of the research was to study cognitive functions in children with sequelae following meningoencephalitis and convulsive syndrome.

Method: Thirty children, after an acute neuroinfection with convulsive syndrome, have been examined. All the patients underwent EEG and dopplerography. We set out to determine a level of indices of cognitive disorders in children with sequelae of neuroinfection with convulsive syndrome. The test of Wexler for children was used to diagnose the intellectual development of patients and test Simernitskaya ≪Luria-90≫ was used to evaluate attention, memory and thinking functions.

Results: Before treatment, EEG revealed diffuse changes in bioelectric activity of the cerebral cortex with a presence of nidal or paroxysmal convulsive activity in all patients. Transcranial dopplerography of the cerebral blood stream in the examined children found a hyperconstrictory reaction of cerebral vessels: mean linear velocity (MLV) in the mean cerebral artery (MCA) was reducing to 30% from an initial one. Results of Wexler and Simernitskaya tests ≪Luria-90≫ exhibited a decrease of the aural-verbal and visual memory, reduction of operative thinking activity and intellectual activity in children.

Conclusion: Thus, results confirmed that children with sequelae of neuroinfection and convulsive syndrome have expressed cognitive disorders, demanding necessary treatment.

p786
PROGNOSTIC VALUE OF CRANIAL ULTRASOUND AND EEG IN NEWBORNS WITH PERINATAL ASPHYXIA

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Purpose: Improvements in perinatal and neonatal care over the last decades have resulted in increased survival of newborn infants with perinatal asphyxia. Neurological disabilities are among the most severe consequences occurring in these infants.

Method: The group of 115 high-risk newborns was examined neurologically, by ultrasound scanning of the brain and EEG during the neonatal period. They were followed up with detailed neurological examinations at three month intervals until one year of age, and thereafter at 18 months and two, three, four and five years of age. According to their neurological outcome, infants were classified into two groups: normal and abnormal.

Results: Normal neurological outcome was found in 44 (100%) of 44 infants with normal neonatal neurological status, in 45 (97.8%) of 46 with normal neonatal ultrasound findings and in 102 (100%) of 102 with normal neonatal EEG findings. Abnormal neurological outcome was found in 9 (12.7%) of 71 infants with abnormal neonatal neurological status, in 8 (11.6%) of 69 infants with abnormal neonatal ultrasound findings and in 9 (69.3%) of 13 infants with abnormal neonatal EEG findings. Specificity and sensitivity of EEG was higher (100% and 69.2%) than of ultrasound imaging of the infant's brain (97.8% and 11.6%) and neurological assessment (100% and 12.6%).

Conclusion: Neonatal neurological assessment, ultrasound and EEG have some prognostic value in newborns with perinatal asphyxia. An integrative approach with the combined use of clinical evaluation and additional diagnostic methods is needed.

p787
CORTICOSTEROIDS FOR THE TREATMENT OF LANDAU-KLEFFNER

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Purpose: The Landau-Kleffner syndrome (LKS) is defined as an acquired disorder of language comprehension arising in a child with centrotemporal epilepsy with either clinical seizures or subclinical epilepsy particularly enhanced by slow-wave sleep. Our aim is to present the clinical, electroencephalographic characteristic of 4 patients with LKS and the language and epilepsy outcome with corticosteroid treatment.

Method: Four children (2 boys and 2 girls) were admitted for LKS. These patients have benefited from complete clinical investigation, awake end sleep EEG and cerebral MRI. All of them had valproic acid as initial therapy and corticosteroids in second intention in 2 patients.

Results: Age of onset ranged from 2 to 6 years (mean 4 years) and epilepsy was the first symptom for all patients. Language regression occurred progressively with an inability to understand spoken words. Awake EEG showed spikes in the temporal cortex and 2 patients had patterns of continuous spike and wave discharges during sleep. MRI was normal in all patients. Valproic acid was used as initial treatment in all patients with seizure control but not language regression. Two patients were treated with hydrocortisone with improvement in language and behaviour. One patient was treated only by VPA with favourable evolution, epilepsy disappeared and he recovered language 10 years after.

Conclusion: Corticosteroids are a safe and effective treatment for patients with Landau-Kleffner syndrome and should be considered as a treatment option for children with Landau-Kleffner syndrome.

p788

ICTAL AND INTERICTAL EEG ABNORMALITIES IN ADHD CHILDREN RECORDED OVERNIGHT BY VIDEO-POLYSOMNOGRAPHY

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Purpose: To look at the prevalence of IEDs in ADHD children during all night video-PSG (vPSG), exploring the possibility of cotreating sleep disorders (SD) and IEDs to improve behaviour and cognition.

Method: Thirty-two children, diagnosed according to DSMIV IC were administered standardised questionnaires and scales: Wechsler Intelligence Scale; attention and short-term memory tests; ADHD-RS, Conners' Teachers (CTRS), Parents (CPRS), SNAP IV RS, and paediatric sleep questionnaire. Standard vPSG also included 18 leads EEG. Sleep and EEG variables were held against cognitive/behavioural scores with Pearson coefficient test.

Results: Most children/parents reported SD confirmed by vPSG (72% SRMD, 37% DOA, 19% SRBD). None of the children showed an intellectual deficit, 6% had a tic disorder, 12% language disorders and 44% learning disorders. No seizure history was reported, but 19% had an abnormal EEG and 53% IEDs on vPSG. Nocturnal seizures were recorded in 2. There was a significant presence of high levels of impulsivity/hyperactivity scoring with RLS. Language disorder was positively related to the presence of rolandic or frontal foci, tic with a temporal occipital focus and RLS, seizures with short-term visual spatial memory deficit. LEV (500–1000 mg) was offered to children with seizures and/or IEDs and with RLS. Seven patients agreed to this regimen. After 6 months, they improved behaviour and social adaptation and nocturnal sleep with cessation of RLS and DOA. No seizures and reduction of IEDs were recorded. A nonparametric analysis between independent variables run by Wilcoxon Test showed statistical significance for improved scoring at CTRS, CPRS, ADHDRS, SNAP IV.

Conclusion: Our study supports data reporting a high prevalence of IEDs in ADHD children and the role of sleep recordings to improve diagnosis of EEG abnormalities and SD in such children, both contributing to the detected cognitive and behavioural abnormalities. LEV holds a promising role as a safe therapeutic tool for EEG and SD in ADHD children.

p789

OUTCOME AND PRESURGICAL RESOURCES IN EPILEPSY SURGERY ON CHILDREN WITH IQ/DQ ABOVE AND BELOW 70

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Purpose: Operations on mentally retarded children are expected to have a poor outcome. We studied whether outcome and resources used for evaluation differed between children with IQ/DQ $>$ 70 (group A) and $<$ 70 IQ/DQ (group B).

Method: Results from a retrospective study of Danish children ($n = 38$) operated between 1996 and 2004 were evaluated. The mean age at operation in group A ($n = 15$) was 13 years 1 month and for group B ($n = 23$) 8 years and 1 month. Nine of group A and 5 of group B were operated in Denmark, the remaining abroad, mainly at Cleveland Clinic. Multiple resection or hemispherectomies were performed in 3 from group A (21%) and 14 (61%) from group B.

Results: Seizure free outcome was found in 66% (group A) and 65% (group B) at one year follow-up. In group A 25% had a decrease and 17% an increase of $>$ 10 IQ/DQ compared to 28% and 14% in group B. Presurgical admittance in Denmark for ictal video EEG and neuropsychological evaluation required 19.9 days (group A) and 15.4 days (group B). 20% had an ictal SPECT (group A) and 39% group B. PET was performed on 46% of group A and 30% of group B.

Conclusion: Seizure and development outcome after epilepsy surgery were the same in children with IQ/DQ above and below 70. Resources in the two groups were comparable.

p790

PREVALENCE OF SLEEP DISORDERS IN CHILDREN AND ADOLESCENTS WITH EPILEPSY: A PILOT STUDY

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Purpose: The pilot study was conducted to examine the sleep habits and the prevalence of sleep disorders in children and adolescents with epilepsy.

Method: From May to September 2005, 65 children and adolescents with epilepsy were investigated via our own questionnaires in the Department of Developmental Neurology, Poznan University of Medical Sciences. The children were admitted to the department to diagnose or treat epilepsy. We created 4 categories dependent on age: preschool (2–6 years old) – 8, grammar school (7–12) – 20, middle school (13–15) – 19, and secondary school (15–18) – 19.

Results: The average of total sleep duration was 9.7 h (ranged from 11.1 h in preschool group to 8.8 h in secondary school group). The mean time of falling asleep in the whole group was 27.0 minutes (ranged from 1 min. to 180 min.). In the investigation, 18 (27.7%) children slept with somebody in the bed, and 48 (73.8%) slept in a common room with family. Awakening during the night sleep were observed in 47.7% and it was more frequent in the preschooler group, 87.5%, than in the middle school group, 31.6%. The presence of different symptoms connected with sleeping disorders were noticed by 87.7% parents. The frequency of sleep disorders reported as parasomnia symptoms like sleep talking 41.6%, bruxism 27.7%, enuresis 26.2%, leg movement 24.6%, nightmares 20.0%, sleep terror 16.9% and sleep breathing disorder symptoms like snoring 47.7% and breathing pauses 13.8%.

Conclusion: Childhood sleep disorders are very common in groups of children with epilepsy. Additional research with a control group is needed to find a correlation between epilepsy and sleep disorders.

p791

A POPULATION-BASED STUDY OF EPILEPSY IN CHILDREN

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Purpose: To establish the rate of incidence and prevalence, age distribution, inheritance, seizure types, epilepsy syndromes and treatment strategies in the county of Uppsala, Sweden.

Method: A population-based study was performed to select children aged from 1 month to 16 years with the diagnoses 'convulsions' or 'epilepsy.' The children were recognised between 1 January 1996 and 31 December 2000, and only those with active epilepsy were included.

Results: 205 children met the study criteria on the prevalence day 31 December 2000. The total prevalence rate was 3.4/1000 with a peak prevalence in the age group 8–11 years. The incidence year 2000 was 40/100000. A majority of patients, 54.0%, had focal or focal plus secondarily generalised seizures. A real syndrome could be diagnosed in 90.7%. The most common syndrome was rolandic epilepsy pure, found in 17%. Different diseases associated with epilepsy were found in 31.7%.

Conclusion: The prevalence and incidence rate in this strictly delineated study are lower than those found in other epidemiological studies in the Western population. The ILAE classification of epileptic syndromes has been used, and the majority of the patients could be classified accordingly. In spite of this well adjusted classification, there are many divergences between reported studies concerning frequencies of different items. This apparently is partly dependent on design, e.g. difference in age groups included, inclusion criteria used, and methodology.

p792

EFFECTS OF LEVETIRACETAM ON EPILEPTIFORM DISCHARGES IN SYMPTOMATIC EPILEPSY IN CHILDREN

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Purpose: To determine the effect of levetiracetam (LEV) as add-on therapy on epileptiform discharges in children with refractory symptomatic epilepsy.

Method: Patients aged 4–15 years suffering from refractory symptomatic epilepsy with partial and generalised partial seizures, and already treated with at least one antiepileptic drug (AED) were included in this retrospective study. LEV was commenced (starting dose 10 mg/kg/day) and up-titrated every 2 days to a maximum dose of 50 mg/kg/day. Concomitant AED doses were not modified. Patients were evaluated by EEG (sleeping and awake) before commencing LEV treatment, and after 3 months.

Results: Thirteen children aged 4–15 (mean 7.6 ± 3.3) years were enrolled. All children completed the titration phase. LEV significantly decreased seizure frequency by ≥50% in 9/13 (69%) patients ($p = 0.0003$). LEV was significantly effective in improving EEG activity, with reduction in frequency of epileptiform discharges in 10/13 (77%) children ($p = 0.0014$). LEV was well tolerated without AEs reported.

Conclusion: LEV is effective in consistently reducing frequency of interictal epileptic activity. Reduction of epileptiform discharges additionally supports a clinically relevant antiepileptic effect. Randomised clinical studies on a larger population are needed to confirm these preliminary results.

p793

PRENATAL CHEMICAL INSULTS INDUCE BRAIN EDEMA AND CHANGES IN EXPRESSION OF AQUAPORINS

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Purpose: Chemical ablation of precursor cells appears to be involved in the genesis of cortical dysplasia (CD) in human brain and animal models. Prenatal exposure to the toxin methylazoxymethanol acetate (MAM) causes cortical dysplasia in rats that partially overlaps with the effects of the angiogenesis inhibitor thalidomide; both vascular and parenchymal factors are thus involved. We wished to investigate the effects of MAM on vascular permeability and cortical development at short intervals after exposure.

Method: MAM (15 mg/kg) was given at E15 and sections processed at E16. Standard immunocytochemical and histological techniques were used.

Results: MAM-treated foetuses exhibited widespread neuronal cell death paradoxically accompanied by increased cortical thickness (308.2 micron ±5.5 vs 181.9 micron ±4.6; $p < 0.05$, $n = 3$ animals). Brain edema was indirectly quantified by measuring tissue optical density (expressed in arbitrary units). MAM treated cortices had a cortical tissue density of 40 ± 0.8 compared to 43 ± 1.1 in control animals. Water channels AQP1 and AQP4 were respectively increased and decreased suggesting a rearrangement of water transport. AQP1 expression was greatly increased in parenchymal cells, while the opposite was observed for AQP4. Both transporters were strongly expressed in association to the cerebral vasculature regardless of treatment.

Conclusion: Brain edema was presumably due to altered water permeability in the glia and blood–brain barrier. Endothelium is an early consequence of chemical induction of cortical dysplasia. Our results suggest that an increase in AQP1 causes cellular edema while A AQP4 decreases may promote greater extracellular or vasogenic edema.

This work was supported by NIH HL51614, NS43284, NS38195, and NS149514 to DJ.

p794

NEUROCOGNITIVE DIFFERENCES BETWEEN FRONTAL AND TEMPORAL SEIZURES IN PAEDIATRIC EPILEPSY

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Purpose: The purpose of this clinical trial was to differentiate the neurocognitive performance between frontal and temporal seizures in paediatric epilepsy. This is an important issue related to measuring the impact of different types of seizure in the neurodevelopment of infants with epilepsy.

Method: We analysed patients with partial epilepsy between 6 and 12 years old, both genders, in the neurology department of the Hospital Infantil de México. After dividing into frontal and temporal epilepsies, we applied a neurocognitive test, evaluating IQ, attention, working memory, executive functions and visuospatial performance. Besides, these infants had an EEG, neuroimaging, social evaluation and physical examination.

Results: Thirty-seven patients, both genders (22 males, 15 females) with partial frontal epilepsy (17) and temporal epilepsy (20) were evaluated. The principal neurocognitive differences between these two types of epilepsy were the IQ (mean 82 in frontal epilepsy and 97 in temporal epilepsy), with more impact in the working memory and visuospatial performance in infants with frontal epilepsy. The patients with temporal epilepsy had more problems in executing attention and long memory tests.

Conclusion: The patients with frontal epilepsy, which started as paediatric epilepsy, had more impact in developmental neurocognitive skills, and we think this is a very important issue to start early support with therapeutic approaches in this group of epilepsy, trying to reverse the impact of seizures over academic and social capacities. Further studies are needed to find whether this impact over neurocognitive skills can be reverted with early therapeutic support.

p795

FOLLOW-UP AFTER SINGLE UNPROVOKED SEIZURE

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Purpose: Most studies have shown that approximately one third of the patients with a single seizure will experience a second one; but there is not any information for the recurrence risk. Therefore, we aimed to evaluate the risk factors for the recurrence of seizures following a single unprovoked idiopathic seizure.

Method: The study comprised 88 patients (mean age 7.9 ± 3.7 years, range 5 months to 13 years, 46 M, 42 F), who were admitted to our paediatric neurology unit with a history of a single episode seizure; and followed for at least 3 years. Patients were divided into 2 groups according to the recurrence of the seizure during the 3 year period; and risk factors such as age, gender, type of seizure, EEG findings, neuroimaging, family history of seizures in first degree relatives and consanguinity were evaluated.

Results: of the 88 patients, 26 (29.5%) had a recurrence within the 5.3 ± 7.3 months (range 4 days to 36 months) after the first seizure. No significant difference was found in terms of age (7.6 ± 3.6 vs 7.1 ± 3.4 years), gender (46.7% vs 50%), seizure type, EEG abnormality (37% vs 34%), neuroimaging abnormalities (3% vs 11.5%), family history (8% vs 23%) and consanguinity (8% vs 15.3%) between the groups ($p > 0.05$ for all parameters).

Conclusion: There is still a dilemma whether a single unprovoked seizure should be treated or not. We tried to find out risk factors for seizure recurrence but we couldn't establish a statistically significant one.

p796

STARTLE DISEASE, AN UNCOMMON NONEPILEPTIC DISORDER: CASE REPORT

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Startle disease is an uncommon and relatively benign nonepileptic neurological entity often confused with epilepsy. Early diagnosis and prompt treatment is important to avoid clinical complications leading to death. We report two cases presenting with hypertonia and exaggerated startle response in neonatal period, diagnosed as startle disease.

p797

RETROSPECTIVE STUDY OF EFFICACY AND TOLERABILITY OF LEVETIRACETAM IN CHILDREN WITH REFRACTORY EPILEPSY

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Purpose: The aim of this retrospective open label add-on study is to assess the efficacy and safety of levetiracetam in refractory partial or generalised epilepsy in children and young adults.

Method: We have retrospectively evaluated 24 patients, 14 males and 10 females, aged between 4 and 18 years, selected from our data base concerning epilepsy patients, according to the following criteria: subjects affected by refractory focal or generalised epilepsy with no more than two baseline AEDs at the moment of LEV add-on and at least six months of follow up. Data included neurological status, cognitive function and neuroimaging; epilepsy type and seizure frequency, and concomitant AEDs treatment. Efficacy was evaluated as seizure freedom, reduction >50% (responders), reduction <50%, unchanged or worsened (non responders). Absent or transient side effects were considered a favourable index of good tolerability.

Results: 24 children or young adults aged between 4 and 19 years were exposed to LEV as add on therapy at doses ranging from 20 to 60 mg/kg/die. 2 patients discontinued treatment before reaching a dose considered effective owing to side effects. Follow up is extended over 3 years in some cases and always longer than 6 months. 4 patients reached complete seizures control, 9 had a >50% seizure reduction, 11 obtained a mild seizure reduction or were unchanged. None deteriorated. Tiredness and somnolence were the most common side effects and in 2 patients lead to drug discontinuation.

Conclusion: Confirming literature data, our study indicates that LEV is quite effective in childhood refractory epilepsies and effectiveness on different types of seizures suggests a broad therapeutic spectrum. Tolerability is also favourable in most cases.

Wednesday July 5, 2006
13:30–15:00
Poster Session 3
Surgical Treatment/VNS

p798

SEIZURE REDUCTION AND QUALITY OF LIFE IN COGNITIVELY CHALLENGED PATIENTS TREATED WITH VAGUS NERVE STIMULATION (VNS) THERAPY

M. Trimble (Institute of Neurology, London, UK)

Purpose: Intractable seizures are common in patients with learning disability (LD), and the seizures may contribute to the LD. Control of seizures in LD represents a clinical challenge, but vagus nerve stimulation (VNS) is one option.

Method: Data from 396 cognitively challenged patients i.e., institutionalised, with LD or developmental delay treated with (VNS) therapy in addition to their regular medication were analysed from the VNS Therapy Patient Outcome Registry at 3, 12, and 24 months. Data on seizure reduction and quality of life (QoL) were analysed at 3, 12 and 24 months after implant.

Results: of 396 patients, 153 (38.6%) were < 18 years, with 80 patients (20.2%) < 12 years of age. Mean age was 24.5 years (range, 2–63). There was a median seizure reduction of 41% after 3 months, 54% at 12 months and 54% at 24 months. Seizure reduction ≥ 50% was reported in 47%, 55% and 55% of the patients after 3, 12 and 24 months, respectively. Seizure reduction ≥ 75% occurred in 26%, 33% and 37% of patients after 3, 12 and 24 months, respectively. Seizure reduction ≥ 90% was observed in 13%, 17% and 23% of patients after 3, 12 and 24 months, respectively. Regarding QoL, the percentage classified as "better" or "much better" were: alertness, 62%, 68% and 66%; mood, 41%, 48% and 45%; and achievements, 24%, 34% and 29%.

Conclusion: VNS Therapy is associated with seizure and QoL improvements in this population of cognitively challenged patients.

p799

AUTISTIC SPECTRUM DISORDER (ASD), ATTENTION DEFICIT AND/OR HYPERACTIVITY DISORDER (AD/HD) AND LEARNING DISABILITY IN CHILDHOOD EPILEPSY SURGERY CANDIDATES AND CANDIDATES FOR VAGUS NERVE STIMULATION (VNS)

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Purpose: Children with medically intractable epilepsy are at an increased risk of neuropsychiatric disorders. Since 2002 all children in the Epilepsy Surgery Programme at Sahlgrenska University Hospital in Göteborg, Sweden are referred for neuropsychiatric assessment before and two years after surgery. We present the results from neuropsychiatric preoperative assessment in candidates for resective surgery and in candidates for VNS.

Method: Children (n = 41) consecutively referred for evaluation before resective surgery or VNS were studied 2002–2005. All children had a clinical neuropsychiatric assessment, including parental questionnaires, and a neuropsychological evaluation. Cases with symptoms and signs on the autistic spectrum were assessed with The Diagnostic Interview for Social and Communication Disorders (DISCO) and the Autism Diagnostic Observation Schedule (ADOS).

Results: In 21 who had resective surgery 24% had ASD, 29% AD/HD and 33% had an IQ level ≤ 70. In 20 who were candidates for VNS treatment 65% had ASD, 50% AD/HD and 90% had an IQ level ≤ 70. The median age of epilepsy onset in the two groups was 4 years and 2.2 years, respectively.

Conclusion: ASD and/or AD/HD are common in children with medically intractable epilepsy being referred for presurgical evaluation. These children are severely impaired with special needs both at home and at school. Behavioural problems and cognitive impairment were more common in the VNS group than in children accepted for resective surgery. Neuropsychiatric assessment is an important part of the epilepsy surgery programme in children, and makes it possible to determine outcome in more aspects than seizure control.

p800

VAGAL NERVE STIMULATION IN DRUG RESISTANT EPILEPSY: EXPERIENCE WITH 7 CASES

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Purpose: In cases of drug resistant epilepsy with no diagnosed focus in clinical evaluation, vagal nerve stimulation (VNS) is a choice of treatment to decrease the seizure frequency or seizure control in 1–2% of cases. This treatment choice was introduced to clinical application in 1998.

Method: VNS was administered to 7 cases of drug resistant therapy by the epilepsy surgery group between 2001 and 2004 at Gulhane Military Medical Academy. Under the authorisation of the epilepsy council, electrodes were placed surgically to the left vagus nerve in the carotid sheath. Electrode cables were directed to the left pectoral region subcutaneously and connected to the pulse generator. Mean surgery time varied between 30 and 60 minutes.

Results: Complications such as infection, vagal nerve injury and vascular injury were not exposed in any of the cases. There was a 27.8% (10–50%) decrease in seizure frequency. There were no cases with total seizure control. VNS application is not intended for total seizure control.

Conclusion: This application can be expected as an adjuvant therapy. In cases with aura, self induction of a pulse generator effectively decreases seizure frequency.

p801

VAGAL NERVE STIMULATION IN CATASTROPHIC EPILEPSY OF INFANCY: EFFECTS ON SEIZURES AND QUALITY OF LIFE

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Purpose: To assess the efficacy of treating catastrophic epilepsy of infancy with vagal nerve stimulation (VNS) and its effects on quality of life (QOL) and behavioural adjustment.

Method: Sixteen patients with Lennox-Gastaut and severe partial epilepsy (pseudo-Lennox-Gastaut) between the ages of 4 and 17 years (mean age: 9 years and 3 months) were implanted and followed-up after 18 months of treatment. Medication and VNS parameters were adjusted for optimal seizure control. Vineland Adaptive Behaviour Scales (VABS) and analogical scale were used to assess postimplantation QOL and behavioural adjustment.

Results: Five out of 16 patients had >90% reduction in seizures, 4 had between 80% and 50%, 4 had <50% and 3 had no change. Pseudo-Lennox-Gastaut (PLG) patients had higher seizure reduction (mean seizure reduction 71%) than Lennox-Gastaut (LG) patients (mean seizure reduction 43%). VABS scores showed no statistical significant improvement. Socialisation subscale showed a trend of decrease in 50% of children, while 50% stayed permanent or slightly improved. Daily living skills and communication subscales showed more permanent and improved scores (respectively 59% and 52%) than decreased scores. No relevant differences were observed between LG and PLG patients. Analogical scale showed significant decrease ($p < 0.05$) in anxiety (especially in PLG) and significant improvement ($p < 0.01$) in attention/concentration skills in both groups.

Conclusion: VNS appear to be an emerging option for treatment of medically intractable catastrophic epilepsy. Its effects appear not to be only restricted to seizure control but also to behavioural skills and to mood and attention/concentration disorders related to epilepsy.

p802

VAGUS NERVE STIMULATION (VNS) THERAPY FOR PATIENTS WITH REFRACTORY SEIZURES ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX

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Purpose: Data from pts with tuberous sclerosis complex (TSC) treated with adjunctive VNS for refractory epilepsy was analysed from the VNS Therapy Patient Outcome Registry, including data on seizure reduction and quality of life (QoL) at 3 and 12 months after implant.

Method: 38 pts (19 M, 19 F) were evaluated. Mean age: 21.58 y (±12.26), mean age at onset: 2.39 y (±4.16); mean duration of epilepsy: 18.99 y (±11.97); 18 pts (47.4%) were < 18 y. Localisation-related epilepsy: 23 pts (60.5%); Lennox-Gastaut syndrome: 7 (18.4%); generalised epilepsy: 5 (13.2%); other: 3 (7.4%).

Results: Median seizure reduction: 52% after 3 months and 46% after 12 months. Seizure reduction ≥50% occurred in 50% and 47% of pts after 3 and 12 months, respectively. The percentage of pts classified as "better" or "much better" was: alertness, 50% and 58%; post-ictal, 61% and 47%; clusters, 55% and 50%; verbal skills, 34% and 32%; mood, 34% and 37%; achievements, 21% and 26%; and memory, 26% and 29% at 3 and 12 months, respectively.

Conclusion: VNS Therapy was associated with seizure reduction (52% and 46% at 3 and 12 months, respectively) and QoL improvements (≥ 50% for alertness and clusters at 3 and 12 months, and for post-ictal period at 3 months) in pts with TSC and refractory epilepsy.

p803

A REVIEW OF OUTCOMES FOLLOWING FIRST 25 VAGAL NERVE STIMULATOR (VNS) IMPLANTATIONS FOR EPILEPSY

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Purpose: We undertook this review to assess the outcomes of patients in our Neurosciences Unit who underwent VNS for the management of intractable epilepsy.

Method: Case notes were reviewed for the 25 patients who had vagal nerve stimulators inserted between 1998 and November 2005. VNS was chosen when reasonable drug options were exhausted and resective brain surgery was not appropriate or declined (2 patients).

Results: of 15 male and 10 female patients, 4 had learning disabilities. Ages ranged from 14y to 58y at implantation. The duration of epilepsy ranged from 11–38y (mean 23y). 19 patients had focal epilepsies, 4 primary generalised and 2 Lennox-Gastaut syndrome. 3 patients had undergone previous surgery: 1 callosotomy, 2 hemispherectomy. Patients were taking a mean of 3 antiepilepsy drugs (range 1–5). 20 patients improved post VNS, including all 4 with primary generalised epilepsy; 5 were unchanged and none worsened. Improvements recorded included reduced seizure frequency (up to 50–75%), more seizure free days, reduced seizure severity (including cessation of tonic–clonic seizures) and improved alertness. No patient became seizure free. Medication was reduced in 1 patient. Many patients experienced side effects with the original VNS settings, but these were easily managed by altering the stimulus parameters.

Conclusion: VNS offers worthwhile palliative benefits to patients with intractable epilepsy, and is well tolerated. Our results are consistent with the published literature, and suggest that VNS can usefully be offered in epilepsy clinics which do not support a full epilepsy surgery programme. .

p804

VAGUS NERVE STIMULATION FOR REFRACTORY EPILEPSY: POOLED RESULTS FROM EPILEPSY CENTRES IN BELGIUM

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Purpose: This study evaluates the long-term outcome for patients treated with vagus nerve stimulation (VNS) for refractory epilepsy in seven different epilepsy centres in Belgium.

Method: Since 1995, 223 patients were treated with VNS in Belgium. We retrospectively assessed seizure frequency reduction, antiepileptic drug (AED) treatment and stimulation parameters in patients with a follow-up of at least one year.

Results: 168 patients (82M/86F) had a mean age of 30 years at time of implantation and a mean postimplantation follow-up of 37 months (range: 12–119). Mean number of AEDs before implantation was 3 (range 1–5). 140/168 patients had complex partial epilepsy, 11 patients had generalised epilepsy and 17 patients were diagnosed with an epilepsy syndrome e.g. Lennox-Gastaut. At maximum follow-up, mean stimulation output current was 1.75 mA (range 0–3.25). In 12 patients (7%), output current was programmed 0 mA due to lack of efficacy. 15 patients were on rapid cycling stimulation. Mean number of AEDs at maximum follow-up remained unchanged. 63 patients (37.5%) were non-responders with a reduction in seizure frequency of <30%. 87 patients (52%) had a >50% reduction in seizure frequency. 13 patients have been seizure-free for at least 12 months.

Conclusion: The long-term experience with VNS in Belgium confirms that VNS is an efficacious adjunctive antiepileptic treatment for patients with refractory epilepsy.

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p805

VISUAL FIELD DEFECT AFTER SELECTIVE AMYGDALOHIPPOCAMPECTOMY IN MESIAL TEMPORAL SCLEROSIS

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Purpose: Visual field defects (VFD) after temporal lobe resection in temporal lobe epilepsy patients are reported to be frequent (50–52%). The aim of this study was to detect the frequency of VFD after selective amygdalohippocampectomy in patients with medically refractory complex partial seizures due to mesial temporal sclerosis.

Method: Twenty patients (13 men, 7 women; age range 12–57 years) underwent selective amygdalohippocampectomy (14 right, 6 left) and were analysed. Mean seizure onset age was 11.5 ± 6 (range 3–25 years). VFD was examined preoperatively by a neurologist ($n = 10$) or by standard Goldmann perimetry ($n = 10$) and postoperatively by standard Goldmann perimetry within 1 to 19 months.

Results: Visual field examination was normal in all patients preoperatively. Postoperative perimetry measurement revealed upper quadrantanopia in 7 patients (35%) although none of them were aware of it. In one year follow-up 16 patients were in class I, 3 patients were in class II, and 1 patient was in class IV according to Engel's outcome classification.

Conclusion: To our knowledge VFD after selective amygdalohippocampectomy has not been reported before. It has been suggested that there is a relation between the extent of resection in the anterior part of the superior temporal gyrus and VFD. A limited resection after selective amygdalohippocampectomy may still cause VFD.

p806

ANTERIOR TEMPORAL LOBECTOMY/AMYGDALOHIPPOCAMPECTOMY FOR MEDICALLY INTRACTABLE COMPLEX PARTIAL SEIZURES

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Purpose: The results and complications of anterior temporal lobectomy/amygdalohippocampectomy (ATL/AH) in patients with medically intractable mesial temporal lobe epilepsy are presented.

Method: Fifteen patients (8 males, 7 females) underwent noninvasive preoperative evaluation (video/scalp EEG, brain MRI, neuropsychological evaluation). Twelve patients were submitted to amytal testing as well. Mesial temporal sclerosis was diagnosed in 12 patients. Two patients had a hippocampal-amygdala tumour (oligodendroglioma: $n = 1$, astrocytoma grade II: $n = 1$) and 1 patient had a fusiform/parahippocampal gyrus astrocytoma grade II. The seizure history ranged from 5 to 40 (mean: 21.3) years. The preoperative seizure frequency ranged from 1 to 100 (mean: 18.6) seizures per month. The patients' ages at operation ranged from 20–58 (mean: 32.5) years. All patients underwent an ATL/AH (right: $n = 9$, left: $n = 6$) and lesionectomy as indicated ($n = 3$), with or without intraoperative electrocorticography. The hospital stay ranged from 4 to 21 (mean: 7) days. The follow-up ranged from 1 to 48 (mean: 23) months.

Results: At the latest follow-up visit 9 patients were seizure-free (60%), 5 were significantly improved (33.3%), and 1 was unchanged (6.6%). According to the ILAE criteria, 9 patients were Engel class I (60%), 4 were Engel class II (26.6%), 1 was Engel class III (6.6.%), and 1 was Engel class IV (6.6%). Postoperatively one patient developed a surgical wound infection (complication rate of 6.6%).

Conclusion: The beneficial ATL/AH outcome (seizure-free and significant improvement) is highly dependent on the accuracy of methods available for patient selection.

p807

HIGH FREQUENCY DEEP BRAIN STIMULATION OF THE HIPPOCAMPUS IN A RAT MODEL FOR TEMPORAL LOBE EPILEPSY

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Purpose: This experimental animal study evaluates the effect of high frequency deep brain stimulation (HFS) on seizures in the Alternate Day Rapid Kindling (ADRK) model, a model for temporal lobe epilepsy (TLE). The target for HFS is the hippocampus, as it is often the seizure focus in human TLE.

Method: Following implantation of recording and stimulation electrodes, all rats ($n = 12$) were fully kindled in the hippocampus according the ADRK-protocol (Lothman et al., *Epilepsy Res* 1993;14:209–20). After this, all rats received 10 kindling stimuli every other day for 3 days. Then, the rats were divided into two groups: a treated group ($n = 7$) received 130 Hz-HFS for 1 week, while the control group ($n = 5$) received no stimulation. After this week, HFS was stopped and both groups were retested with 10 kindling stimuli every other day for 3 days. One week of wash-out was allowed, before continuously stimulating the HFS-group again for 1 week. During this week of HFS, 10 additional kindling stimuli every alternate day for 3 days were given. The control group only received the kindling stimuli. For each rat, the afterdischarge duration (ADD), the afterdischarge threshold (ADT) and the afterdischarge latency (ADL) were compared before, during and after HFS.

Results: HFS significantly reduced the ADD when comparing before HFS with during HFS ($p < 0.001$) and after HFS ($p < 0.05$). Also the ADL was significantly increased in the HFS-treated group comparing before HFS with during HFS ($p < 0.001$) and after HFS ($p < 0.001$). This was also found for the ADT. The control groups showed no significant difference in ADD, ADT and ADL.

Conclusion: Long-term high frequency stimulation of the hippocampus in epileptic rats shortens the afterdischarge duration and increases the afterdischarge threshold.

p808

NEURONAVIGATION ASSISTED SUBDURAL STRIP ELECTRODE POSITIONING: A SIMPLE METHOD TO INCREASE THE ACCURACY OF STRIP LOCALISATION IN EPILESY SURGERY

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Purpose: When localising the epileptogenic zone in cases of clinical focal epilepsies, imaging and different electrophysiological methods are in use. In some cases intracranial electrodes are used. The proper positioning of subdural electrodes is always challenging for the neurosurgeon. CT and MR techniques are the gold standard by which to localise the real postoperative position of the electrode contacts over the gyri. However, the exact localisation of the electrodes on the patient's brain remains uncertain for the surgeon during insertion. Intraoperative visualisation of the electrodes during positioning through a burr hole with the combination of navigation systems and fluoroscopy was not found in the literature.

We introduce the real time parallel use of intraoperative neuronavigation and x-ray for colocalising subdural strips and the cortical gyri during an operation to increase the accuracy of subdural strip electrode placement.

Method: For describing the proper electroclinical seizure pattern and localising the epileptogenic zone of patients with drug resistant epilepsy, subdural strip electrodes were implanted before long-term video EEG monitoring. We demonstrate our method with 3 cases of focal drug resistant epilepsies.

Brain Lab Vector Vision neuronavigation system was used in the operating room (OR) to select our entry point and visualise our region of interest and target point on the cortical surface. The radiopaque navigation

probe was placed on the skin, over the target point under the control of C-arm (Siemens, Siremobil 2000). The stainless steel, radiopaque strips (DIXI Medical) were introduced through the burr hole to the target point. The intracranial target point was visualised on the skin surface by the radiopaque navigation probe that was kept in place during strip insertion.

Results: We were able to visualise the target point, which was the region of interest on the convolutions of the patient's cortex with neuronavigation and localise the strips during insertion with the C-arm. With the help of the nonradiolucent neuronavigation probe the two modalities could be fused during the procedure. We controlled our accuracy intraoperatively with the navigation system and postoperative MR (1,5T GE) and less then 1 mm registration error was found.

Conclusion: Combining neuronavigation and intraoperative X-ray is a simple and feasible method to get precise intraoperative localisation of subdural strips used for long term video EEG monitoring of patients with drug resistant epilepsy.

p809

OUTCOMES OF SURGICAL TREATMENT OF SYMPTOMATIC EPILEPSY FOR CHILDREN WITH BRAIN TUMOURS

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Purpose: To determine the factors influencing results of surgical treatment of symptomatic epilepsy for children with brain tumours.

Method: The results of surgical treatment of 58 children with symptomatic epilepsy caused by intracerebral tumours were analysed. The age of children was from 3–16 years. Duration of a symptomatic epilepsy before operation was from 1–14 years. A postoperative catamnesis was from 1–5 years.

Results: 43 (74.1%) patients became seizure free after operation (Engel I), 6 (10.3%) patients had no more than two seizures per year (Engel II), and for 9 (15.5%) patients the frequency of seizures decreased (Engel III).

Conclusion: The best results of surgical treatment were for patients with a smaller interval from the beginning of seizures to operations. The best results were for patients with tumours of medial parts of a temporal area when in volume of a resection the amygdalohippocampal complex was included. The treatment of symptomatic epilepsy was more effective in patients with tumours in a temporal area when focal epileptic activity was recorded in ipsilateral frontal and parietal areas. Conservation of a zone of epilepsy activity after the resection of tumours is a principal cause of decrease of efficiency of treatment of seizures. Use in such cases of corticography can specify the centre of irritation and raise the efficiency of surgical treatment of symptomatic epilepsy.

p810

ANTIEPILEPTIC DRUG TREATMENT IN LONG-TERM FOLLOW-UP AFTER EPILEPSY SURGERY IN PATIENTS WITH OCCIPITAL LOBE EPILEPSY

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Purpose: To evaluate the long-term antiepileptic drug (AED) regime with regard to medication reduction/discontinuation trials after epilepsy surgery in patients with occipital lobe epilepsy (OLE).

Method: Out of the total Bonn surgical sample (1988–2002), we were able to identify 37 patients with surgery for therapy refractory OLE and obtained postsurgical follow-up data for 36 patients (18 women). Additionally, patients were surveyed via a standardised telephone interview which addressed medication reduction/discontinuation trials.

Results: Overall postoperative outcome according to Engel classification I A and B is 58%. The average number of AED in postoperative treatment was reduced for all patients. Two initially seizure-free patients lost seizure freedom in the first two postoperative years following moderate dosage reduction. One of these patients could be reevaluated and reoperated. One patient had one isolated generalised tonic–clonic seizure four years after operation due to alcohol, sleep deprivation and noncompliance. After reestablishing continuous medication he was seizure-free for another 5 years. All 8 patients who reduced medication stayed completely seizure free for an average follow-up duration of 8.5 years. Two initially nonseizure-free patients became seizure-free in the first two postoperative years (five/eight years follow up) after changing medication.

Conclusion: If medication could be partially withdrawn without seizure recurrence complete withdrawal of AED did not change long-term surgical outcome. In postoperative non seizure-free patients, changing AED treatment can ultimately lead to long-term seizure freedom.

p811

INTRACRANIAL VIDEO-EEG MONITORING AT GHENT UNIVERSITY HOSPITAL

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Purpose: To evaluate the outcome of patients with refractory epilepsy who underwent invasive video-EEG monitoring at Ghent University Hospital.

Method: We retrospectively analysed seizure frequency, treatment with antiepileptic drug (AED) treatment and other types of subsequent intervention in patients who underwent invasive video-EEG monitoring with subdural grids and strips and/or depth electrodes.

Results: Between October 1990 and January 2006, 800 patients were admitted at the video-EEG monitoring unit for presurgical evaluation. From January 1992 until January 2006, 66 of these patients were selected for invasive recording due to incongruent findings during non-invasive presurgical evaluation. 12/66 patients were lost in follow-up. Mean follow-up of 54/66 patients was 51 months (range 3–141). 26/54 patients underwent resective surgery (RS) of whom 21 (81%) became seizure-free; in 3/26 patients AEDs were completely stopped. 12/54 patients underwent deep brain stimulation of whom 1 became seizure-free and in 6/12 AEDs could be tapered, but not stopped. The remaining 16/54 patients received ongoing AED treatment (6/16), multiple subpial transections (MST) (2/16), combination of MST and RS (1/16) or vagus nerve stimulation (VNS) (7/16, of which 2 are being scheduled). In those 16 patients, seizure-freedom was obtained in 1 patient with AEDs, in 1 patient with MST and in 1 patient with VNS. Tapering of the AEDs in those patients was not possible.

Conclusion: In the group of 66 patients who underwent invasive video-EEG monitoring, different treatment options were possible depending on the results of the monitoring. Seizure-freedom and the tapering of AEDs were most likely in patients who underwent RS.

p812

VALUE OF FDG-PET IN SCREENING FOR TEMPORAL LOBE EPILEPSY SURGERY

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Purpose: The decision-making process for temporal lobe epilepsy (TLE) surgery includes a number of diagnostic tests, starting with patient history, MRI, and video-EEG monitoring. When the decision for TLE surgery cannot be reached with these tests, ancillary tests are performed, usually PET and intracranial EEG monitoring. We studied the value of FDG-PET and the implications on intracranial EEG monitoring.

Method: This nationwide, retrospective diagnostic study included all consecutive patients referred for screening for TLE surgery. The impact of FDG-PET results on the decision-making process for TLE surgery was assessed. Furthermore, we assessed the influence of the FDG-PET on the need to perform intracranial EEG monitoring.

Results: of 803 included patients, 186 (23%) had indecisive results after MRI and video-EEG monitoring and underwent a FDG-PET. In 111 patients (60%), a decision could be reached after the FDG-PET:

68% were eligible and 32% ineligible for TLE surgery. The 75 patients for whom FDG-PET also showed indecisive results consecutively underwent intracranial EEG monitoring. After intracranial monitoring, 71% were considered eligible and 29% ineligible for TLE surgery. The outcome after surgery of our study population was comparable to that reported in the literature: 58% Engel Score 1A one year after surgery.

Conclusion: FDG-PET can set the decision for TLE surgery in the majority of patients with indecisive results after MRI and video-EEG monitoring. Performing a FDG-PET in these patients can avoid intracranial EEG monitoring, which is an invasive and burdening test.

p813

ELECTROCORTICOGRAPHIC-HISTOPATHOLOGIC CORRELATIONS IN TEMPORAL LOBE EPILEPSY DUE TO CORTICAL MALFORMATIONS, HIPPOCAMPAL SCLEROSIS AND DUAL PATHOLOGY

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Purpose: To correlate intraoperative electrocorticographic (ECoG) recordings with histopathologic findings in patients with temporal focal cortical dysplasia (CD), hippocampal sclerosis (HS) and dual pathology (DP).

Method: Twenty-nine (16 F, 13 M) patients with drug-resistant temporal lobe epilepsy due to pathologically confirmed CD (5), HS (13) and DP (11) who underwent intraoperative ECoG recordings with electrodes placed over the anterolateral surface of the temporal lobe, were included. The analysis of spike activity of the most active fragments ECoG 10 to 15 minutes recording was performed and compared in three histopathologically different groups. In all patients a tailored anterior temporal lobe resection was performed.

Results: All 13 patients with SH, had ECoG recordings with frequent burst of spikes with periods of voltage depression. In all patients spikes and polyspikes were generalised over almost all temporal electrodes. Most patients with DP (7 of 11) showed ECoG recordings with generalised bursts of spikes with periods of depression. On the other hand 4 of 11 patients had focal rhythmic discharges of spikes and sharp waves. In 5 patients with pure focal cortical dysplasia, 3 recordings showed bursts of generalised spikes or polyspikes with periods of depression. Only 2 had focal temporal rhythmic or semirhytmic discharges of spikes and sharp waves.

Conclusion: Hippocampal sclerosis correlated with ECoG generalised bursts of spikes with periods of voltage depression. Dual pathology and focal cortical dysplasia also correlated with similar activity; however, a small group of cases with the focal rhythmic discharges without generalisation was disclosed.

p814

EARLY LESIONECTOMY IN A CASE OF OHTAHARA SYNDROME WITH A LEFT TEMPOROPARIETAL CORTICAL DYSPLASIA (POLYMICROGYRIA)

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Purpose: Epileptic seizures are rare in the neonatal and early infantile period. Two epileptic encephalopathies characterised by frequent seizures have been described in this period of life: early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy with suppression-bursts (EIEE), or Ohtahara syndrome (OS). There is no effective pharmaceutical treatment for either of them.

Method: We report a surgically treated case of Ohtahara syndrome associated with polymicrogyria.

Results: Clusters of brief, repetitive tonic spasms of the upper limbs, with clonic jerks of the eyelids, head-eye deviation to the left and munching movements, first occurred at the age of 40 days. Interictal electroencephalogram repeatedly demonstrated a suppression-burst pattern throughout awake and sleep states. Magnetic Resonance Imaging revealed focal cortical dysplasia (polymicrogyria) in the left temporoparietal lobe. Medical treatment with combinations of anticonvulsive drugs and steroid therapy was only mildly effective. The patient underwent lesionectomy at the age of 5 months. Five months postoperatively, during follow up, the infant showed a decrease of seizures to only one brief cluster of eyelid jerks every 8–9 days, mild hypertonia of the right upper limb and a graduate psychomotor development.

Conclusion: This report provides further evidence that early surgical intervention can be safe and promising in selected cases of Ohtahara syndrome with focal cortical dysplasia. We present our acknowledgements to Dr Alexis Arzimanoglou (Robert-Debre Hospital-Paris) for presenting this case to the French paediatric epilepsy surgery multidisciplinary network and the surgeon Pr Christian Sainte-Rose (Necker Hospital Enfants Malades-Paris) for realising the surgical treatment.

p815

"EPILEPSY SURGERY CENTRE" OF ATHENS UNIVERSITY: RESULTS OF SURGICAL MANAGEMENT

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Purpose: Surgical therapy for epilepsy is nowadays an established therapy for drug resistant partial epilepsy. We present the protocol of the presurgical evaluation and the results of surgical treatment of epilepsy in our Epilepsy Surgical Centre.

Method: Presurgical evaluation protocol and surgical procedures.

Results: Outcomes for 35 patients, aged 12–47 years old, 19 men and 16 women, who underwent surgical treatment for their refractory epilepsy, are presented.

Conclusion: About 80% of patients with drug-resistant epilepsy of the mesial temporal lobe are seizure-free after surgical treatment. The percentage of patients with other types of drug-resistant epilepsy who were treated surgically and remain seizure-free is 55%.

p816

RESULTS OF SURGERY IN DRUG-RESISTANT, SLEEP-RELATED FRONTAL LOBE EPILEPSY

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Purpose: To retrospectively evaluate the anatomo-electroclinical features, histological substrate and outcome on seizures of 21 surgically treated patients with drug-resistant, sleep-related frontal lobe epilepsy (4% out of 522 operated on cases).

Method: There were 11 males and 10 females; mean age at seizure onset was 6.2 years and mean age at surgery was 23.8 years. Seizure frequency was high in most cases. Magnetic resonance imaging (MRI) disclosed a focal anatomical lesion in one frontal lobe in 11 cases and it was unrevealing in 10. Scalp video-EEG monitoring was performed in all cases. Three patients were operated on after non-invasive investigations. In the remaining 18 patients a stereo-EEG investigation was performed for a better definition of the epileptogenic zone. In all cases the presurgical investigations indicated a frontal lobe origin of seizures. Surgery consisted of cortical resection in 10 patients, in a lesionectomy with cortical resection in 9 and in a lesionectomy in 2. Two patients were operated on twice for poor results on seizures of first surgery.

Results: Histology revealed a Taylor's focal cortical dysplasia (FCD) in 16 patients, an architectural FCD in 4 and was negative in 1 case.

Outcome on seizures (mean follow-up 42.5 months) according to Engel was: 16 patients (76%) in class Ia, 3 in class II, 2 in class III. All the patients in class Ia had a Taylor FCD.

Conclusion: Surgery in frontal lobe sleep-related epilepsy provides better results on seizures than in frontal lobe epilepsy in general. Taylor's FCD may represent a histological substrate which supports the occurrence of seizures during sleep.

p817

HUMANISTIC IMPACT SEVERITY AS A DETERMINANT OF HIGHER COSTS IN PATIENTS WITH REFRACTORY EPILEPSY: A SPANISH PERSPECTIVE

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Purpose: To explore the association between humanistic impact (quality of life, depression, anxiety and health status) and costs in adult patients with refractory epilepsy in Spain.

Method: Secondary analysis of a cross-sectional study carried out to determine humanistic impact and cost of refractory epilepsy. Consecutive male and female adult patients (over 18 years) fulfilling criteria for refractory epilepsy were analysed. Health-related quality of life (HRQoL), anxiety and depression were assessed by QoLIE-10 and HAD scales, and health status by a 0–100 mm visual analogue scale. Costs were estimated from health care and non health care resources used.

Results: A total of 762 consecutive patients [728 valuables, (95.5%); 50.8% males, 40.5 (13.5) years, 24.3 (13.4) years of evolution] were analysed. Total yearly costs were associated with poorer HRQoL scoring according to patients segmentation in QOLIE-10 deciles; from a mean yearly total cost of €11,494 (€11,668) to €809 (€2,904), first and ten deciles respectively, $p < 0.001$. Severe levels of anxiety and depression were both associated with higher costs. Anxiety (from normal to severe): €6,192 (€7,546) and €9,959 (€9,950), respectively, $p < 0.01$. Depression (from normal to severe): €5,968 (€6,704) and €12,691 (€11,746), respectively, $p < 0.001$. Subjects with health status below 50 showed higher costs [€9,828 (€10,709)] than those above 50 [€5,897 (€6,749)], $p < 0.001$.

Conclusion: Costs of refractory epilepsy were associated with higher negative humanistic disease impact: the higher the negative impact the higher the costs. Health decision makers and clinicians should be aware when making health decision. This study has been financed by Pfizer Spain.

p818

INTRACAROTID PROPOFOL TEST FOR SPEECH AND MEMORY DOMINANCE IN PRESURGERY EPILEPSY STUDY

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Purpose: Since 2000 amobarbital has not been available in Spain and scarcely in other countries. To evaluate the usefulness of propofol as an alternative drug to amobarbital for the Wada test, we analysed 11 cases with refractory epilepsy who were candidates for neurosurgical therapy and thus underwent the Wada test as a preoperative evaluation.

Method: The authors analysed the recovery time of muscle power to manual muscle testing (MMT) Grade 3 (T3/5) and Grade 5 (T5/5), onset time of the first verbal response and nonverbal response. These times were similar to amobarbital results in the bibliography. Analysis of EEG background activity during the Wada test was performed. The median dosage was 10 mg for 5 seconds.

Results: T0/5 was presented to 3–17 seconds. T5/5 was presented in 2–6.20 minutes. Lateralities of language were identified in all patients and memory lateralities in 7 of 11 patients. A case presented transitory ipsilateral eye pain; no other complications with direct intracarotid injection were observed.

Conclusion: With direct intracarotid propofol injection, the Wada test was satisfactorily performed in all 11 patients without any complications. The times of first response and the recovery were similar to the times described with amobarbital.

p819

AN EPILEPSY CENTRE'S ROLE IN EPILEPSY SURGERY IN CHILDREN OF LOW IQ

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Purpose: The Children's Assessment Service provides new solutions to old and intractable problems. Surgical treatment is not always considered for children with complex epilepsy including learning difficulties. This study, a natural development of clinical audit, describes the opportunities for and the effects of, epilepsy surgery among children referred to us.

Method: 287 children had a period of residential assessment. We got to know them and their parents well. We had a part in assessing 7 patients for surgery (group 1; 3 had hemispherectomy, 3 temporal lobectomy and 1 had a frontal lobe lesion resected) and played a part in the rehabilitation of 7 patients (group 2) operated elsewhere (4 resections, and 3 procedures likely to provide only moderate improvement). We contacted the parents of as many of the children from both groups as we could, seeking information about current seizures, drug treatment, behaviour, living situation and their views about the surgery. The longest follow-up study was 12 years.

Results: Six of 7 children in group 1 had good results by internationally agreed standards. 5 of 7 were seizure free. 1 was living independently. All parents who replied were grateful their child had surgery. One child in group 2 had deteriorated cognitively and behaviourally and continued to have seizures. The effect of surgery on 6 out of 7 in group 2 was neutral.

Conclusion: Children with learning disability can benefit from epilepsy surgery programmes.

p820

EARLY RESULTS OF MEDICALLY RESISTANT FOCAL EPILEPSY SURGERY WITH NEURONAVIGATION ASSISTANCE

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Purpose: Our aim was to evaluate the use of neuronavigation (NN) in focal epilepsy surgery and early clinical outcome.

Method: The study period was from 2000 until 2005. NN by Zeiss SMN system, Medtronic Stealth Station Treon. In all cases lesionectomy was performed. Patients who were totally operated numbered 41 (male: female 23:18). Age range was 4–68 (mean 35). Epilepsy anamnesis: 29 (70.8%) 1–3 months; 7 (17%) 2 years; 2 (4.9%) 10–15 years; 3 (7.3%) more than 15 years; mean 16 months. Preoperative EEG: 29 (70.3%) epileptic focus found; 9 (22%) abnormal, no focus; 3 (7.7%) normal, close to normal. Antiepileptic medication was administered preoperatively to 25 (61%) patients. Operated lesions: 29 (70%) cerebral tumour; 4 (9.8%) arteriovenous malformation; 4 (9.8%) gliosis; 4 (10.4%) other. Size of lesion from 0.8 to 7.5 cm. Lesion topography (lobes): 15 (36.5%) frontal; 16 (39%) temporal; 8 (19.5%) parietal; 2 (5%) occipital. In 5 cases more than 1 lesion was operated simultaneously. The size of lesions were from 0.8 to 7.5 cm (mean 4.3 cm).

Results: Postoperative follow-up period was 3 months. EEG control 8–10 weeks after operation. Clinically: 35 (85%) no epileptic seizures; 6 (15%) less frequent. EEG results: 11 (26.8%) epileptic focus seen; 23 (56%) abnormal, no focus; 7 (17.2%) normal, close to normal. Patients on antiepileptic medication: 13 (31.7%).

Conclusion: Neuronavigation is useful in focal minimally invasive epilepsy surgery and in extirpation of more than one cerebral lesion simultaneously. So far we have achieved good results, but must still continue long-term evaluation.

p821
THE LONG-TERM OUTCOME OF EPILEPSY SURGERY: HOW MANY PATIENTS DISCONTINUE ANTIEPILEPTIC MEDICATION?
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Purpose: Epilepsy can be regarded as cured by surgery if the individual remains seizure-free having discontinued antiepileptic drugs (AEDs). We determined how common this optimal outcome is over long-term follow-up, and identified factors associated with successful discontinuation of AEDs.

Method: 473 patients who had epilepsy surgery at the National Hospital for Neurology and Neurosurgery in 1990–2003 were followed for 2–15 years, analysed in 5 year cohorts. Seizure outcome was classified according to the 6-point ILAE Epilepsy Surgery Commission scale, at the latest follow-up available and it was noted whether they remained on AEDs. Data are so far based on a cohort of 144 patients for whom there are complete follow-up data.

Results: 69% were seizure-free (Group 1) and 31% continued to have seizures, including auras (groups 2–6). The former comprised 19% off AEDs and 50% on AEDs. Gender did not influence the rate of seizure freedom. However, 14% of seizure-free men were off AEDs and 55% on AEDs; whilst 23% of women were off AEDs and 46% on AEDs. The seizure freedom rate was lower in the 1990–1994 cohorts (55%), possibly reflecting improving methodology with time, and that longer follow-up increases the risk of relapse.

Conclusion: The greater proportion of seizure-free women who discontinued AEDs probably reflects concerns about teratogenesis and the higher percentage of men who continue on AEDs may be due to concerns about driving. With current criteria, only 19% could be said to be cured of epilepsy by surgery; a further 50% are seizure free but continue on AEDs.

p822
USE OF A DECISION SUPPORT SYSTEM (DESSA) FOR THE SURGICAL TREATMENT OF EPILEPSY
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Purpose: The validation of a newly developed decision support tool for the early identification of candidates for surgical treatment in epilepsy.

Method: The DESSA tool is the result of a close collaboration between engineers, medical doctors, and market analysts. Its architecture provides the user with an integrated electronic working domain handling diverse types of information and medical records. DESSA enables the doctor-user to make a decision based on the identification of critical interaction factors amongst predefined data categories through a correlations model on the integrated clinical picture of the patient in real time. The term integrated clinical picture refers to the ability of the system to record, describe, and classify in time the epileptic events on the basis of their type, frequency of occurrence, duration of symptoms, and correlation with respective pharmacological treatment and period of its application as well as respective specialised EEG and vEEG pictures. For the validation of the new tool 24 drug-resistant epilepsy patients were entered in the database and their presurgical assessment has been analysed.

Results: At this first stage of implementation, the DESSA tool seems to provide a holistic view on the patient's assessment and enables the easier identification of candidate patients for surgical treatment.

Conclusion: The current phase of development of the tool is a good platform for the development of markers regarding the cross-reactivity of treatments as well as at a later stage postsurgical scenarios.

p823
SURGICAL MANAGEMENT OF PATIENTS WITH PAEDIATRIC ONSET EPILEPSIES IN SLOVENIA
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Purpose: Slovenia's population is too small for an epilepsy surgery programme. Following noninvasive presurgical assessment, patients are referred abroad for further evaluation and surgery. To assess outcome, data for patients referred from the Center for Epilepsy (Child and Adolescent) to foreign surgery centers were evaluated.

Method: Retrospective data analysis of 40 referrals from 1985 to 2005.

Results: Epilepsy surgery was performed on 22 patients (55% of referrals), 15 were declined (37.5%), while 3 were waiting phase II assessment. Positive trends in the number of referrals and in shortening the duration of epilepsy before surgery (from 16.5 to 7.5 years) were observed. The majority had procedures in frontal lobes (13/22), followed by temporal (5/22) or parietal lobe surgery (1/22), while 3 had callosotomy. Seizure outcome in 12 of 19 patients was Engel I in the first year and 8/19 after follow-up (mean 4.5 years; 3 missing). One of 2 patients starting as Engel III switched to Engel IV. Perioperative complications were transient (7 of 18; 4 missing). The use of AEDs and quality of life parameters were followed after surgery.

Conclusion: Referrals for epilepsy surgery abroad offers benefits related to type of pathology and age of the patient but also carries logistic problems in planning strategies and communication. The high proportion of patients declined reflects specific pathology of severe paediatric epilepsy. Further shortening the duration of epilepsy before surgery by earlier referrals is a desired and possible goal. Specific and tailored rehabilitation after surgery may reduce problems with social integration.

p824
CHARACTERISTICS AND OUTCOME OF OCCIPITAL LOBE EPILEPSY SURGERY GUIDED BY MONITORING WITH SUBDURAL ELECTRODES
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Purpose: Occipital lobe epilepsy is uncommon in epilepsy surgery series and difficult to assess due to rapid propagation and misleading seizure semiology. Ictal recordings with surface electrodes may not properly define the seizure onset zone, and intracranial recordings are often indicated. In this study we present our experience with individually tailored resections of occipital lobe epileptic foci guided by monitoring with subdural electrodes.

Method: Clinical characteristics, interictal/ictal surface and intracranial recordings, neuroimaging, type of resection, pathology and outcome of 7 patients are presented.

Results: The most common seizure was complex partial with temporal lobe semiology; 5 patients reported visual auras. Two patients had semiology of the supplementary motor area seizures and 1 patient had temporal and frontal seizure propagation. Neuroimaging showed lesions in 6/7 patients. Pathological studies revealed cortical dysplasia and tumours as most common causes. Intracranial recordings (6/7 patients) revealed focal onset in 2 patients, regional onset in 2, and diffuse onset in 2. Resections were performed according to intracranial recordings restricting resections in cases with focal seizure onset (even in large dysplastic lesions) and performing wider resections in patients with regional or diffuse onset. Five of 7 patients are seizure free after 12–55 months (mean 24.3). The 2 remaining patients may be classified as Engel 2b and 3a.

Conclusion: This series of occipital lobe epilepsy surgery shows that even in patients with cortical dysplasias restricted resections may have a good outcome and that intracranial monitoring is usually necessary in order to design an individually tailored resection.

p825

PRIMARY TEMPORAL LOBE TUMOURS PRESENTED WITH SEIZURES

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Purpose: Seizures are observed in 20–45% of primary brain tumour patients (PBT) depending on tumour type and location. Temporal lobe tumours (TLT) are common in patients with temporal lobe epilepsy requiring surgery. The aim of this study was to analyse the association between primary TLT and seizures in terms of localisation, age at onset, type and outcome after surgery.

Method: Clinical, pathological features, MRI and EEG results and outcome data of 89 patients with PBT were analysed; 43 patients (21 women/22men, age range: 2–46 years) with TLT who presented with seizures and underwent surgerybetween 1992 and 2005 were studied separately.

Results: Mean age at seizure onset 14.0 $\pm$ 9.1 years, mean interval between seizure onset and surgery 7.9 $\pm$ 8.3 years. Tumours were localised on the right in half of the patients. Mesial in 22 (52.4%), lateral 15 (35.7%), mesiolateral 6. The histological investigation revealed ganglioglioma in 18, dysembryoplastic neuroepithelial tumour (DNET) 12, oligodendroglioma 5, others in 8 patients. Gangliogliomas were significantly more common under the age of 18 ($p < .05$). Mean follow-up was 4.4 $\pm$ 3.2 years. EEG showed focal epileptiform activity or slow waves in the majority of patients. Seizure-freedom was achieved in 52.4% of all patients and 64.3% of patients had no postoperative residual tumour ($p < .05$). Postoperatively, 56.3% of DNET and 45.5% of ganglioglioma patients were seizure free. No significant statistical association was found among localisation, EEG, onset, pathology and outcome of the tumours.

Conclusion: This study indicates that the majority of primary TLT presented with seizures are low grade glioneuronal tumours and long-term good seizure control may be influenced by the presence of postoperative residual tumour.

p826

ANTIEPILEPTIC DRUG REGIMEN STATUS BEFORE AND AFTER CORTICOAMYGADALO HIPPOCAMPECTOMY IN PATIENTS WITH UNILATERAL MESIAL TEMPORAL SCLEROSIS

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Purpose: The surgical outcome after temporal lobe resections regarding seizure frequency has been extensively reported over the last decades. On the other hand, the status of the antiepileptic drug (AED) regimen of these patients has been poorly studied, especially over long follow-up periods. We describe the status of the AED regimen in a series of patients with mesial temporal sclerosis submitted to corticoamygdalohippocampectomy.

Method: Forty-one patients with refractory unilateral temporal lobe epilepsy were studied. Mean postoperative follow-up time was 4.3 $\pm$ 1.1 years. MRI disclosed unilateral mesial temporal sclerosis (MTS) in all patients. All patients had interictal EEG recordings. All patients were submitted to corticoamygdalohippocampectomy at the side determined by MRI. The AED regimen status was recorded before and at the last follow-up visit.

Results: Thirty-nine patients (95, 1%) were classified as Engel's Class I (70.6% Engel I-A) and two (4.9%) as Engel's Class II, postoperatively. Eleven patients (26.8%) were not taking any AED. Mean pre- and postoperative doses (mg) for the different AED were as follows: carbamazepine = 1059/608; phenobarbital = 113.6/96.4; phenytoin = 280/200; oxcarbazepine = 900/0; valproic acid = 733.3/1000; clonazepam = 2/4; lamotrigine = 125/0; clobazam = 20/20; topiramate = 150/0 and gabapentin 1200/0.

Conclusion: One quarter of the patients were taking no AED at late follow-up. The majority of the others were taking much lower dosages of AED. Valproic acid was the only AED more extensively used postoperatively in this series; it is currently used in the treatment of postoperative hypomania seen in some of these patients.

p827

SPIKES ON POSTOPERATIVE SCALP EEG DO NOT CORRELATE WITH SEIZURE OUTCOME AFTER SELECTIVE AMYGDALOHIPPOCAMPECTOMY

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Purpose: Patients with mesial temporal lobe epilepsy-hippocampal sclerosis (MTLE-HS) have a favourable prognosis after surgery. However, up to 20–30% still may not benefit form standardised surgical approaches. A tailored surgery resecting residual spikes is expected to have an impact on outcome. After standard surgery, residual spikes on scalp EEG may be a predictor for the outcome. The aim was to understand the role of postoperative scalp EEG to make future projections about seizure outcome in patients with MTLE-HS.

Method: Forty-five patients who underwent selective amygdalohippocampectomy were enrolled in the study. EEG recordings of 30 minutes in duration with double longitudinal montage were performed in three consecutive stages: early stage (1–3 months), median stage (6-9 months), and late stage (12–18 months). The frequency of spike activities but not their spatial distribution were taken into consideration and they were classified as more than 5 in one minute (I), 1–5 per minute (II), less than 1 per minute (III), random (IV) and none (V). Seizure outcome was classified according to Engel's seizure outcome classification.

Results: One hundred and one EEG recordings of 45 patients were evaluated. Mean age was 28.6 years (12–52). The mean follow up period after the surgery was 49.29 (12–120) months. Spike activities on early EEG recordings were compared to the following EEG's and revealed no change in spike frequencies in time, or statistically. Spike activities on three consecutive postoperative scalp EEG recordings were not statistically significant with final seizure outcomes ($p = 0.6, 0.4, 0.9$, respectively).

Conclusion: Routine scalp EEG is not a good predictor for seizure outcome in patients with MTLE-HS after surgery.

p828

FEBRILE SEIZURES ARE NOT A RELEVANT PREDISPOSING OR PROGNOSTIC FACTOR IN A HOMOGENEOUS SERIES OF PATIENTS WITH UNILATERAL MESIAL TEMPORAL SCLEROSIS SUBMITTED TO CORTICOAMYGDALOHIPPOCAMPECTOMY

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Purpose: The occurrence of febrile seizures in patients who would later develop refractory temporal lobe epilepsy has often been noted. Although the causal relationship of these events to the development of refractory epilepsy has been extensively discussed, no consensus has been reached. We studied the prevalence of febrile seizures and its relation to the surgical outcome in a homogeneous series of patients with unilateral mesial temporal sclerosis submitted to surgery.

Method: Forty-one patients with refractory unilateral temporal lobe epilepsy were studied. The presence or not of early febrile seizures was documented in all of them. MRI disclosed unilateral mesial temporal sclerosis (MTS) in all patients. All patients were submitted to corticoamygdalo-hippocampectomy at the side determined by MRI.

Results: Febrile seizures occurred in 10 patients (24.39%). Nonfebrile seizures started 7.61 $\pm$ 9.25 years afterwards in these patients. There was no statistically significant relationship between the presence of febrile seizures and the age of onset of nonfebrile seizures. Additionally, there was no statistical difference regarding neurophysiologic or surgical outcome findings in patients with or without febrile seizures. Overall, interictal EEG showed unilateral epileptiform discharges compatible

with MRI findings in 37 patients; in 4 out of the 41 patients, bilateral discharges were found. Mean follow-up time was 4.3 ± 1.1 years. Thirty-nine patients (95.1%) were classified as Engel's Class I (70.6% Engel I-A). Two patients (4.9%) were rated as Engel's Class II. All patients in whom bilateral discharges were found were in Engel's Class I. Pathological examination showed mesial temporal sclerosis in all patients.

Conclusion: Although frequently recognised during the initial clinical work-up of patients with refractory temporal lobe epilepsy, the presence of febrile seizures does not seem to be an important predisposing or prognostic issue in patients with mesial temporal sclerosis.

p829

CASE REPORT OF A PATIENT WITH REFRACTORY EPILEPSY DUE TO EXTENSIVE MULTIFOCI EPILEPTOGENIC ZONE TREATED WITH COMBINED SURGICAL PROCEDURE

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Purpose: We report the case of a patient with symptomatic refractory epilepsy due to a wide epileptogenic zone, who was successfully treated by a surgical approach.

Method: A 15-year-old boy suffered from complex partial seizures with frequent secondary generalisation for the last 9 years. Despite the antiepileptic regimen, seizures were not controlled. Brain MRI revealed a lesion in the right temporal lobe, with poorly defined margin. The presurgical evaluation demonstrated the lateralisation of the epileptogenic zone, but not the exact localisation. Invasive recording was needed. An epidural grid and depth electrodes were put on the right frontal-temporal-occipital region, followed by a prolonged video-ECG monitoring in order to find the epileptogenic zone.

Results: The electrocorticography revealed a multifocal wide epileptogenic zone from the right occipital lobe to mesial temporal lobe. A right amygdalohippocampectomy with a tailored removal of the tumour and the surrounding tissue, and multiple subpial transections modified by Morrell in the temporal-occipital region were performed. The patient has experienced no seizures since then (already 16 months).

Conclusion: Combined video-ECG tailored surgical procedures could be a significant and irreplaceable method for surgical treatment of epilepsies with wide epileptogenic zone.

Sunday July 2, 2006

Sunday July 2, 2006
7:30 – 9:00
Hall 5A
Teaching Session
Neurocognitive functioning in children with epilepsy

NEUROLOGICAL AND DEVELOPMENTAL OUTCOME OF CHILDREN WITH EPILEPSY; EPIDEMIOLOGICAL PERSPECTIVE

M. Kerr (Cardiff University, Wales, UK)

Epilepsy is common in childhood with annual incidence rates range between 50–80 per 100,000 children and prevalence ranges around 0.5%. The outcomes of these epilpesies are varied. Adult population studies identify people with epilepsy as having decreased life expectancy, poor quality of life, increased levels of mental illness, decreased educational achievement, social isolation and a high prevalence of intellectual impairment. The question for pediatric care is of course how these apparent epilepsy related outcome can be predicted and whether they can be modulated.

This presentation will explore the epidemiology of epilepsy in childhood in terms of prevalence, incidence, seizure type and syndrome and associated comorbidity.

Epilepsy parameters include the likelihood of remission off drug and seizure related mortality.

Other outcomes include the potential associations with developmental disabilities and educational achievement these will be explored and where available information on prediction of outcome presented.

Workshop attendees will be expected to attain an understanding of the neurodevelopment outcomes of epilepsy from an epidemiological perspective.

COGNITIVE FUNCTIONING IN CHILDREN WITH SYMPTOMATIC EPILEPSY

A. Kolk (University of Tartu, Department of Paediatrics, Estonia)

Seizure disorders in childhood may adversely influence the maturation and maintenance of normal brain function. Intense seizure activity in early life can be functionally as damaging as status epilepticus in mature tissue.

We investigated the children with symtomatic epilepsies what are the heterogenous group of epilepsies with some common characteristics, including uncertain prognoses, frequent resistance to antiepileptic treatment, localized origin of seizures and frequent associations with neurological/mental abnormalities. These children need neuropsychological examination to predict the prospective cognitive development and educational need in each individual case.

We present resent data in the field of cognitive development, including profiles of mildly retarded children, also gender differences, and findings of humour development in epileptic children.

1. Visual-perceptual and visuo-constructive development testing (TVPS-R and Rey tests) in 36 children with symptomatic epilepsy (18 boys and 18 girls) and 36 healthy controls revealed that the children with epilepsy were delayed about 12 months on visuospatial perception. Localized impairment in the parietal lobe or central parts had the most negative effect on the visuospatial abilities. Co morbidity with speech disorder was associated with main deficit in visual sequential memory. The boys outperform girls in visuospatial tasks.

2. A study of 12 hemiparetic children with epilepsy and 10 children with newly diagnosed epilepsy revealed a higher incidence of cognitive impairment in symptomatic epilepsy cases, especially in immediate memory and logical learning. Children with left hemisphere lesions were impaired not only in language and reading abilities, but also in attention. Boys were more affected. Children with temporal lobe epilepsy often demonstrate material specific memory deficits.

3. Examination of 10 boys and 10 girls with epilepsy and mild intellectual disability demonstrated low scores in attention, executive, language and sensorimotor functions. In case of duration of epilepsy >5 years dysfunctions were noted in all 6 cognitive domains without gender differences.

4. The study of humour understanding in 17 epileptic children (7 boys, 10 girls) showed that they appreciated clear and easily understandable jokes as funnier; and did not appreciate jokes with aggressive/scary tone.

COGNITIVE FUNCTIONING IN CHILDREN WITH NON-SYMPTOMATIC EPILEPSY

K. Eriksson (Pediatric Research Centre, Medical School, University of Tampere and Department of Pediatric Neurology, Tampere University Hospital, Finland)

Nonsymptomatic childhood epilepsies, i.e., idiopathic focal or generalized epilepsy syndromes and 'cryptogenic' epilepsies account for 70–80% of all childhood onset cases. The risk for impairment of cognitive functioning and neurological development are significant hazards for children with epilepsy. The prevalence of cognitive dysfunctioning (up to mental retardation) in children with epilepsy, as a group, is increased and specific neurocognitive difficulties have been described also in the children with 'epilepsy only' i.e., without any evident other neurological or cognitive problems. A significant proportion of neurologically otherwise normal children with epilepsy also need special educational services.

The cause for specific cognitive dysfunction in children with nonsymptomatic, uncomplicated epilepsy is related to unrecognized etiological factors (e.g., genetic traits), various epilepsy related factors (e.g., age at onset, ictal and interictal EEG abnormalities, type of epilepsy syndrome, seizure type/localization/frequency and antiepileptic drug treatment) as well as to many psychosocial and socioeconomic factors. Most cognitive problems have a multifactorial origin and these factors combined are responsible for the specific features of cognitive functioning in individual cases.

In children with benign and/or idiopathic focal (BCECTS, COE) or generalised (CAE, JME) epilepsies the most often reported specific neurocognitive dysfunctioning include problems in language, attention, memory, phonological processing, visuospatial skills and verbal fluency but the test results have not always been consistent. Some of these problems seem to exist already before seizures emerge and the direct causal link to epilepsy is not always evident.

It should be remembered that child's prediagnostic learning and behavioral histories and contextual variables (e.g., psychosocial, parenting habits) jointly with epilepsy related variables are important for understanding the cognitive and behavioral problems in children with epilepsy only. Parents' guidance and neuropsychological as well as educational multidisciplinary interventions to support neurological development of children with epilepsy should therefore be emphasized.

THE EFFECTS OF ANTIEPILEPTIC DRUGS ON COGNITIVE FUNCTIONING IN PEDIATRIC PATIENTS WITH EPILEPSY

A. Aldenkamp (Maastricht University Hospital, Department of Neurology, The Netherlands)

Although the causes of cognitive impairment in patients with epilepsy have not been completely elucidated, three factors are clearly involved: the underlying etiology of epilepsy, the effects of seizures themselves, and the central nervous system effects of antiepileptic drugs (AEDs). All commonly used AEDS have some effect on cognitive function and behaviour, and the effect may be substantial when crucial functions are involved, such as learning in children or driving ability in adults, or when already vulnerable functions are involved, such as memory in elderly patients. This will be illustrated using a metanalysis for all commonly used AEDs: valproate, carabamazepine, phenytoin and phenobarbitone.

The available evidence is insufficient to support definite conclusions about the cognitive effects of three of the newer AEDs, tiagabine,

gabapentin, and levetiracetam. Better evidence is available for lamotrigine, topiramate, and, to a lesser degree, oxcarbazepine. Oxcarbazepine appears not to affect cognitive function in healthy volunteers or adults with newly diagnosed epilepsy, but its cognitive effects in children and adolescents have not been systematically studied. A relatively large number of studies are available for lamotrigine, which has demonstrated a favorable cognitive profile overall, both in volunteers and in patients with epilepsy. Although dose and titration speed may be confounding factors in some of the studies of topiramate, there is clear evidence that this agent does affect cognitive function, with specific effects on attention and verbal function. For lamotrigine, attempts have been made to correlate cognitive effects with what is known of the drug's mechanism of action; this is an area of research that deserves further exploration with regard to other AEDs, especially topiramate, as well.

Sunday July 2, 2006
7:30 – 9:00
Hall 5B
Teaching Session
Epilepsy and genetics

A GENETICIST'S VIEW

O. Steinlein (Institute of Human Genetics, University of Munich, Germany)

The term epilepsy describes a heterogeneous group of disorders, with a lifetime cumulative incidence of 3%. In the majority of epilepsies genes are a minor if not even the only etiological factor. There is a large subgroup of epilepsies that are suspected or proofed to be mainly genetic in origin. This group of epilepsies has been named idiopathic, and during the last decade several genes have already been identified for various idiopathic epilepsies. On the other hand there is a large group of epilepsies and disorders with epilepsy that have been termed "symptomatic" because they are due to known metabolic, neurodegenerative or structural brain damage. Many of these disorders have by now shown to be caused by clearly defined genetic factors. Seizures and myoclonus are common to many neurodegenerative and metabolic disorders, but are also a major feature in patients with structural chromosomal arrangements or neuronal migration disorders. In this talk exemplary members of both groups will be discussed to illustrate principal etiological categories of the disorder "epilepsy" and trace the various genetic pathways to epileptogenesis.

A CLINICIAN'S VIEW

J. Serratosa (Fundación Jiménez Díaz, Unidad De Epilepsia, Servicio De Neurología, Madrid, Spain)

No abstract received.

GENETICS IN FOCAL EPILEPSIES

E. Brodtkorb (Department of Neurology and Clinical Neurophysiology, Trondheim University Hospital, Norway)

Clinical Genetics in Focal Epilepsies

Idiopathic focal epilepsies are considered to be exclusively caused by genetic factors, but only in a few a monogenetic origin has been proven.

Autosomal dominant frontal lobe epilepsy (ADNFLE) causes characteristic hyperkinetic nocturnal seizures in the form of episodes of complex motor activity during light sleep, ranging from subtle paroxysmal awakenings to violent jerks and posturing. Seizures are usually numerous and occur in clusters. They are assumed to represent disinhibition phenomena from subcortical structures. Mutations in genes coding for subunits of the nicotinic acetylcholine receptor have been identified. Penetrance is incomplete and the course may be variable. Some patients demonstrate pharmacoresistence. Curiously, nicotine consumption appears to modulate the symptomatology in a number of patients, and transdermal nicotine has been reported to be effective against seizures.

Autosomal dominant lateral temporal lobe epilepsy (ADLTE) has recently been found to be associated with mutations in the leucine-rich, glioma inactivated 1 (LGI1) gene, previously considered a candidate tumour suppression gene for glioma. It is not encoding an ion channel, but may regulate axonal guidance and cell migration. Acoustic auras are common, but a range of other ictal phenomena from the lateral temporal lobe have been reported, among them aphasia. Another peculiar feature is its reflex character. In a number of patients, seizures can be triggered by auditory stimuli. Clinical, EEG as well as evoked response studies predominantly indicate left-sided brain abnormalities and a role of the LGI1 gene in the functional development of the dominant hemisphere has been hypothesized.

The progress in the field of genetics now contributes enormously to the development of epileptology. The current discoveries suggest new neurobiological mechanisms for familial epilepsy, which may elucidate the pathophysiology of the epilepsies in general.

GENETICS AND PATHOPHYSIOLOGICAL CONCEPTS OF GENERALISED EPILEPSIES

H. Lerche (University of Ulm, Neurological Clinic and Department of Applied Physiology, Germany)

Idiopathic epilepsies are genetically determined syndromes not associated with structural brain lesions and featuring characteristic epileptic seizures and EEG abnormalities. In recent years, an increasing number of mutations cosegregating with the disease status in families with idiopathic epilepsies has been identified in genes encoding subunits of voltage- or ligand-gated ion channels which play a fundamental role in brain excitability. Namely axonal conduction of action potentials is mediated by voltage-gated channels and signal transduction from cell to cell (synaptic transmission) by ligand-gated channels. Thus from a pathophysiological point of view, it is plausible that mutation-induced channel dysfunction can induce neuronal hyperexcitability and epileptic seizures. The mutations can affect ion channels which on one hand have been known since several decades to be crucial for neuronal function, such as the voltage-gated sodium channel or the $GABA_A$ receptor, or on the other hand were newly identified within the last decade as KCNQ potassium channels or the ClC-2 chloride channel. Functional studies characterizing the molecular defects of the mutant channels point to an important role of GABAergic synaptic inhibition in the pathophysiology of IGE. Furthermore, newly discovered genes may be suitable as novel targets for pharmacotherapy such as KCNQ channels for the anticonvulsant drug retigabine. Altogether, these genetic and pathophysiological investigations will enhance our knowledge about the understanding of epileptogenesis and can help to improve anticonvulsive therapy.

Sunday July 2, 2006
7:30–9:00
Hall 5C
Teaching Session
Nonconvulsive status epilepticus – clinical definitions and biological framework

REVIEW OF BASIC MECHANISM IN STATUS EPILEPTICUS

J. Epsztein (INMED-INSERM U29, France)

Ongoing epileptiform activity without seizures in the postischemic hippocampus: a permanent shift of the excitatory-inhibitory synaptic balance in resistant pyramidal neurons

Ischemic stroke are often associated to late-onset epilepsy but the underlying mechanisms are poorly understood. In the hippocampus, that is one of the regions most sensitive to ischemic challenge, global ischemia induces a specific neuronal loss of CA1 pyramidal neurons while the resistant CA3 pyramidal neurons display a long-term hyperexcitability several months after the insult. The mechanisms of this long-term hyperexcitability remain unknown despite their clinical implications. The aim of the present report was to analyze the long-term morpho-functional consequences of global ischemia on glutamatergic and GABAergic systems in the CA3 area of the hippocampus that could account for the hyperexcitability of resistant CA3 pyramidal cells. Using chronic in vivo EEG recordings and in vitro field recordings in slices, we report spontaneous interictal epileptiform discharges (IEDs) in the CA3 area of the hippocampus from post ischemic rats several months after the insult. However, none of the recorded postischemic rats showed behavioral or electrographic seizures in the hippocampus during the recording period. Whole cell recordings from CA3 pyramidal neurons revealed a permanent reduction in the frequency of spontaneous and miniature GABAergic inhibitory postsynaptic currents (IPSCs) and a parallel increase in the frequency of spontaneous and miniature glutamatergic excitatory postsynaptic currents (EPSCs). Global ischemia also induced a dramatic loss of GABAergic interneurons and terminals together with an increase in glutamatergic terminals in the CA3 area of the hippocampus. Altogether our results show a morpho-functional reorganization in the CA3 network several months after global ischemia resulting in a net shift in the excitatory-inhibitory balance towards excitation that may constitute a substrate for the generation of epileptiform discharges in the post-ischemic hippocampus.

SIMPLE AND PARTIAL COMPLEX STATUS EPILEPTICUS

H. Meierkord (Charité – Universitätsmedizin Berlin, Germany)

Focal forms of nonconvulsive status epilepticus may or may not include altered contact with the environment. In simple partial status epilepticus (SPSE) consciousness is not compromised. In contrast, in complex partial status epilepticus (CPSE) changes in behaviour or mental state are associated with impairment or loss of consciousness. This classification is not entirely satisfactorily since impairment of consciousness may be difficult to prove or to rule out. In this presentation the various subtypes of SPSE such as somatosensory, psychic, autonomic and aphasic SPSE will be discussed. The clinical phenomenology and EEG changes and aetiologies, treatment and prognosis will be presented. Propagation of epileptic activity is an important neurobiological phenomenon well suited to explain various clinical and EEG features that may be encountered in status epilepticus. All types of SPSE may evolve into CPSE but a reversal of such an evolution is rare if not impossible. CPSE for many years was thought to be a rare condition. In an epidemiological study by DeLorenzo et al. (1996), CPSE was reported to account for only 3% of all cases of status epilepticus. Only recently European population-based studies revealed that the proportion of CPSE of all cases ranges from 16 to 43% (Vignatelli et al. 2003, Knake et al. 2001). CPSE poses greater diagnostic and therapeutic challenges compared to SPSE. Typically, the condition evolves gradually and is fluctuating with waxing and waning symptoms including restlessness, fearful and/or agitated behaviour and automatisms. CPSE most often arises from temporal or frontal lobe regions and the spectrum of aetiologies causing CPSE is wide. Regarding prognosis available human data indicate that NCSE itself seems to be a rather benign condition regarding morbidity and mortality. Poor outcome in most cases results from the underlying aetiology and associated complications.

NONCONVULSIVE STATUS EPILEPTIC AND COMA

G. Bauer (University Hospital for Neurology Innsbruck, Austria)

Coma is a state of unarousable psychologic unresponsiveness in which the subjects lie with eyes closed (Plum, F, Posner, JB: The Diagnosis of Stupor and Coma. 3rd ed. F.A. Davis Company, Philadelphia, 1980). In coma, the diagnosis of an enduring epileptic condition rests on epileptiform EEG abnormalities. EEG changes with coma are multifaceted and exhibit continuous epileptiform patterns in advanced cases (Bauer, G: Coma and Brain death. In: Niedermeyer, E, Lopes da Silva, F: Electroencephalography, Basic Principles, Clinical Applications and Related Fields, 5th ed. Lippincott Williams & Wilkins, Philadelphia 2005, p 471–487). A second criterion for an epileptic condition would be a beneficial effect of antiepileptic drug (AED) treatment on EEG and the clinical state. Several papers deal with the question, how aggressive the AED treatment should be and if it is beneficial or even harmful. The outcome does not depend on treatment but on etiology and is bleak in most cases. Therefore, the differential diagnosis-NCSE or deep coma with epiphenomenal spikes-remains undecided. In most cases, coma with NCSE designates an acute and serious cerebral insult. NCSE in the form of coma rarely if ever occurs in pre-existing chronic epilepsies.

Several generalized and lateralized EEG patterns prompted the classification of deep coma states as NCSE: continuous spikes, periodic epileptiform complexes, several types of burst suppression pattern, triphasic waves, periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs (BI-PLEDs) and unilateral suppression burst pattern. All these abnormalities are unspecific with regard to etiology and the relation to NCSE, but reflect the depth of coma. With generalized patterns, the most frequently observed etiologies are cerebral anoxia, toxic and metabolic encephalopathies, CNS infections and space occupying lesions with irreversible tentorial herniation. Lateralized EEG abnormalities occur with acute hemispheric lesions. The relation of EEG changes to epileptic cellular mechanisms is controversially discussed. Generally, coma accompanied by continuous epileptiform EEG pattern has a dismal prognosis. A few exceptions exist. Intoxications with triphasic waves or suppression burst pattern recover after the elimination of the toxic substance. In these cases, the treatment with sedative AEDs clearly would be counterproductive. Remote symptomatic epilepsies following a cerebral vascular infarct frequently exhibit PLEDs in the postictal unconscious state. Most of these patients recover promptly without immediate i.v. AED treatment.

ABSENCE STATUS EPILEPTICUS THROUGHOUT THE LIFE CIRCLE

P. Thomas (Service de Neurologie, Unite Fonctionnelle EEG-Epileptologie, Hopital Pasteur, Nice, France)

Absence status (AS) is a polymorphic condition that can complicate many epileptic syndromes, and can occur at any age. Diagnosis is difficult on the basis of clinical semiology alone, and requires emergency EEG. On a nosographic point of view, literature indicates that 4 types of AS may be recognized. Typical AS occurs as part of an idiopathic generalised epilepsy most often characterized by absences. Isolated impairment of consciousness, at times with subtle jerks of the eyelids, is the essential symptomatology. The EEG correlates with repetitive absence seizures and shows symmetric and bilateral synchronous SW or PSW complexes faster than 2.5/3 Hz. The immediate prognosis is excellent. Atypical AS occurs in patients with symptomatic or cryptogenic generalized epilepsies and is characterized by a fluctuating confusional state with more prominent tonic and/or myoclonic and/or lateralized ictal manifestations than occur in typical AS. The EEG shows continuous or intermittent diffuse irregular slow SW or PSW complexes. The immediate prognosis is guarded, as these episodes tend to recur and to be resistant to medication. “De novo” absence status of late onset is characterized by toxic or metabolic precipitating factors in middle-aged or elderly subjects with no previous history of epilepsy. Patients often have a history of psychiatric illness with multiple psychotropic drug intake. The electroclinical characteristics and the immediate prognosis are variable. These episodes of AS generally represent acute symptomatic seizures and may not recur if the triggering factors can be controlled or corrected. Long-term antiepileptic drugs may thus not be needed. Absence status with focal characteristics occur in subjects with a preexisting or newly developing partial epilepsy, most often of extratemporal origin. The EEG shows bilateral but often asymmetric ictal discharges. The immediate prognosis is variable. Some of these cases are difficult

to distinguish from complex partial status epilepticus of frontal lobe origin.

Sunday July 2, 2006
9:30 – 11:30
Hall 1
Discussion Group Session
Clinical neuropathology of epilepsy associated cortical malformations

RECENT DEVELOPMENTS IN THE CLASSIFICATION OF CORTICAL MALFORMATIONS

A. Palmini (UZ Gasthuisberg, Leuven, Belgium and Porto Alegre Epilepsy Surgery Program, Porto Alegre, Brazil)

Furthering the knowledge about focal epilepsies will depend on a detailed understanding of the determinants of epileptogenicity, other functional properties, clinical and electrographic presentations, and imaging features of specific types of lesions. A crucial step in this direction is to precisely define the histopathological features of epileptogenic lesions.

Interestingly, high resolution MRI has led to a puzzling scenario in which lesions are often identified and described in global, categorical terminology, distracting the attention to differences between specific types of lesions that present 'roughly' with the same imaging picture. This situation has been witnessed in relation to the identification and treatment of cortical malformations associated with epilepsy, particularly the focal dysplastic lesions.

Therefore, an effort was made to develop a histopathological classification system for focal dysplastic lesions that could be correlated with imaging, clinical, neurophysiological, functional, surgical, and prognostic aspects. This classification proposes the clustering of minimal histopathological abnormalities that do not disrupt cortical architecture (such as small clusters of heterotopic neurons in the white matter) in a specific category, thus abandoning the terminology "microdysgenesis." In addition, the classification distributes focal dysplastic lesions in which cortical dyslamination is a major feature along a continuum of histological abnormalities which in one end is represented by dyslamination only, and proceeds to more complex histopathological patterns characterized progressively by immature yet 'nondysplastic' cellular elements, dysplastic neurons, and, finally, in the opposite end, by lesions harboring dysplastic neurons and balloon cells.

Several clinical studies incorporating this classification system have appeared in recent years, and have confirmed that specific histopathological types of focal dysplastic lesions are indeed associated with more or less specific imaging, neurophysiological, functional and prognostic features. Some of these studies will be presented in the symposium.

IMAGING, CLINICS, AND HISTOPATHOLOGY OF FOCAL CORTICAL DYSPLASIAS

R. Spreafico (Istituto Nazionale Neurologico "C. Besta," Milano, Italy)

Since the original observation of Taylor et al. (1971) the focal cortical dysplasia (FCD) are increasingly revealed by high resolution MRI and most of the patients with this type of malformation are affected by drug resistant epilepsy and thus candidate for epilepsy surgery. However it should be noticed that despite the technological improvements, MRI is still failing in detecting some of the cortical malformations in about 10–20% of the cases recognized by neuropathological studies after surgery. While some forms of MCD are clearly defined, FCD are variously grouped using disparate terminology and numerous attempts have been made in the last ten years to classify the FCD. Recently the classification proposed by Tassi et al. (2002) subsequently refined by Palmini et al (2004) are recognising four main distinct morphological subtypes: type IA architectural dysplasia (AD), Type IB cytoarchitectural dysplasia (CD),Type II A Taylor's type dysplasia (TFCD) without balloon cells and Type II B Taylor's type dysplasia (TFCD) with balloon cells. This classification based on easily recognized histopathological characteristics, avoiding complicated terminology, were confirmed not only by more sophisticated immunocytochemical procedures but also by electroclinical data, MRI characteristics and localization and by the surgical outcome of the operated patients. These data indicate that the recognized subgroups of FCD define clinically homogeneous groups and that a presumptive diagnosis and prognosis could be possible based on electroclinical and imaging data.

DIFFERENTIAL EXPRESSION OF CYTOKINES AND NEUROTROPHIN RECEPTORS IN MALFORMATIONS OF CORTICAL DEVELOPMENT

E. Aronica (Department of (Neuro)Pathology, Academic Medical Center, University of Amsterdam, The Netherlands)

Malformations of cortical development (MCD) are recognized causes of epilepsy in children and young adults. Although genes that are responsible for selected MCD have been identified, the histogenesis of several MCD (such as focal cortical dysplasia, FCD and glioneuronal tumors, GNTs) is not completely understood and it is still unclear whether different MCD share common pathogenetic and epileptogenic pathways. An increasing number of observations suggest an important and complex role for both neurotrophins and inflammatory cytokines in epilepsy-associated pathologies.

We have analyzed the expression of both high (trkA, trkB, trkC) and low affinity (p75) neurotrophin receptors (NTRs) in FCD and GNTs specimens from patients with medically intractable epilepsy. All three trk receptors were encountered in high levels in the neuronal component of these developmental lesions. Strong trkA, trkB and trkC IR was found in neurons of different size, including dysmorphic neurons and balloon cells in FCD cases. Astrocytes showed predominantly IR for trkA. In addition $P75^{NTR}$ IR was observed in a population of cells of the microglial/macrophage lineage. These data indicate that the neuronal and the glial components of both neoplastic and malformative developmental lesions can be controlled by neurotrophin influences through specific receptors, potentially influencing both the development and the epileptogenicity of these lesions.

The presence of NTRs on glial cells suggests a role for neurotrophins in the regulation of several aspects of glial cell activation and function. Interestingly, not only astrocytes, but also microglial cells are highly represented within MCD specimens and may contribute to epileptogenesis through production of inflammatory cytokines, such as IL-1β. IL-1β may also exert neuroprotective effects via production of neurotrophins. The specific cellular distribution of IL-1β and its functional receptor (IL-1RI) and the possible involvement of the IL-1β system in the complex functional network of MCD will be presented and discussed.

ARCHITECTURAL MALFORMATIONS OF CORTICAL DEVELOPMENT: NEUROPATHOLOGICAL APPROACHES TO AN ENIGMA

I. Blümcke (Department of Neuropathology, University of Erlangen, Germany)

Neurosurgical treatment modalities in epilepsy patients with cortical dysplasia offer the intriguing opportunity to microscopically confirm the structural correlate of epileptogenic brain lesions. However, the spectrum of neuropathological alterations is large ranging from prominent to only minute changes and there is yet no international classification system available to reliable predict postsurgical outcome. Histopathological lesions associated with Focal Cortical Dysplasia (FCD) type I include architectural disturbance of cortical lamination as well as ectopic neurons in white matter. However, two major subgroups of patients can be identified. Almost 30% of patients with hippocampal sclerosis present with type I FCD within the ipsilateral temporopolar region and neurosurgical resection associates with successful seizure

control. On the other hand, young children with catastrophic epilepsies often show neuroradiological features of FCD, a hypoplastic neocortex within the affected hemisphere and microcolumar arrangements of cortical layers as histopathological hallmark. Neurosurgical resection do not always sufficiently control seizure activity in these young patients. Whether similar pathomechanisms operate in both patient groups remain to be determined and the common diagnosis of FCD type I may not reliably clarify different clinicopathological histories and outcome.

FCD type II present with gross histopathological changes including dysplastic neurons (FCD type IIA) and/or balloon cells (FCD type IIB). These lesions can be readily observed in MRI (transmantle sign) and histopathological examination of surgical specimens usually corroborates the diagnostic subtype. However, there may be additional clinico-pathological variants hidden and our recent molecular-biological approach targeting the insulin–growth factor receptor cascade indicate that FCD type IIA and IIB are distinct. The latter appears to share pathogenetic similarities with cortical tubers, although most patients fail to present with additional stigmata of TSC.

Neuropathological examination of surgical specimens is mandatory to classify variants of cortical dysplasias and to allow for subsequent molecular-genetic and/or –biological studies. This neuropathological approach will help to establish a comprehensive classification system as prerequisite to support the design of clinical outcome studies and targeted search for new antiepileptic drugs.

MOLECULAR GENETICS OF FOCAL CORTICAL DYSPLASIAS WITH AND WITHOUT TAYLOR TYPE BALLOON CELL

A. Becker (Department of Neuropathology, University of Bonn Medical Center, Germany)

Focal cortical dysplasias (FCD) constitute glioneuronal lesions, which predispose individuals to recurrent pharmacoresistant seizures. In FCD, a broad spectrum of structural changes can be observed, that is related to changes in migration and differentiation of neural precursors in cortical development. A frequent variant of FCD is composed of dysplastic cytomegalic neurons and "Taylor"-type balloon cells (FCD_{IIb}), distinguished from FCD_{IIa} that lack balloon cells. Those resemble cells, which are found in cortical tubers in the autosomal dominant inherited disorder tuberous sclerosis (TSC). This phacomatosis is caused by mutations in the *TSC1* or *TSC2* genes. Recent data have indicated a pathogenetic role of *TSC1* also in FCD_{IIb}. TSC1 represents a key factor in the phosphatidylinositol 3-kinase (PI3K) pathway. In order to further understand the molecular pathology of FCD_{IIb}, we have analyzed additional major components of the PI3K-cascade in FCD_{IIb}, i.e., PTEN and Akt, which operate upstream of TSC1.

Mutational screening of *PTEN* was performed by single-strand conformation polymorphism analysis (SSCP) in 37 FCD_{IIb}. Immunohistochemistry with antibodies against phospho-Akt (Ser473) was carried out in FCD_{IIb} ($n = 33$).

SSCP in combination with laser assisted microdissection revealed a silent polymorphism of *PTEN* in exon 2 ($n = 2/37$ vs. 1/100 controls) and another polymorphism in exon 8 ($n = 1/37$ vs. 0/100 controls). An FCD_{IIb} showed a mutation, i.e. amino-acid exchange at nucleotide position 834 (*PTEN* cDNA, GenBank AH007803.1) in exon 8 with replacement of phenylalanine by leucine (F278L). Intriguingly, increased immunoreactivity for phospho-Akt was observed in balloon cells and dysplastic neurons but not in adjacent normal CNS.

Increase of phosphorylated Akt is in line with altered PI3K pathway signaling in FCD_{Iib}. The present findings constitute an important prerequisite in order to functionally address epileptogenesis of glioneuronal lesions.

Supported by DFG SFB TR3, BMBF and BONFOR.

Sunday July 2, 2006
9:30–11:30
Hall 5A

Discussion Group Session
Seizures, hippocampus, and memory

FUNCTIONAL APPROACH TO MEMORY DEFICITS ON HIPPOCAMPAL DAMAGE

H. Markowitsch (Physiological Psychology, University of Bielefeld, Bielefeld, Germany)

Memory deficits belong to the most frequent concomitants of epilepsy-related hippocampal degeneration. Nevertheless, present-day neuroscience requires a refined determination of structure-function relations between areas within the hippocampal formation and different memory systems. For one, hemispheric-specificity has to be taken into account: the left hemisphere is seen as primarily engaged in verbal and the right one in nonverbal memory functions. Secondly, within the hippocampal formation there is an unequal sensitivity towards epilepsy-related damage (e.g., the special vulnerability of the CA1 region within the hippocampus proper). And thirdly, neuropsychological and neuroscientific evidence strongly emphasises the existence of process-specific memory functions ('implicit memory,' 'explicit memory') and of different subsystems of memory.

It is distinguished between five basic long-term memory systems: procedural memory, priming, perceptual, semantic, and episodic memory systems. Different neuroanatomical networks are proposed to be active during encoding, storage, and retrieval of information belonging to each of these systems. Especially the hierachically highest memory systems (semantic and episodic memory) are strongly dependent on a well-functioning hippocampal system.

Aside from manifest tissue damage, the high number of glucocorticoid receptors in the hippocampal region makes this structure vulnerable to environmental stress and may lead to mnestic block syndromes.

Epilepsy-related memory deficits as well as other causes of hippocampal damage/dysfunction-related memory deficits will be discussed both from structural-anatomical and from functional-behavioural viewpoints.

MEMORY PERFORMANCE IN EPILEPSIES IS GENETICALLY INFLUENCED?

A. Gambardella (Università Magna Graecia, Cattedra di Neurologia, Catanzaro, Italy)

No abstract received.

SPECIFIC LONG-TERM EFFECTS ON MEMORY AFTER SURGERY

W. Alpherts (Epilepsy Institute of the Netherlands (SEIN))

Resections in the left temporal lobe (LTL) that include hippocampus, amygdala and lateral neocortex are generally accompanied by a decline in verbal memory. There are only a few publications with a follow-up of one year or two years after surgery. The effect of surgery on memory in the long-term is not fully known. The one study with a comparison of early (one year post-op) and late (at least 9 years post-op) cognitive changes showed a long-term decline of verbal memory in LTL.

We assessed verbal memory performance as measured by a verbal learning test before surgery, and at three specific times after temporal lobe surgery: six months, two years and six years in 85 patients. An amygdalo-hippocampectomy and a neocortical temporal resection between 2.5 and 8 cm were carried out in all patients. LTL patients showed an ongoing memory decline for consolidation and acquisition of verbal material (both 2/3 SDs) for up to two years after surgery. RTL patients at first showed a gain in both memory acquisition and consolidation, which vanished in the long-term. Breaking the group up into a mesiotemporal (MTS) group and a non-MTS group showed clear differences. The group with pure MTS showed an overall lower verbal memory performance than the group without MTS, in the LTL group more pronounced than in the RTL group. After surgery, both pathology groups showed an ongoing decline up to two years post-op, but the degree of decline

was greater for the LTL patients with MTS compared with the non-MTS group.

Becoming and remaining seizure free after surgery does not result in a better performance in the long-term. Predictors of postoperative verbal memory performance at 6 years after surgery were: side of surgery, preoperative memory score and age.

HIPPOCAMPAL STIMULATION INDUCES MEMORY CHANGES?

G. Alarcón (King's College Hospital, London, UK)

We investigated the role of medial temporal structures (MT) on recognition memory by studying the effects of unilateral and bilateral electrical stimulation of MT with single pulses during encoding and recognition of a yes-no recognition memory test in patients with epilepsy implanted with bilateral electrodes in MT structures. One millisecond electrical pulse was time-locked to item presentation during encoding and recognition. Four material types were presented (words, objects, geometrical figures and faces). It was assumed that each electrical pulse disrupts normal function during approximately 400 ms (the duration of the early response). All 18 patients studied carried out a baseline memory test (with no stimulation), a memory test with stimulation of right MT and a memory test with stimulation of left MT. Six of the 18 patient carried out an additional memory test with bilateral stimulation of MT. Performance during baseline was compared with performance during unilateral and bilateral stimulation. No differences were found in memory performance between baseline and unilateral stimulation, either in the total score or in material-specific deficits. In contrast, a pronounced decrease (50%) in total memory scores was seen when bilateral stimulation was applied ($p<0.05$). Decrements in performance with bilateral stimulation compared to baseline were seen for all materials, and the difference was significant for words and faces ($p<0.05$). The findings confirm that localised 1-ms electrical pulses can disrupt cognitive function and that MT are involved in processing recognition memory. The presence of memory deficits only with bilateral stimulation suggest that memory is stored in both hippocampi and processed independently by both hippocampi. This technique could be used to predict memory deficits of unilateral hippocampal resections.

ANTIEPILEPTIC DRUG TREATMENTS AND MEMORY CHANGES

R. Kälviäinen (Kuopio Epilepsy Center, Department of Neurology, Kuopio University Hospital, Finland)

Slowing of mental or motor speed and attentional deficits are well known adverse effects of the many antiepileptic drugs (AEDs). It is generally assumed that AEDs do not specifically impair memory and that patients' memory complaints are secondary to the changes in their attentional level or mental processing speed induced by AEDs. However, underlying pathologies in the mesial temporal structures and their associated neocortices, epileptic discharges, and untoward effects of AEDs alone or together may disturb memory formation, retention, or retrieval.

There are several lines of evidence suggesting an independent potential for AEDs to induce or exacerbate memory impairment. Patients treated with monotherapy show fewer cognitive effects, including memory deficits, than those treated with polytherapy, particularly at higher doses. In animal studies on spatial working memory in nonepileptic rats, the largest disruptive effects on working memory, as measured by percentage of correct responses, are produced by the benzodiazepines, phenobarbital and ethosuximide. More modest but significant disruption is produced by carbamazepine and topiramate, whereas tiagabine, valproate, gabapentin, phenytoin, lamotrigine, and levetiracetam are without significant effects on spatial working memory. Studies in healthy volunteer adults and patients with epilepsy have demonstrated that several AEDs can impair memory and that there appear to be differential effects across AEDs. Most significant changes have been demonstrated with benzodiazepines and phenobarbital, whereas newer drugs seem to produce fewer problems. Elderly patients and children appear to be at the greatest risk. Unfortunately, evaluation of memory impairment has been limited in most studies.

In conclusion, although the memory impairments in epilepsy are multifactorial in nature, AEDs can clearly reduce memory performance. At the moment, however, there are inadequate data to delineate completely the independent effects of AEDs on memory and to determine the interaction of AEDs with seizures, interictal discharges, and underlying brain disease.

Sunday July 2, 2006
9:30–11:30
Hall 5B
Discussion Group Session
Ictal and interictal autonomic dysfunction: symptoms, signs, and potential consequences

AUTONOMIC SEIZURES: AN OVERVIEW OF SEMIOLOGY AND ANATOMICAL SUBSTRATE

C. Baumgartner (Department of Neurology, Medical University of Vienna, Austria)

Autonomic symptoms during epileptic seizures can either represent the sole or predominant seizure manifestation as in simple autonomic seizures or accompany complex partial or generalized seizures. Autonomic symptoms consist of cardiovascular changes, respiratory manifestations, gastrointestinal symptoms, cutaneous manifestations, pupillary symptoms, genital and sexual manifestations as well as urinary symptoms. Autonomic symptoms are mediated by an activation of the central autonomic network which comprises (1) the insular and medial prefrontal cortex, (2) the central nucleus of the amygdala and the bed nucleus of the stria terminalis, the preoptic region and the hypothalamus, (4) the midbrain periaqueductal gray matter, (5) the pontine parabrachial Kölliker-Fuse region, (6) the nucleus of the solitary tract and (7) the intermediate reticular zone of the medulla. Inputs to the CAN are multiple, including viscerosensory inputs relayed on the nucleus of the tractus solitarius and humoral inputs relayed through the circumventricular organs. The CAN in turn controls preganglionic sympathetic and parasympathetic, neuroendocrine, respiratory and sphincter motor neurons. Due to a hemispheric specific representation of the CAN certain autonomic symptoms provide lateralizing and sometimes localizing information on the seizure onset zone. Autonomic symptoms indicating a seizure onset in the non-dominant hemisphere include ictal vomiting and retching, spitting automatisms and ictal urinary urge. Autonomic symptoms range from subtle seizure manifestations which become apparent only during meticulous seizure analysis to severe, sometimes life-threatening events. Cardiovascular and respiratory autonomic symptoms are discussed as the mechanisms underlying sudden unexpected death in epilepsy (SUDEP). When autonomic symptoms represent the sole seizure manifestation, they can pose problems in the differential diagnosis against various non-epileptic conditions. Finally, autonomic seizure symptoms open a unique window on the functional organization of the central autonomic network and on brain function in general.

ICTAL CARDIAC ARRHYTHMIA

C. Elger (University of Bonn, Department of Epileptology, Germany)

Heart rate alteration in relation to epileptic seizures has been a well-known phenomenon for over 50 years. A number of publications exist which deal particularly with TLE. The aim of this presentation is to provide a brief summary of the published data and to add the results we obtained from the presurgical evaluation.

When studying ictal cardiac arrhythmia (ICA), two opposing views are of interest: the first concerns the consequences of ICA; the second, its causes. For a few patients, the consequences may result in dramatic risks when extreme tachy-/bradycardia or cardiac arrest are involved and this may be one of the reasons SUDEP is assumed. Inversely, searching for

the causes of ICA may contribute to the differential diagnosis or classification and, hypothetically, even to the individual focus localization. In this field, the standard reference is still Blumhardt's work. He documents a high incidence of tachycardia (91%) for TLE patients and a 57% HR increase prior to seizure onset.

We performed a retrospective data analysis of 82 consecutive patients who were examined during the presurgical evaluation. Inclusion criteria were: final diagnosis and a successful operation for either frontal or temporal lobe epilepsy. A total of 700 seizures were analyzed, the majority of which were done via intracranial (hippocampal depth, temporal strip, orbitofrontal grid) electrodes. From R-R intervals, ictal heart rate courses were automatically calculated and parameterized. Our results for the TL seizures generally confirm those of Blumhardt (tachycardia > 90%). Compared to TL seizures, tachycardia exceeding 160 bpm occurred significantly more often in FL seizures (23%). The most exciting aspect reported in this study was finding that the microanalysis of the HR course in correlation with intracranial registrations can directly reflect the waxing and waning involvement of cerebral structures.

METHODS TO ASSESS CARDIOVASCULAR REGULATION IN EPILEPSY

H. Ansakorpi (University of Oulu, department of Neurology, Finland)

It is well known that the heart is one of the most delicate organs reflecting cardiovascular autonomic regulatory function. The heart rate (HR) during normal sinus rhythm is not uniform but the interval between the two R spikes in the electrocardiographic (ECG) recordings fluctuates. Respiration, neurohumoral factors and cardiovascular regulation are the main effectors on the RR interval. HR variation reflects the competence of this regulatory system, diminished HR variation being a sign of dysfunction of the autonomic nervous system.

Cardiovascular autonomic reflexes in humans are essential for the maintenance of arterial blood pressure (BP) during the orthostatic stress adopting a standing posture and for preventing wide fluctuations of arterial BP in response to adaptive responses. To examine cardiovascular reflexes, a standardised laboratory test pattern, in which HR and BP responses at rest and to certain stimuli are measured, is often used. The method is easy to perform and it has an established role as the most used method assessing autonomic functions. The test pattern includes the measurement of HR and BP during normal and deep breathing, the Valsalva maneuver, the tilt test and the isometric work test.

HR variability can also easily be analysed from 24-hour ECG recordings. Information about tonic autonomic effects on the heart can be obtained by the traditional time and frequency domain measures based on linear fluctuations of HR. Since the genesis of HR variability also involves nonlinear mechanisms, several newer methods have been developed to quantify the complex HR dynamics. Whereas the magnitude of the variability is assessed by the traditional HR variability measures, methods of analysis derived from the nonlinear system theory provide information on the quality, scaling and correlation properties of the HR signal.

HEART RATE VARIABILITY IN EPILEPSY: POSSIBLE RELEVANCE FOR SUDEP

T. Tomson (Department of Clinical Neuroscience, Karolinska Institutet, Sweden)

Impairment of cardiovascular regulation has been discussed as a possible contributing mechanism for SUDEP. Autonomic cardiac control can be assessed clinically by analysis of heart rate variability (HRV) based on ECG recordings. HRV is of special interest in the context of SUDEP since a reduced HRV has been shown to predict sudden death in other conditions than epilepsy. Several studied have assessed HRV in patients with epilepsy to explore whether there are any indications of an impairment of the autonomic cardiac control and in particular if HRV is reduced in populations with a particularly high risk of SUDEP. Most cross-sectional studies suggest a decreased HRV, and thus an impaired autonomic cardiac regulation, in patients with chronic temporal lobe epilepsy. This decrease might be more pronounced during night than at daytime. The reason for the reduced HRV is probably multifactorial and possibly related to the epilepsy, the underlying etiology, as well as the antiepileptic drugs. Epilepsy surgery candidates are considered to be at particularly high risk of SUDEP. Patients rendered seizure free after epilepsy surgery, seem to have a lower risk whereas the incidence is high among surgery failures. Impaired HRV has been reported in studies of epilepsy surgery candidates. Interestingly, preoperative HRV was decreased among surgery failures and significantly lower than in patients seizure free after temporal lobe surgery. Data on the effects of epilepsy surgery on HRV are more conflicting. Nevertheless, the available information confirms that patients with epilepsy have a reduced HRV and suggest that this decrease is more pronounced among those with a high SUDEP risk. This indicates that a decreased HRV might be a marker for an increased risk of SUDEP in line with recent preliminary observations of lower HRV in patients who later died in SUDEP compared with epilepsy and nonepilepsy controls.

Sunday July 2, 2006
9:30 – 11:30
Hall 5C
Discussion Group Session
Neonatal seizures

AETIOLOGY AND OUTCOME OF NEONATAL SEIZURES

M. Levene (University of Leeds, UK)

Neonatal convulsions are common and can manifest themselves in many ways. There is a very varied aetiology but are due in full-term infants most commonly to hypoxic-ischaemic injury. Other important causes include hypoglycaemia, inborn errors of metabolism, intracranial haemorrhage, cerebral artery infarction and infection.

The prognosis depends to a relatively large degree on the cause of the convulsions. Moderate HIE has a 25% risk of disability and severe HIE has almost 90% risk of death or disability. It is difficult to disentangle the effect of the convulsions from their cause.

Recent animal studies have mimicked the relatively short-lived but frequent seizures seen in the newborn. These studies have shown that short convulsions in the neonatal period do not increase the rate of neuronal necrosis/apoptosis but affect the brain functioning later in adolescent life of the animal. In addition it is thought that later exposure to convulsions have a worse outcome when the animal has had sensitizing neonatal convulsions.

This recent data has shifted the pendulum more towards effective and safe anticonvulsant management of neonatal seizures.

DIAGNOSING NEONATAL SEIZURES: THE ROLE OF THE EEG

R. Pressler (Department of Clinical Neurophysiology, National Hospital for Neurology, UK)

The EEG is an important investigation in the diagnosis and treatment of neonatal seizures. Electrophysiological seizures consist of rhythmic activity with a sudden and distinct beginning and end lasting >10 sec (>5 sec if background activity is abnormal). They may consist of sharp waves or spikes, monomorphous delta or theta waves, sequence of alpha or beta frequencies or transient suppression. Neonatal seizures are nearly always partial, but secondary generalisation is not uncommon.

Seizures are not usually sustained, with 97% lasting less than 9 minutes. In preterm infants seizure duration is shorter than at term. Multifocal seizures (simultaneous independent focal electrographic seizures) are common in severe encephalopathies and are more often associated with neurological sequelae than unifocal seizure discharges. A characteristic feature of neonatal seizures is the phenomenon of electroclinical dissociation: seizures can be electroclinical, electrographic (subclinical) or clinical only. Treatment with antiepileptic drugs increases electroclinical dissociation and electrographic seizures may persist without clinical

correlate. Subtle seizures are the most common seizure type in term and preterm infants and may manifest as ocular, oral or autonomic phenomena, or fragmentary body movements. Prolonged video-EEG has shown that the majority of infants with subtle seizures will exhibit rhythmic epileptiform activity at least during some seizures. The absence of ictal EEG discharges, however, does not necessarily rule out seizures. Neonatal status is currently defined as a total seizure time occupying 50% of a 30 minutes recording. Discharges of less than 10 s duration have been termed BIRDs (Brief Interictal Rhythmic Discharges or Brief Ictal Rhythmic Discharges) and are of uncertain significance. However, BIRDs have been associated with seizures in the same or subsequent EEG and with poor neurodevelopmental outcome.

THE ROLE OF AMPLITUDE INTEGRATED EEG (aEEG)

L. de Vries (Wilhelmina Children's Hospital, Utrecht, Netherlands)

Immediate access to aEEG monitoring in full-term infants with neonatal encephalopathy (NE), often admitted at night or during the weekend is one of many advantages of the amplitude integrated EEG (aEEG), which is easy to learn by senior and junior doctors as well as the nursing staff. aEEG will provide immediate information about the background activity and presence of seizures within hours after birth. This information will be required as soon as possible after birth for selection of patients for neuroprotective intervention, and for early prediction of neurodevelopmental outcome.

A rapid rise of both the lower and the upper margins of the aEEG tracing is suggestive of an ictal discharge. Seizures can be recognised as single seizures, repetitive seizures and as a status epilepticus. The latter usually looks like a "saw-tooth" pattern. Correct interpretation is greatly improved by simultaneous raw EEG recording available on the different digital devices, which are now mostly used. Since the increased use of continuous monitoring, it has become apparent that subclinical seizures are common and tend to be seen following administration of the first antiepileptic drug. Using a single channel or even using two channels will not allow detection of all seizures. Due to the nature of the technique it is clear that very brief seizure activity as well as focal seizure activity will be missed.

The long duration of the aEEG registration however appears to outweigh the limitations of obtaining detailed information during a much shorter, 30 minutes standard EEG registration, which is usually available in the neonatal care setting.

NEONATAL SEIZURE DETECTION: OTHER PHYSIOLOGICAL MODALITIES

G. Boylan (Department of Paediatrics & Child Health, University College Cork, Ireland)

Seizures in the newborn are notoriously difficult to diagnose and clinical signs may be very subtle or completely absent. In addition, there is considerable mismatch between clinical and electrographic diagnosis of neonatal seizure. Diagnosis becomes even more problematic following antiepileptic treatment, when clinical suppression of seizure activity is common.

Multichannel video-EEG monitoring is the only reliable method available for the detection of all neonatal seizures. Video-EEG does require special expertise for acquisition and interpretation and this expertise is not always available to many neonatal intensive care units (NICU), particularly on a 24-hour basis. Many clinicians rely instead on simpler systems that provide the compressed and filtered amplitude integrated EEG (aEEG) signal. These systems have proven very useful for monitoring background EEG activity but have some limitations for seizure detection in the hands of nonexperts (Rennie JM, Chorley G, Boylan GB, Pressler R, Nguyen Y, Hooper R. Non-expert use of the cerebral function monitor for neonatal seizure detection. *Arch Dis Child Fetal Neonatal Ed* 2004;89(1):F37–F40).

It is not surprising therefore that there have been many attempts to automatically detect seizures in neonates using the EEG. To date, none of these methods have proven suitable for clinical use (Faul S, Boylan GB, Connolly S, Marnane WP, Lightbody G. An Evaluation of Automated Neonatal Seizure Detection Methods. *Clinical Neurophysiology*, 2005;116(7):1533–1541). Automated neonatal seizure detection is however important work, and is a rapidly developing field. Newly emerging signal processing methods are constantly being applied to the problem of seizure detection using EEG.

The aims of this presentation are to:

- Examine the EEG characteristics of neonatal seizures
- Review current automated neonatal seizure detection techniques
- Discuss changes that occur in other physiological signals such as heart rate, respiration and cerebral blood flow during neonatal seizures
- Explore the possibility of combining information from many physiological sources to increase neonatal seizure detection reliability in the NICU.

TREATMENT OF NEONATAL SEIZURES

J. Rennie (University College Hospital, London, UK)

The first line treatment for neonatal seizures (phenobarbitone) has not changed for over thirty years. Phenobarbitone is effective in controlling seizures in about a third to a half of babies, and is more likely to work if the seizure burden is low and the background EEG is normal (Boyland GB, Rennie JM, Pressler RM, et al. *Archives of Disease in Childhood*, 2002;86:485–489). These cases have a better prognosis than those whose seizures are resistant to treatment and whose seizure burden is large.

Phenobarbitone has theoretical disadvantages but there is considerable experience with it, and in our view it should remain the drug of first choice. There is no evidence that giving a dose of more than 40 mg/kg is of benefit.

Babies whose seizures are resistant to treatment with phenobarbitone are a high risk group. Many different AEDs have been tried as second line, although few have been evaluated using EEG assessment of the response. Amongst the AEDs which have been evaluated with EEG quantification of the seizure burden, phenytoin and has been shown to be of some benefit (Painter MJ, Scher MS, Stein AD, et al. *N Engl J Med*, 1999;341:485–489), and others report good experiences with lignocaine (Hellstrom-Westas L, Westgren U, Rosen I, Svenningsen NW, *Acta Paediatrica Scandinavica*, 1988;77:79–84). Experience with midazolam is variable; there is one report of 100% control after a bolus of 150 microg/kg followed by an infusion rate starting at 60 microg/kg/min and escalating to a very high dose of 1080 microg/kg/hr (Castro Conde JR, Borges AAH, Martinez ED et al. *Neurology*, 2005;64:876–879). In contrast, we did not find a midazolam loading dose of 60 microg/kg followed by an infusion rate of 150 microg/kg/hr to be of benefit (Boylan G, Rennie JM, Chorley G, et al. *Neurology*, 2004;62:486–488).

Much work remains to be done in this important area. Advances in the study of neonatal seizures at a cellular level, using animal models, suggest that drugs such as levetiracetam (Keppra) would prove more effective than existing agents.

Sunday July 2, 2006
9:30–11:30
Hall 3A
Discussion Group Session
Lessons learned from local epidemiological studies

EPIDEMIOLOGY OF EPILEPSY IN ESTONIA

A. Õun (Department of Neurology and Neurosurgery, University of Tartu, Estonia)

Epidemiological data about epilepsy from central and eastern Europe is controversial. A modern study on prevalence and incidence of epilepsy in Estonia has been carried out on children–prevalence of active epilepsy was 3.6/1,000, and incidence 45/100,000 person-years being essentially similar to those in developed countries. In an adult populaton review of all databases and lists related to epilepsy in Tartu supplemented by re-examination of patients to identify all persons with active epilepsy aged

≥20 years on January 1, 1997. Special attention was paid to extensive adoption of definitions and criteria proposed by Guidelines for epidemiologic studies. The incidence rate was 35/100,000 person-years. The age-specific rates tended to increase with advancing age. The prevalence rate was 5.3/1,000. The largest syndromic categories were localization-related symptomatic and cryptogenic epilepsies, which are very likely due to the age-distribution of the study. The risk factors for epilepsy were identified in 39.6% cases of the prevalent cases. Of the subjects 19% did not take an entiepileptic drug on the prevalence day, 83% of them were taking a single drug. The most common agent was carbamazepine (68%), followed by barbiturates. Epidemiologic rates in the adult, as well as in the total population of Tartu was comparable to those reported from the developed countries. The large percentage of medication-free epileptics, notably small figures for polytherapy, and the associating low aggregate antiepileptic drug sales in Estonia, indicate a tendency for moderate medication in the epileptic population.

EPIDEMIOLOGY OF EPILEPSY IN SCANDINAVIAN COUNTRIES

L. Forsgren (Department of Neurology, Umeå University Hospital, Umeå, Sweden)

Purpose: To give an overview of results from epidemiological studies on epilepsy in the Scandinavian countries. Studies from Iceland are also included.

Methods: Survey of epidemiological studies from Denmark, Iceland, Norway and Sweden published during the last 30 years. Focus on results from population-based studies.

Results: Prevalence and incidence studies confirm or have later been confirmed by results from studies in other high income countries in the world. The prevalence of active epilepsy is around 5–6 per 1000 and slightly more common in males than females in most studies. Around 40% of patients in epilepsy populations have been seizure free for at least one year, and 10–20% have one or more seizures per week.

The annual incidence of epilepsy is 35–45 per 100,000 and 45–60 when single unprovoked seizures are included. Young children and in the elderly have the highest age-specific incidence. Stroke is the most common identified cause of epilepsy, followed by cerebral tumors, early brain damage and dementing diseases.

Patients with remote symptomatic causes of epilepsy have significantly higher recurrence rate for seizures compared with patients with unknown cause. The effect of treatment during the first year is a significant predictor for long-term prognosis.

Mortality is increased in patients with remote symptomatic etiology, particularly during the first years following diagnosis.

Learning disability/mental retardation (MR) occurs in 20–25% of adults and 40% of children with active epilepsy. In a MR-population around 20% have active epilepsy. The epilepsy in this group is often poorly controlled with at least 10% having daily seizures. Mortality is increased.

Conclusions: Epidemiological studies from Scandinavia and Iceland have provided important contributions to our knowledge on causes, magnitude and prognosis of epilepsy.

EPIDEMIOLOGY OF EPILEPSY IN FINLAND

T. Keränen (University Hospital of Tampere, Finland)

No abstract received.

EPIDEMIOLOGY OF EPILEPSY IN RUSSIA

A. Guekht (Russian State Medical University, Russia)

Rationale: The epidemiological study of epilepsy in people over 14 years old has been performed in 12 regions in European and Siberian parts of Russia. The total population of the studied regions was 517642. In each region studied population was representative and sufficient (for instance, 109436 in Moscow, 28609 in Irkutsk).

Methods: All established or suspected cases were identified from available medical information sources. Possible epilepsy cases were then evaluated by the neurologists or epileptologist. Majority of patients underwent EEG, and a part–neuroradiologic investigations or both.

Results: The crude prevalence rate of active epilepsy was 3.39 per 1000, age-adjusted rate was 3.41 per 1000. Men had higher prevalence rate than women (4.53 vs 2.49; age adjusted −4.49 vs. 2.51, $p < 0.0001$). The highest age-specific prevalence was found in patients 50–59 years old (4.21 per 1000). The prevalence of epilepsy in the Eastern (Siberian) regions was significantly higher then in the Western (European) regions (4.11 vs. 2.82 per 1000, $p < 0.0001$). Partial seizures with or without secondary generalization were more common (78%) than generalized seizures. Localization-related symptomatic or cryptogenic epilepsies were the largest syndromic category. No cause of epilepsy was identified in 40% of patients. The most important etiologic factors of epilepsy in all regions were brain trauma, stroke, tumor, perinatal pathology and infections.

Significant proportion of patients, especially in Siberian regions, received suboptimal treatment. That explained the high level of disability. It was significantly higher in Siberian regions (66.2%) compared to European (39.6%, $p < 0.0001$).

Conclusions: Epidemiological data on epilepsy in European part of Russia suggest a lower prevalence than in Siberian part. Special attention to improvement of epilepsy care is required.

Acknowledgement: The author thank Professors W. Hauser and E. Gusev for the most valuable recommendations during the study, and Drs. Balhanova, Golovanova, Kabakov, Kotov, Milchakova, Pisova, Shprakh, Spirin, Volkova for their contribution.

Sunday July 2, 2006
9:30–11:30
Hall 3D
Discussion Group Session
Plastic modifications during the transition between a normal brain and an epileptic one

THE ROLE OF NEUROGENESIS FOR THE DEVELOPMENT OF AN EPILEPTIC FOCUS IN A MOUSE MODEL OF TEMPORAL LOBE EPILEPSY

J. Fritschy (University of Zurich, Institute of Pharmacology and Toxicology, Switzerland)

Adult hippocampal neurogenesis is enhanced in response to acute seizures. However, the significance of neurogenesis in temporal lobe epilepsy (TLE) remains disputed. Unilateral intrahippocampal injection of kainate (KA) in adult mice models morphological features (e.g., neuronal loss, granule cell dispersion) and occurrence of chronic recurrent seizures observed in human TLE. In this model, KA injection transiently increased cell proliferation bilaterally in the subgranular zone (SGZ). As a result, neurogenesis was stimulated in the contralateral dentate gyrus. In contrast, the epileptic hippocampus exhibited strongly reduced neurogenic potential, even after onset of recurrent seizures. Therefore, neurogenesis does not contribute towards the formation of the epileptic focus and may be affected when granule cell dispersion occurs. To investigate further the relationship between epileptogenesis and neurogenesis, we compared the differentiation of cells born shortly before and after KA injection. Immunohistochemical staining for doublecortin and PSA-NCAM, two markers of young neurons, revealed rapid down-regulation of both markers ipsilaterally, whereas they were increased transiently on the contralateral side. To determine whether KA treatment directly affects SGZ neural progenitors, dividing cells were prelabeled with 5'-bromo-2'deoxyuridine (BrdU) treatment before unilateral injection of KA. Double staining with the proliferation marker PCNA showed that prelabeled BrdU cells survived KA exposure and proliferated bilaterally. Unexpectedly, the neuronal differentiation of these cells, as assessed after two weeks with doublecortin and NeuN triple staining, occurred to the same extent as in control. Therefore, SGZ progenitor cells that were committed to a neuronal phenotype before KA treatment completed their differentiation despite the rapid down-regulation of doublecortin and PSA-NCAM. These findings suggest impaired fate commitment of proliferating cells in the lesioned dentate gyrus. Loss of neurogenesis in this TLE model likely reflects an irreversible alteration of the SGZ germinal

niche during development of the epileptic focus and may therefore be relevant for human TLE.

ACCUMULATION OF BDNF IN THE DENDRITES: A LINK WITH EPILEPTOGENESIS?

M. Simonato (Department of Clinical and Experimental Medicine, Section of Pharmacology, University of Ferrara, Italy)

Targeting of mRNA into dendrites, followed by a local, extrasomatic, protein synthesis is a mechanism that enables neurons to synthesize proteins in close proximity to the postsynaptic site of stimulated synapses. Here, we demonstrate that epileptogenic stimuli induce a dramatic accumulation of BDNF mRNA and protein in the dendrites of hippocampal neurons in vivo. BDNF mRNA and protein accumulate in dendrites in all hippocampal subfields after pilocarpine seizures, and in selected subfields after other epileptogenic stimuli (kainate and kindling). BDNF accumulates selectively in discrete dendritic laminae, suggesting targeting to synapses that are active during seizures. Dendritic targeting of BDNF mRNA occurs during the time when the cellular changes that underlie epilepsy are occurring, and is not seen after intense stimuli that are non-epileptogenic including electroconvulsive seizures and high frequency stimulation. MK801, an NMDA receptor antagonist that can prevent epileptogenesis but not acute seizures, prevents the dendritic accumulation of BDNF mRNA, indicating that dendritic targeting is mediated via NMDA receptor activation.

We have also investigated the molecular determinants of BDNF mRNA trafficking. BDNF is encoded by multiple, alternatively spliced, transcripts whose function is still unknown. We have analyzed the trafficking of five rat BDNF mRNA splice variants in hippocampal neurons following kainate or pilocarpine injection. Both kainate and pilocarpine seizures induce a dramatic accumulation of isoforms IIa, IIb and IV in the dendrites of hippocampal neurons, while exon I and III transcripts remain in the soma.

These results suggest that dendritic accumulation of BDNF mRNA and protein play a critical role in the cellular changes leading to epilepsy. Experiments are ongoing to challenge this hypothesis by means of siRNAs specifically directed against the different BDNF mRNA splice variants.

h-CHANNEL PLASTICITY DURING EXPERIMENTAL EPILEPTOGENESIS

M. Shah (University College London, UK)

The hyperpolarization-activated cation channel (h-channel) has been suggested to be involved in the changes in neuronal excitability in many different types of epilepsy. During chronic temporal lobe epilepsy (TLE), the expression of the hyperpolarization-activated cation non-selective (HCN) subunit (molecular correlate of h-channels) was found to be altered in hippocampal CA1 pyramidal neurons (Brewster et al., *J Neurosci*, 2002;22:4591–9; Bender et al. *J Neurosci*, 2003;23:6826–36), leading to a shift in the activation curve for the resultant h-current, I_h (Chen et al. *Nat Med*, 2001;7:331–7). I_h is also modified in entorhinal cortical (EC) layer III neurons during the process of epileptogenesis as my colleagues and I have recently demonstrated (Shah et al. *Neuron*, 2004;44:495–508). Interestingly, in these neurons I_h is downregulated within 24 hr of experimentally induced seizures and remains substantially reduced for at least 1 week following their termination (Shah et al. *Neuron*, 2004;44:495–508). The decrease in I_h occurred prominently in the dendrites. As a consequence, excitatory synaptic potential (EPSP) integration was reduced, resulting in a higher propensity for action potentials to occur. Thus, the excitability of individual EC layer III neurons was considerably enhanced and can be predicted to cause enhanced network activity of the EC. Indeed, electroencephalographic (EEG) recordings showed interictal spikes in the EC during this time period, suggesting that EC neuronal network excitability was increased in vivo. Alterations in EC neuronal network activity are particularly significant since EC layer III neurons provide the predominant excitatory drive to hippocampal CA1 neurons during chronic TLE. Hence, I_h plasticity in EC neurons may be an important factor in the development of chronic TLE, and upregulation of I_h may be therapeutically beneficial in the treatment of the disorder.

PLASTICITY OF LOW-THRESHOLD CURRENTS IN EPILEPSY

H. Beck (University of Bonn Medical Center, Department of Epileptology, Germany)

Seizures potently modify the expression of voltage-gated ion channels in neurons, leading to changes in intrinsic firing properties. Recent data indicate that changes in the expression and modulation of voltage-gated currents active in the subthreshold potential range may be particularly important. This presentation will therefore focus on epilepsy-related changes in low-threshold ion channels, such as T-type Ca^{2+} currents, persistent Na^{+} currents, and different types of K^{+} currents. The molecular mechanisms underlying changes in these current types will be discussed, as well as how changes in these currents shape discharge behavior of hippocampal neurons in the chronically epileptic brain.

REORGANISATION OF GLUTAMATERGIC AND GABAergic PATHWAYS DURING EPILEPTOGENESIS

M. Esclapez INSERM U751, Falculté de Médecine de la Timône, Marseille, France

Temporal Lobe Epilepsy (TLE), one of the most common forms of partial epilepsy in adult is characterized by the occurrence of spontaneous recurrent seizures associated to the excessive and synchronous discharges of pyramidal cells (PC) which may result from imbalance between excitation and inhibition (E-I). We address this issue in the pilocarpine model of TLE by studying the morpho-functional reorganization of the glutamatergic and GABAergic hippocampal networks and consequences on the E-I balance in CA1 PCs at the different stages of development of the epilepsy. Our data demonstrated cell death of GABA neurons in the stratum oriens of CA1 and in the hilus of the dentate gyrus (DG) that occurred after the status epilepticus (SE). Remaining GABA neurons showed already from the latent period on, a marked up-regulation of the vesicular GABA transporter and synthesizing enzymes of GABA at the gene and protein levels reflecting the hyperactivity of these interneurons. Glutamatergic hilar mossy cells degenerated during the latent period as revealed by the loss of VGLUT1 mRNA-containing hilar neurons and VGLUT1-containing terminals in the inner one-third of the DG molecular layer. Plasticity of glutamatergic neurons, characterized by axonal sprouting of glutamatergic principal cells, was not evident before the end the latent period. Recovery of VGLUT1-immunolabeling in the inner molecular layer started at the end of the latent period and increased massively at the chronic stage due to the progressive development of mossy fibers sprouting. An increased labeling of VGLUT1-containing axon terminals in the CA1-CA3 regions was not detected before the chronic stage. These overall reorganizations and the measures of GABAergic and glutamatergic drives received by CA1 PCs demonstrated that E-I imbalance is an early outcome of SE that evolves dynamically during epileptogenesis in a cell domain dependent manner. Epilepsy may occur when critical E-I imbalance threshold is reached.

Sunday July 2, 2006
9:30–11:30
Ballroom 1
Discussion Group Session
The role of opioids in epilepsy

OPIOID RECEPTORS: WHAT, WHERE AND HOW?

I. Kitchen (University of Surrey, UK)

There are four opioid receptors, three sensitive to the opioid antagonist naloxone (MOP, DOP and KOP) and a related receptor (NOP) that mediates the effect of the endogenous peptide, nociceptin. Three other families of endogenous peptides, (including □-endorphin, dynorphins and the enkephalins) act on the MOP, DOP and KOP receptors. All the receptors are seven transmembrane structures and are G-protein coupled. There are receptor agonists and antagonists available, though not all are sufficiently selective or in vivo active. The characterisation of the receptors and their ligands has been greatly helped by gene knockout mice, created for all four receptors and their peptide families. MOP receptors are widely distributed throughout fore, mid and hindbrain regions, and quantitatively the MOP receptor is the most highly expressed. The DOP receptor shows a more prominent expression in forebrain, whilst the KOP receptor, although widely distributed, is expressed at a much lower level in most rodent species. The NOP receptor also exhibits dense rostral to caudal labeling but with distinct expression patterns compared to MOP, DOP and KOP receptors. The presence of all of the opioid receptors in key motor, limbic, reward, endocrine and sensory structures suggest broad roles for these receptors in many biological functions. Whether there are receptor subtypes is still a contentious issue, and evidence for alternative splicing of the MOP gene might suggest this plays a role in receptor variants. However, some of the evidence that has suggested subtypes of the KOP receptor can be dismissed as misinterpretation of data with nonselective ligands. There is certainly evidence for receptor cross-talk and heterodimerisation of the KOP and DOP receptor has been demonstrated in cell systems. Finally evidence from peptide gene knockouts shows that the ligands act and regulate more than one receptor subtype and that this regulation is region specific.

OPIOID PEPTIDES IN EPILEPSY

G. Sperk (Department of Pharmacology, Medical University Innsbruck, Austria)

The prodynorphin gene is one of three opioid peptide genes. Prodynorphin is processed to various peptides, dynorphin A and B and α– and β-neoendorphin, all of which are C-terminal extensions of Leu-enkephalin. These peptides are of different length, however have similar pharmacological properties. Within the brain, prodynorphin-derived peptides (here termed as dynorphin) are contained mainly in limbic areas such as the hippocampus, amygdala, entorhinal and cingulated cortex. Changes in prodynorphin mRNA and dynorphin-immunoreactivity were extensively investigated in the hippocampus by several groups. In summary, in most models of TLE dynorphin levels decrease in the hippocampus during an initial status epilepticus due to release of the peptide. At the same time, prodynorphin mRNA levels increase in the granule cell layer of the dentate gyrus and in other brain areas indicating its augmented resynthesis. This increase in prodynorphin mRNA is transient and subsides in most models after 24 to 48 hrs. Also the subsequent increases in dynorphin levels are only transient, indicating that the upreguation of dynorphin is dependent on acute seizure activity. In the hippocampus of TLE patients, also pronounced upregulation of dynorphin mRNA is seen in dentate granule cells and dynorphin-immunoreactivity is contained at high concentrations in mossy fibers. It is used as immunohistochemical marker of mossy fibers and depicts aberrant mossy fiber projections to the inner dentate molecular layer in the TLE hippocampus. In contrast the faint dynorphin-immunoreactivity in the outer molecular layer of the dentate gyrus presumably contained in afferent perforant path fibers is reduced in TLE. Dynorphin primarily acts through κ-opiate receptors. In contrast to stimulation of μ-opiate receptors, infusion of dynorphin or of dynorphin agonists like U-54494A exert anticonvulsive actions. Dynorphin thus may act as an endogenous anticonvulsant and its κ-opiate receptors may be a drug target for anticonvulsant treatment.

EVIDENCE FROM GENETIC STUDIES: THE PDYN PROMOTER POLYMORPHISM

F. Zimprich (Department of Neurology, Medical University of Vienna, Austria)

Opioid peptides play an important role in modulating the excitability of many different neuronal networks. There is particularly strong evidence that opioids regulate hippocampal circuits, thus setting the threshold for seizures originating in the temporal lobe.

A key component in the opioid system is the prodynorphin gene (*PDYN*) which codes for dynorphins, opioid peptides with an inhibitory function in the hippocampus. Recently, a polymorphism in the regulatory region of this gene was identified that features a 64 bp long element tandemly repeated one to four times with each repeat containing a transcription factor binding site. Interestingly, this polymorphism was shown to be functional by influencing the activity of the PDYN promoter.

The relevance of this promoter polymorphism has recently been further strengthened by evolutionary genetic studies. A comparison of the sequence of this polymorphism between primates and different human population groups has shown that it has undergone sweeps of strong positive selection during human evolution. Although the exact significance of these findings is still unknown a role of this promoter polymorphism in epilepsies appears likely given the results of several association studies. A meta-analysis of all published studies suggests that alleles with a low-promoter activity predispose patients with a familial background for seizures to temporal lobe epilepsy.

EVIDENCE FROM HUMAN PET STUDIES

M. Koepp (Institute of Neurology, UCL, London, UK)

Background: Opioid peptides act as mediators of use-dependent synaptic activity and as cotransmitters to modulate the actions of the primary transmitter, glutamate. There is a large, sophisticated and at times controversial body of animal data showing endogenous opioid release may occur following induced and spontaneous seizures. There is consensus that endogenous opioids released following seizures contribute to a raised seizure threshold. Previous interictal PET studies in temporal lobe epilepsy (TLE) have shown increased binding in the lateral temporal neocortex with the μ-receptor specific ligand [11C]carfentanyl as well as with the δ-receptor specific ligand [11C]methyl-naltrindole, but no side-to-side differences of [11C]diprenorphine (DPN) binding, which is a partial δ and κ agonist, but antagonist at μ-subtypes. Only dynamic studies, looking at receptor binding in the same subject over time, can prove the role of a given receptor / ligand system in some event. PET studies have shown a dynamic decrease in specific binding of [11C]DPN in association cortices during hyperventilation-induced absences and lower binding in reading-associated areas during reading-induced seizures in reading epilepsy compared to baseline scans.

Rationale: To measure changes in opioid receptor availability following spontaneous seizures in patients with TLE by means of a two-scan paradigm.

Methods: We performed [11C]DPN PET scans as soon as possible after a spontaneous seizure; a second scan aquired after as long a seizure free period as achievable in a given patient served as an intrasubject control. In addition, healthy control subjects were scanned twice in the same manner to establish normal fluctuation of receptor availability.

Results: Large increases of opioid receptor availability were observed specifically in the temporal pole which mediates temporal lobe seizures. These changes correlated with time since the last seizure, but could not be explained by a number of behavioural variables measured.

Conclusion: We were able to show a regionally specific upregulation of opioid receptor availability in the temporal pole and fusiform gyrus on the side of the seizure focus following seizures. This provides direct evidence for opioid receptor plasticity over a time course of hours following neural events.

Sunday July 2, 2006
12:00–14:00
Hall 5A
Bursary Award Symposium
New insights in temporal lobe epilepsy

MICROARRAYS HAVE IDENTIFIED NEW GENES, PATHWAYS AND PROCESSES IN THE NEUROPATHOLOGY OF TEMPORAL LOBE EPILEPSY

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Purpose: Temporal lobe epilepsy (TLE) is a severe type of epilepsy with serious clinical symptoms. The aetiology remains elusive but appears to be multifaceted, with genetic, environmental and developmental factors all implicated. In terms of pathophysiology, the hippocampus appears to be the predominant substrate in this disorder. Therefore, we have investigated genome wide gene expression in the hippocampus of epilepsy patients and normal autopsy controls.

Method: Oligonucleotide microarrays (21,521 genes) were used to compare gene expression of hippocampal resections from hippocampal sclerosis (HS) and nonhippocampal sclerosis (non-HS) TLE patients and autopsy controls using a common reference design. Data were normalised using the Lowess algorithm. Statistical analysis was performed by Statistical Analysis of Microarrays (SAM) and Gene Ontology classification was performed with Panther Software (www.pantherdb.org).

Results: Comparing expression in autopsy controls with HS and non-HS patients, 566 and 642 ($q < 0.002$) genes and comparing HS with non-HS patients, 218 ($q < 0.005$) genes were differentially regulated. Several genes were validated by qPCR. Pathway analysis identified down regulation of glutamatergic pathways in non-HS and more severely in HS patients. Gene ontology analysis implicated immunity and defense genes in HS patients ($p < 0.002$) and to a lesser extent also in non-HS patients.

Conclusion: The use of pathway and gene ontology analysis on our data set from clinically well defined TLE patients provides a unique, unbiased insight in the neuropathology of the human epileptic hippocampus. Next to obvious differences, striking similarities were found between HS and non-HS epileptic hippocampi.

INNATE AND ADAPTIVE IMMUNE MECHANISMS DURING EPILEPTOGENESIS AND SPONTANEOUS SEIZURES: EVIDENCE FROM EXPERIMENTAL MODELS AND HUMAN TEMPORAL LOBE EPILEPSY

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Purpose: The rodent brain shows a rapid and lasting innate inflammatory response to seizures involving glial and neuronal production of inflammatory mediators. Inflammatory processes decrease seizure threshold and promote neurodegeneration. We explored the relative contribution of innate and adaptive immunity in perpetuating brain inflammation during epileptogenesis and in the chronic phase of spontaneous seizures (SS).

Method: The immunohistochemical pattern of microglia (CD-11b/c, HLA-DR), T-(CD3, CD4, CD8) and B-lymphocytes (CD45RA), monocytes/macrophages (ED-1, CD68), NK (NKR-P1A) and granulocytes (HIS48) was assessed in rats 4-36h and 3-7d after the onset of pilocarpine-induced status epilepticus (SE) and during SS, and in hippocampal specimens from medically intractable TLE with or without hippocampal sclerosis (HS).

Results: Activated IL-1beta-expressing microglia was observed within 4h after SE in rat forebrain while abundant parenchymal macrophages were found from 36h onwards. Both cell populations persist in rats with SS. Granulocytes appeared between 36h-3d only. Scarce B and T-lymphocytes and NK cells ($\geq$3d) were found associated with microvessels. No changes occurred in pilocarpine+phenobarbital treated rats. In human TLE with HS, IL-1beta-expressing microglia and clusters of perivascular monocytes/macrophages occurred in the hippocampus; CD3- and CD8-positive cells were scarce and B cells were lacking.

Conclusion: Microglia activation sustains the early phases of inflammation after SE and, together with macrophages, contributes to its persistence both in rat and human epileptic tissue. Granulocytes are transiently recruited during epileptogenesis while B-, T-, NK-cells are scarce or absent. These findings together with functional studies in experimental models strongly suggest that innate, but not adaptive, immunity significantly contributes to epileptogenesis. Supported by Fondazione Mariani Onlus (A.V.) and National Epilepsy Fund (E.A., K.B.).

BRAIN MATURATION AND THE EVOLUTION OF DIFFERENT AXES OF TEMPORAL LOBE SEIZURE SEMIOLOGY

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Purpose: To examine objectively the effects of age on different aspects of temporal lobe (TL) seizure semiology.

Method: We performed a video analysis of 605 archived seizures from 155 consecutive patients (85 males; 95 with hippocampal sclerosis (HS); age 10 months to 49 [mean 17.1 $\pm$ 12.6] years) selected by post temporal lobectomy seizure-free outcome. Beside semiological seizure classification (*Epilepsia* 1998;39:1006–13.), we assessed age-dependency of four axes of seizure semiology: (i) number of different lateralising signs (*Brain* 2001;124:1683–1700.), occurrence of ictal (ii) emotional and (iii) vegetative signs, as well as (iv) the ratio of motor seizure components (*Epilepsia* 2002;43:638–43.).

Results: One-hundred patients were <12 and 29 of them <6 years of age. From the 155 patients, 39 had ictal emotional and 51 had vegetative signs at least once during their seizures. Altogether 369 (median: 2/patient) different lateralising signs were recorded. Univariate analysis of variance (ANOVA) revealed that age of patients, controlled for the presence of HS, showed an association with the number of different lateralising signs ($p < 0.001$) and an inverse correlation with the ratio of motor seizure components ($p < 0.001$). The occurrences of emotional and vegetative signs were independent of age.

Conclusions: Our findings support that brain maturation significantly influences the evolution of some important aspects (motor seizures, lateralising signs) of TL seizure semiology. Conversely, other aspects (emotional and vegetative signs) are independent of the maturation process. According to our knowledge, this is the first age-dependent assessment of TL epilepsy comprehensively analysing different axes of seizure semiology.

LIMBIC ENCEPHALITIS—A FREQUENT CAUSE OF ADULT-ONSET MEDIOTEMPORAL LOBE EPILEPSY

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Purpose: Mediotemporal lobe (MTL) epilepsy (MTLE) accounts for the majority of human localisation-related epilepsies. In the majority of cases, the morphological substrate of the epileptogenic area is Ammon's horn sclerosis (AHS). In these cases, epilepsy usually starts in childhood. For adult-onset MTLE, the aetiology, disease course, and therapeutic outcome are unknown.

Method: From the database of the Department of Epileptology, we collected all patients between 1 January 1999 and 30 September 2005 fulfilling the following criteria: (1) Manifestation of epilepsy at the age of >20 years. (2) Time between disease manifestation and presentation <6 years. (3) History, brain MRI and neuropsychological testing available. (4) MTL lesion on brain MRI. Patients were diagnostically classified by histopathology, autoantibodies, brain MRI, brain PET, neuropsychology, and clinical parameters. Outcome was assessed based on seizure frequency and neuropsychological performance.

Results: The causes for the 84 cases were: limbic encephalitis 25% (11% definite, 14% probable), tumours 21% (14% WHO I°/II°, 7% WHO III°/IV°), AHS 21%, amygdala sclerosis 12%, posttraumatic 6%, other 15%. After surgical treatment, 6/9 AHS and 9/12 tumour patients (WHO I°-IV°) with follow-up assessment were seizure-free. 11/13 LE cases improved on immunotherapy.

Conclusion: Quite unexpectedly, the most frequent cause of adult-onset MTLE in this sample of early-on diagnosed patients from a tertiary epilepsy referral centre is limbic encephalitis. Thus, immune-mediated epilepsy plays the most important role for adult-onset MTLE. The outcome of adult-onset MTLE is generally favourable, especially for the AHS and tumour patients if surgical treatment is possible, and for limbic encephalitis if (early) immunotherapy is provided.

MAGNETIC RESONANCE SPECTROSCOPY OF THE THALAMUS IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY AND HIPPOCAMPAL SCLEROSIS

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Purpose: To investigate possible neuronal dysfunction of the thalamus in patients suffering from mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE/HS).

Method: We examined 10 epilepsy patients with MTLE/HS (7 females, 3 males) and 11 healthy volunteers (8 females, 3 males). The mean age in the patient group was 40.64 ± 8.96 years (from 21 to 55 years; median 42 years); the mean age in the control group was 40.40 ± 7.53 years (from 28 to 51 years; median 40.50 years). We performed ^{1}H MR spectroscopic imaging of the right and left thalamus in all patients and controls. In addition both hippocampi in a patient group were investigated by MRS-single voxel technique. MR examinations were carried out on a 1.5 T Siemens scanner. A *t*-test was performed to compare the distribution of NAA concentration within thalamic and hippocampal structures.

Results: Statistical analysis of compared data in both groups demonstrated that the thalamic NAA/Cr + Cho ratio was significantly decreased in patients with MTLE as compared to healthy controls. Comparison of right and left thalami separately, between patients and healthy controls, also showed statistically significant reduction of NAA/Cr + Cho ratio. A significant correlation between the patients' thalamic NAA/Cr + Cho values and the duration of the epilepsy and their age was revealed. When comparing MRS data of thalamus ipsilateral to diseased hippocampus no significant decrease in NAA/Cr + Cho ratio was observed, however the significant reduction of these values was present in the contralateral thalamus.

Conclusion: Our results suggest widespread metabolic dysfunction and possible involvement of bilateral subcortical structures in patients with MTLE/HS.

IMPACT OF INTERICTAL DISCHARGES ON RESTING STATE BRAIN ACTIVITY

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Purpose: A brain network comprising precuneus, medial frontal and temporoparietal cortices is overall more active during conscious rest than during goal-directed behaviour but also than during states of reduced consciousness. These areas have been proposed to underpin a "default mode" of brain function. We have previously shown their activity to decrease during generalised spike and wave discharges (GSW) in absence epilepsy, with associated thalamic activity increase. We investigated whether there is a common association between interictal discharges (ID) and deactivation of "default mode" brain regions in focal epilepsy.

Method: Using continuous electroencephalography-correlated functional magnetic resonance echo planar imaging (EEG-fMRI) during relaxed wakefulness we investigated the blood oxygen level-dependent correlates of ID in 19 consecutively recruited patients with focal epilepsy who had 1-20 ID/minute.

Results: We found significant ID-related deactivations in the named "default mode" brain regions in the 9 patients with temporal lobe epilepsy (TLE) at the group level. Significant activations were seen in the ipsilateral medial temporal lobe. No significant deactivations were found in the 10 patients with extra-TLE.

Conclusion: TLE and extra−TLE seem to be distinct with respect to their perturbation of resting state brain activity. Deactivation of brain areas that are active during conscious rest by temporal IDs suggests a widespread disruption of normal brain function and may contribute to cognitive dysfunction. In the propagation of ID in TLE, the hippocampus may have an analogous role to that of the thalamus in GSW, both resulting in deactivation of "default mode" brain regions.

CLOSING REMARKS: MESIAL TEMPORAL LOBE EPILEPSY: WHAT HAVE WE LEARNED?

J. Engel Jr. (UCLA, Los Angeles, CA, USA)

Mesial temporal lobe epilepsy (MTLE) is arguably the most common epilepsy condition, and among the most pharmacoresistant. Research to elucidate the fundamental neuronal mechanisms leading to the development of mesial temporal lobe epilepsy and to the initiation of limbic seizures has been greatly facilitated due to opportunities for invasive basic research on patients with MTLE in the epilepsy surgery setting, and a number of excellent animal models of this condition. Results of this research will not only provide insights into novel targets for treatment, but ideally they will lead to effective approaches for the prevention and cure of MTLE. The papers in this symposium represent the application of diverse, cutting-edge, research technologies in both patients with MTLE and animal models. Microarray analysis of gene expression and investigation of inflammatory processes are revealing the molecular basis of epileptogenesis, while functional magnetic resonance imaging and magnetic resonance spectroscopy provide crucial evidence for widespread neuronal networks that are involved in the manifestation of limbic seizures. Both the molecular and systems approach also must take into account the fact that the maturational state of the brain influences epileptogenesis and epileptogenicity. Studies like these are ongoing at hundreds of laboratories throughout the world, and form the basis of the transitional research necessary for realizing our goals of improved treatment, prevention, and cure for temporal lobe epilepsy.

Sunday July 2, 2006
12:00–14:00
Hall 5B
Neurobiology Symposium
In vivo imaging of neurobiology of epileptogenesis

MRI AND MRS AS NONINVASIVE TOOLS TO INVESTIGATE EXPERIMENTAL MODELS OF EPILEPSY

D. Gadian (UCL Institute of Child Health, UK)

Magnetic resonance imaging (MRI) and spectroscopy (MRS) techniques have found widespread application in the investigation of patients with epilepsy. Applications in animal models of epilepsy are perhaps less well established, but they provide important opportunities for probing pathophysiological changes that may be difficult to characterise in humans. A key feature of animal studies is that they enable us to carry out longitudinal examinations, from prior to the onset of seizures onwards. Comparisons of data obtained before, during and after seizures can greatly facilitate the detection of brain abnormalities that may be functionally important and yet cause only subtle changes in magnetic resonance characteristics. Moreover, the longitudinal magnetic resonance data can be correlated with end-point histopathology.

This presentation will report on our ongoing clinical and experimental magnetic resonance studies of status epilepticus. Convulsive status epilepticus (CSE) is the most common medical neurological emergency

in childhood, and is associated with significant morbidity and mortality. Although many patients will have no obvious sequelae, possible outcomes from childhood CSE include epilepsy as well as permanent neurological or cognitive deficits. However, much remains to be learned about the pathophysiology associated with CSE and about the relationship between CSE and subsequent epilepsy. Modern magnetic resonance methods, applied both in patients and in experimental models, provide an opportunity to understand in more detail the temporal evolution of brain abnormalities associated with CSE. This may in due course lead to the development of new therapeutic approaches.

TRACT TRACING OF CIRCUITRY REORGANISATION DURING EPILEPTOGENESIS WITH MRI

O. Gröhn (A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Finland)

Mossy fibers are granule cell axons that can loose their normal postsynaptic cellular targets due to neurodegeneration caused by epileptogenic brain insults. As a consequence, mossy fibers sprout and innervate abnormal targets. Even though it is still under dispute whether mossy fiber sprouting is a critical factor for seizure generation, it has been shown to be present both in mouse, rat, and human brain with symptomatic epilepsy. The presence of aberrant sprouting before spontaneous seizures provides a rationale for its use as a surrogate marker for epileptogenesis.

Mn^{2+}-enhanced magnetic resonance imaging (MEMRI) has potential to reveal functional, structural and connectional alterations in high spatial resolution. We injected Mn to entorhinal cortex of rats to characterize activity-dependent plasticity in the mossy fiber pathway after kainic acid induced status epilepticus in rats. High-resolution 3D T_1-wt MRI at 4.7T and volume-rendered 3D reconstruction allowed for visualization of the lamellar organization of the mossy fibers in vivo. Increased accumulation of Mn into to dentate gyrus and CA3 of rat hippocampus was correlated with histologically determined mossy fiber sprouting. Our preliminary results show that also systemically administered Mn accumulates in the same hippocampal subregions and may provide a robust MEMRI approach for detection of mossy fiber sprouting, in vivo.

The present study demonstrates that MRI can detect plasticity changes in axons. This is expected to be of great value as axonal plasticity is a part of several pathologic processes, including epileptogenesis.

IMAGING EPILEPTOGENESIS INDUCED BY FEBRILE SEIZURES

T. Baram (University of California at Irvine, USA)

Finding biomarkers for the epileptogenic process is important, because it will allow to monitor this process, to determine the mechanisms involved, and eventually, to intervene and abort the development of Epilepsy. Signal changes on magnetic resonance imaging (MRI) may provide early markers for changes in neuronal integrity that may promote epileptogenesis. In addition, this tool is helpful, because it is non-invasive and can be used repeatedly. We have previously established that prolonged experimental febrile seizures (FS) provoke an epileptogenic process that results in frank Epilepsy in ~35% of seizure-experiencing immature rats (Dube et al., *Brain*, 2006). Here we discuss the use of serial MRIs, obtained before and at several time-points following the seizures, (Dube et al., *Ann Neurol*, 2004) as a biomarker of the epileptogenic process.

A 7 Tesla magnet provided detailed anatomy of brain regions, including the hippocampus and limbic cortices (piriform and entorhinal), that are involved in FS and in its putative consequence in humans, temporal lobe epilepsy (TLE). Experimental FS evoked both visually apparent changes as well as deviations from normal T2 values, determined using 'absolute' T2 maps. To understand the meaning of these changes in T2, that were found 1,8 and 30 days after the seizures, we studied the presence of neuronal injury and death (damage). The signal changes in hippocampus, amygdala and piriform/ entorhinal cortex were not accompanied by evidence of neuronal injury or death in these regions, as assessed using the Fluoro-Jade method. In addition, the T2 signal changes were correlated with water content as determined in tissue samples from imaged rats. In summary, experimental prolonged FS provoke epileptogenesis, and to abnormal MRI signal in temporal lobe structures, that may denote pathological cellular processes that promote epileptogenesis.

THE USE OF IMAGING TECHNIQUES TO UNDERSTAND EPILEPTOGENESIS IN AN ANIMAL MODEL OF TEMPORAL LOBE EPILEPSY

A. Nehlig (INSERM U 666, Faculty of Medicine, Strasbourg, France)

In patients with temporal lobe epilepsy (TLE), hippocampal sclerosis and lesions of the temporal lobe, amygdala and thalamus are frequently observed. Their respective role in epileptogenesis is unclear. To identify the structures critical in the epileptogenic process, we used the lithium-pilocarpine model of epilepsy which reproduces most clinical and neuropathological features of TLE. While all adult rats subjected to status epilepticus (SE) become epileptic, only a subset of 21-day-old (PN21) rats develop epilepsy. The use of T_2-weighted MRI (4.7 T) revealed that, in adult rats and PN21 rats that became epileptic, entorhinal and piriform cortices were the initial structures exhibiting a significant signal change (as soon as 6 h after SE onset) reflecting rapid and massive neuronal injury and death. In the subset of PN21 rats that did not become epileptic, the absence of signal in the piriform and entorhinal cortices confirmed their critical role in the early establishment of epileptic networks. In contrast, MRI signal change in the hippocampus appeared only 36–48 h after SE onset and progressively worsened to sclerosis. The use of ^{13}C NMR spectroscopy showed that the flux through the glutamate-glutamine cycle was decreased in temporal cortices but not in hippocampus while astrocytic metabolism was unchanged in both regions. Moreover, metabolic levels measured in the hilus of the dentate gyrus of adult and PN21 epileptic rats by ^{14}C-2-deoxyglucose autoradiography was normal during the latent and chronic phases although neuronal loss reached 60–75%. This relative hypermetabolism reflects the involvement of the hilus during circuit reorganization and epilepsy. In conclusion, these data demonstrate the usefulness of imaging techniques in the identification of the key structures at various steps of the epileptogenic process.

Monday July 3, 2006

Monday July 3, 2006
7:30–9:00
Hall 5A
Teaching Session
Coping with the side effects of antiepileptic drugs (AEDs)

ASSESSMENT OF ADVERSE EFFECTS: METHODOLOGICAL ISSUES

E. Perucca (Institute of Neurology, IRCCS C. Mondino Foundation, and Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Italy)

Because antiepileptic drugs (AEDs) have a narrow therapeutic index, adverse effects (AEs) represent a major determinant of health-related quality of life in persons with epilepsy. Optimizing the assessment of AEs is essential not only in differentiating risk/benefit ratios of AEDs in formal studies, but also in ensuring best care in clinical practice. There is no simple methodological approach that can be recommended in all settings, and complementary information can be obtained with different methods. Selection and assessment bias are best minimized with double-blind controlled trials, but enrolment criteria and dosing regimens in these trials may be poorly representative of routine practice, and sample size and trial duration are usually inadequate to identify rare or delayed AEs. Relying on spontaneous reports for detection of AEs leads to underestimation of AEs, whereas use of checklists leads to overestimation, and neither approach is free from bias. Specialized tests and testing protocols may be required to assess certain categories of AEs, such as cognitive dysfunction or metabolic effects. Elusive AEs include those which are rare, those which only occur in special patients' groups (for example, young children), and those which mimic the manifestations of underlying pathology or reproduce disorders which have a high incidence of spontaneous occurrence. Further work is needed to optimize assessment protocols to be used in routine clinical practice. Recent work suggests that use of standardized self-administered questionnaires can be valuable in identifying AEs in individual patients, and sensitizing physicians to the need of reducing the AEs burden.

PREVENTING AND MANAGING SIDE EFFECTS AT ONSET OF TREATMENT

E. Ben-Menachem (Institution for Clinical Neuroscience and Physiology, Sahlgrenska University Hospital, Göteborg, Sweden)

When clinical trials are performed especially for approval of drugs for epilepsy, only ideal patients are included that fit inclusion criteria and no exclusion criteria. When a drug is then marketed, it is used in patients who have many risk factors, many concomitant medications and comorbidities. These patients are those who will be most prone to experience side effects not even seen in the clinical trials when starting treatment. The recommendations for adequate dose level and titration rates are usually based on rigid protocols in the clinical trials. These in turn are built on hypotheses about the adequate dose most effective and tolerated by patients which, in turn, are usually founded on animal studies and phase I normal control trials in healthy people not on concomitant antiepileptic drugs.

Because the results of clinical trials determine that the majority of the included patients tolerate a certain titration rate and dose level, these become the recommended doses and methods for starting the drug in all patients after approval of the drug. Many examples, however, are now in the literature about how these recommendations can be inadequate, causing side effects in unsuspecting patients.

The side effects most often seen are somnolence and other sleep disturbances, headache, dizziness, ataxia, rash and other allergic reactions, depression and cognitive and behavioral changes.

Side effects at initiation can be prevented using two procedures: slow titration along with titration of dose to the effective level where the patient has least amount of seizures with least amount of side effects. That way the patient may be maintained at dose levels far below that recommended by the pharmaceutical company. This, however, is not accomplished quickly and can even take several months. Of course it is desirable to initiate an effective treatment all at once at an effective level, but that is exactly how acute side effects appear. Patients with refractory epilepsy with a chronic seizure condition are usually in no hurry. However, the situation may be different in specific cases and in patients with new onset epilepsy. Still, even in the naïve patient just starting an AED, slow titration can improve compliance, minimize side effects and increase the trust of the patient in the doctor and the treatment itself.

With slow titration to effective dose, with the patient keeping a record of seizure frequency and side effects, then if acute side effects occur the dose can be down titrated to the level below where no side effects had appeared previously. Often waiting at that lower level for an extended period enables the increase in dose later on, enhancing the ability of the patient to remain on the drug.

The term: "start low-go slow" applies for the initiation of most AEDs and is the most advantageous way to prevent and manage side effects at onset of treatment.

RECOGNISING AND MANAGING SIDE EFFECTS EMERGING DURING LONG-TERM TREATMENT

P. Genton (Centre Saint-Paul-HHG, France)

While severe idiosyncratic side effects (SE) of antiepileptic drugs (AED), and acute, often transient SE at initiation of therapy are the main concerns of epileptologists, patients will often complain about the long-term, daily, "benign" SE, especially when they emerge progressively, or may exhibit the long-term, hidden but dangerous consequences of long-term therapy. Most of these used to be of little concern to doctors, and were considered "a price to pay," but modern attitudes stress the importance of quality of life: a longlasting problems like epilepsy should be controlled with minimal somatic and social impairment. Most of such SE are fairly common, but patients exhibit specific sensitivities that may be related to genetic factors: this sector of epileptology is a potentially fertile ground for pharmacogenetic research. Beneficial SE may also be noted, e.g., as some AED are efficient mood regulators and painkillers.

Long-term deleterious effects are often interrelated, usually multifactorial, occur insidiously, and recent concerns have focused on:

- cosmetic SE, with mainly weight changes (gain with valproate, vigabatrin, gabapentin and pregagalin, and to a lesser extent with carbamazepine, or loss with topiramate, felbamate and zonisamide), but also acnea, hirsutism, gum hyperplasia and coarse facies (phenytoin).
- cognitive SE, with variable iimpact of AEDs, the highest risks occurring with topiramate.
- effects on mood and behaviour, which may be superimposed on disease-related anxiety, depression, or psychotic traits.
- effects on bone mineral balance, with a clear increase in severity of age-related osteomalacia due to enzyme-inducing AEDs that interfere with vitamin D metabolism,
- effects on reproductive and sexual functions.

The right attitude is to inform patients about potential risks, putting them into perspective in terms of incidence and severity, and to review treatment whenever a specific side effect is present or very likely in a given patient. The relationship between doctor and patient with epilepsy is necessarily a long-term one, and should be based on trust and clarity.

RECOGNISING AND COPING WITH SIDE EFFECTS FROM AED INTERACTIONS

G. Krämer (Schweiz Epilepsie-Zentrum, Zurich, Switzerland)

Interactions of antiepileptic drugs (AEDs) are a common problem in clinical practice. As long as drugs are prescribed by the same physician (e.g., neurologist or neuropediatrician) dosage adjustments are more common and prevent increased side effects. However, patients are treated by several physicians simultaneously or my have acute comorbidities requiring additional drugs.

In women AEDs may influenec endogenous as well as exogenous hormones and vice versa. AEDs that induce hepatic microsomal enzymes interact with hormonal contraception by increasing the metabolisation of estrogen metabolism and the protein binding of progesterone's and decreasing concentrations of both hormones. Thus they are reducing the efficacy of oral contraceptives (OC) and incraesing the isk of unplanned pregnancies. Recently it was discovered that at least one AED (lamotrigine) is signifantly influenced by hormones (OC as well as pregnancy).

In elderly people with epilepsy, drug interactions are of sepcial importance. In principle, they are not different from those in younger patients, but they are more common and their effects are often stronger. The almost always present polytherapy in elderly patients is the cause of an increased incidence of interactions which, in turn, can result in intoxications or losses of activity or the antiepileptic drugs as well as other undesired drug reactions. The few investigations performed on this topic have found a prevalence for potential interactions of 2–17% of all drug prescriptions in 6–42% of all elderly patients.

Another example are patients with brain tumors. In these patients drug interactions can cause insufficient tumor or seizure control or lead to unforeseen toxicity. The interactions between AEDs, chemotherapeutic drugs, and corticosteroids are of special importance. Conversely, chemotherapy may lower serum concentrations of AEDs and corticosteroids.

Monday July 3, 2006
7:30–9:00
Hall 5B
Teaching Session
To treat or not to treat the EEG in paediatric epilepsy syndromes

THE AMBIGUITY OF INTERICTAL SPIKES AND SUBCLINICAL SEIZURES

U. Brandl (Friedrich-Schiller-Universität, Jena, Germany)

No abstract received.

SUPPRESSION OF INTERICTAL EPILEPTIFORM DISCHARGES IMPROVES BEHAVIOUR IN CHILDREN WITH EPILEPSY

R. Pressler (Department of Clinical Neurophysiology, National Hospital for Neurology, UK)

Treatment of interictal discharges can improve behaviour in children with epilepsy

Increased behavioural problems in children with epilepsy are a consequence of various factors including underlying brain lesion, age of onset, antiepileptic drugs, psychosocial issues**,** seizure type and frequency, and interictal EEG abnormalities. Suppression of discharges will improve behaviour in children with nonconvulsive status epilepticus presenting as pseudo-dementia or more subtle behavioural changes, and in children with prolonged nocturnal discharges such as ESES. The effect of intermittent interictal EEG discharges on behaviour and cognition is still controversial. Whether cognitive and behavioural problems can be directly caused by discharges or are a coexisting phenomenon can be determining through improvement of cognition and behaviour, if EEG discharges are suppressed.

In children with drug resistant epilepsy and learning difficulties suppression of discharges was associated with improvement in global rating of psychosocial function. In children showing interictal discharges but without epilepsy, suppression of discharges showed no definite effect. In children with well-controlled or mild epilepsy, improved behaviour was only observed in children who showed a reduction of discharges during active treatment, but not in patients without a change in discharge rate.

The issue of 'treating the EEG' remains controversial. The question is not whether to treat the EEG, but whether seizures, so subtle as to be recognisable only by EEG and behavioural monitoring, produce disability sufficient to justify treatment.

LESSONS FROM CHILDREN WITH BENIGN IDIOPATHIC FOCAL EPILEPSIES

T. Deonna (Neuropaediatric Unit, CHUV, Lausanne, Switzerland)

There is a consensus that most children with benign partial epilepsies (rolandic epilepsy) do not need prophylactic antiepileptic drug therapy to prevent recurrence of seizures. These are usually short, harmless, of low frequency and occur mainly during sleep. There is no morbidity associated with the seizure, despite the sometime alarming symptoms (sylvian seizures with pharyngeal contractions). A different problem is the issue of trying to suppress EEG discharges which are now suspected to be the potential cause of various cognitive/behavioural problems, increasingly reported in these children, despite normal intelligence. Recent longitudinal studies have shown that these difficulties sometime arise and regress in direct relationship with the activity of the epileptic disease as shown by the epileptic EEG activity during the waking and sleep state. Knowing also that prolonged acquired oromotor, speech and language problems can develop in the course of initially typical BEPRS, there is now some basis to think that even some more minor cognitive/behavioural problems could also be of direct epileptic origin.

When a child is diagnosed as having BEPRS and has some behavior/cognitive problems it is usually uncertain whether it could be is the direct consequence of the paroxysmal EEG epileptic activity present at the time, because there may be many other possible explanations. The same is true in those children who had already been recognized and treated beforehand for a developmental disorder, a learning disability or a behaviour problem. When the problems are clearly of recent onset or that a cognitive stagnation, regression or marked fluctuations of the symptoms can be documented, an antiepileptic drug trial aiming at suppressing the EEG discharges is justified. If in doubt, a documentation of the present cognitive status and school achievements with close clinical and EEG follow-up every few months may be proposed before a decision is made. Some EEG features, in addition to the typical FSW have been found to predict a higher risk of future cognitive problems. At the present time, no single antiepileptic drug or controlled group study has definitively proven the benefit of this approach, but there are several suggestive ongoing trials clearly justifying an open, individually based attitude.

LESSONS FROM CHILDREN WITH EPILEPTOGENIC LESIONS

H. Holthausen (Behandlungszentrum Vogtareuth, Germany)

Background: There is increasing data that in children with benign idiopathic focal epilepsies (BIFEC) or just benign focal idiopathic epileptiform discharges of childhood (BIFEDC) a complete suppression of the epileptiform discharges in addition to seizure control may have a favourable impact on their cognition and / or behaviour. Whether this is also the case in children with epileptogenic lesions is even less well documented.

Patients and methods: Patient groups have been selected from the Vogtareuth epilepsy-surgery-database because of the meticulous documentation of seizures, ictal EEG, interictal EEG, cognition and behaviour and of the situation on follow-up investigations.

3 Groups were selected:

Group 1: patients with one type of etiology at one localization–chosen were patients with frontal Type II-FCD.

Group 2: Patients with marked cognitive problems, who have been operated on despite control of clinical seizures, because it was hypothesized that their cognitive deficits were the result of subclinical seizure spread / secondary bilateral synchrony as documented during presurgical evaluation.

Group 3: Patients with BIFEDC in addition to their symptomatic focal epilepsies in whom their BIFEDCs were successfully suppressed by change of medication.

Results:

Group 1: A clear tendency was noticed that it is the combination of 1) early onset of epilepsy plus 2) spread of epileptiform activity to the contralateral hemisphere which puts children at a very high risk for a mental retardation.

Group 2: On follow-up investigations all patients showed a better developmental pace; best results were achieved in patients with a relative late onset and a short duration of the epilepsy.

Group 3: In 50% of the patients of this subgroup a marked improvement in their cognition and / or behaviour was noticed.

Conclusions: With respect to mental development and / or behaviour, there are subgroups of patients with symptomatic focal epilepsies for which suppression of "interictal" sharp waves or subclinical seizures may be as equally important as is the control of clinical seizures.

Monday July 3, 2006
7:30–9:00
Hall 5C
Teaching Session
Diagnostic methods in presurgical workup—what's new?

MODELLING AND VISUALISATION OF BRAIN ELECTRIC ACTIVITY IN EPILEPSY

M. Scherg (University Hospital Heidelberg, Germany)

No abstract received.

ADVANCED STRUCTURAL AND FUNCTIONAL MRI TECHNIQUES IN EPILEPSY

L. Lemieux (Institute of Neurology, University College London, UK)

The principal aims of developments in MRI applied to epilepsy are the detection and visualisation of ever more subtle abnormalities and networks that sustain epileptic activity, with a view of improving patient management. Furthermore, advanced MRI can provide quantitative morphological, connectivity and perfusion data which are essential to study the mechanisms that underlie epileptogenicity, its consequences and the effects of treatment. Recent developments from our lab in the following areas will be reviewed and illustrated with data acquired in patients: structural MR acquisition sequences (diffusion tensor imaging, T1 and T2 mapping and magnetisation transfer ratio); morphological and connectivity image analysis (tractography, segmentation and quantification of change in serial data); functional MRI (language pathway mapping and EEG-correlated fMRI; BOLD and perfusion).

THE NEW AND THE VERY NEW PET TRACERS IN EPILEPSY

M. Koepp (Institute of Neurology, UCL, London, UK)

Studies using positron-emission-tomography (PET) have advanced our pathophysiological and biochemical understanding of focal and generalised epilepsies. Neurotransmitters are directly responsible for modulating synaptic activity and PET allows quantification of specific ligand-receptor relationships which are important for epileptogenesis and spread of epileptic activity. The following neurotransmitter systems have recently been examined: (1) GABAergic neurotransmission using [^{11}C]flumazenil, which images the benzodiazepine/GABAA-receptor complex; (2) serotonergic neurotransmission using alpha[^{11}C]methyl-tryptophan, which reflects the uptake of tryptophan into the brain and in physiological conditions it is thought to relate to the synthesis of serotonin, using either [^{18}F]MPPF, [^{18}F]FCWAY or [^{11}C]WAY-100635 reflecting 5-HT$_{1A}$ receptor binding, (3) glutamatergic neurotransmission using [^{11}C]ketamine or [^{11}C]CNS5161 as potential PET tracers for open NMDA receptor associated ion channels; (4) opioid neurotransmission using the μ-receptor specific ligand [^{11}C]carfentanyl, the δ-receptor specific ligand [^{11}C]methylnaltrindole and [^{11}C]diprenorphine, which is a partial δ and κ agonist, but antagonist at μ-subtypes; (5) dopaminergic neurotransmission using [^{18}F]fluoro-L-Dopa and the D2-receptor antagonist [^{18}F]Fallypride. In this review, we aim to define the potential of the new PET tracers in clinical and experimental epileptology.

MAGNETOENCEPHALOGRAPHY IN PATIENTS WITH EPILEPSY—AN UNDERUSED TOOL

H. Stefan (University Erlangen-Neurber, Neurological Clinic, Epilepsy Centre, Germany)

No abstract received.

Monday July 3, 2006
9:30–11:30
Hall 1
Chairmans Symposium
Promoting European collaboration in epilepsy research

EUROPEAN COLLABORATIVE INITIATIVES IN BASIC SCIENCE, EXAMPLES FROM EPILEPSY RESEARCH

G. Avanzini (Istituto Nazionale Neurologico C.Besta, Milano, Italy)

As many as 6 million people in Europe currently have active epilepsy that has major implications not only for health but also for independent living. The synergy between experimental and clinical research led to significant advances in identifying new etiological factors (e.g., cortical dysplasia, epilepsy genes) pathogenetic mechanisms (e.g., channel dysfunction) and rational therapeutic strategies (e.g., molecules targeted to specific epileptogenic mechanisms, new surgical approaches). However Several important problems are still open.

Although the European epileptological community has an important tradition of scientific research contributing by one third to the worldwide scientific production in the field (see the European White Paper on Epilepsy, 2001), the great potential of collaborative research has been so far underexploited because of a lack coordination.

In 2005 The EPICURE multisciplinary integrated project has been developed aimed at mobilizing the potential synergies of 30 research groups from 14 European countries.

The project will last 4 years and will include:

- identification of epilepsy genes and characterization of the functional alteration affecting the encoded proteins, in relation to their epileptogenic function
- identification of acquired channelopathies and network reorganisation in human temporal lobe epilepsy and clinically relevant animal models, with the aim of identifying protective strategies and new therapeutic targets
- identification of mechanisms controlling age related epileptogenesis in children suffering from brains maldevelopment
- development and testing of new strategies for prevention and treatment of epilepsies and identifications of mechanisms which account for pharmacoresistance

The expected results will advance European epilepsy research and bring about novel therapeutic benefits to patients.

EURAP: A REGISTRY OF ANTIEPILEPTIC DRUGS AND PREGNANCY AND AN EXAMPLE OF A EUROPEAN COLLABORATIVE INITIATIVE

T. Tomson ((Karolinska Institutet, Sweden)

The treatment of epilepsy during pregnancy and the potential teratogenic effects of antiepileptic drugs (AEDs) and other fetal and maternal risks associated epilepsy during pregnancy is one of the most important health issues for women with epilepsy. Yet we are short of data necessary for a rational approach to the management of women with epilepsy that are of childbearing potential, because we lack conclusive comparative data on the teratogenic potential of different AEDs.

This is mainly due to the difficulties to enroll sufficient numbers of pregnancies. Collaborative efforts are necessary to overcome this problem and assessment of the comparative teratogenicity of AEDs is therefore particularly suitable for an international collaboration.

Based on these considerations, research groups in Europe agreed on a common protocol and in 1999 launched EURAP in the first two countries. EURAP has since then been extended to 40 countries in Europe and other regions. EURAP is a prospective registry aimed at assessing the comparative risk of malformations following intake of AEDs during pregnancy. EURAP is organized through networks of reporting physicians, national coordinators and a central registry based in Milan, Italy. Women taking antiepileptic drugs at conception are enrolled in early pregnancy Baseline information and follow-up data are collected on-line and immediate feedback between the central registry and reporting physicians allows collection of missing data. By March 2006, more than 8,000 pregnancies have been enrolled and approximately 3,500 have completed one-year follow-up after birth. EURAP is an example of a European research collaboration, who's success depends on voluntary work of more than 700 physicians dedicated to a common cause and on the development of on-line interaction between collaborators at different levels, which serves to strengthen this extensive network.

FONDE : FOLLOWING OUTCOMES IN NEWLY DIAGNOSED EPILEPSY—A MAJOR NEW RESEARCH INITIATIVE

M. Brodie (Epilepsy Unit, University of Glasgow, Glasgow, Scotland on behalf of the EUCARE Management Group, UK)

EUCARE (European Concerted Action and Research in Epilepsy) is a joint initiative of the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), sponsored by an unrestricted educational grant from UCB. The major plank of its research activities is FONDE (Following Outcomes in Newly Diagnosed Epilepsy), which is a prospective observational study of the pharmacological and lifestyle consequences of newly diagnosed epilepsy in the different countries of Europe. The objective is to assess clinical and social outcomes for people with newly diagnosed epilepsy from the age of 2 years upwards in relation to a variety of prognostic factors, including age at onset, seizure and syndrome classifications, pharmacological treatment, and socioeconomic background. Data will be collected on an electronic case record form (CRF). FONDE investigators will be invited to enter the clinical details of 10 or more patients each year in whom they have made a diagnosis of epilepsy (see www.eucare.org for information and application form). Each patient will be followed up prospectively for a minimum of 3 years. The primary outcome variable is the proportion seizure free for at least 1 year. Secondary outcome variables include time to reach 1, 2 and 3 years remission, proportion of patients discontinuing each drug due to inefficacy or side effects, lifestyles/social parameters and morbidity and mortality. This study will provide prospective data in assessing outcomes and responses to treatment, insights into the lives of people with epilepsy and levers to implement political change in improving epilepsy services across Europe.

AEDs TRIALS ACROSS EUROPE: OPTIMISING THE RESOURCES AND INCREASING THE POTENTIAL

M. Baulac (Service de Neurologie, Hopital Pitie-Salpetriere, Paris, France)

No abstract received.

HOW CAN ILAE AND THE COMMISSION ON EUROPEAN AFFAIRS (CEA) FACILITATE EUROPEAN RESEARCH COLLABORATION?

P. Wolf (National Hospital Copenhagen and Danish Epilepsy Centre Dianalund, Denmark)

To encourage and facilitate research is one of the primary objectives of the ILAE. The traditional ways comprise the publication of *Epilepsia* and the organization of international congresses. Much attention has successfully been paid to continuously improve the quality of both congresses and journal. Epilepsy research increasingly needs large databases (e.g. to study the genetics of epilepsy syndromes with polygenic inheritance or teratogenic effects of antiepileptic drugs), or addresses relatively rare conditions where as many cases as possible need to be collected. Therefore, epilepsy research often ideally is collaborative research of multinational groups. These can develop spontaneously from the initiative of few people, but they may also be facilitated by appropriate means. Various mechanisms have been installed and others are envisaged.

In 1996, the European Epilepsy Academy (EUREPA) was founded as an initiative of the CEA, and one of its objectives is to facilitate transnational research. Since EURAP, the Registry of Antiepileptic Drugs and Pregnancy was implemented, EUREPA provides logistics for its financial management. EUREPA also has access to an informal network of European researchers which has been able within days to organize an expression of interest with multinational, multicentre European participation in response to a research announcement. These possibilities are still little known but can be activated for new projects at any moment.

Advanced courses and summer schools, of which the CEA will soon be offering 2–3 per annum, are fora for young investigators to meet and establish connections between each others and with seniors who may act as tutors for collaborative research.

The ILAE is starting to invest funds into the development of education, structure of epilepsy care and translational research, and research scholarships, bursaries and mentorship programmes are being considered which all should contribute to the expansion of research networks.

Monday July 3, 2006
15:00–17:00
Hall 1
Finnish Epileptology Symposium
Unverricht-Lundborg disease in Finland and elsewhere

THE CHANGING CLINICAL PICTURE OF UNVERRICHT-LUNDBORG DISEASE

P. Genton (Centre Saint-Paul-HHG, France)

Unverricht-Lundborg disease (ULD) was reported under multiple names, mainly from the Baltic and Mediterranean areas, as a severe, invalidating condition with limited life expectancy, much as other progressive myoclonus epilepsies (PME). Recent years have witnessed dramatic changes in the overall picture, which occurred in several phases:

1. The disease was unified as ULD on clinical grounds, and this process was validated by the a single genetic cause, i.e., mutations (dodecamer repeats in most) in the cystatin B (stefin) gene on chromosome 21. However, this unification has been challenged recently by the possibility of other loci, which might be associated with slight clinical variations.
2. The avoidance of aggravating drugs, e.g., phenytoin, and the use of efficient and adapted anticonvulsant and antimyoclonic agents (in historical order, phenobarbital and primidone, benzodiazepines and valproate) helped many paitents gain control of myoclonus and seizures and enjoy a much better qualitiy of life.
3. The emergence of new, very active agents like piracetam, zonisamide, topiramate and levetiracetam brought further progress.

Nowadays, ULD appears as a comparatively mild form of PME, without shortened life expectancy, and in recent long-term studies indeed the

disease tends to level off in adulthood. Its present clinical picture can thus be summarized in the following way:

- onset in late childhood or early adolescence with GTCS and action myoclonus,
- coexistence of very benign and very severe cases, even within sibships,
- absence of associated dementia or sensory deficits,
- GTCS and clonic seizures that tend to remit after 8–10 years,
- EEG changes, including photosensitivity, that also tend to disappear,
- myoclonus progressing over 2–8 years then stabilizing at a given level.

ULD thus appears to have limited progression. The overall prognosis, which is highly variable, can be acurately made within 2–3 years of onset.

MOLECULAR BASIS OF UNVERRICHT-LUNDBORG DISEASE: WHERE ARE WE TODAY?

A. Lehesjoki (Folkhälsan Institute of Genetics and Neuroscience Center, University of Helsinki, Finland)

The gene underlying progressive myoclonus epilepsy of Unverricht-Lundborg type (Unverricht-Lundborg disease, EPM1) was identified ten years ago as the one coding for cystatin B (CSTB), a ubiquitously expressed inhibitor of several lysosomal cysteine proteases, cathepsins. Since then, significant advances have been made in understanding the molecular genetic basis of EPM1. An unstable dodecamer repeat expansion in the regulatory promoter region of the *CSTB* gene accounts for 90% of disease alleles worldwide, the majority of the patients being homozygous for this mutation. Seven rare mutations that, with one exception, occur in compound heterozygous form with the expansion mutation have also been reported. Molecular diagnostics for EPM1 is currently readily available and used on a routine basis in clinical work. In a number of patients only one copy of the minisatellite expansion mutation have been identified, the other abnormal allele remaining undetected. Moreover, a number of patients with clinical features compatible with EPM1 do not have mutations in the *CSTB* gene, suggesting the presence of other genes in the genome accounting for the same phenotype. A locus for one such, *EPM1B*, has been localized to chromosome 12q. *Cstb*-deficient mice that have been produced by targeted disruption of the mouse *Cstb* gene develop progressive ataxia and myoclonic seizures resembling the human phenotype and can thus be used to model the human disease. These mice show apoptotic death in cerebellar granule cells, less marked neuronal apoptosis in the hippocampal formation and entorhinal cortex, neuronal atrophy and gliosis. Findings in the mouse model suggest differential neuronal sensitivity to CSTB deficiency. Even if advances have been made in functional analyses of cellular and animal models for EPM1 the molecular mechanisms underlying the development of EPM1 remain, however, still largely unknown.

NEUROPHYSIOLOGY OF UNVERRICHT-LUNDBORG DISEASE

S. Franceschetti (National Neurological Institute C. Besta, Italy)

Progressive myoclonus epilepsies (PME) share some clinical aspects, including action myoclonus, epileptic seizures (Marseille Consensus group), and neurophysiological features reflecting a hyperexcitable condition of the cerebral cortex. However, PME result from heterogeneous genetic disorders with different pathogeneses that result in uneven physiopathological mechanisms of excitability. We summarize here the electrophysiological characteristics found in a population of patients with Unverricht-Lundborg disease (ULD).

Most ULD patients submitted to neurophysiological evaluation showed mildly enlarged "early" (P25-N33) components of somatosensory evoked potentials and consistently enhanced long-loop "cortical reflexes." Moreover, coherence analysis of EEG-EMG relationship invariably showed the presence of pathological cortical rhythms driving recurrent myoclonic burst with a time-transfer consistent with a corticospinal conduction in all patients.

"Paired-pulse" stimulation protocols performed by means of transcranial magnetic stimulation indicated a short-term increased excitability/decreased inhibition of motor cortex.

Postmovement EEG synchronization in beta-band, considered as a marker of cortical inhibition, was weak or lacking in ULD patient, and the degree of its impairment correlated with the severity of action myoclonus.

All the neurophysiological findings indicated a homogenous neurophysiological profile in ULD due to the hyperexcitability of a consistent circuitry, prominently involving the motor cortex and resulting in a short-term increased excitation/decreased inhibition. These findings appeared to be suitable to describe the ULD phenotype, to differentiate it from other forms of PMEs, to assess the severity of neurological impairment at the time of patient observation and to give measurable parameters during the follow-up.

The persistence of a precise dysfunctional profile in patients rationally treated with antiepileptic and antimyoclonic drugs (usually capable of controlling epileptic seizures and photosensitivity) well matches with the poor sensitivity of action myoclonus to pharmacological treatments. This could also suggest a prominent susceptibility of specific cerebral structures to the damage due to cystatin B deficiency characterizing ULD.

PROSPECTS FOR ANTIEPILEPTIC TREATMENT IN UNVERRICHT-LUNDBORG DISEASE

G. de Haan (SEIN, Heemstede, Netherlands)

Treatment of Unverricht-Lundborg disease (ULD) and other progressive myoclonic epilepsies (PME) should encompass seizures and myoclonus, and treatment of the underlying neurological disease.

The objective of the presentation is to give an overview of the current state of anticonvulsant treatment. In the first years after onset of ULD the seizures and myoclonus may be responsive to medication, but after a few years myoclonus may become refractory. Valproate has been widely accepted as drug of first choice, often with adjunctive treatment for the myoclonus. A number of new drugs may be interesting, due to reported effectiveness in the treatment of myoclonus. Other drugs, such as carbamazepine, phenytoine, and lamotrigine may be ineffective and even may increase myoclonus. Phenytoin may have a detrimental effect on the course of ULD, and should therefore be avoided.

Progression of ULD is particularly pronounced in the first years after onset. Causal treatments may be developed now the causative molecular mechanisms are being unraveled. Such treatment should start as early as possible in the course of the disease, in order to prevent irreparable damage to the nervous system.

After this presentation the listener should be informed about current treatment options for ULD, and we hope a discussion will be encouraged about the importance of early diagnosis and possibility of measures slowing down progression.

Monday July 3, 2006
15:00–17:00
Hall 5A
Discussion Group Session
Role of electrocorticography, stereo-EEG, subdural grids, ictal SPECT and magnetoencephalography in the preoperative evaluation of patients with focal dysplastic lesions

ROLE OF ELECTROCORTICOGRAPHY IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH FOCAL DYSPLASTIC LESIONS

A. Palmini (UZ Gasthuisberg, Leuven, Belgium and Porto Alegre Epilepsy Surgery Program, Porto Alegre, Brazil)

Acute electrocorticography (ECoG) is a time-honoured procedure to delineate the distribution of interictal spikes in the cortical area exposed

by the craniotomy, and which has been previously demonstrated to (hopefully) contain the epileptogenic zone (EZ). Although the precise relevance of these acutely recorded interictal spikes to the final localization of the EZ is still unclear, significant advances in this regard have been made in patients with refractory epilepsies due to focal dysplastic lesions. These dysplastic lesions have at least two important features which can be fruitfully explored by ECoG electrodes, particularly individualized, carbon-ball electrodes: (i) microscopic dysplastic abnormalities are often found surrounding the MRI-visible lesion, and these can often be identified (or at least suspected) by specific patterns of ECoG spikes, and (ii) focal dysplastic lesions commonly extend to the depths of sulci, and completeness of resection may be helped by the identification of spikes in these deeper regions, not easily probed by purely surface electrodes. Nevertheless, a major caveat of this procedure is the virtual impossibility to record seizures in the short duration of the recording.

It is with these assets and caveats in mind that one should conceptualize the role of acute ECoG in the resection planning of patients with focal dysplastic lesions. Should independent, 'non-neurophysiological' surrogates of the ictal onset zone be accepted in patients with focal dysplastic lesions, acute ECoG may often obviate the need for chronic recordings with intracranial electrodes. More specifically, when the lesion is visible and concordant with focal ictal hyperperfusion (as probed by SISCOM), acute ECoG spikes may help the final tailoring of resection. Long-term results of a large surgical series obtained with the help of acute ECoG and without resorting to chronic intracranial recordings will be presented to feed the discussion on the role of ECoG for these patients.

ROLE OF STEREO-EEG IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH FOCAL DYSPLASTIC LESIONS

F. Chassoux (Department of Neurosurgery, Centre Hospitalier Sainte-Anne, Paris, France)

Focal cortical dysplasias (FCDs) are associated with severe partial epilepsy that can be cured by surgery if complete resection can be performed. High resolution MRI can detect the dysplastic tissue but limits of the lesion are often difficult to determine on imaging. Moreover, MRI can be normal in 20 to 30% of cases. Stereo-EEG recordings have been proved to be useful to delineating the extent of dysplastic tissue. The main electrophysiological criteria corresponding to FCDs consist of: 1) interictal subcontinuous rhythmic spiking activity persisting after diazepam injection; 2) lack of background activity; 3) site of ictal discharge onset after brief speeding of rhythmic spikes; 4) site of elicited seizures either by low or high frequency electrical stimulation; 5) early reappearance of rhythmic spikes after ictal discharges.

Using these criteria, 24 patients (11 females) aged from 7 to 40 years (mean 22.6) have been operated during the 5 last years with favourable outcome (class I) in 23 cases. In these patients, MRI was considered as normal in 11 cases. Focal resections have been performed in eloquent areas (central, pre-or postcentral areas) in 13 cases without permanent motor deficit. Others resections were performed in the frontal lobe (8 cases), the parietal lobe (2 cases) and the occipital lobe (1 case). FDG-PET was performed in all patients, demonstrating a good concordance between the extent of hypometabolic areas and the epileptogenic zone determined by stereo-EEG. Taking into account these data, eight others patients with frontal (6 cases) or central FCDs were recently successfully operated without invasive procedure.

Stereo-EEG has allowed to greatly improving surgical strategy and outcome in FCDs. In our experience, it remains useful in cases of FCDs with normal MRI ("cryptogenic cases") and some poorly delineated FCDs located in functional areas.

ROLE OF SUBDURAL GRIDS IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH FOCAL DYSPLASTIC LESIONS

I. Najm (Cleveland Clinic, USA)

Subdural electrodes (stainless steel or MR-compatible platinum) electrodes are embedded in strips or sheets of polyurethane or other synthetic material and are implanted subdurally over the suspected epileptogenic and/or functional dysplastic regions. Subdural grids are inserted through either open craniotomy or burr-hole openings and registered stereotactically for extraoperative mapping. The cortical covering may extend beyond the visualized cortical area, as grids may be slid beyond the edges of the craniotomy to cover adjacent areas for the purpose of better electrocorticographic (EcoG) and/or functional sampling. Beside the EcoG recordings and direct electrical stimulation studies, grids can be used to record somatosensory evoked potentials after stimulation of the trigeminal (lip) or median nerves for central sulcus localization.

Advantages of chronic, extraoperative subdural recordings include the ability to record cortical ictal events and to determine the functionality of the underlying cortex. Additionally, direct cortical recordings are performed in the well-controlled environment of the epilepsy monitoring unit on a relaxed, cooperative patient without the time constraints of the operating room environment.

As this procedure involves the insertion of foreign bodies into the cranial vault, the surgical risks include wound infection, flap osteomyelitis, acute meningitis, cerebral edema, and hemorrhage. Concerns about increased intracranial pressure may limit the maximal number of electrodes that can be inserted and therefore may result in limited epileptic mapping from large cortical areas. Other limitations may include the anatomic location of the proposed area of sampling (e.g., mesial orbitofrontal) and "redo" surgeries with cortical adhesions. In areas of difficult surgical access, like the mesial surface of the hemispheres or in deep regions of the brain, stereotactic placement of depths electrodes (stereo-EEG), alone or combined with subdural grids, are good options, promoting an adequate coverage and precise targeting of the desired areas.

General indications for invasive electrode implantation in the evaluation of patients with epilepsy:

When noninvasive studies remain nonconcordant or inconclusive regarding the localization and the extent of the seizure onset zone and/or the eloquent cortex, invasive studies using subdural grids and/or depth electrodes may be needed. Jayakar proposed the following relative indications for the evaluation with subdural grids: normal structural imaging, extratemporal location, divergent noninvasive data, encroachment on eloquent cortex, tuberous sclerosis, and cortical dysplasia. Rosenow and Lüders recommended the use of subdural electrodes only in patients with focal epilepsy (single focus) in whom there is a clear hypothesis regarding the location of the epileptogenic zone (derived from non invasive studies),

In patients with focal CD, the two main indications for the use of extraoperative invasive electrode recordings are: 1) definition of the epileptogenic region and 2) mapping of the eloquent areas.

1. Definition of the epileptogenic zone in patients with focal CD

The epileptogenic zone is the area of the cortex that is indispensable for the generation of epileptic seizures and whose resection or complete disconnection leads to seizure control. In most cases of focal CD, the data generated from noninvasive EEG recordings and other electrophysiological/neuroimaging techniques are sufficient to define the approximate location of the epileptogenic zone.

Various studies using direct electrocorticographic recordings showed that focal CD lesions are intrinsically epileptogenic. The need for invasive monitoring to define the location and extent of epileptogenicity in focal CD is warranted by the fact that the epileptogenic area in patients with CD is frequently larger than the visually identified CD. Moreover, in CD lesions with severe FLAIR signal increase (balloon cell-containing dysplastic lesions) epileptogenicity mainly arises from the surrounding dysplastic cortex that is devoid of balloon cells.

2. Localization of the functional ("eloquent") cortical regions in focal CD.

As most CD lesions are often localized in the frontal lobe (therefore in potentially "eloquent" cortex), an understanding of the functional status of the involved region(s) and of its anatomical and pathological correlates is of prime importance. We recently assessed the functional status (as identified by direct cortical electrical stimulation) of focal CD and its relationship with imaging, and in situ electrocorticographic (ECoG) characteristics in patients who underwent focal neocortical resection for the treatment of medically intractable epilepsy. Our results showed that some focal CD lesions that are typically characterized by significant FLAIR signal increase on MR imaging and are located in anatomically functional areas (primary motor, Broca area, etc) are not functional upon direct electrical stimulation, the same lesions did not show evidence of

intrinsic epileptogenicity as assessed through the mapping of the ictal onset zones. On the other hand, CD lesions with mild or no FLAIR signal increase were functional and at times epileptogenic. These results are in agreement with previous reports that showed the persistence of eloquent function in CD that are devoid of balloon cells. Similar EcoG patterns were reported in patients with low-grade glial tumors (e.g dysembryoplastic neuroepithelial tumor; DNET and ganglioglioma) whereas dysplastic and epileptic cortical areas were found in the immediate surroundings of these lesions. Moreover, these results show that functional cortex may be displaced within the same hemisphere and therefore may have direct implications on the options for epilepsy surgery.

Proposed indications for use of subdural grids in patients with focal CD: As the limited success after surgical resection in epileptic patients with CD is likely related to a lack of an accurate definition of the "true margins" of the epileptogenic lesion, direct electrocorticographic recordings using subdural grids are needed.

We believe that subdural electrodes should be used in the evaluation of epileptic patients with suspected focal CD after the diagnosis of focal epilepsy is confirmed through the careful analysis of the seizure semiology, noninvasive scalp EEG recordings and other anatomic and functional neuroimaging techniques. The goals from the invasive evaluation should be clear (mapping of epileptogenicity and function) with the understanding of the limitations and risks of the evaluation

The continuous improvement in current functional imaging techniques (such as EEG triggered functional MRI) and the future development of micro imaging techniques that would potentially map the molecular markers of epileptogenicity will obviate the need for invasive recordings.

ROLE OF ICTAL SPECT AND SISCOM IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH FOCAL DYSPLASTIC LESIONS

W. Van Paesschen (UZ Gasthuisberg, Neurology, Leuven, Belgium)

Background: Invasive EEG studies are often considered necessary to localize the epileptogenic zone in partial epilepsies associated with focal dysplastic lesions (FDL). Our aim was to evaluate the relationships between SISCOM hyperperfusion clusters and MRI-visible FDL, and to establish a preliminary algorithm for a noninvasive presurgical evaluation protocol for MRI-visible FDLs in patients with refractory epilepsy.

Methods: Fifteen consecutive patients with refractory partial epilepsy and a single MRI-visible FDL underwent a noninvasive presurgical evaluation including SISCOM. Each hyperperfusion cluster was visually analyzed, automatically quantitated, and its distance form the lesion as outlined on the MRI was measured. In patients who underwent surgery, the volumes of resected brain tissue containing the FDL, the SISCOM hyperperfusion cluster, and surrounding regions were assessed on postoperative MRI and correlated with surgical outcome.

Results: Fourteen of the 15 patients (93%) showed SISCOM hyperperfusion overlapping with the FDL. The FDL was detected only after re-evaluation of the MRI guided by the ictal SPECT in 7 of the 15 patients (47%). Four distinct hyperperfusion patterns were observed, representing different degrees of seizure propagation. Nine patients have been operated. Five have been seizure free since surgery and one since a reoperation. The degree of resection of the MR-visible FDL was the major determinant of surgical outcome. Full resection of the SISCOM hyperperfusion cluster was not required to render a patient seizure free.

Conclusion: Detailed analysis of SISCOM hyperperfusion patterns is a promising tool to detect subtle FDL on MRI and to establish the epileptic nature of these lesions non-invasively. Overlap between the SISCOM hyperperfusion cluster and MR-visible FDL in a non-invasive presurgical evaluation with concordant data may suffice to proceed to epilepsy surgery aimed at removing the MR-visible FDL and the part of the hyperperfusion cluster within and immediately surrounding the FDL.

ROLE OF MAGNETOENCEPHALOGRAPHY IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH FOCAL DYSPLASTIC LESIONS

T. Bast (Department of Pediatric Neurology, University Hospital Heidelberg, Germany)

Rational: Magnetoencephalography (MEG) simultaneous to EEG is a non-invasive diagnostic tool with high temporal resolution. Localization accuracy of inverse source analysis is satisfactory presenting some advantages of MEG over EEG, i.e., lower influence of volume conduction. The subject matter consists in the role of MEG in the diagnostic workup of patients with focal dysplasias.

MEG in focal dysplastic lesions: Several MEG/EEG studies have confirmed the concept of intrinsic epileptogenicity of dysplasias (i.e., focal cortical dysplasia, polymicrogyria), since sources modeling interictal epileptiform activity were mostly localized within the lesion as defined from MRI, invasive recordings and resection outcome. However, MEG provides information exclusively regarding the interictal irritative zone, as seizures generated by the epileptogenic cortex are rarely recorded. Only 3 out of 20 patients with FCD investigated by our group had a seizure during MEG acquisition. Source analysis of ictal MEG patterns in these cases localized the dipole within the dysplasia. None of the methods of inverse analysis in MEG or EEG can provide an accurate estimation of the extent of an activated cortical area. Although MEG source analysis may identify the maximum center of an irritative or even epileptogenic zone, other methods are required to tailor a resection (mainly MRI, eventually PET/SPECT). However, MEG may be helpful even in clear, MRI-defined cases, because identified maxima of irritative or epileptogenic zones should be covered by the resection or at least by invasive electrodes. A special role of MEG can be presumed in cases of cryptogenic focal epilepsies. Since MEG sources usually localize within the FCD in "clear" lesions, the same can be assumed for cryptogenic cases, in many of which a FCD is revealed through histopathology. To our experience, MEG source analysis was crucial for later epilepsy surgery in a series of 6 patients with cryptogenic frontal lobe epilepsies caused by FCD.

Conclusion: MEG with simultaneous EEG analysis is a non-invasive and helpful tool in the process of presurgical epilepsy evaluation in patients with focal dysplastic lesions.

Monday July 3, 2006
15:00–17:00
Hall 5B
Discussion Group Session
From functional brain anatomy to clinical seizure semiology

THE MOTOR SYSTEM AND SEIZURE SEMIOLOGY

C. Baumgartner (Department of Neurology, Medical University of Vienna, Austria)

Motor manifestations during epileptic seizures include focal clonic motor seizures, seizures with asymmetrical tonic posturing and seizures with hypermotor automatisms. Focal clonic motor seizures are generated by epileptic activity in the primary motor cortex and consist of unilateral, jerky, usually rhythmic movements, frequently also tonic components like tonic postural signs and tonic face contractions can be observed. Most frequently they start in the face or hand due to their large representation in primary motor cortex and due to a lower seizure threshold of these cortical regions. Asymmetric tonic seizures or supplementary motor area (SMA) seizures are mediated by epileptic activity in the supplementary sensorimotor area or the premotor cortex, but can also be generated by epileptic activity in other frontal lobe regions. Because frequently somatosensory auras like feelings of pulling, pulsing, heaviness, numbness or tingling which can occur ipsi-, contra- or bilaterally occur the term "supplementary sensorimotor seizures" has been introduced. Asymmetric tonic seizures are characterized by bilateral, asymmetric, tonic or dystonic posturing of the extremities and facial grimacing resulting in tonic posturing. Vocalizations frequently occurring during asymmetrical tonic seizures can be a reactive phenomenon, can be caused by a tonic contraction of the diaphragm and laryngeal muscles and finally can be a consequence of an activation of Broca's area or SMA. While hyperkinetic or 'hypermotor' automatisms are not associated with a seizure onset in any specific region within the frontal lobes. They are

characterized by prominent and complex, coordinated, purposeless or semipurposefull movements (trembling, waving, rotating, stepping, cycling, rocking, hopping etc.) with an agitated or frenetic appearance. Vocalizations often are explosive and pronounced which seems to be unique for frontal lobe seizures with hypermotor automatisms. Seizures with hypermotor automatisms usually are associated with a loss of consciousness and therefore also are referred to as frontal lobe complex partial seizures.

THE CENTRAL AUTONOMIC NETWORK AND SEIZURE SEMIOLOGY

J. Janszky (University of Pecs, Hungary)

No abstract received.

CONSCIOUSNESS AND SEIZURE SEMIOLOGY

A. Ebner (Department Presurgical Evaluation, Epilepsy Center Bethel, Bielefeld, Germany)

Semiology of epileptic seizures depends on what part and how much of the brain is involved by pathologic ictal activation. One among many observable clinical ictal signs is alteration or even loss of consciousness, pragmatically defined as loss of contact, inability to respond to external stimuli, and loss of memory of what occurred during the seizure. These alterations can take place gradually in the course of a focal seizure, for example, beginning with the perception of an aura, an initial ability to respond to the environment, but then followed by a more or less complete loss of responsiveness. The initial auras may be remembered or not, the latter probably being a sign of a more rapid spread of seizure activity to the contralateral hemisphere (Schulz et al. *Epilepsy Res* 2001;43:201–10). Automatisms in complex partial seizures (automotor seizures) of temporal lobe origin are usually associated with loss of consciousness and occur at the time of spread to the contralateral temporal lobe. However, in temporal lobe seizures arising in the non-dominant hemisphere showing no spread, impairment of consciousness may be very mild or absent even in the presence of vivid distal oral and/or manual automatisms (Ebner et al. *Neurology* 1995; 45: 61–4). Loss of consciousness can also set in immediately at the beginning of a complex partial seizure, probably indicating rapid spreading of the seizure activity to the contralateral temporal lobe, which is also associated with bitemporal disease and amnesia for auras (Schulz et al. *Neurology* 1995;45:231–5). Hypermotor seizures characterized by proximally accentuated and often violent automatisms can also be accompanied by preserved or impaired consciousness and memory, partially depending on the duration of the seizure.

Pathophysiologically, there is evidence that impairment of consciousness has a strong association with secondary hyperperfusion in the thalamic/upper brainstem region as revealed by an ictal SPECT study (Lee et al. *Neurology* 2002;59:841–6). These authors suggest that the spread of epileptic discharges or a trans-synaptic activation (diaschisis) of these structures is an important mechanism in the alteration of consciousness during seizures of focal origin.

In focal seizures a gradual impairment of consciousness can often be observed with disturbance of only some of the constituents representing "consciousness" such as memory, language, etc.

In absence seizures loss of consciousness is the hallmark of seizure semiology although sometimes occurring together with motor symptoms that are usually mild. Loss of consciousness occurs abruptly and is indispensably associated with generalized spike wave activity in the EEG. Several pathophysiological hypotheses exist to explain this sudden interruption of the stream of consciousness and emphasize either the leading role of cortical or subcortical (thalamic or reticular systems) mechanisms. The new theory of a "cortical focus" for generalized absence epilepsy bridges cortical and thalamic theories (Meeren H et al. *Arch Neurol* 2005;62:371–6. From this focus, seizure activity generalizes rapidly over the cortex. During the first cycles of the seizure the cortex drives the thalamus, while thereafter cortex and thalamus drive each other, thus amplifying and maintaining the rhythmic discharge.

EMOTION AND SEIZURE SEMIOLOGY

A. Gil-Nagel (Hospital Ruber Internacional, Madrid, Spain)

Affective states are regulated by different brain structures and change in relation to internal and external situations, creating a range of emotions. Numerous studies have demonstrated abnormal emotional responses in relation to focal lesions of the central nervous system, mostly those involving the prefrontal cortex, the cingulate gyrus and the amygdala, however these studies also suggest that many other areas in the frontal and temporal lobes, the hypothalamus and beyond are also involved in the physiology of emotional responses and the changes in the autonomic nervous system that often are associated with the manifestation of emotions. Clinical research suggests that the generation of mirth and laughter requires integrity of right hemisphere structures, while gloom and cry are more related to the left hemisphere. Several studies have also evaluated the ictal semiology of emotions and its clinical implications. These studies analyze emotional behavior during seizure or at the time of electrical stimulation during epilepsy surgery. Most of these studies agree with other anatomical analysis and tend to show a predominance of ictal emotions in patients with focal epilepsies involving the temporal and frontal lobes. In a series of 134 seizures analyzed with ictal video-EEG recordings 34 seizures (25%) showed ictal emotions, the most common were anxiety and fear; other emotions were laughter, crying, kissing and restlessness. 74% of seizures showing emotional features had a temporal lobe origin and 12% were frontal, there were no significant differences between left and right hemispheres. Laughter is a usual manifestation of hypothalamic hamartomas, and is related to activation of the hamartoma. In addition, weeping and crying are more often observed in psychogenic seizures than in epileptic seizures. Therefore, the analysis of emotions may have practical value in the evaluation of epilepsy, however, larger studies with multimodal diagnostic analysis are necessary in order to provide guidelines about its clinical significance.

Monday July 3, 2006
15:00–17:00
Hall 5C
Discussion Group Session
Nosology and pathophysiology of the epilepsies in the first three years of life

ARE THERE RECOGNISABLE EPILEPSY SYNDROMES IN NEWBORNS?

P. Plouin (Hopital Necker Enfants Malades Paris, France)

Since the last classification of epilepsies and epileptic syndromes, which was adopted in 1989, 4 epilepsy syndromes appear in neonates.

Two of them are considered as benign: Benign Familial Neonatal Seizures (BFNS), and Benign Idiopathic Neonatal Seizures (BINS). The first one is quite rare but easy to recognize as there is a constant family history, a normal clinical examination, seizures are stereotyped, focal, brief and never lead to a status epilepticus. It was the first syndrome with a genetic background assessed from 1989. On the other hand, BINS are no more frequent among neonates, as it was when described in the seventies. In this condition, the diagnosis remains one by exclusion, facing a long lasting status of seizures (around 2 days).

The 2 other syndromes can be associated as "Neonatal Epileptic Encephalopathies with Suppression Burts." In Early Myoclonic Encephalopathy the main seizure type is myoclonia, erratic or generalized, as in Ohtahara syndrome, epileptic spasms and focal seizures are predominant. It is not always easy to discriminate the 2 conditions and this may be important considering etiology ant treatment. Ictal electro-clinical and interictal EEG patterns may help a lot in this purpose. Some etiologies as glycine encephalopathy on one hand or hemimegalencephaly on the other hand are quite easily recognizable.

Since 1989, new syndromes have been reported, among them Migrating Partial Seizures in Infancy (MPSI). In this syndrome seizures may

start from birth, and the multifocal character of the seizures as well as the "subnormal" interictal EEG are a good orientation to the diagnosis.

Still nearly 30% of cases of neonatal seizures do not get any syndromic nor etiological classification, and the outcome is very difficult to assess in these conditions.

Definition of epilepsy syndromes among neonates remains an important challenge considering treatment and prognosis.

IDIOPATHIC SYNDROMES IN INFANTS: THE GENETIC BACKGROUND

f C. (Neurogenetics Laboratory, Department of Child Neurology and Psychiatry, IRCCS Fondazione Stella Maris, Italy)

Seizures occurring in the first 3 years life might be associated with serious underlying structural brain disease or metabolic abnormalities. However, there are several idiopathic syndromes beginning in the first few days of life or in infancy with a genetic aetiology. Benign familial neonatal seizures (BFNS) begin around day 3 and are caused by mutations in the potassium channel genes *KCNQ2* and *KCNQ3*. Benign familial infantile seizures (BFIS) begin around 6 months of age and may be associated with paroxysmal dyskinesias in later childhood. Linkages to chromosomes 19 and 16 were reported but gene defects have not yet been identified. A mutation in the *ATP1A2* gene was reported in one family in which there was partial cosegregation of familial hemiplegic migraine and infantile seizures. Families with an intermediate variant–benign familial neonatal-infantile seizures (BFNIS)–have also been described carrying missense mutations in the gene coding for the $\alpha 2$ subunit voltage-gated sodium channel *(SCN2A*).

Febrile seizures are the most common type of seizures in children occurring between age 6 months to 6 years. The mode of inheritance has been hypothesised to be autosomal dominant in some families and polygenic in others. Several loci have been published but no genes have yet been identified. The variant of febrile seizures plus (FS^+) in which febrile seizures extend past the age 6 years and/or afebrile seizures occur at any age, is part of the generalized epilepsy with febrile seizures plus spectrum ($GEFS^+$). Mutations in the genes coding for the $\alpha 1$ and $\beta 1$ subunits of the voltage-gated sodium channel *(SCN1A* and *SCN1B)* and the $\gamma 2$ subunit of the $GABA_A$ *(GABRG2*) have been identified in few families. Severe myoclonic epilepsy of infancy (SMEI) has also been described in few families with $GEFS^+$. De novo mutations of *SCN1A* are present in about 70% of SMEI patients.

SYMPTOMATIC SYNDROMES IN INFANTS: ETIOLOGY AND ELECTROCLINICAL PATTERNS

R. Guerrini (Department of Child Neurology and Psychiatry, University of Pisa, Italy)

A concept that challenges our ability to understand the relationships between brain structure and function is that of epileptic encephalopathy (EE), often occurring in symptomatic early onset epilepsies. EEs occur when seizures, epileptiform EEG abnormalities, or both, result in impaired neurological and cognitive development and functioning. EEs represent about 40% of all epilepsies occurring in the first three years of life. Some children (for example those suffering from Dravet syndrome) have no detectable lesions, in which case most of the entire clinical picture is usually attributed to epilepsy, as suggested by the temporal relationship between the onset of seizures and evidence of developmental impairment. When a brain lesion is present, however, the concept of epileptic encephalopathy is not easily delineated, since an evaluation of the extent to which epilepsy is likely to interfere with residual developmental potential could be arbitrary. There is no doubt, however, that the area of dysfunction that originates from a lesion may spread to anatomically intact areas and circuits that are distant from the primary lesion and drag them into a dysfunctional network.

Vigorous early pharmacological or surgical treatment is often advocated on the assumption that epileptic activity would cause or worsen the encephalopathy per se. However, for many of these conditions there are no established endpoints of treatment and drug adjustments are very empirically established. Complete seizure control should not be presented as a fundamental target to the child and parents. The main goal should be minimizing seizure frequency to an extent that seizures, per se, do not represent an impossible obstacle to social integration. This target can be reached by trying to find the right balance between side effects and seizures. For those syndromes, in which a definite structural abnormality underlying epileptogenesis is recognized, and drug treatment fails, surgical treatment can be very successful and can prevent or 'cure' the epileptic encephalopathy.

EARLY EPILEPSY AS AN EXPRESSION OF INBORN METABOLIC DISORDERS IN NEWBORNS AND INFANTS

R. Surtees (UCL Institute of Child Health, London, UK)

Early-onset, treatable metabolic epileptic encephalopathies

Seizures are a common symptom in many metabolic diseases. However, few present with epilepsy; yet some of these are treatable. Here I will review the clinical features and treatment of early onset, treatable, metabolic epileptic encephalopathies. These naturally divide into two groups: vitamin-responsive epileptic encephalopathies; and, some other metabolic epileptic encephalopathies. Vitamin responsive epilepsies comprise: pyridoxine dependant epilepsy; folinic acid responsive epilepsy; pyridoxal phosphate oxidase deficiency and biotinidase deficiency. Other, potentially treatable metabolic epilepsies are glucose transporter 1 deficiency, creatine deficiency syndromes and serine deficiency syndromes.

Monday July 3, 2006
15:00–17:00
Hall 3A
Discussion Group Session
Cognitive dysfunction in children with temporal lobe epilepsy

NEUROPSYCHOLOGICAL DEFICITS IN CHILDREN WITH TEMPORAL LOBE EPILEPSY: ARE THEY SPECIFIC?

F. Vargha-Khadem (Institute of Child Health, Development Cognitive Neuroscience Unit, London, UK)

No abstract received.

INPUT OF FUNCTIONAL AND STRUCTURAL NEUROIMAGING TECHNIQUES WHEN STUDYING COGNITION IN CHILDREN WITH TLE

M. Seeck (University Hospital of Geneva, Switzerland)

Temporal lobe epilepsy (TLE) in children is less frequently diagnosed than extratemporal lobe epilepsy as compared to adult patients; however, TLE in adults is often traced back to childhood. TLE in children varies greatly with respect to etiology, severity or age of onset. While clinical observations find similar deficits as in adult TLE, the seizure disorder may be more severe and thus comes earlier to medical attention. Earlier onset, higher seizure frequency and longer exposure to chronic seizure disorder are associated to a poorer cognitive status, which may counterbalance "brain plasticity." The vast majority of imaging studies are devoted to the identification of the epileptogenic focus, and imaging studies on cognitive functioning in pediatric epilepsy are rare. Several studies correlated cognitive dysfunction with hippocampal or global brain atrophy, using 3D-MRI and volumetry. In recent years, knowledge on physiological changes in the aging brain could be obtained in subjects starting as early as 7 years. MR-spectroscopy may be another tool, and some data on MRS-components and cognitive function could be obtained in children. Pediatric PET-or SPECT studies in TLE-children are hampered by the fact that control exams in non-epileptic children cannot be obtained for ethical reasons. A large body of fMRI studies explored language-related networks and their reorganization; however, the imaging of memory functions in pediatric TLE-patients has not yet

been addressed. Multichannel scalp EEG, examining frequency changes or cognitive evoked potential changes related to specific cognitive tasks, might provide another avenue of research, given that it is non-invasive, allow measuring control subjects of all ages, and is less critical for motion artifacts.

COGNITIVE AND MOOD EFFECTS OF ANTIEPILEPTIC DRUGS

G. Baker (Division of Neurosciences University of Liverpool, UK)

Purpose: Understanding the impact of antiepileptic drugs on the psychological and neuropsychological well being of children with epilepsy is of critical importance in the management of their condition. Previous studies have identified that the older antiepileptic drugs may have a deleterious impact on learning and memory and subsequently influence performance and behaviour at home and in the school. Little however is known about the newer antiepileptic drugs.

Methods: The author has searched the Cochrane Epilepsy Group trial register, the cochrane central register of controlled trials and Psychoinfo and cross references from identified publications. In addition a hand search of relevant journals was undertaken.

Results: There are very few studies that have carefully examined the effects of newer antiepileptic drugs on cognitive and behavioural functioning. Those studies that have been published often fail to meet the rigorous scientific standards required to meet the criterion for level A scientific evidence. This review will present the available knowledge on the impact of AEDs on neuropsychological and psychological functioning.

Discussion: There is a need for well designed studies to establish the impact of AED treatment but also to determine what is the most beneficial strategy to ameliorate the effects for children's day-to-day functioning

COGNITIVE DYSFUNCTION AND TLE IN CHILDREN: DO WE DISPOSE OF SUFFICIENT DATA TO PRAISE EARLY SURGERY?

A. Arzimanoglou, Agathe Laurent, Monica Zilbovicius, Scania de Schonen, and the French Network for Epilepsy Surgery in Children (Service de Neurologie Pédiatrique et des Maladies Métaboliques, Hôpital Robert Debré (AP-HP), Paris, France)

Traditionally paediatricians, including many child neurologists, consider epilepsy surgery the last treatment option for patients with focal nonidiopathic epilepsy. The average duration of surgically treatable epilepsy among young and middle-aged adults referred for epilepsy surgery is about 20 years. The main arguments usually advanced for such an approach are: the availability of a great number of drugs to be tried; the potential cognitive and behavioural affects on a child when operated on early; the fact that little is known about the natural history, particularly the time course of development, of refractory epilepsy; and the risks of surgery. As a consequence a number of available studies mainly aim to early identification of factors suggesting intractability to drugs, which then can be used as one of the main criteria to suggest early surgery.

Another approach would be to take under consideration: available robust data on the effectiveness and safety of surgery for patients with some types of epilepsy (temporal lobe epilepsy, epilepsy related to some defects of migration or to the presence of a well circumscribed lesion, etc.); available data on quality of life, education and professional achievements in patients that became seizure free following surgery, even late surgery; available data on cognitive and behavioural affects on children with drug resistant versus drug sensitive epilepsies; available data suggesting that alternation between remission and relapse is one of the inherent features of a number of focal epilepsies, probably depending on aetiology. Lack of robust data, on the behavioural and neuropsychological outcome of children with focal non-idiopathic epilepsies operated on early or controlled by AEDs, must also be taken into account. On the basis of all the above, clinical trials of early surgical intervention including children and adolescents can be designed. The *sine qua non* condition for such studies to provide the medical community with solid data favouring (or not) early surgery, is to change today's clinical practice and to refer all patients that fail two drugs for a presurgical evaluation in centres that dispose of all available means for a global and comprehensive approach, as recently suggested by the ILAE subcommission on paediatric epilepsy surgery.

Focusing on temporal lobe epilepsy and on the basis of available data, from the literature and from our studies on influence of seizures on auditory and visual perceptual processing, we will highlight the limits of drug treatment, the successes and risks of epilepsy surgery and the need for early implementation of educational interventions. We will insist on the limits and methodological issues for prospective research projects assessing the neuropsychological profile of these children. A step further would be a better understanding of the ways to evaluate the installation process, and the underlying mechanisms, of such dysfunctions.

We dispose of sufficient data on the results of surgery on seizures. What remains to be done are prospective follow-up studies on global development and social integration of children operated-on early in the course of their disease. But how much early is "early"?

Monday July 3, 2006
15:00–17:00
Hall 3D
Discussion Group Session
Programmed cell death pathways in seizure-induced neuronal injury and epileptogenesis: human and animal data

INHIBITOR OF APOPTOSIS PROTEINS IN SEIZURE-INDUCED BRAIN INJURY

D. Lindholm (Uppsala University, Department of Neuroscience, Sweden)

No abstract received.

CASPASES IN EPILEPTOGENESIS: ANIMAL AND HUMAN DATA

S. Narkilahti (A.I.Virtanen Institute for Molecular Sciences, University of Kuopio and Regea Institute for Regenerative Medicine, University of Tampere, Finland)

Caspases form a group of proteolytic enzymes that are activated during programmed cell death. These enzymes are responsible both for initiating the death signaling and for cleaving of cellular substrates resulting ultimately in cell death. Since caspases are typically inactivated in normal cells, inhibition of their activity prior or during neurodegenerative events might result in reduced cell death and in a better functional outcome.

To model human TLE, several animal models of TLE have been developed in which an initial brain insult, that is, status epilepticus (SE), causes epileptogenesis and epilepsy. In these models, both pathological and electrophysiological features of human TLE can be mimicked. Importantly, in the experimental models brain samples can be collected in every phase of the epileptic process, while from human patients' tissue samples are only available after epilepsy surgery in the chronic phase of the disease.

The main aim was to investigate the detailed temporal and spatial expression and activation patterns of caspases acutely after SE, during epileptogenesis and epilepsy in a rat model of TLE. Further, the effect of pharmacological inhibition of caspases after SE on neurodegeneration and development of epilepsy was evaluated. In addition, presence of caspases in the hippocampal specimens derived from patients operated on for drug refractory TLE was assessed.

The main findings were: 1) in addition to acute phase after SE, caspases are enzymatically activated during the epileptogenesis. 2) Individual caspases have differential cellular and subcellular expression patterns during the course of epilepsy. 3) Caspase 3 inhibition reduces neuronal

damage after SE but it does not prevent epilepsy. 4) In TLE patients, caspase 2 localizes to the remaining neurons of the hippocampus.

In summary, these results provide new data about the role of caspases in epileptogenic processes both in rats and humans.

DEATH RECEPTORS AND BCL-2 PATHWAYS IN EPILEPSY: EXPERIMENTAL AND HUMAN DATA

D. Henshall (Royal College of Surgeons in Ireland)

Prolonged seizures (status epilepticus) and repetitive seizures over time may cause damage to temporal lobe structures such as the hippocampus. Evolving experimental data have demonstrated programmed cell death (apoptotic) signaling pathways are triggered by seizures and may contribute to acute injury as well as participate in network remodeling during epileptogenesis. Classically, such cell death cascades are engaged following dysfunction of intracellular organelles such as mitochondria (intrinsic pathway) or via activation of surface-expressed death receptors of the tumor necrosis factor receptor (TNFR) family. Initiation or progression of these pathways may involve recruitment and activation of pro-apoptotic members of the Bcl-2 gene family, which function up- and downstream of the caspase family of cell death proteases which effect cell death. Since seizures trigger intracellular calcium overload, it has been presumed that the intrinsic cell death pathway mediated by mitochondrial dysfunction would instigate neuronal death following seizures. However, our work suggests that the extrinsic cell death pathway is also engaged and may precede or initiate the damage program.

Focally-evoked status epilepticus in rats or mice induced hippocampal neuronal death, assembly of TNFR1 signaling complexes and activation of caspase-8. Bcl-2 family member Bid was activated downstream, with subsequent processing of executioner caspases 3/7. The functional significance of this pathway was supported by the neuroprotective efficacy of pharmacologic inhibition of caspase-8. Examination of resected temporal lobe material from refractory epilepsy patients reveals TNFR1 signaling complexes and their components are also upregulated. However, such presumably pro-apoptotic responses may be partially kept in check via concurrent modulation of anti-apoptotic Bcl-2 proteins or downregulation of pro-cell death genes.

These data highlight unexpected roles for death receptors in seizure-induced neuronal death and the ongoing neuronal stress and injury responses in patients with refractory seizures which may have significant implications for approaches to neuroprotection after damaging seizures and anti-epileptogenesis.

Monday July 3, 2006
15:00–17:00
Ballroom 1
Discussion Group Session
Blood–brain barrier and epilepsy

STRUCTURE AND FUNCTIONAL PROPERTIES OF THE BLOOD–BRAIN BARRIER

I. Blasig (FMP, Berlin-Buch, Germany)

No abstract received.

INFLAMMATION AND THE FUNCTION OF THE BLOOD–BRAIN BARRIER

D. Janigro (Cleveland Clinic Foundation, USA)

One of the most commonly used animal model of status epilepticus (SE) is based on the intra peritoneal injection of the cholinergic agonist pilocarpine. While in vivo administration leads to acute SE in approximately the 70% of the cases, in vitro electrophysiological studies have shown that pilocarpine causes epileptogenic activity preferentially when co-applied with other proconvulsants. Moreover, radioactive tracer experiments suggested low brain accumulation of pilocarpine. We measured the potency of pilocarpine when directly applied to hippocampal slices and we compared the in vitro pilocarpine ED_{50} with the levels measured in the brain after i.p. injection of 350 mg/Kg before (Stage 4) and at SE. Staging of pilocarpine effects were performed by video EEG monitoring. At concentrations up to 500 □M, synchronized epileptiform activity in vitro was never seen. Similar in vitro potency was observed when using a guinea pig whole brain preparation. In contrast, kainic acid induced dramatic electrographic seizures when applied at 4 □M. Surprisingly, pilocarpine brain levels measured after i.p. injection never exceed 60 □M and were on average around 5% of serum levels. We measured blood-brain barrier permeability by ^{14}C-Sucrose, ^{3}H-Diazepam and FITC-albumin to determine if altered BBB function may affect pilocarpine penetration. Before SE, only modest modifications of BBB permeability to FITC-albumin or radiotracers was observed. Pilocarpine permeability was compared to the permeability of sucrose and diazepam to reveal significantly lower permeation than predicted by its lipophilicity. Beside CNS cholinergic effects, significant pro-inflammatory changes (increased serum levels of IL-1□ and changes in the CD4:CD8 T-Cells) were observed after pilocarpine injection and before Stage 4 or SE. Our results show a discrepancy between the in vivo and in vitro pilocarpine proepileptogenic effects and reveal, in vivo, the occurrence of an early peripheral inflammatory event that may cooperate to the establishment of SE.

THE BLOOD–BRAIN BARRIER AS A SOURCE OF DC POTENTIAL GENERATION

J. Voipio (Department of Biological and Environmental Sciences, University of Helsinki, Finland)

Slow shifts in the human EEG have been generally assumed to result from changes in the level of tonic excitation of cortical pyramidal neurons. However, prolonged large-amplitude shifts can be readily induced without an evident change in cortical gross excitation. For instance, voluntary hyperventilation by healthy adult subjects results in a prompt negative shift with amplitudes rising up to −2 mV within 3 min at the vertex (Cz) (Voipio et al., *J Neurophysiol* 2003;89:2208–14). Such responses have an extremely steep dependence (up to 100 μV/mmHg) on end-tidal P_{CO2}, and blocking hypocapnia with 5% CO_2 in air during a similar breathing pattern blocks the negative DC shift. Hypoventilation or breathing 5% CO_2 in air at the normal respiratory rate induces a positive shift. On the other hand, shifts up to 250 μV can be evoked by manoeuvres that alter intracranial brain hemodynamics with little effect on breathing pattern or cortical excitation (jugular vein compression, head-up/down tilt, Valsalva and Mueller manoeuvres; Vanhatalo et al., *Clin Neurophysiol* 2003;114:1744–54). The large amplitude of such responses is not consistent with a neuronal origin.

The potential difference that prevails across the blood–brain barrier (V_{BBB}) is capable of generating extracortical volume currents and stationary potential gradients on the scalp, which together with the known pH/P_{CO2} sensitivity of V_{BBB} readily accounts for the hyperventilation-induced responses. Moreover, hemodynamic changes detected using near-infrared spectroscopy correlate with slow EEG shifts. Although the role of neuronal activity and other factors in affecting V_{BBB} are poorly understood, the blood–brain barrier should be considered as a factor contributing to infra-slow EEG activity (Vanhatalo et al., In: Niedermeyer and Lopes da Silva (eds.), *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, 5th edition, pp. 489–493. Lippincott Williams & Wilkins, 2005).

MECHANISMS UNDERLYING EPILEPTOGENESIS UNDER BLOOD–BRAIN BARRIER DISRUPTION

A. Friedman (Ben-Gurion University, Beer-Sheva, Israel)

No abstract received.

Tuesday July 4, 2006

Tuesday July 4, 2006
7:30–9:00
Hall 1
Orphan Drug Symposium

THE CONCEPT OF RARE OR ORPHAN DISEASES IN EPILEPSY

M. Baulac (Service de Neurologie, Hopital Pitie-Salpetriere, Paris, France)

Although epilepsy is one of the commonest neurological disorders, certain epileptic syndromes or diseases are nonetheless fulfilling all the criteria, in terms of epidemiology and severity, for being qualified as rare diseases. These epileptic conditions indeed are distinct entities, affecting no more than 5 in 10,000 persons in Europe, carrying a risk of chronic impairment, severe debilitation, and mortality, and there is a lack of specific treatments with durable effects on the seizures and the neuropsychological disorders.

Most of the epileptic encephalopathies can be qualified as rare diseases. They include Ohtahara syndrome / early myoclonic encephalopathy, migrating partial seizures in infancy, West syndrome, Dravet syndrome or severe myoclonic epilepsy in Infancy (1/30,000), Lennox-Gastaut syndrome (2/10,000), Landau-Kleffner syndrome, continuous spike-wave during sleep, etc. . . In these specific conditions, the intense ictal and interictal epileptic activity contributes to the progressive disturbance in brain function. These epileptic encephalopathies can themselves be caused by rare mutations or other rare diseases, for instance tuberous sclerosis in West syndrome. Orphan drugs, which are still in development, have been designated by the EMEA for the Dravet syndrome (stiripentol) and for the Lennox-Gastaut syndrome (rufinamide).

In other situations, epilepsy is the predominant clinical expression of a disease of genetic, metabolic or inflammatory origin, which is responsible for progressive brain damage. Progressive myoclonic epilepsies (less than 1/20,000) for which brivaracetam was recently designated, and Rasmussen encephalopathy (approximately 1 case per big center per year) are good examples.

It is very important for our patients and their families to ensure that these conditions are well acknowledged as rare diseases, and that they can benefit from the various governmental and EU incentives dedicated to specific research and Orphan drugs development.

ORPHAN DRUGS: REVIEW OF THE EU PROGRAM

S. Del Signore (European Medicines Agency EMEA)

The EU Orphan Regulation was adopted in December 1999. It defines the criteria for designation as orphan medicinal products and offers incentives to assist sponsors in the development of medicinal products for patients affected by rare diseases. This is with a view to ultimately provide medicinal products to patients in the shortest possible time-frame. The Regulation incentives include a 10-year period of market exclusivity once authorised throughout the EU, protocol assistance from the European Medicines Agency (EMEA), eligibility for Community and Member State initiatives which support research and development of orphan medicinal products, access to the centralised procedure and the possibility to request fee reductions.

The EMEA is responsible for opinions on designation through its Committee for Orphan Medicinal Products (COMP), which is comprised of health professionals representing each of the Member States, three patient representatives, and three representatives recommended by the EMEA. The European Commission takes the administrative decision.

A medicinal product is designated as an orphan medicinal product in the EU based on the following criteria: (a) rarity of the condition (no more than 5 in 10,000 patients in the EU), or lack of sufficient return on investment, (b) a serious or life-threatening condition and (c) absence of satisfactory method(s) of diagnosis, prevention or treatment of the condition in question, or if methods exist, significant benefit to those affected by the condition. In this context, 'significant benefit' has been defined in legislation as a clinically relevant advantage or a major contribution to patient care.

In April 2006, the COMP adopted its 385th positive opinion recommending orphan designation.

Twenty-six designated orphan medicinal products have gone on to receive marketing authorization in the EU. As a consequence, up to approximately 1 million patients suffering from these orphan diseases in the Community stand to benefit from availability of these new treatments.

OVERVIEW OF BRIVARACETAM FOR PROGRESSIVE MYOCLONIC EPILEPSIES (UCB)

P. von Rosenstiel (Clinical Program Director, Therapeutic Area Neurology/Psychiatry, UCB, Belgium)

Introduction: Orphan drug legislation offers the possibility to pharmaceutical industry to develop innovative treatment options in rare diseases with a high medical need.

Brivaracetam orphan drug program: Brivaracetam is a novel SV2A ligand with sodium-channel inhibiting properties and a clearly distinct pharmacological profile from levetiracetam. It has shown at least ten-fold higher potency in animal models of epilepsy and posthypoxic myoclonus, as well as more complete seizure suppression in several of these models. First clinical data in a photoparoxysmal response study have confirmed these preclinical data, with significant effects throughout the tested dose range. Clinical development programs are currently ongoing in partial onset epilepsy and other indications.

Recently, brivaracetam has been granted orphan drug status for the treatment of symptomatic myoclonus in the US and progressive myoclonic epilepsies (PMEs) in Europe. UCB is currently in the preparatory phase for a clinical development program in Unverricht-Lundborg disease (ULD, EPM1).

The program, which will be run in Europe and North America, will consist of two studies as well as an open-label extension study. The program will combine dose-finding, confirmation of efficacy, and proof of long-term safety, tolerability and maintenance of efficacy. Additional significant benefit with regard to currently used treatments is to be demonstrated by an adequate trial design. While patients in Europe are discretely distributed in certain geographical regions and treated in a limited number of specialised centers, patients suffering from ULD are widely dispersed in the US. This makes novel approaches to find and recruit patients for clinical trials necessary. Among others, the cooperation with research centers and patient organizations is crucial in this endeavor.

If the clinical development program is successful, it will make a new treatment option available for patients suffering from a severely disabling disease, while at the same time allowing the sponsor to demonstrate efficacy in an extremely difficult to treat indication.

Conclusion: UCB's development program in ULD is a good example of the positive effects of orphan drug legislation on the development of new pharmaceuticals:

- It allows industry to perform controlled clinical trials, which would be difficult to fund from public sources, advancing our knowledge of these rare diseases
- It makes new treatment options for patients suffering from rare and unsatisfactorily treated disorders available, ideally leading to an improved quality of life for patients and a reduced burden of these diseases for society.

OVERVIEW OF STIRIPENTOL FOR SMEI (DRAVET SYNDROME) (BICODEX)

C. Chiron (Service de Neurologie et Metabolisme, Hopital Necker, Paris, France)

Stiripentol (STP) is a new antiepileptic compound made by Biocodex (France). It is structurally unrelated to all currently marketed

antiepileptic products. It recently proved to increase the GABAergic transmission using patch-clamp techniques in the hippocampus of immature rats. STP increases both the release of GABA and the duration of the activation of GABA-A receptors through a barbiturate-like effect.

Clinical studies were based on the fact that STP also inhibits cytochromes P450 (CYP3A4, CYP1A2, and CYP2C19) in vivo in epileptic patients, leading to increase plasma concentrations of concomitant antiepileptic drugs and to potentiate their antiepileptic efficacy. When it is associated with clobazam (CLB), STP inhibits the hydroxylation of the active metabolite of CLB, nor-clobazam through a mechanism mediated by CYP2C19. The adjunction of STP to clobazam and valproate proved to be superior to placebo ($p < 0.002$) in severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), a highly refractory, but homogeneous epilepsy in infancy, and a limited number of patients was enough to show similar results in two independent randomized controlled trials in France and Italy. Efficacy was maintained in about half the patients at long term follow-up. Adverse events were reported in about half of the patients, including drowsiness, hyperexcitability, loss of appetite, and loss of weight, but they could be minimized by optimizing the dose of clobazam and valproate. The protracted experience in compassionate use in France now provides tolerability data available on 400 patient–years. It confirms the loss of appetit as the first side effect reported, provided the interactions of STP are carefully taken into account by adjusting the doses of the combined AEDs. Based on these results, STP is going to grant orphan drug status for the treatment of Dravet syndrome and about to become the first orphan antiepileptic drug for children in Europe.

Tuesday July 4, 2006
9:30–11:30
Hall 1
Main Session
Brain imaging from molecules to networks

IMAGING BRAIN STRUCTURE AND THE NETWORK OF BLOOD FLOW AND METABOLIC CHANGES

W. Van Paesschen (UZ Gasthuisberg, Neurology, Leuven, Belgium)

High resolution MRI is the method of choice to study the brain structure in epilepsy. The MRI-identified lesion is important for the prognosis to render a patient seizure free with antiepileptic drugs and epilepsy surgery. Quantitative MRI is useful for research purposes, may facilitate the detection of focal dysplastic lesions, and has been shown to correlate with cognitive morbidity. 3 T MRI can improve the presurgical evaluation of patients with partial epilepsy when compared to 1.5 T studies.

Ictal hyperperfusion may localize the seizure onset zone and seizure propagation pathways accurately. Seizure propagation is characterized by "hour-glass" patterns. Postictal and interictal SPECT studies are less useful to localize the ictal onset zone. Subtraction ictal SPECT coregistered with MRI (SISCOM) improves the localization of the area of hyperperfusion. Detailed analysis of SISCOM hyperperfusion patterns is a promising tool to detect subtle focal dysplastic lesions in around 15% of "MR-negative" partial epilepsies and to establish the epileptic nature of these lesions noninvasively.

Statistical parametric mapping (SPM) analysis of groups of selected ictal-interictal difference images has the potential to demonstrate the evolution of cortical, subcortical and cerebellar perfusion changes during a particular seizure type, and to provide new insights into the pathophysiology of seizures. In a comparative study of ictal SPECT during complex partial seizures (CPS) and interictal FDG-PET in mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS), hypometabolism was greatest in the ipsilateral frontal lobe, and represented a seizure-related dynamic process in view of further ictal decreases. Crossed cerebellar diaschisis suggested that there was a strong ipsilateral frontal lobe inhibition during CPS. This surround inhibition in the frontal lobe may be a dynamic defense mechanism against seizure propagation, and may be responsible for functional deficits observed in mTLE-HS.

VISUALISING THE CHEMISTRY OF THE BRAIN

M. Guye (INSERM U 751 & CNRS UMR 6612, Faculte de Medecine de Marseille, France)

Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) is a metabolic imaging technique providing non-invasive quantification of several brain metabolites. This method has always been considered as particularly interesting to assess in vivo the biochemical alterations underlying human epilepsy. However, its clinical use has been limited because of: 1) technical difficulties (i.e., low signal to noise ratio, high susceptibility to magnetic field, difficulties for absolute quantification, overlap of signals coming from different metabolites. . .) and 2) the lack of knowledge concerning the interpretations of metabolites alterations. Indeed, since the first use of ^{1}H-MRSI in the early nineties, studies had identified more or less reproducible modifications of metabolites concentrations: mainly N-acetyl-aspartate (NAA), Creatine (Cr) and Choline (Cho). However, the significance of such alterations has only been clarified recently. This was due to: 1) technical improvement overcoming several methodological pitfalls, 2) studies investigating not only histological but also functional and electrophysiological correlates of such metabolites alterations. An overview of recent advances and findings of chemical shift imaging technique will be presented. MRS studies of amino-acids such as GABA and Gutamine-Glutamate (Glx) and their usefulness in the in vivo assessment of human epilepsy will also be discussed.

IMAGING NEUROTRANSMISSION

E. Kumlien (Department of Neuroscience, Neurology, University Hopsital, Uppsala, Sweden)

Epilepsy research imaging neurotransmission with positron emission tomography (PET) has been used to elucidate the pathophysiological mechanisms underlying both focal and generalised epilepsies. The most important clinical contribution of PET has been in the presurgical evaluation of patients with medically refractory partial epilepsy. □-Aminobutyric acid (GABA) is the major inhibitory transmitter in the brain. ^{11}C-flumazenil is a useful marker of the central GABA-benzodiazepine receptor complex. The binding of the tracer is reduced in mesial temporal lobe epilepsy reflecting localized neuronal and synaptic loss in the epileptogenic region. In extratemporal lesions the binding pattern is less distinct and decreased as well as increased uptake may be seen. Interictal studies of the opiate receptor system have shown increased binding of the □-agonist ^{11}C-carfentanil in lateral temporal cortex in temporal lobe epilepsy (TLE) indicating an antiepileptic and inhibitory role of the endogenous opiod system.

Eexperimental models have suggested a potential role for serotonergic transmission in epilepsy, and interest in this research has been increased by the development of ligands specific for 5-hydroxytryptamine (5-HT) receptors and serotonin synthesis. 5-HT_{1A}-binding measured with ^{11}C-WAY or ^{18}F-FCWAY is reduced in TLE. In children with tuberous sclerosis □^{11}C-methyl-L-tryptophan (AMT) can help to identify epileptogenic tubers. Glutamate is powerful excitatory neurotransmitter mediating its effect through glutamate and NMDA receptors. NMDA receptor dysfunction may underlie epilepsy, ischemia and neurodegenerative disorders. Attempts to visualize the NMDA receptor with ligands such as ^{11}C-S-ketamine have yielded ambiguous results. In addition the cholinergic and dopaminergic transmitter systems have been subjected to human PET-studies.

IMAGING NORMAL AND ABNORMAL CEREBRAL ACTIVATION

F. Woermann (MRI Unit, Bethel Epilepsy Center, Bielefeld, Germany)

To avoid postsurgical morbidity, the lateralization/localization of primary motor cortex, of language and of memory have to be known prior to epilepsy surgery.

Functional MRI (fMRI) is a timely method to visualize cerebral activation with the aim to delineate areas of eloquent cortex from epileptogenic lesions. Compared to other methods (Wada test, subdural grids, depth electrodes), fMRI is noninvasive, free from ionizing radiation, widely

available, and relatively inexpensive. The method "fMRI" is in the process to demonstrate that it can be used in the majority of epilepsy patients (incl. children); that fMRI acquisition and assessment are easy and reproducible; and that fMRI provides typical and atypical results in large number of individual cases in concordance with a gold standard (e.g. postsurgical outcome etc.).

FMRI visualizes functional networks and shows either even bilateral or unilaterally scattered activations which can be displayed as very circumscript areas—ultimately as a result of statistical thresholding. Whether these activation areas of statistical significance are of clinical relevance and carry essential parts of cognitive and motor functions, can be investigated by correlating fMRI results with deactivating methods or with outcome: e.g., in patients with congenital hemiparesis and in the presence of bilateral fMRI activity, transcranial magnetic stimulation identified ipsilateral fMRI activation controlling the paretic hand (Staudt, 2004); fMRI predicted the absence of essential language areas compared to intraoperative stimulation (Rutten, 2002); greater left hippocampal activity in memory fMRI predicted a greater postoperative decline in memory (Richardson, 2006).

While motor and cognitive fMRI seem to approach a certain level of clinical relevance, the technically challenging, but scientifically certainly promising combination of EEG and fMRI (to image abnormal epileptic activity) is at an earlier stage of development and has no current role in the presurgical evaluation of patients with epilepsy.

VISUALISING THE NETWORKS OF THE BRAIN

R. Powell (Institute of Neurology, UK)

The relationship between brain structure and function is fundamental to understanding both cognitive neuroscience and clinical neurology. There is good reason to expect a strong correspondence between regional brain function and the underlying architecture, however studying this relationship is complicated by the intricacy of the brain's connections, and the lack of techniques for exploring structural connectivity in vivo. Recent advances in neuroimaging now allow brain connections to be studied noninvasively. Tractography, a derivative of diffusion tensor imaging allows the mapping of white matter tracts and the exploration of the anatomical connectivity of regions involved in particular functions.

Tractography has a number of roles in the evaluation of patients with epilepsy. An important clinical role will be in the presurgical evaluation of epilepsy patients, and in particular in the prediction of visual and language deficits. This potential as a presurgical tool can be illustrated by the mapping of the optic radiations preoperatively, and how this information can be used to predict, and minimize the risk of, visual field defects following anterior temporal lobe resection.

Tractography can also demonstrate subtle structural changes in epilepsy patients, for example the structural connections underlying functionally defined language regions. The structural connectivity of language areas in left and right TLE are different from controls, with a decrease in connections ipsilateral to the focus and a contralateral increase, providing an insight into the basis of functional plasticity.

A further evolving role of tractography is to potentially demonstrate networks involved in seizure propagation, such as the connections of the medial temporal lobe.

Tuesday July 4, 2006
9:30–11:30
Hall 5A
Main Session
Epileptogenesis, seizures, and epilepsy

INTRINSIC NEURONAL PLASTICITY: ROLE IN HYPEREXCITABILITY AND PHARMACORESISTANCE

H. Beck (University of Bonn Medical Center, Department of Epileptology, Germany)

The input-output relationship of neuronal networks depends both on their synaptic connectivity and on the intrinsic properties of their neuronal elements. Long-term changes in this relationship can thus be achieved by changes in synaptic and/or intrinsic neuronal properties. Recent data clearly demonstrate that seizures can modulate the functional and molecular characteristics of voltage-gated ion channels, leading to persistent changes in neuronal discharge behavior. We suggest that this intrinsic plasticity is a potent mechanism that, in conjunction with synaptic plasticity, can fundamentally alter the input-output properties of neuronal networks in the mammalian brain. Furthermore, changes in voltage-gated ion channels that constitute targets for antiepileptic drugs can cause them to become unresponsive to these agents, thus constituting one potential molecular cause for drug-resistance.

MOLECULAR BASIS OF EPILEPTOGENESIS IN CHANNELOPATHIES

S. Baulac (INSERM U679, France)

Epileptic syndromes have very diverse etiologies involving genetic factors and/or brain insults and injuries. While human epilepsies with a mendelian inheritance are not common, numerous genes have been identified over the last decade. Until recently, genes linked to idiopathic epilepsies with monogenic inheritance were all thought to encode subunits of ion channels or transmitter receptors. Thus, potassium channel mutations cause benign familial neonatal convulsions; sodium channel mutations are linked to generalized epilepsy with febrile seizures plus and severe myoclonic epilepsy of infancy; $GABA_A$ receptors to generalized epilepsy with febrile seizures plus and autosomal dominant (AD) juvenile myoclonic epilepsy; nicotinic receptors to AD nocturnal frontal lobe epilepsy, and chloride channels mutations cause idiopathic generalized epilepsy. However the identification of idiopathic epilepsies as channelopathies, which alter synaptic transmission or neuronal excitability, has been challenged by two recent reports describing mutations in human idiopathic epilepsy that affect unknown proteins, EFHCI and LGI1. Gaining knowledge on the physiological role of new proteins within the central nervous system may throw light to normal brain function and to new mechanisms of epileptogenesis.

IMAGING PROGRESSIVE CHANGES IN EPILEPSY

L. Lemieux (Institute of Neurology, University College London, UK)

Serial MR imaging has increased our understanding of the way structural changes evolve in epilepsy. Applications include identifying the structural consequences of status epilepticus or repeated brief seizures on the brain and the monitoring of lesion size e.g. tumours over time. This presentation focuses on the secondary effects of seizures.

Various imaging techniques show selective sensitivity to different stages of the acute postictal period. Methodological considerations are divided into those MR imaging modalities used to (1) detect acute hippocampal changes in the immediate postictal period, and (2) those used in identifying subtle volumetric change over a more prolonged period.

Our results and that of others, have demonstrated increases in the T2-weighted signal, possibly reflectings eizure-induced alterations in haemodynamic and cell membrane permeability as the result of seizures, fluctuations in the apparent diffusion coefficient on diffusion-weighted imaging and metabolite changes detectable using proton and phosphorus MRS.

Volumetric changes following status epilepticus and repetitive seizures are best studied using serial volumetry incorporating coregistration to improve sensitivity to change. Manual hippocampal volumetry remains the most common quantitative measure used in imaging progressive changes in epilepsy although automated techniques may play a greater role in the future. Region- and voxel-based tools for detecting cerebellar and neocortical change have also been used. Methodological aspects of serial imaging are discussed, along with examples of their application. "Our results in a population-based study support the concept of early volume loss resulting from an initial insult followed by age-related volume loss within the normal range."

Serial imaging provides valuable information on the timing and pathogenesis of structural changes in epilepsy, and the findings could have

important implications in devising timely and targeted neuroprotective strategies.

EPILEPTOGENESIS AND DISEASE MODIFICATION—ARE THEY REALISTIC NOVEL TREATMENT INDICATIONS?

A. Pitkänen (University of Kuopio, A.I.Virtanen Institute for Molecular Studies, Finland)

Epileptogenesis refers to abnormal neuronal reorganization occurring over a long period of time following a cerebral insult (e.g., traumatic brain injury, stroke) leading to the occurrence of spontaneous seizures. To prevent epileptogenesis or modify the disease process in such a way that developing epilepsy is milder and easier to treat will require (i) clinically relevant animal models for studies on basic mechanisms of epileptogenesis as well as for preclinical testing of novel treatments, (ii) molecular targets for development of novel therapies, (iii) compounds that affect the targets without compromizing the normal brain function or the recovery process that occurs in parallel with epileptogenesis, and (iv) surrogate or biomarkers that can be used to identify individuals at risk of epilepsy after brain damaging insult as well as to follow the effects of treatments in preclinical and clinical trials. This presentation will review the developments in these fields over the recent years. As the data show there have been major progress in epileptogenesis research providing novel ideas how to proceed in the design of studies aiming at preventing or modifying the disease process that eventually leads to acquired symptomatic epilepsies.

Tuesday July 4, 2006
15:00–17:00
Hall 1
Discussion Group Session
Neurostimulation for epilepsy

DEEP BRAIN STIMULATION IN EPILEPTIC PATIENTS IN 2006, WHAT IS THE EVIDENCE?

P. Boon (Laboratory for Clinical and Experimental Neurophysiology (LCEN) and Department of Neuology, Ghent University Hospital, Belgium)

Acute deep brain stimulation (DBS) in various thalamic nuclei and medial temporal lobe structures has recently been shown to be efficacious in small pilot studies of patients with medically refractory epilepsy. Only limited data on chronic thalamic and amygdalohippocampal stimulation are available. Chronic DBS in these structures requires resolving many conceptual and technical issues. There is little evidence based information on rational targets and stimulation parameters. Currently available depth EEG recording electrodes are unsuitable for chronic use. Inversely, the use of DBS electrodes for intracranial EEG recording and localization of the ictal onset zone prior to stimulation has only been reported by a few groups. Results from feasibility and pilot studies in the most recent literature will be presented. The experience with DBS in temporal lobe epilepsy using quadripolar DBS electrodes bilaterally implanted in the amygdalohippocampal region to identify and subsequently stimulate the ictal onset zone will be described. This work has yielded a significant decrease of seizure counts and interictal EEG abnormalities during long-term follow-up. Various hypotheses on the possible mechanism(s) of action of DBS for epilepsy using EEG, cerebral blood flow and metabolic measures including results from animal experiments have recently been developed. Data from open pilot studies suggests that chronic DBS for epilepsy may be a feasible, effective and safe procedure that reduces interictal EEG abnormalities and seizures. Further trials with larger patient populations, controlled and randomised designs should be initiated.

BASIC MECHANISM OF DEEP BRAIN STIMULATION, WHAT IS REALLY KNOWN?

W. Wadman (SILS Center for Neuroscience, University of Amsterdam, Netherlands)

Deep brain stimulation (DBS) is one of the therapeutic alternatives under development for pharmacoresistant patients in particularly for those for which surgical resection of the epileptic focus is not an option. The major advantages for such a treatment are its reversibility e.g., when new drugs become available and its controllability, eventually allowing "on-demand" stimulation. Most current treatments for epilepsy aim at seizure suppression, but DBS could also play a role by interfering with epileptogenesis. Fortunately DBS technology exists and the technique has been proven quite successful in patients that suffer from Parkinson's disease.

There are at least four distinct mechanisms by which DBS could work: 1) the release of endogenous substances (as most likely occurs in Vagal Nerve Stimulation) 2) the acute manipulation of the neuronal membrane voltage by an external electrical field 3) the manipulation of synaptic coupling by mechanisms that induce Long Term Potentiation or Long Term Depression and 4) the manipulation of mechanisms involved in the intrinsic scaling of excitability. For all four mechanisms proofs of principle exist, but none of them has already been employed in a fully successful protocol against epileptic seizures.

In particularly for the human situation many questions need to be resolved: 1) what is (are) the best region(s) to stimulate, 2) which are the optimal parameters (frequency, intensity, duration, specific patterns) of the stimulation protocol, 3) are continuous, intermittent or "on demand" stimulations possible and preferable, and 4) who are the best patients to treat. For the latter question it is clear that trials will start with patients that are pharmacoresistant, but if DBS would counteract epileptogenesis the patient selection will enter a new phase.

RESPONSIVE (CLOSED-LOOP) STIMULATION, IS IT REALLY FEASIBLE?

F. Mormann (Department of Epileptology, University of Bonn, Germany)

Deep brain stimulation is a promising new technology for the treatment of medically intractable seizures. Apart from the question where in the brain the stimulation should take place (e.g., cerebellum, thalamus, basal ganglia, or direct stimulation of the epileptic focus) there are different possibilities of how to stimulate.

In principle, neural stimulation can be carried out either in an open-loop, duty-cycle design, e.g., in the form of continuous or periodic stimulation, or in a closed-loop, responsive design in which the patient's electroencephalogram is used to trigger on-demand stimulation. This type of responsive stimulation can be based, e.g., on seizure detection algorithms or on seizure prediction algorithms.

Controlled clinical trials are currently being carried out both for duty-cycle stimulation and for responsive stimulation based on seizure detection algorithms. The results reported to date must be regarded as preliminary and do not allow a conclusive comparison of these two stimulation techniques.

Deep brain stimulation based on seizure prediction algorithms does not appear to be justified at this stage as it is not clear whether prospective prediction algorithms can indeed perform significantly better than a random prediction.

VAGUS NERVE STIMULATION IN 2006, WHAT IS THE EVIDENCE?

K. Vonck (Ghent University Hospital, Reference Centre for Refractory Epilepsy, Department of Neurology, Ghent, Belgium)

Vagus nerve stimulation, a state-of-the-art

Introduction: Electrical stimulation of the vagus nerve (vagus nerve stimulation, VNS) is one treatment modality for refractory epilepsy. Clinical efficacy of VNS has been established in randomized controlled studies. Important issues that still need to be cleared up are mode of action, optimum stimulation parameters, long-term efficacy and side effects, cost-efficacy and potential other treatment indications.

Recent literature on the use of VNS in refractory has looked at efficacy in terms of changes of seizure frequency and concommittant AED treatment in different types of epilepsy. Side effects and cost-efficacy

analysis in terms of decreases in hospital admission days, clinic visits and laboratory investigations were also assessed. Mechanism of action was studied by positron emission tomomgraphy (PET) and single photon emission tomography (SPECT) studies performed immediately after initial stimulation to evaluate VNS induced changes in regional cerebral bloodflow (rCBF) and serial SPECT measurements during follow-up in these patients to assess temporal evolution of rCBF changes and correlate findings to clinical efficacy.

Clinical efficacy of VNS in long-term observational studies is in accordance with the results of the initial controlled studies. In one third of the patients a more than 50% reduction in seizure frequency is found. Up to 10% of patients become seizure free for a period of 12 months or longer. A trend towards improved seizure control with longer use of VNS was observed. Response during the first 3 months of treatment seemed predictive of long-term response. VNS is mostly studied in patients with refractory partial epilepsy but appears to be equally efficacious in patients with different forms of generalized epilepsies.

Side effects are mostly related to peripheral stimulation effects on the laryngeus recurrens nerve and other branches of the vagus nerve including hoarseness, throath pain or discomfort and coughing and appeared to decrease with longer treatment. Despite early reports on cardiac arrythmias occurring at the time of first stimulation during the implantation procedure, no serious life-threatening adverse events have been reported. VNS has a promising cost-efficacy profile. Epilepsy related direct medical costs were reduced significantly after treatment with VNS, the reduction in hospital admission days being the most important factor. Cost-efficacy analysis suggests that the cost of VNS is saved within 2.5 years following implantation. VNS induces rCBF changes immediately after initial stimulation that can be studied with SPECT and PET. Ipsilateral thalamic hypoperfusion was the most significant finding. VNS-induced changes in the thalamus may play an important role in suppression of seizures.

Conclusions: VNS is an efficacious, safe and cost-effective treatment for patients with refractory epilepsy, who are not candidates for resective surgery. Further studies are needed to elucidate the anti-seizure mechanism of action of VNS.

Tuesday July 4, 2006
15:00–17:00
Hall 5A
Discussion Group Session
The spectrum of temporal "plus" epilepsy

FAILURES OF TEMPORAL LOBE SURGERY

D. Schmidt (Epilepsy Research Group, Berlin, Germany)

Temporal lobe surgery is the nonpharmacological treatment of choice for carefully selected patients with drug resistant temporal lobe epilepsy. On average, two of three patients undergoing surgery will become seizure free or nearly seizure free after surgery with continued antiepileptic drug (AED) treatment. We limit our discussion to failure to achieve long term surgical seizure control which can occur in three groups of patients. One, surgery fails with respect to seizure control with continued AEDs in one of three cases who never become seizure free after surgery. Two, a small subgroup of patients who were seizure free after surgery on AEDs will not remain seizure free in the long run. This is another group of patients in whom surgery may be considered to have failed. When AEDs are stopped in patients who have been seizure free after temporal lobe surgery for several years, one in three patients has a seizure recurrence. This is a third subgroup of patients in whom surgery has failed, particularly in a small group in whom reinstitution of AEDs after seizure recurrence fails to regain seizure freedom. Despite all these instances of failure, temporal lobe surgery is a very useful procedure and the only one which achieves seizure freedom in 50% of patients with drug resistant temporal lobe epilepsy, approximately in 20% of patients with AEDs and in 30% without AEDs.

TEMPOROORBITAL EPILEPSY

F. Dubeau (Montreal Neurological Hospital and Institute, McGill University, Canada)

There is a subset of epileptic patients with temporal lobe (TL) seizures where the definition of limbic or neocortical TL epilepsy does not seem to apply: a TL syndrome can be produced by extratemporal physiological or structural abnormalities. The concept of temporal "plus" epilepsy was introduced to define this group of patients with TL semiology and electrophysiological characteristics, but poor results after standard TL resections. These patients are believed to have multilobar epilepsy, or widespread epileptogenicity, which includes TL and extra-TL structures; the later likely functionally linked to the mesial or neocortical TL, explaining the main temporal electroclinical features. Kahane and Ryvlin (*Curr Opin Neurol* 2005;18:125–127) proposed to divide patients with temporal "plus" epilepsy in temporoorbital (orbitofrontal, or OF), perisylvian (opercular and insular) and posterior temporal (parietooccipitotemporal) epilepsy.

The definition of frontal lobe (FL) semiology is relatively clear, but the interpretation of FL epileptic semiology remains difficult particularly if epileptic activity shows poor localizing value or, even more, if no lesion can be detected. The clinical presentation for OF epilepsy is variable, and OF seizure discharges may be associated sometimes with typical FL semiology, but often can be silent until they propagate to other structures such as the adjacent TL. The OF cortex has extensive connections with other parts of the brain, including virtually all limbic structures, the amygdala, hippocampal formation, entorhinal area and insula, and the anterior temporal cortex. A few cases of OF epilepsy have been described and often they felt into a broader category of regional epilepsy. On the other hand, mesial TL epileptic discharges preferentially spread to the mesial FL, especially to the OF cortex, an important route for the clinical expression of TL seizures.

To address the issue if the existence of temporoorbital epilepsy explains some of the surgical failure in patients with a diagnosis of TLE, we reviewed a series of patients investigated between 1995 and 2005, in our institution, with intracranial SEEG recordings exploring simultaneously the TL and FL structures. The data were compared with our current knowledge on the electrophysiopathology of OF and temporoorbital epilepsy.

TEMPOROSYLVIAN EPILEPSY

P. Kahane (Epilepsy Unit, Neurology Department, Grenoble University Hospital, France)

The term of temporosylvian epilepsy (TSE) has been proposed 25 years ago (Munari et al. 1980) to describe specific forms of multilobar epilepsies characterized by a complex epileptogenic network including the temporal lobe (TL), the frontal and parietal operculum, and the insula. There are, however, only few published data on this topic (Kahane et al. 2001, Isnard et al. 2004) and, because of this, the identification of this form of epilepsy has remained largerly ignored. Yet, some patients submitted to TL surgery who continue to experience seizures postoperatively might suffer from TSE, and identifying those patients using invasive recordings might lead to perform a more extensive and more effective cortectomy, according to the surgical possibilities and limits (Munari et al. 1995). For instance Kahane et al. (2001) showed that 6 of the 7 patients studied by intracerebral electrodes and in whom seizures arose from temporal and suprasylvian opercular cortices were totally seizure-free after surgery when an adequate TS resection could be achieved. By contrast, TL surgery alone was unsuccessful in the 2 temporoinsular cases of Isnard et al. (2004) since it allowed to suppress the seizures of TL origin but not those which arose from the insula. Thus, though limited, these examples emphasize the interest to better delineate the spectrum of TSE, in as much as patients suffering from this form of epilepsy might be at higher risk of sudden death than those suffering from ≪pure≫ TLE (Persson et al. 2005). Therefore, whether the diagnosis of TSS can be suspected non invasively remains an important issue and particular attention must be paid, in the context of TLE, to the presence of early ictal signs suggesting the involvement of the perisylvian region (somatosensory, gustatory, vestibular and auditory auras, hypersalivation, laryngeal constriction, hemifacial motor signs). Also, the presence

of bilateral or precentral interictal EEG abnormalities might be suggestive of an epileptogenic zone extending outside the anatomical boudaries of the TL (Barba et al. In preparation). In such cases, invasive recordings should be considered, even when MRI shows a hippocampal sclerosis.

POSTERIOR TEMPORAL EPILEPSY

S. Francione ("Claudio Munari" Epilepsy Surgery Centre, Ospedale Niguarda Ca' Granda, Milano, Italy)

Extending a temporal lobe resection to the neighbouring occipital or parietal cortex can be a useful surgical therapeutic option in selected cases. In order to analyse the clinical characteristics of this type of "temporal-plus" epilepsies we selected—from a population of 91 patients with drug-resistant partial epilepsy operated on in the posterior part of the brain presented elsewhere (Francione et al, this Congress)—25 patients in which a temporooccipital (22) or temporo-parietal (3) resection was performed. Selection criteria followed both anatomical (localization of surgical resection) and clinical (semiological features resembling temporal lobe seizure) parameters.

Studied patients are 15 males and 10 females, age at surgery: 3–54 years (28 ± 11.9; 2 patients operated on before the age of 16 years), mean age at seizures onset: 7.9 ± 4.8 (birth-16 years), mean epilepsy duration: 19.9 ± 11.7 (3–46 years). Seizures were monthly in 3 patients(12%), weekly in 19(76%) and daily in 3(12%).

Five patients have a familiarity for epilepsy, none presented febrile convulsions in his personal history.

Preoperatory MR was negative in 7 cases(28%), showed a localised lesion in 17(68%) and a bilateral double cortex in 1. All the patients but 1 were studied by Video-EEG, and in 21 cases (84%) the extension of the resection was defined on the basis of an intracerebral stereo-EEG study. Surgery was right-sided in 17(68%) and left-sided in 8(32%). After a mean follow-up of 46 months surgical outcome following Engel's classification is: 18 patients: Class I(72%), 5 patients: Class II (20%), 2 patients: Class IV(8%).

Histological examination accounted for: 11 MCD (44%), 9 neoplastic lesions(36%), 4 cryptogenic (16%) and 1 scar. In conclusion, posterior temporal resections, mainly defined by invasive recordings, seem to represent an effective surgical option; further analysis, especially concerning ictal electroclinical features, will be presented with the aim of characterising a possible "syndromic" entity.

SURGERY FOR TEMPORAL PLUS EPILEPSY

P. Ryvlin (Hospices Civils de Lyon, France)

Introduction: Temporal-plus (T+) epilepsy is defined by an epileptogenic zone (EZ) primarily encompassing temporal lobe structures, but extending to neighboured areas beyond the boundaries of anterior temporal lobectomy (ATL), such as the insula, the frontal and parietal operculum, the orbitofrontal cortex and the temporoparietooccipital (TPO) junction. In this study, we compared the surgical outcome in T+ epilepsy versus pure temporal lobe epilepsy (TLE).

Methods: We included 283 consecutive patients who underwent an epilepsy surgery procedure in our institutions that affected at least part of the temporal lobe. The distinction between pure TLE and temporal plus epilepsy was made according to the final conclusion of the presurgical assessment which has prompted surgery. The diagnosis of temporal plus epilepsy was always based on invasive stereo-EEG (SEEG) data, whereas that of pure TLE could be made on non invasive data only. The completness of removal of the epileptogenic zone was evaluated on post-operative MRI.

Results: Among the 283 patients, 183 who underwent a stereo-EEG (65%), and 59 proved to suffer from T+ epilepsy (21%). Surgery was considered as resulting in a complete resection of the EZ in 97% of "pure" TLE patients and 69% of T+ epilepsies. Incomplete resection was related to hippocampal remnant in pure TLE (3%), and to the decision to perform an ATL or a suboptimal cortectomy in T+ epilepsy due to the presence of eloquent cortex within the EZ. A regressive tree analysis demonstrated that the main factor that significantly affected seizure outcome was the completness of removal of the epileptogenic zone ($p < 0{,}0001$), followed by the type of epilepsy (TLE versus T+: $p < 0{,}001$). In patients who benefited from a complete removal, a class I outcome was achieved in 92% of pure TLE and in 76% of T+ epilepsy.

Conclusion: Fair surgical results can be obtained in T+ epilepsy, provided an appropriate identification and complete resection of the EZ.

Tuesday July 4, 2006
15:00–17:00
Hall 5B
Discussion Group Session
Mesial temporal epilepsy is an extrahippocampal disease

EXTRAHIPPOCAMPAL NEUROPATHOLOGICAL CHANGES IN MESIAL TLE

I. Blümcke (Department of Neuropathology, University of Erlangen, Germany)

Hippocampal sclerosis comprises the most frequent histopathological alteration in mesial TLE. However, there are some extrahippocampal areas severely compromized in many TLE patients, i.e., the amygdala, entorhinal cortex, subiculum and temporal neocortex (pole region). A major issue to be discussed is whether these lesions arise from an independent pathogenesis, i.e., as dual pathology, or underlie rather HS-associated pathomechanisms.

Amygdala sclerosis represent with severe neuronal cell loss in at least two subnuclei of the human amygdala, mainly from the basolateral complex. A major obstacle for histopathological examination is the compound anatomical organization, which is often not well preserved in surgical specimens. However, our analysis of 20 en bloc samples of the human amygdala identifies neuronal cell loss and astrogliosis in the majority of cases. Ultrastructural analysis further characterize synaptic circuitries of local interneurons as well as projection neurons to be severely affected (i.e., loss of perisomatic inhibitory synapses). These data point to altered networks between the amygdala and hippocampus, which is likely to contribute to mesial epileptogenesis in chronic mTLE patients. Furthermore, amygdala related pathology can be observed in various TLE animal models, including kindling or kainite-induced status epilepticus.

Architectural dysplasia of the temporal neocortex is another hallmark of mTLE. However, there are some concerns with respect to classification issues. Disturbance of cortical lamination as well as abundant ectopic neurons in white matter are frequent microscopical features of compromized areas. Whereas some authors consider these lesions as FCD type I and dual pathology, respectively, other labs regard these patterns as HS associated pathology. Nonetheless, epileptogenicity appear with these temporal lobe regions and surgical removal is benefical for the majority of patients to control seizure activity.

The knowledge of extrahippocampal pathologies is mandatory to better characterize the etiology and pathogenesis of chronic seizure in mTLE patients and to further improve surgical as well as pharmacological treatment strategies.

EXTRAHIPPOCAMPAL VOLUMETRIC CHANGES IN MESIAL TLE

N. Bernasconi (Mc Connell Brain Imaging Centre/Montreal Neurological Institute, Canada)

For many years, temporal lobe epilepsy (TLE) was considered to be mainly related to hippocampal pathology.

In the last decade, volumetric MRI has been used to evaluate the structural integrity of mesial temporal lobe structures in TLE. The entorhinal cortex and the hippocampus are the most atrophic structures within the mesial temporal lobe, whereas the perirhinal and posterior parahippocampal region are less commonly affected. This pattern of preferential damage is possibly consequence of a disruption of

entorhinal-hippocampal connections as a result of privileged dialogue between these two structures. Whole-brain voxel-based morphometry has revealed that GM and WM pathology in TLE extends beyond the hippocampus involving other limbic areas such as the cingulum and the thalamus, as well as extralimbic areas, particularly the frontal lobe. This is suggestive of disconnection involving preferentially frontolimbic pathways in TLE.

It is now generally recognized that epilepsy is not a static disorder and that important structural brain changes may take place over time. Volumetric MRI has shown that progressive volume loss of mesial temporal lobe structures in relation to duration of epilepsy is not restricted to the hippocampus and also affects the amygdala and the entorhinal cortex. On the other hand, entorhinal and hippocampal volumes seem to be already low at the time of onset of recurrent seizures, indicating that the effect of TLE may be present before the clinically obvious onset of seizures.

Although, the cause of the disease is still unknown, it seems too simplistic to consider that evaluation of the hippocampus alone is sufficient to fully understand TLE. Indeed, MRI studies have allowed us to view TLE not as a disease of single structure disease, but as one involving many structures interconnected through a network.

EVIDENCE FOR EXTRAHIPPOCAMPAL SEIZURE ONSET WITH INVASIVE RECORDINGS IN MESIAL TLE

F. Bartolomei (INSERM U751 and Clinical Neurophysiology Department Timone Hospital, Marseille, France)

The role of extrahippocampal mesial temporal lobe structures in the genesis of mesial temporal lobe seizures (MTLs) is unclear. In particular, the role of the rhinal region (entorhinal cortex, EC) in MTLs genesis has been proposed, mainly based on indirect MRI evidence. We will summarize several studies conducted in patients having depth electrodes-SEEG recordings in whom we recorded both hippocampus and extrahippocampal areas. The main finding of these studies is to show that the ictal onset zone in MTLs is made of several structures forming a network instead of a simple "hippocampal" focus.

The respective role of hippocampal and non hippocampal structures in these networks will be discussed in the light of S-EEG signal analysis.

EXTRAHIPPOCAMPAL INVOLVEMENT IN MESIAL TLE USING FUNCTIONAL IMAGING METHODS

W. Serles (Universitätsklinik fuer Neurologie Wien, Abteilung für Klinische Epilepsieforschung, Austria)

Structural brain abnormalities are widespread in drug resistant mesial temporal lobe epilepsy (mTLE). There is compelling evidence that extrahippocampal volume loss occurs in patients with mTLE which is more pronounced ipsilateral to hippocampal sclerosis. Specifically, involvement of the amygdala, the rhinal cortices, the temporal pole, the lateral regions of the temporal lobe, but also contralateral temporal lobe areas and extratemporal brain regions have been found. However, besides neuronal loss, extrahippocampal abnormalities are also seen in functional imaging methods measuring different aspects of neuronal dysfunction.

Diffusion tensor imaging (DTI) provides evidence for extrahippocampal network abnormalities as do interictal PET methods and proton MR spectroscopy.

Diffusion abnormalities have been reported to extend to lateral temporal structures, to the contralateral mesial structures and remote extratemporal regions. In FDG-PET, various patterns in temporal and extratemporal areas including the insula have been described. Finally, mTLE is associated with extrahippocampal and extratemporal spectroscopic abnormalities. The pathophysiological implications of these findings for understanding epileptogenesis and neural networks in mTLE are discussed.

Tuesday July 4, 2006
15:00–17:00
Hall 5C

Discussion Group Session
Pharmacokinetics of concern for women with epilepsy of childbearing potential

CONTRACEPTIVES AND AEDS, INTERACTIONS IN TWO DIRECTIONS

M. Bialer (Department of Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel)

Antiepilpetic drugs (AEDs) can be categorized into three groups based on their potential to cause induction-drug interactions (DDI) with combined oral contraceptives (OC). The old AEDs such as phenobarbital, phenytoin and carbamazepine (CBZ) induce CYP-mediated metabolic pathways as well as glucuronide conjugation. Consequently, these enzyme-inducing AEDs reduce OC levels during concomitant administration and may cause contraceptive failure. A second group of AEDs includes topiramate (TPM), felbamate and oxcarbazepine (through its active monohydroxy metabolite or entity - licarbazepine), which are less potent inducers of CYP isozymes, but have been shown to alter OC plasma concentrations. A third group of AEDs includes valproic acid, gabapentin, lamotrigine (LTG), levetiracetam and tiagabine, which do not alter OC pharmacokinetics. A recent study evaluated the TPM-OC interaction in comparison to CBZ. Coadministration of TPM at daily doses of 50, 100, 200 mg did not have a statistical significant effect on the mean exposure or area under the curve AUC of ethinyl estradiol (-12%, $+5\%$ and -11%, respectively). A similar nonsignificant difference was observed with the norethindrone AUC and plasma levels ($p > 0.05$). In contrast to TPM, CBZ significantly decreased AUC values of norethindrone and ethinyl estradiol by 58% and 42%, respectively, and increased their respective oral clearance (CL/F) by 69% and 127% ($p < 0.05$). These results show that in the above OC-DDI classification TPM should be categorized by the dose used. At daily doses below 200 mg, TPM belongs to the third group rather than the second one. Given the significant effect that CBZ coadministration (600 mg/day) had on the reduction of plasma levels and AUC values of norethindrone and ethinyl estradiol, it is clear that TPM does not cause a similar effect.Sabres et al. 2001 & 2003, showed that OC treatment reduces LTG plasma levels by more than 50%, which may require LTG dose adjustment. Withdrawal of OC may double LTG plasma levels. Reimers et al. 2005, demonstrated that it was the ethinyl estradiol component of the combined OC that interacted with LTG by inducing its metabolic glucuronide conjugation. Such an interaction might be expected with other AEDs that are metabolized primarily by glucuronidation mediated by the same glucuronide isozymes as LTG (e.g. UGT 1A4). In conclusion, DDI between AEDs and OC should indeed be looked at from both directions. On one side, both the estrogen and progestin complements of combined OC are very susceptible (sensitive) to enzyme inducation even by mild inducers such as OXC or TPM (>200 mg/day). On the other side, ethinyl estardiol as the estrogen component of combined OC may induce AEDs that are metabolized primarily by glucuronidation.

ALTERATIONS IN AED KINETICS IN PREGNANCY, DO THEY MATTER?

T. Tomson (Department of Clinical Neuroscience, Karolinska Institutet, Sweden)

The pharmacokinetics of many antiepileptic drugs (AEDs) undergo changes during pregnancy due to a combination of several factors. Such alterations are of particular importance because they may be relevant not only for seizure control and adverse effects in the pregnant women with epilepsy, but also for the extent of exposure of the fetus to potentially teratogenic drugs. The clinical consequences of the frequently observed decline in serum concentrations during pregnancy will depend on the mechanisms behind the alterations. A decreased binding of a drug to plasma proteins will result in a fall in total serum concentrations but essentially unchanged unbound serum concentrations. It is the unbound concentration that exerts the drug's pharmacological effects and it also reflects the fetal drug exposure. A reduced plasma protein binding will

thus not alter the effect of the drug treatment but measuring total drug concentrations may underestimate the effects under such circumstances. Such changes can be seen during gestation with valproic acid and phenytoin. Increased metabolic or renal elimination will on the other hand lead to decline in total as well as unbound drug concentrations and can thus be expected to result in reduced efficacy of the treatment. This mechanism is also relevant for phenytoin but has been reported for other AEDs such as phenobarbital and carbamazepine. A particularly pronounced decline in serum concentrations due to enhanced metabolism is seen with lamotrigine and probably also with oxcarbazepine, drugs eliminated by glucuronidation. For these AEDs plasma levels may fall in late gestation to 30% of prepregnancy levels, which clearly must be clinically relevant. Very little is known about the other new generation AEDs in this respect.

The gestational effects on the kinetics thus differ between drugs but also display marked interindividual variability. Therapeutic drug monitoring could be particularly useful in pregnancy because of this unpredictability.

FETAL AND NEONATAL DISPOSITION OF AEDs

P. Patsalos (Institute of Neurology, UK)

Because it is a common therapeutic strategy to continue antiepileptic drug (AED) treatment during pregnancy in women with active epilepsy, AEDs can pass from the maternal blood supply via the umbilical cord to the fetus and via breast milk to the nursed neonate. This passage forms the basis of fetal and neonatal AED disposition which is dependent in part on maternal blood concentrations, extent of transfer to breast milk and the amount of milk intake by the neonate. Additionally, neonatal disposition is dependent on gastrointestinal absorption, AED distribution and metabolic elimination, processes that are immature compared to adults. In order to determine fetal disposition cord blood is used and cord/maternal blood concentration ratios are close to 1 for most of the first generation AEDs, with valproate being slightly higher. Ratios close to unity are also observed for the new AEDs, lamotrigine, topiramate, levetiracetam, oxcarbazepine and zonisamide. For gabapentin a ratio of 1.7 has been reported indicating fetal accumulation which may be the consequence of active transport. Milk/plasma ratios vary from 0.04 −0.19 (phenytoin, valproate, vigabatrin), through to 0.6–0.86 (lamotrigine, gabapentin, topiramate), and to 0.93–1.0 (ethosuximide, levetiracetam, zonisamide) indicating respectively minimal, substantial and considerable breast milk transfer. At birth, processes involving hepatic cytochrome P450 metabolism are immature and consequently AEDs that are cleared in this manner are eliminated from the neonate slowly. Furthermore, UGT activity is absent, with adult levels being reached by 3–4 years, and consequently the neonate is unable to eliminate lamotrigine, which is exclusively metabolized by UGT. Finally, in neonates, and particularly premature neonates, where kidney function is low, elimination of AEDs that are excreted exclusively renaly is slow (gabapentin, pregabalin, vigabatrin).

BREAST-FEEDING AND AEDS, WHAT DO WE KNOW AND WHAT DOES IT MEAN?

S. Johannessen (The National Center for Epilepsy, Sandvika, Norway)

The common strategy to continue AED treatment during pregnancy in most women with active epilepsy may have implications also for the perinatal period and for the question whether breast-feeding is advisable. Most drugs can pass from maternal serum to breast milk and thus be transferred to the nursed infant. The amount that the infant will be exposed to through breast-feeding depends on maternal serum concentration, extent of transfer to the breast milk, and amount of milk intake by the infant. Drug exposure is also dependent on the infant's absorption, distribution, metabolism, and elimination. In particular, metabolism and excretion may be different in the newborn compared to in children and adults and also vary with the drug in question.

Phenobarbital can accumulate in the suckling infant and sedation has been reported. Similar sedation may occur due to exposure to benzodiazepines if taken chronically by the nursing mother. However, such adverse effects do not occur in all nursed infants. Infant serum concentrations of ethosuximide and lamotrigine may occationally reach levels at which pharmacological effects could be seen. There is no clear support for the occurrence of adverse effects in the nursed infants. For phenytoin, carbamazepine, and valproate only small to moderate amounts are transferred. For oxcarbazepine, topiramate, levetiracetam, and gabapentin excretion into breast milk is considerable, but serum levels in the suckling infants are generally so low that pharmacological effects are unlikely to occur.

For several of the newer AEDs (vigabatrin, zonisamide, and tiagabine) data on breast-feeding are scarce or lacking and warrants further studies. The potential adverse or unknown effects must be weighed against the unquestionable medical development, social and economic benefits of breast-feeding. Women with epilepsy should in general, be encouraged to nurse their infants. The risk of adverse effects due to exposure through breast milk is in most cases negligible.

Women who nurse while taking AEDs that might affect the suckling infant should be advised to monitor their infant for side effects such as sedation or poor suckling, rather than being discouraged from breast-feeding. Monitoring maternal and infant AED serum levels is advisable.

Tuesday July 4, 2006
15:00–17:00
Hall 3A
Discussion Group Session
Psychogenic pseudoepileptic seizures; a critical review of etiological factors, diagnostic procedures, and treatment outcomes

PSYCHOGENIC ETIOLOGICAL FACTORS ASSOCIATED WITH DEVELOPMENT OF PSYCHOGENIC PSEUDOEPILEPTIC SEIZURES

B. Schmitz (Department of Neurology, Campus Virchow-Klinikum, Charité, Berlin, Germany)

The diagnosis of dissociative seizures is not difficult in the majority of cases. The prognosis is however much poorer than the prognosis of epileptic seizures and treatment strategies have not been systematically evaluated. Surprisingly little research has focused on psychological mechanisms underlying the development of pseudoseizures.

The lecture will summarise the existing literature on psychological etiological factors including traumatic events and childhood abuse as well as gender aspects in patients with exclusive pseudoseizures and in patients with epilepsy plus pseudoseizures.

DIAGNOSTIC PROCEDURES IN THE DIFFERENTIAL DIAGNOSIS OF EPILEPTIC VERSUS PSEUDOEPILEPTIC SEIZURES

J. Alving (Danish Epilepsy Center, Dianalund, Denmark)

Differentiating between epileptic seizures (ES) and psychogenic nonpileptic seizures (PNES) often is a challenge. In specialized centers, 10–30% of patients referred for intractable epilepsy have PNES, alone or in combination with ES.

Video-EEG is considered the most important procedure, but it is resource demanding and quite often a good preliminary diagnosis can be made from qualified clinical observation including video recordings.

In comparative studies, rather few out of many clinical features studies are of high discriminative value. These are e.g., variability in seizure duration, eyes and mouth closed versus open, facial myoclonias, ictal stuttering, occurrence out of sleep. Reported seizure occurrence during night-time, however, is not discriminative.

Of paraclinical investigations, ictal EEG demonstrating pseudoepileptiform artifacts during motor episodes or normal alpha in apparent unconsciousness are very powerful indicators of nonepilepsy, but it must be remembered that not all epileptic seizures give rise to scalp EEG abnormalities.

Biochemical markers (mostly prolactin and neuronal specific enolase) have by and large been disappointing, as there is a considerable overlap in prolactin rise between ES and PNES.

In differentiating between generalized tonic–clonic seizures and "convulsive" PNES, monitoring of oxygen desaturation may be of some help; however, according to a study in our center, the sensitivity of pulse oximetry was only 34% in detecting generalized tonic–clonic seizures.

It is important that the diagnosis of PNES versus ES is based on a whole set of data including seizure response to antiepileptic medication and its withdrawal. No single observation can stand alone.

TREATMENT OUTCOMES OF PSYCHOGENIC PSEUDOEPILEPTIC SEIZURES; A COCHRANE REVIEW

J. Brooks (Walton Centre for Neurology & Neurosurgery, UK)

Purpose: Nonepileptic seizures (NES) have the outward appearance of epilepsy in the absence of physiological or electroencephalographic correlates. There is a growing literature on the treatment of NES which includes psychological and nonpsychological therapies such as cognitive behavioural therapy (CBT), hypnotherapy and paradoxical therapy. The purpose of this Cochrane Review of the current literature was to establish the evidence base for the treatment of NES.

Methods: The authors searched the Cochrane Epilepsy Group trial register (7/9/05), the Cochrane Central Register of Controlled Trials (9/9/05) and PsychInfo (12/9/05) and cross references from identified publications. A hand search was conducted in *Seizure, Epilepsy & Behaviour, Epilepsia*, and *Epilepsy Research* between 20/09/05 and 29/9/05. Reference lists of retrieved studies were checked for additional reports of relevant studies.

Results: Only three small studies met the inclusion criteria. Methodological quality was considered poor. These studies were not comparable due to their different designs. Two of the studies used hypnosis and one used paradoxical therapy. There were no detailed reports of improved seizure frequency or quality of life, although reduction in seizure frequency was mentioned. All three studies concluded that the intervention used was beneficial in the treatment of NES.

Conclusions: Despite the existence of many journal articles suggesting efficacy of various treatment methodologies for NES, there have to date been no well designed randomized controlled trials of any therapeutic intervention. There is currently therefore no reliable evidence available on the optimum treatment for NES.

PSYCHOGENIC PSEUDOEPILEPTIC SEIZURES; ASPECTS OF CARE

N. Bodde (Epilepsiecentrum Kempenhaeghe, Heeze, Netherlands)

Psychogenic nonepileptic seizures (PNS) are a relatively frequently reported symptom. For example, 7–10% of the patients referred to a specialized epilepsy centre in The Netherlands have PNS. We will discuss a review on possible psychogenic factors that underlie the development of PPS.

One of the crucial factors in clinical practice is that Information on the long-term effects of psychogenic nonepileptic seizures (PNS), is limited. We therefore report on a study in which we reassessed patients, 4–6 years after the initial diagnosis of PNS. Patients with epilepsy and PNS as a comorbid symptom were not included. Reassessments were aimed at possible psychogenic factors.

Seizure frequency showed a statistically significant reduction from baseline to endpoint. At time of diagnosis none of the patients were seizure free or had only yearly seizures, whereas at endpoint about 30% of the patients were completely in remission and 10% had only occasional seizures. The number of patients with daily seizures dropped from 25% to 8%. It is not fully clarified which factors caused this improvement, but the common denominator is that a definitive expert diagnosis in a tertiary centre was made and all possible efforts were made to inform the patient in a respectful manner about this diagnosis. On the other hand, the fact that there is a more than seven year delay between seizure onset and time of diagnosis (7.2 years) also opens the possibility that other factors have influenced the outcome; in addition to the seizure reduction, there is an improvement on a wide range of personality traits, showing a reduction of psychological stress an increase of selfcontrol, a more active attitude towards social contact, a reduction of dissociative features, such as amnesia and a reduction of feelings of dissatisfaction and passive avoidant behaviour. These changes may have preceded the improvement of seizure control.

The consequences for treatment strategies will be discussed

Tuesday July 4, 2006
15:00–17:00
Hall 3D
Discussion Group Session
Large scale mRNA and protein expression profiling in epilepsy—where we are and where we are going

MOLECULAR PROFILING OF TEMPORAL LOBE EPILEPSY

M. Majores (Department of Neuropathology, University of Bonn Medical Center, Germany)

Microarray analysis of temporal lobe epilepsy in surgical tissue specimens and experimental animal models.

Ammon's horn sclerosis (AHS) is a frequent observation in human temporal lobe epilepsy (TLE). In AHS hippocampi neuronal loss occurs in CA1 and CA4, whereas dentate gyrus (DG) granule and CA2 pyramidal cells are more resistant. Molecular pathways involved in stage and subfield specific hippocampal epileptogenesis have yet to be determined. Since many patients with pharmacoresistant TLE undergo surgical treatment with removal of hippocampi, we have the unique opportunity to analyze pathogenetic mechanisms in human brain tissue. In addition, animal models of TLE with induction of an episode of status epilepticus (SE) by application of pilocarpine to rats allow the generation of gene expression profiles during epileptogenesis, i.e., the seizure free latency interval between SE and onset of chronic recurrent seizures.

We have used oligonucleotide microarrays to carry out expression profiling as a valuable approach to determine transcript patterns in both human and experimental TLE. In rats, the transcriptional response to SE revealed early upregulation of genes linked to stress and cell damage associated signaling cascades. It was followed by upregulation of transcription factors, neurotransmitter receptors and calcium-signaling or structure related molecules in the initiation of chronic seizures. In human tissue, expression patterns from hippocampi with the pattern of AHS were compared to profiles of "epileptic controls," i.e., hippocampi of pharmacoresistant TLE patients with extrahippocampal lesions. In these patients the hippocampus does not show the pattern of AHS but is to be resected for seizure control.

Expression profiling allows to determine transcript patterns in anatomically heterogeneous structures such as the brain and to monitor genomic responses in complex diseases such as TLE. The identification of genomic networks and pathways specifically involved in key aspects of human epileptogenesis opens the perspective to develop new therapeutical strategies in order to target the stage of epileptogenesis and prevent the onset of recurrent chronic epileptic seizures.

Supported by DFG (SFB TR3), Bundesministerium für Bildung und Forschung, Deutsche Krebshilfe, BONFOR.

LARGE SCALE mRNA AND PROTEIN EXPRESSION PROFILING IN EPILEPSY

H. Potschka (University of Veterinary Medicine, Department of Pharmacology, Toxicology, and Pharmacy, Germany)

Research taught us a lot about seizure- and epileptogenesis-associated changes in brain structure and function. However, still a complete description of the factors determining seizure susceptibility and epileptogenesis remains elusive.

Available methods for expression analysis allow to perform large scale or even genome-wide expression profiling, providing insight into the whole ensemble of molecular events taking place in epileptic tissue. Using tissue obtained from experimental epilepsy models or obtained from

surgical resection in epileptic patients, expression profiling has delivered a large amount of data which can teach us about the pathophysiological mechanisms of ictogenesis, epileptogenesis, and pharmacoresistance. In addition, a variety of studies have been designed to identify new target sites, and to learn about interactions of antiepileptic drugs with gene expression. In order to gain information from expression data, this needs to be amended by a thorough bioinformatical analysis considering available knowledge about biological pathways. Furthermore, selected data must be validated by more traditional methods focusing on expression of one gene or protein, and by a functional analysis, e.g., using RNA interference mediated knockdown or mouse mutants.

Genes which proved to be regulated during epileptic processes belong to a variety of functional classes, e.g., including those involved in transcriptional regulation, protein synthesis, protein degradation, synaptogenesis, ion channels, cytoskeleton, cation transport, calcium homeostasis. When gene lists are compared between different studies, there is relatively little overlap. This must be attributed to variations in study design, including differences in time points and differences in methodological aspects.

Despite of some drawbacks, simultaneous profiling of thousands of genes or proteins is a valuable tool to learn more about coregulated molecules that function in concert, to identify common traits in epileptogenesis, and to identify surprising and unexpected changes which can lead to new targets for antiepileptic drug development.

MOLECULAR PROFILING OF THE EPILEPTIC BASOLATERAL AMYGDALA

K. Majak (A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Finland)

Lateral and basal nuclei of the amygdala play critical role in the emotional learning. During development of temporal lobe epilepsy (epileptogenesis) the lateral and basal nuclei of the amygdala are damaged. So the aim of the study was to reveal the differences in gene expression pattern during emotional learning in rats undergoing epileptogenesis. Electrical stimulation of the left lateral nucleus induced status epilepticus (SE) which triggers epileptogenesis. Five days after SE, habituation to the fear conditioning apparatus started (it continued for 3 days). During the whole experiment video-EEG monitoring was performed to make sure that animals do not have spontaneous seizures. 8 days after SE control and epileptic animals received training session composed of two presentation of either paired or unpaired tone and footshock. 3h after training animals were sacrificed. Then the lateral and basal nuclei of the amygdala were microdissected using Leica AS LMD Laser System. 30 ng of total cellular RNA underwent 2 rounds of amplification. Then aRNAs animals in 4 experimental groups: epileptic paired (EP), epileptic unpaired (EU), control paired (CP) and control unpaired (CU) were pooled (2 animals per group) and hybridized to GeneChip Rat Genome 230 2.0 Array (Affymetrix). Comparisons of genes expressed in basolateral amygdala between experimental groups revealed that different genes change their expression level during Pavlovian fear conditioning in rats undergoing epileptogenesis comparing to controls, that is epileptogenesis substantially affects molecular processes underlying emotional learning in the basolateral amygdala. Many genes were up- or down-regulated in the rats undergoing epileptogenesis and they are much more numerous than genes involved in emotional learning, which indicates the complexity of the epileptogenic process.

Acgnowledgements: Array experiments were conducted in Center for Biotechnology, University of Turku, Finland. The study was financially supported by Finnish Academy of Science, Medical Council.

MICROARRAY DATA FOR ANALYSIS OF GENE REGULATORY SEQUENCES

M. Dabrowski (Nencki Institute, Poland)

Knowledge of genomic sequence of several vertebrate species permits—by their comparison—identification of putative regulatory regions of genes on the scale of whole genomes. Analysis of these sequences together with data on gene expression permits identification of cis-regulatory features that are associated with particular patterns of expression. This task can be simplified by first decomposing (by singular value decomposition–SVD) the expression profiles into sums of modes, analogous to the modes of a vibrating violin string, followed by analysis of regulation separately for of each mode. We applied SVD to the published time-series dataset (*J Mol Neurosci* 2005;25:285–98) from expression profiling of rat hippocampus following injection of kainate or saline. I will focus on analysis of regulation of mode 3, which is the most important kainate-specific mode. Mode 3 represents a component of an increase in expression at the early time-points (1h, 6h) following the injection of kainate. Distribution of loadings of mode 3 shows a group of about 20 genes with very high loadings of this mode, separating them from the rest of the population. This group overlaps heavily with the group of genes listed in a review (*Neurochem Int* 2001;38:485–501) as the genes up-regulated in all hippocampal subfields following the injection of kainate. In the putative cis-regulatory regions of the 20 genes with highest contribution of this mode, identified by rat-human comparison, we identified a statistical overrepresentation (corrected p-values 10^{-4}–10^{-3}) of sequences containing the motif CRE known to bind CREB/ATF and two other motifs sharing the same consensus sequence. Of the 13 genes in this group that contain the motif CRE, 7 were recently identified (personal communication, G. Schutz) as affected in CREB/CREM knockout, thus validating our in silico prediction of a regulatory role of the CREB-binding motifs for this group of genes.

Tuesday July 4, 2006
15:00–17:00
Ballroom 1
Discussion Group Session
Is epileptic activity during sleep an ignored cause of neuropsychological disorders in children?

EPILEPTIC ACTIVITY AND COGNITIVE IMPAIRMENT

D. Kasteleijn-Nolst Trenité (University La Sapienza (Rome), Italy and University of Utrecht, Netherlands)

Epileptic activity can disturb cognition even when no clinical signs or symptoms are present. These short-lasting discharges of 10 seconds or less are called subclinical EEG-discharges and can occur during sleep or wakefulness. Not only are these discharges an expression of underlying brain dysfunction, but also they have themselves a negative effect on performance of tasks. Since 1939 research has been undertaken to unravel the impact of these subclinical discharges, either isolated and focal or long-lasting and generalised. It is by far easier to determine the direct impact of short lasting epileptiform discharges on cognition when the patient is awake than when asleep and most studies were performed even during evoked epileptiform discharges using hyperventilation or photic stimulation. The more complex the task, the more disturbance can be found. Individual differences are important and interaction between performance of the task and occurrence of epileptiform discharges complicates matters further.

Much more recently long-term follow-up studies have been undertaken in patients with rolandic and occipital epilepsy and those with epileptic activity during sleep to determine their cognitive evolution. Mainly transient deficits were found and these appeared to be correlated in time with worsening of the EEG in the active phase

Besides scientific purposes, insight into the various factors involved in cognitive impairment in patients with subclinical EEG-discharges is of practical importance.

Grant: European Cie–Marie Curie Actions.

CSWS AND LKS—THE EXTREME OF A SPECTRUM?

C. Tassinari (University of Bologna, Department of Neurological Sciences - Bellaria Hospital, Italy)

No abstract receceived.

EPILEPTIC ACTIVITY DURING SLEEP IN CHILDREN WITHOUT SEIZURES BUT WITH COMMON DISORDERS OF BEHAVIOUR AND LEARNING—THE OTHER EXTREME?

J. Wilson (The National Centre for Epilepsy, Norway)

Children without a seizure history, but with interictal spike-wave activity, enhanced or exclusively during sleep, share the spectre of cognitive and behavioural disorders that can afflict children with Rolandic Epilepsy.

105 children were recruited to perform a 24 hr EEG recording, in the time span of 2 years, by encouraging referrals of children with Attention Deficit and /or Hyperactivity Disorder, and/or other moderate cognitive disorders, but no seizure history and no known brain lesion.

46 of these children had abundant focal spike-wave activity, mainly or exclusively during slow sleep. Spike-wave morphography and topography was in most cases indistinguishable from that found in rolandic epilepsy. Most cases had a single focus in one or the other perisylvian region, a few had either an occipital, frontal or lateral temporal focus, a few had bilateral independent foci, and a few had propagation from one perisylvian area to the other. Spike-wave indexes during slow sleep ranged from 25 to over 90% of slow sleep time. There was a slight clustering of right-sided focus in children with interactional problems and temper tantrums, and left-sided focus in children with language or speech deficits.

The findings are not population based, thus a reliable assessment of the prevalence of interictal focal spike wave activity during sleep in children with moderate disorders of behaviour and cognition can not be made, and the children may have been atypical and subject to referral bias. Nonetheless, nearly half of the referred children had substantial, sometimes abundant, epileptic activity during sleep, indicating that epileptic pathology can be a grossly underdiagnosed cause of cognitive and behavioural disorders in children that do not have overt seizure history.

Some of the empirical and neurophysiological evidence as to the clinical relevance of interictal epileptic activity, especially during sleep, is discussed; as well as some comments on therapeutical implications.

CSWS AND LKS SYNDROME: FROM CHILDHOOD TO ADULTHOOD

T. Deonna (Neuropaediatric Unit, CHUV, Lausanne, Switzerland)

Childhood partial epilepsy syndromes with major effects on cognitive functions, acquired epileptic aphasia (Landau-Kleffner syndrome) and epilepsy with continuous spike-waves during sleep (CSWS) constitute a special neurophysiological situation with rarely studied long term consequences. Although these syndromes share a marked activation of the epileptic EEG abnormalities during sleep (CSWS), Landau-Kleffner syndrome is defined by its cognitive consequences (auditory agnosia) whereas epilepsy with CSWS is the name given for those children whose epileptic cognitive dysfunction is not predominantly in the language domain, and in fact encompasses all other cognitive and behavioral problems directly linked to the epilepsy. Importantly, children with LKS almost never have an identifiable focal cortical lesion, whereas one increasingly finds out that the other children with CSWS have recognizable lesions, either cortical or in the thalamus. In the idiopathic cases, the deficits observed in adulthood is the result of whatever epilepsy did to the affected part of the developing brain during the active period of the disease. Such conclusions are possible only if the early deficit and its direct relationship to epilepsy has been demonstrated from the onset and that evolution has been monitored for a long period, and more precisely in the affected domain. Personal long-term studies of children followed to adulthood will be presented as well as other recently published cases. These cases were not diagnosed and studied as early and treated as effectively as occurs nowadays. Disappearance of CSWS (an age-related phenomenon) does not mean that epilepsy has necessarily remitted. Persistent deficits in very specific domains (i.e., phonologic decoding) are seen in LKS whereas executive deficits and special behavioural syndromes can be seen in those with CSWS and frontal epilepsy. As there is a great variability in age at onset, severity, duration and reversibility (medical control) of the epileptic disease, prolonged follow-up of all cases, and not only of the most severe ones, is necessary to find out which variables are the most important for prognosis and also to find out for how long there is potential for late recovery. This seems greater than initially anticipated.

Wednesday July 5, 2006

Wednesday July 5, 2006
7:30–9:00
Hall 5A
Teaching Session
Epileptic syndromes: from childhood to adulthood

IDIOPATHIC PARTIAL EPILEPSIES IN ADULTHOOD

B. Dalla Bernardina (Clin. Ped. Università-Borgo Roma, Verona, Italy)

No abstract received.

WEST SYNDROME IN ADULTHOOD

V. Komárek (Epilepsy Centre Motol, Prague, Czech Republic)

The first description of infantile spasms was published in Lancet (1941) by West (British pediatrician) in his own son. In 1952, Gibbs and Gibbs identified the "interictal" hypsarrhytmia pattern associated with infantile spasms. West syndrome is related to the combination of infantile spasms and hypsarrhytmia, with or without cognitive impairment.

The epidemiological studies show differences (from 1:1900 to 1:4000) in incidence among ethnic and national groups. There is no doubt about the age-dependent nature of the syndrome: it begins exclusively during the first year of life, with maximum frequency between 3 and 7 months. The semiology of spasms consist of sudden intensive flexion of the head, trunk and limbs ("jack knife," "salaam" convulsions). The essential characteristics of spasms is their occurence in series (cluster). The etiological factors of symptomatic forms are multiple: predominantly brain malformation, cortical dysgenesis, tuberous sclerosis complex, perinatal anoxia-ischemia, and different form of brain infections.

From the therapeutic point of view early treatment with steroids (ACTH) or vigabatrine improved unfavourable prognosis of children suffered from IS. However there are unsufficient data about long-term outcome when the patients are adults.

We analysed published studies of adults with history of infantile spasms as well as our own data obtained from patients with cerebral palsy, tuberous sclerosis and autism. The most relevant informations about IS long-term outcome were published by Riikonen (1981, 1996, 2001, 2004). In 214 Finnish patients followed up for 20–35 years or untill death, one third of patient died (the most of them in first decade), one third of survivors were seizure-free, twenty percent patients with daily seizures were on the oposite endpoint of the outcome spectrum.

The most important positive prognostic factors are: early identification and intervention as well as prompt therapeutic response (cessation of spasms and hypsarrythmia). The mental/cognitive and social outcome correlates with severity of underlying etiology, however the quality of medical care and social services play crucial role for definitive quality of life of patients with IS history.

Supported in part by IGA MZ NR 8287.

THE LENNOX-GASTAUT SYNDROME IN ADULTHOOD

G. Bauer (University Hospital for Neurology, Medical University Innsbruck, Austria)

The definition of the Lennox-Gastaut syndrome (LGS) still is controversial. A descriptive definition encompasses the following main criteria: (a) polymorphous epileptic seizures (atypical absence, tonic and atonic seizures); (b) EEG patterns consisting of slow spikes and waves and runs of rapid spikes; and (c) cognitive and emotional disturbances (Genton P, Dravet C. Lennox-Gastaut syndrome and other childhood epileptic encephalopathies. In: Engel J, Pedley TA (eds.): *Epilepsy:A Comprehensive Textbook*. Lippincott-Raven, Philadelphia 1997, pp 2355–66). The LGS represents an age-dependant condition with onset before 8 years, with a peak between 3 and 5 years. Several papers reported epilepsies with all features of LGS except age at onset (Oller-Daurella L. Un type spéciale de crises observées dans le syndrome de Lennox-Gastaut d´apparition tardive. *Rev Neurol* 1970;122:459–62; Lipinski CG. Epilepsies with astatis seizures of late onset. *Epilepsia* 1977;18:13–20; Stenzel E, Panteli C. Lennox-Gastaut-Syndro des 2. *Lebensjahrzehntes. Jahrestag*. Dt. Sektion Int. Liga gegen Epilepsie, Marburg 1981; Bauer G, Aichner F, Saltuari L. Epilepsies with diffuse slow spikes and waves of late onset. *Eur Neurol* 1983;22:344–50; Roger J, Remy C, Bureau M, Oller-Daurella L, Beaumanoir A, Favel P, Dravet C. Le syndrome de Lennox-Gastaut de l´adulte. *Rev Neurol* 1987;143:401–5).

LGS patients can maintain the complete syndromic profile into adulthood. Frequently, the severity of the seizure disorder and neurological disturbances decreased. In many cases the profound cognitive decline and behavioral abnormalities represent the major problem compared to seizures. 27 out of 68 LGS patients with persistent seizures transformed into severe focal or multifocal epilepsies (Othahara S, Ohtsuka Y, Kobayashi K. The Lennox-Gastaut syndrome: A new vista. *Psychiatry Clin Neurosci* 1995;49:179–183). The development of focal aspects might be confined to EEG without a significant change in the generalized seizure semiology.

A second group of late onset LGS compromise patients starting with an idiopathic generalized epilepsy syndrome (IGE) turning into a full blown LGS. As a cause of this "Lennoxisation" overdosage with AEDs or abrupt withdrawal and consecutive status epilepticus has been identified in some cases. The malignisation of the IGE can be transient, but there are patients with enduring LGS-like features.

In rare cases the LGS starts in the second or even third decade of life. These patients had a normal neurological and mental status before the start of seizures, an uncharacteristic seizure disorder until all features of LGS emerged, no identifiable etiology and a somewhat better social status compared with the other forms of late LGS. This group seems to represent the old end of the Gaussian age distribution of cryptogenic LGS.

LONG-TERM OUTCOME OF SEVERE MYOCLONIC EPILEPSY IN INFANCY (DRAVET SYNDROME)

[1]C. Dravet, [2]G. Daquin, [2]N. Villeneuve, [2]D. Viallat, [2]P. Genton, [2]D. Broglin, and [1]A. Ferrari ([1]IRCCS Fondazione Stella Maris, Pisa, Italy, [2]Centre Saint-Paul-Hôpital Henri Gastaut, Marseille, France)

Among more than one hundred patients examined at the Centre Saint-Paul with a diagnosis of severe myoclonic epilepsy in infancy (SMEI), forty are now 15 years old or more (up to 40 years). For thirty patients enough information was obtained either because they were regularly followed or by letters and telephone calls. Their age was between 15 and 19 years for ten, and between 20 and 40 years for twenty. Four died after the age of 15. In all the others, epileptic seizures have persisted in spite of treatment but their frequency and their severity have decreased. All patients had a cognitive deficit, of variable degree, but the behavioral disturbances had a tendency to improve. None could have a normal job and the majority was institutionalized or remained at home. Seizure type and frequency, electroencephalographic features, neurological signs, psychological evaluation, response to treatment, social situation of these patients will be presented.

Wednesday July 5, 2006
7:30–9:00
Hall 5B
Teaching Session
Pharmacogenomics: possibilities, realities, and difficulties

THE PROMISE OF PHARMACOGENOMICS

S. Sisodiya (UCL Institute of Neurology, UK)

Whilst drug resistance in epilepsy is difficult to define, there are clearly patients for whom no antiepileptic drug brings about seizure control,

whilst other patients, with the same types of epilepsy, may be rendered seizure-free with currently available antiepileptic drugs. Even for the majority of patients who do obtain response, and seizure freedom, from current antiepileptic drugs, the choice of drug remains empirical for an individual patient. Antiepileptic drugs also have potential for generating harm, with adverse effects that may or may not be reversible, and that can be life-threatening. Currently, there are no rigorous, useful predictors of responsiveness in general, or of responsiveness to specific antiepileptic drugs, or of harm that may ensue from antiepileptic drug treatments. Syndrome-specific trials of particular drugs may provide such information, especially if individual cases within trials can be more precisely described—the trials could then be conceptualised as disease-specific trials, for example in genetically-defined conditions. Even syndrome-specific trials are rare, and it is unlikely that appropriate, sizeable studies will be undertaken for already-licensed agents. On the other hand, significant advances in theoretical and practical aspects of genetics offer the possibility of more closely linking particular therapeutic options to individual patients. Early progress will be reviewed. Whilst significant challenges remain, and it is possible that no clinically useful benefit will derive from studies in epilepsy pharmacogenetics, existing knowledge of drug transport, metabolism and activity on the one hand, and variation in the genes encoding the relevant proteins on the other suggest further benefit is likely to accrue. Formal assessment of the cost-effectiveness of treatment-related genotyping will be necessary. In combination with other investigations, including formalised assessment of pharmacometabonomics, pharmacogenetics holds at least theoretical promise for improving treatment decisions in patients with epilepsy.

THE CHALLENGE OF PHARMACOGENOMICS

D. Goldstein (Duke Institute for Genome Sciences & Policy, USA)

Pharmacogenetics–lessons from antiepileptic drugs

Many clinical challenges remain in the treatment of epilepsy, including the optimization of dosing, the control of adverse reactions, and perhaps most importantly the significant minority of patients who do not respond well to pharmacological treatment.

The potential modes of action of most antiepileptic drugs are known, permitting detailed candidate gene and candidate pathway screens for gene variants that may influence response. Such variants would be of potential relevance in the treatment of epilepsy and other in other indications that make use of antiepileptic drugs. Here I report the results of a search for genetic determinants of predisposition to epilepsy and response to anti epileptic drugs in a data set of 3000 SNPs drawn from 300 candidate genes related to the action of anti epileptic drugs.

PHARMACOKINETIC PHARMACOGENOMICS AS APPLIED TO EPILEPSY

M. Johnson (Imperial College London, Charing Cross Hospital, UK)

Pharmacokinetic variability in antiepileptic drug (AED) response is under considerable clinical as well as genetic control, including age, sex, weight, nutritional status, pregnancy, drug formulation, comorbidity and comedication influences. Genetic influences can be considered to act at peripheral (Phase I and II metabolism) and central (transport proteins regulating the flux of drugs across the blood brain barrier) mechanisms. With respect to peripheral mechanisms, genotyping to determine drug metabolism alone probably has a limited role in epilepsy for two main reasons (1) for many AEDs, there is not a clear relationship between plasma concentration and efficacy/adverse events; (2) AEDs are successfully titrated up slowly and concomitant clinical and blood level monitoring usually gives an accurate idea if patients are slow or fast metabolizers. To date, pharmacogenetic analysis of pharmacokinetic factors influencing drug response in epilepsy has focused on a single central pharmacokinetic mechanism P-glycoprotein, the product of the ABCB1 gene. Case control association studies of a single variant C3435T and a 3 SNP haplotype containing C3435T have produced discordant findings, which reflect the complexities and pitfalls of pharmacogenetic analysis. Potential statistical explanations for the discordant findings have been well rehearsed, but less well considered are the potential biases of the retrospective case control design or problems of non-standardized definitions of outcome when assessing the genetic basis of AED response.

PHARMACODYNAMIC PHARMACOGENOMICS AS APPLIED TO EPILEPSY

C. Depondt (Université Libre de Bruxelles, Belgium)

Pharmacodynamics is the interaction of a drug with its target(s) at the cellular level, e.g., binding to a receptor or inhibition of an enzyme. The aim of pharmacodynamic pharmacogenomics in epilepsy is to identify polymorphisms in genes encoding antiepileptic drug (AED) targets that affect response to AEDs. These polymorphisms may have an influence on AED efficacy and/or adverse drug reactions. They may also play a role in the pathogenesis of drug refractory epilepsy.

Except for levetiracetam, which acts on synaptic vesicle protein SV2A, all currently licensed AEDs of which the mechanism of action is known, act through one or several of the following three mechanisms: modulation of voltage-dependent ion channels, enhancement of GABA-mediated inhibitory neurotransmission, and attenuation of excitatory (particularly glutamate-mediated) transmission. This knowledge allows drafting of a list of candidate genes for pharmacodynamic pharmacogenomics. Other candidate genes besides the genes encoding the actual AED target are those encoding effector proteins downstream in the pathway of AED action and target.

Only a handful of genetic associations relating to pharmacodynamics have been reported in epilepsy to date. These will be discussed, with special emphasis on the association of a putative functional polymorphism in the *SCN1A* gene with clinical use of phenytoin and carbamazepine.

Many other candidate genes remain to be examined. Major advances in the field of genetics have significantly facilitated large-scale candidate gene studies, and even whole genome scans. Therefore it is likely that further genetic associations in epilepsy pharmacodynamics will emerge in the near future. It is hoped that this knowledge will ultimately lead to a more efficacious and less harmful drug treatment of patients with epilepsy, as well as to the development of new, more efficient AEDs.

Wednesday July 5, 2006
7:30–9:00
Hall 5C
Teaching Session
Imaging language and memory

IMAGING LANGUAGE FUNCTIONS USING fMRI

F. Woermann (MRI Unit, Bethel Epilepsy Center, Bielefeld, Germany)

Cognitive functional MRI (fMRI) is noninvasive, but often produces maps with bilateral activations.

There is a large variety of literature describing fMRI results of language functions in normal subjects. These interesting group studies are designed to describe the normal pattern of cortical representations of speech, reading and auditory language. Aiming to reveal regions responsible for specific cognitive components, very similar tasks are contrasted, which do not necessarily reveal all essential language areas and might have only insufficient power to produce activations in individuals.

This approach differs substantially from what is needed in the presurgical evaluation of individual patients with epilepsy (simple tasks; contrasted with a baseline condition which allows to visualize the entire network; statistics aiming to reduce false negatives; individual concordance with a gold standard). Studies in patients with epilepsy show a high concordance between language fMRI and Wada test (Woermann, 2003). FMRI predicted the absence of essential language areas when compared with intraoperative electrocortical stimulation (Rutten, 2002). Use of preoperative fMRI predicted language deficits from epilepsy surgery (Sabsevitz, 2003).

FMRI studies of language in patients with epilepsy contribute to the discussion on reorganization of cognitive functions. A longitudinal fMRI

study of language pre- and postseizures demonstrated false lateralization of language cortex after a cluster of seizures and subsequent recovery (Jayakar, 2002). A crossectional study on language fMRI in patients with left sided hippocampal sclerosis showed EEG spiking frequency associated with atypical language lateralization (Janszky, 2006). A longitudinal fMRI study of reading skills after left anterior temporal lobe resection used operated patients as human lesion model and described mechanisms maintaining function postoperatively (Noppeney, 2005).

Atypical language lateralization is more frequent in patients with epilepsy and associated with left sided (extra)temporal epilepsy, left-handedness, younger age at epilepsy onset and at early precipitating injury.

IMAGING MEMORY FUNCTIONS USING fMRI

M. Richardson (King's College London Institute of Psychiatry, UK)

In determining the site and extent of surgical resection, the anatomical location of the epileptogenic zone needs to be established. Additionally, the functional capacity of regions affected by resection needs to be taken into account. Mesial temporal structures, especially hippocampus, play a crucial role in long-term memory function. Mesial temporal resection can impair memory function; preoperative assessment of memory function and evaluation of the risk of postoperative memory impairment is routine in presurgical investigation. It has been established that patients with a relatively larger hippocampus, or with relatively well-preserved preoperative memory function, are at greatest risk of significant postoperative memory decline. Furthermore, the intracarotid amobarbital test (IAT, 'Wada test') may provide information about the risk of an amnesic syndrome. However, none of these tests has a strong predictive value for postoperative memory outcome. The suboptimal value of these tests motivates a search for an improved means to examine preoperative memory function using functional MRI (fMRI). A number of techniques have been applied to epilepsy patients to examine memory function using fMRI. These include; comparison of the brain activity during viewing of visual scenes versus viewing 'scrambled' pictures; comparison of the activity during covert recall of a familiar route versus a rest state; and comparison of the activity during presentation of items subsequently remembered at a postscan recognition test versus items not remembered. These approaches have different advantegs and disadvantages, and activate somwhat different brain regions. Initial attempts have been made to optimise the way in which fMRI data from patients is examined, and to compare the predictive value of fMRI with existing tools. In this session, current fMRI techniques to assess memory function in epilepsy patients will be reviewed, and important problems and pitfalls discussed. An attempt will be made to suggest directions for further work in this area.

IMAGING STRUCTURAL AND FUNCTIONAL CONNECTIVITY OF MEMORY AND LANGUAGE USING TRACTOGRAPHY

R. Powell (Institute of Neurology, UK)

Understanding the relationship between brain structure and function would be enhanced by a detailed knowledge of the anatomical connections of the white matter fibres linking functional regions. The combination of functional magnetic resonance imaging (fMRI) to identify cortical regions involved in specific functions and MR-tractography to visualise pathways connecting these regions offers an opportunity to increase our understanding of brain functioning.

A number of fMRI studies have demonstrated a reorganisation of language function in patients with left temporal lobe epilepsy (TLE) with greater involvement of the nondominant hemisphere however the structural brain connections supporting this atypical language dominance have not previously been identified. Preliminary findings using tractography have demonstrated a structural reorganisation of white matter pathways that reflects the reorganisation of language function seen in TLE patients. Correlations were shown between structure and function, with subjects with more lateralised functional activation having more highly lateralised connecting pathways. This combination of fMRI and tractography offers a promising research and clinical tool to supersede the Wada test for studying language function in many neurological conditions and may prove useful in predicting language deficits following temporal lobe surgery.

The connections of the medial temporal lobe are important for seizure propagation and memory function in TLE patients. In vivo visualisation of these pathways using tractography has shown a pattern of connections in keeping with information from histological tract-tracing studies in animals. Tractography may prove a useful presurgical investigation for predicting postoperative memory outcome, as well as providing insights into the networks involved in memory function and seizure spread.

GAMMA OSCILLATIONS DURING MEMORY AND LANGUAGE TASKS

J. Lachaux (INSERM, Lyon, France)

While functional neuroimaging studies have helped elucidate major regions associated with reading, the dynamics of activation within those regions and the actual neural phenomena underlying reading within that network are still virtually unknown. We used intracranial EEG recordings in ten epileptic patients to measure directly the neural activity occurring in the temporal and frontal lobes during reading. The patients were presented with visual letters strings and performed a classic hierarchical reading paradigm contrasting semantic processes (an animacy decision task with words), phonological processes (a rhyme decision task with pseudowords) and visual processes (a visual analysis of consonant strings). We found that reading was associated with transient and local neural synchronization in the gamma frequency range, in distributed brain regions including the fusiform gyrus, the anterior and middle superior temporal gyrus, the inferior frontal gyrus, and the dorsal prefrontal cortex. Reproducible gamma band deactivations were also observed in the ventral lateral prefrontal cortex. Further, we observed that those effects were amplified by attention. The reproducibility in timing and task-sensitivity of those gamma band responses made it possible to reach robust conclusions regarding the dynamics of neural activation within the reading network and regarding the function of each of its components.

Wednesday July 5, 2006
9:30–11:30
Hall 1
Main Session
New concepts in pharmacotherapy

CIRCUMVENTING MULTIDRUG RESISTANCE MEDIATED BY EFFLUX PROTEINS

H. Potschka (University of Veterinary Medicine, Department of Pharmacology, Toxicology and Pharmacy, Hannover, Germany)

Local limitation of antiepileptic drug brain access by overexpression of efflux-transporters at the blood–brain barrier has been substantiated as a mechanism of multidrug resistance of epilepsy by numerous studies.

Awareness of this mechanism now renders a basis for the development of new therapeutic strategies aimed to overcome efflux-transporter mediated pharmacoresistance. Modulation of transporter function by coadministration of inhibitors proved to be efficacious in experimental set ups including a model of pharmacoresistant epilepsy. First clinical data also indicate that inhibition of efflux transporter function may be one means to improve therapeutic success. Alternatively, efflux-transporter expression can be downregulated by RNA interference. Both strategies have the potential to reduce efflux function at the blood–brain barrier, thereby enhancing brain permeability of transporter substrates including antiepileptic drugs. However, these concepts must take into consideration the putative complications of such modulation in view of the general protective role of efflux-transporters.

Thus, by-passing of efflux-transporters seems to be a more elegant strategy to overcome transporter mediated drug resistance. This may imply the use of immunoliposome-based drug delivery systems targeted

to the blood–brain barrier or modes of administration which are suitable to circumvent the blood–brain barrier.

Instead of dealing with the problem of overexpressed transporters in multi-drug resistant individuals, it is a promising approach to prevent seizure-induced upregulation of efflux-transporters. In this context, we currently study the cascades which are involved in seizure-induced upregulation in order to identify targets for resistance prophylaxis.

In summary, knowledge about a correlation between efflux-transporter expression and multidrug resistance renders a basis for new therapeutic concepts, which need further thorough validation with regard to effectiveness and tolerability. When heading to clinical studies it will be important to select appropriate patients, taking into consideration that drug resistance per se must be considered a complex phenomenon that is likely to involve many mechanisms.

EXPANDING MECHANISTIC DIVERSITY OF ANTIEPILEPTIC DRUGS

G. Sills (University of Glasgow, Scotland, UK)

The last two decades have witnessed an unprecedented development of novel antiepileptic drugs (AEDs) and a quantum leap forward in our understanding of how these agents work at the cellular level. From a handful of compounds with unknown pharmacology discovered by serendipitous means, we now possess an extensive and well-characterised pharmacopoeia with which to treat seizure disorders. Despite these significant advances, current evidence suggests that the majority of established and modern antiepileptic agents exert their effects by one or more of just three principal mechanisms of action; blockade of voltage-gated cation channels (sodium, calcium), potentiation of the inhibitory effects of the neurotransmitter γ-aminobutyric acid (GABA) and inhibition of the excitatory effects of the neurotransmitter glutamate. This relatively narrow pharmacological spectrum is most likely symptomatic of a drug development process that continues to rely on experimental models first employed in the identification of phenytoin in the 1930s. It may also be indicative of a chemical and mechanistic "me-too" philosophy that is aimed at minimising risk, at the potential expense of therapeutic advantage, in the identification of novel compounds. It is reasonable to speculate that for some epilepsy types, or some individuals, this pharmacological spectrum is inadequate and that new AEDs with innovative mechanisms of action are required to address the important clinical issue of non-response to medication. In this regard, the recent introduction into clinical practice of compounds with novel cellular effects, such as $\alpha_2\delta$-subunit selective calcium channel blockade and SV2A protein inhibition, may be a useful indicator of whether expanding mechanistic diversity is a worthwhile pursuit in AED development and one which can genuinely improve the outcome of treated epilepsy.

DELIVERING DRUGS DIRECTLY TO THE BRAIN VIA VECTORS OR DEPOTS

P. Boon (Laboratory for Clinical and Experimental Neurophysiology (LCEN) and Department of Neurology, Ghent University Hospital, Belgium)

The inability of currently available antiepileptic drug treatment to provide seizure freedom in about 30% of patients and the limitations of resective, disconnective or stimulation-based surgical techniques provide a strong impetus for developing new treatment strategies. In this context delivering agents with antiepileptic properties directly to the brain tissue seems an attractive avenue. Two major strategies are conceivable. The first one is to locally administer antiepileptic drugs in various technical ways (via catheters, implanted polymeric wafers,); the other is to graft tissue or cells that locally produce antiepileptic agents.

The majority of epileptic patients are taking antiepileptic drugs orally on a bid or tid basis. In developing innovative antiepileptic drugs, increasing the bioavailability is a key issue. The drawbacks of systemic delivery are well recognized and the potential benefits of local delivery can be easily anticipated. Key difficulties for local delivery are associated with bringing in and keeping antiepileptic drugs in the brain, by temporarily breaking, circumventing or "cheating" the blood brain barrier. Moreover, there is a need for safe and minimally invasive drug delivery systems that can locally release drugs from a large enough reservoir in a controlled fashion. Finally, locally delivered antiepileptic agents may have to be pharmacologically quite different from the antiepileptic drugs that are currently used and much attention should be focused on developing such new molecules. Once appropriate agents and delivery systems are available these could be used in a closed loop system provided a reliable seizure detection or anticipation algorithm is also available.

Local grafting of cholinergic, GABAergic, noradrenergic or serotonergic cells or cells engineered to secrete adenosine or neuropeptides such as galanin are alternative strategies that may result in a direct and potent antiepileptic effect locally but also in an alteration of the epileptic network beyond the immediate area of transplantation. Key issues are the long-term survival of transplanted cells and the control of cell growth and release of antiepileptic agents. Intensive animal experiments are in progress to address these issues before any human experiment can be undertaken.

EXPLOITING PHARMACOGENOMICS TO INDIVIDUALISE PRESCRIBING

N. Delanty (Epilepsy Programme, Beaumont Hospital, Royal College of Surgeons in Ireland, Dublin, Ireland)

Pharmacogenomics may be defined as the use of genomic data from an individual's genotytpe to help predict drug efficacy and adverse effects of drug therapy. Pharmacogneomics also has the potential to advance our understanding of the biology of disease. Pharmacogenomics (or pharmacogenetics) is still at its infancy as a clinical science, and overall has so far failed to deliver on its promise to revolutionise therapeutics and allow for individualised prescribing. However, pharmacogenomics offers huge potential to significantly improve therapy in many areas of medicine and obviate the "controlled trial and error" approach to therapeutics. These areas include psychiatry (depression, schizophrenia), cardiology (hypertension), oncology, and neurology (epilepsy, multiple sclerosis, Parkinson's disease). The epilepsies are particularly amenable to pharmacogenomic study because of heterogeneity of disease, the significant proportion of patients with refractory epilepsy, and the clinical problem of antiepileptic drug adverse effects.

To date, pharmacogenomic association studies in epilepsy have been hampered by conflicting results in cohorts of small size. No pharmacogenomic study has yet to significantly change the way patients with epilepsy are treated in the clinic. It is now appreciated that such studies need to be completed in large cohorts and positive associations with specific phenotypes should be confirmed in another collaborative cohort to attempt to avoid the publication of misleading false positive association. The numbers required for study depend on the individual phenotypic question but overall are significantly greater (thousands) than the cohort sizes studied to date (hundreds). Therefore, there is now increased awareness of the importance of collaboration in epilepsy pharmacogenomics, and the fruits of such collaboration will be eagerly awaited over the coming years.

Thus far, pharmacogenomics has yielded important but clinically limited information in the areas of pharmacokinetics (related to cytochrome P450 2C9/2C19 metabolism of phenytoin), pharmacodynamics (related to dosing requirements of phenytoin and carbamazepine and a polymorphism of the SCN1A gene), and idiosyncratic adverse effects of AEDs (carbamazepine hypersensitivity). Studies on the importance in variation in multi-drug transporter genes as a mechanism of refractory epilepsy has yielded conflicting results. We have recently explored the pharmacogenomics of vigabatrin retinopathy, in an effort to resurrect this drug as an important AED. Currently we are also examining associations in a multigene, multi-SNP collaborative project using an Illumina-based platform.

Despite the promise of individualised prescribing enabled by pharmacogenomic data, we are some way off exploiting genomic data in everyday clinical practice. Significant obstacles remain in the way before we can routinely prescribe by genotype. These include poor understanding of the biology of disease and the molecular basis of important side effects of therapy, the need for large-scale well-phenotyped collaborative pharmacogenomic research consortia, challenges in bioinformatics and statistical analysis, and cost of both research and clinical genotyping.

We may be at the dawn of a new age of genomic therapeutics, but the sun is barely rising.

Wednesday July 5, 2006
9:30–11:30
Hall 5A
Main Session
Brain maturation in epilepsy evolution

DEVELOPMENTAL PLASTICITY OF THE SENSORIMOTOR NETWORKS

R. Khazipov (INSERM U29/INMED, France)

Early in development, cortical activity is characterized by particular patterns of activity that disappear upon maturation. Using extracellular and patch-clamp recordings from somatosensory (S1) cortex of neonatal rat in vivo we have shown that the principal cortical pattern of activity is spindle-burst. S1 spindle bursts were tightly correlated with characteristic motor activity in the neonatal rat myoclonic twitches. S1 spindle bursts were reliably triggered in a somatotopic manner by myoclonic twitches of hindlimbs, forelimbs and whiskers. Direct sensory stimulation of various parts of the body also evoked S1 delta brushes in somatotopic manner. Sensory deafferentation by spinal cord transaction reduced the frequency of delta brushes, but did not completely suppress them. These results suggest that spindle bursts are generated by circuits intrinsic to immature brain but can be triggered by sensory feedback resulting from spontaneous movements. Study in the preterm human neonates revealed that similar scenario also operates in human, in which homologous pattern of delta brushes was tightly correlated with the neonate spontaneous myoclonic jerks and could be evoked by sensory stimulation in a somatotopic manner. These results suggest that basic functional properties of immature cortical networks are conserved through mammalian evolution making the neonatal rodent an excellent model to study early cortical activity and associated plasticity during the developmental period corresponding to the fetal stage in human.

IMAGING PLASTICITY OF LANGUAGE IN CHILDREN WITH EPILEPSY

L. Hertz-Pannier (Pediatric Radiology and INSERM U663, Necker-Enfants Malades Hospital, Paris, and SHFJ, CEA, Orsay, France)

Despite methodological difficulties, brain functional MRI (fMRI) is a unique tool to study the development of language functions in healthy children, as well as to assess functional reorganization following early brain lesions and/or epilepsy, with the possibility of multi-tasks and longitudinal studies.

The early left lateralisation of language networks during perceptive tasks was demonstrated in infants, with fMRI activation patterns comparable to those of adults despite obvious differences in linguistic skills. Subsequently, the hemispheric language specialisation progresses with age, until at least the end of adolescence. This functional profile is paralleled by structural asymmetric focal changes of both grey and white matter.

It is well known that language development and/or recovery following left lesions is largely better in children than in adults. The organization of language networks in right perisylvian regions, homotopic of those usually observed in the left hemisphere, seems to be the modality of choice of brain plasticity in cases of destructive or large brain lesions, or in early refractory epilepsy. Contrarily to adults, children with focal epilepsy restricted to the left temporal lobe do not exhibit a higher risk of atypical dominance. This suggests a role for a "chronic plasticity" related to duration and/or intensity of the epileptic activity. However, the respective contribution of various factors such as age at onset, duration of epilepsy, type and location of lesion, etc. is still highly debated. The recovery of efficient language, along with right-sided shift of language networks can occur after left hemispherotomy performed as late as 10 years of age.

At a clinical level, the assessment of possible reorganization of language networks is critical in the presurgical work-up of intractable focal epilepsies. High quality multitask fMRI can advantageously replace the Wada test in cases of clear left dominance, but mixed representations may still benefit from invasive techniques.

BRAIN MATURATION AND THE EVOLUTION OF EPILEPSY SYNDROMES

R. Guerrini (Epilepsy, Neurophysiology and Neurogenetics Unit, Unicversity of Pisa and IRCCS Stella Maris Foundation, Pisa, Italy)

A main achievement is the definition of age related epilepsy syndromes, for which after onset in a given period of life, course and outcome will be relatively predictable. However, assessment of children with age related epilepsy must be very careful as slight deviations from the "typical" clinical picture may result in atypical cases with entirely different course. Seizure onset outside the usual age range for a specific syndrome may be accompanied by a different than expected course and outcome. There are several other factors that may be related in the typical or atypical evolution of epilepsy syndromes during infancy, childhood and adolescence. However, in human epilepsy such factors can be inferred from clinical observation and neurophysiological analysis but cannot be proven. A fundamental difference resides in the idiopathic or symptomatic nature of epilepsy. Symptomatic epilepsies, in turn, have a different propensity to undergo age related changes according to the type of structural abnormality. For example, focal cortical dysplasia only cuases focal epilepsy and, in some cases, asymmetric infantile spasms, but always has a focal expression and never changes to other forms of epileptogenesis. Polymicrogyria, on the other hand, often starts as focal epilepsy and then translates into ESES (or CSWS) during school age to reverse to focal epilepsy after a variable time. This evolution demonstrates that even a fixed lesion can undergo age related influences that modify epileptogenesis and outcome. Another main factor influencing epileptogenesis is the age related area specific cortical hyperexcitability often observed in idiopathic epilepsies. Early onset occipital idiopathic epilepsy, rolandic epilepsy and the photosensitive epilepsies are typical examples and there may be overlap of these forms in the same patient. Although our knowledge about phenomenolology of clinical and electrographic changes related to age is greatly increased, our understanding of pathophysiology of age related epileptogenesis is very poor.

BRAIN MATURATION AND SURGICAL STRATEGIES IN CHILDREN

H. Holthausen (Behandlungszentrum Vogtareuth, Germany)

Developmental aspects always play a major role, when it comes to the discussion, if, when and how a child with drug-resistant seizures should be operated on. "When" usually means "timing."

The most often comment with respect to "timing" is "the earlier, the better." But this is an oversimplistic attitude towards a complex issue. There is no doubt that children with onset of epilepsy within the first 2 years of life and drug-resitant focal seizures are in general at great risk for a permanent mental retardation and that a surgical intervention should be discussed earlier. But today we are able to identify better those, who are at a great risk and those where this risk is much lower.

Timing of surgery is also a major issue in children with epileptogenic lesions bordering or overlapping language-areas.

Plasticity of the sensorimotor system is very limited beyond the first year of life—therefore to rush for a better sensorimotor outcome is seldom justified.

And there is also no pressure for a rush towards surgery with respect to visual outcome, because there is no or almost no "plasticity" as far as the visual cortex is concerned.

At centers specialized in epilepsy surgery for children in more than half of the patients etiology of the drug-resistant seizures is focal cortical dysplasia (FCD).

In FCD-type I the limits of the lesion is extremely difficult to visualize at all ages.

To get an idea about the exact extend of this peculiar type of pathology before completion of myelination is one of the most challenging tasks

during the presurgical evaluation. It is not rare that one has to decide, whether surgery should be carried out soon for reasons of a better mental outcome of whether the surgical internention should be done somewhat later, after the repetition of the MRI with the hope that the delineation of the extend of the resection would then be somewhat easier.

Considerations about "brain maturation and surgical strategies in children are not limited to the very young age-group.

Wednesday July 5, 2006
15:00–17:00
Hall 1
Discussion Group Session
Translational research in design and development of new antiepileptic drugs (AEDs): from academia to commercialisation and clinical utilisation

ACADEMIC INITIATIVES AND IDEAS FOR DEVELOPMENT OF NEW AEDs

M. Bialer (Department of Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel)

Currently the following three approaches are the major strategies for the development of new antiepileptic drugs (AEDs): 1) The animal model approach that utilizes screening of new compounds in various anticonvulsant animal (rodent) models; 2) The second-generation approach that designs follow-up compounds or second-generation AEDs by modifying the structure of existing AEDs and 3) The mechanism-based approach that designs new drugs by targeting them to specific physiological substrates or macromolecules. Academia can contribute ideas and initiatives to any one of these strategies.

In the last decade ten new AEDs have been introduced that offer appreciable advantages in terms of their favorable pharmacokinetics, improved tolerability and lower potential for drug interactions. However, in spite of the large therapeutic range of old and new AEDs about 30% of patients with epilepsy are still not seizure-free and consequently, there is a substantial need to develop new AEDs. The new AEDs currently in development can be divided into two categories: a) Drugs with completely new chemical structures such as lacosamide, retigabine, rufinamide and talampanel. Most of these drugs were developed utilizing the animal model strategy with some involvement of the mechanism-based approach in two fo the AEDs. b) Drugs that are derivatives or analogues of existing AEDs that can be regarded as second-generation to established AEDs. The second-generation compounds are: eslicarzepine acetate or BIA 2–093 and 10-hydroxy carbazepine (MHD) (carbamazepine derivatives); valrocemide and NPS 1776 (valproic acid (VPA) derivatives); XP13512 (a gabapentin derivative); brivaracetam (ucb 34714) and seletracetam (ucb 44212) (levetiracetam derivatives); and flurofelbamate (a felbamate derivative). In addition, some lead compounds of a series of VPA derivatives currently in preclinical stage have a promising potential to become new antiepileptics and CNS drugs. For these follow-up compounds to become successful second-generations to an existing AED, they must be more potent, safer and possess favorable pharmacokinetics (PK) including low potential for PK and pharmacodynamic (PD) drug interactions.

The design and development of new AEDs by any strategy should incorporate PK-based design considerations to minimize the failures in clinical trials due to PK shortcomings or drawbacks. The PK of new drugs can be better predicted from in vitro or animal data than PD. By implementing PK considerations in early stages of development, it is possible to design molecules based not only on their intrinsic PD activity (intrinsic potency and lack of toxicity), but also based on their PK profile and predesign metabolic and elimination pathways.

Although the development of second-generation AEDs based on PK- and/or PD-based design can complement existing strategies in drug development, other needs must also be addressed. Consequently, new AEDs that are currently being developed, should also have a potential in nonepileptic CNS disorders such neuropathic pain, migraine prophylaxis and bipolar disorder. This can triple the market potential of any new AED and will make its costly development worthwhile despite the ten new AEDs that have entered the market in the last decade.

Second-generation AEDs are likely to work in a mechanism of action similar to that of their parent compounds and thus may, not provide the incentive of a new mechanism of action. However, this disadvantage might be outweighed by the advantage of having extensive information about PK, toxicological and PD problems associated with the parent drug and by relying on the vast array of anticonvulsant animal models that have proven reputation and predication capabilities since the discovery of phenytoin in 1938. In addition, the design of second-generation AEDs is less risky economically for the industry than the development of a completely new chemical entity that possesses a new mechanism of action. Thus, it is not too speculative to predict that eslicarbazepine acetate is more likely to become a second generation to CBZ than a CBZ derivative with a new mechanism of action like ADCI.

In the holy scripture it is written: "If there is not flour there is no Torah." This has meaning for academia and industry as well. To achieve commercialization, academic initiatives must present an incentive to the pharmaceutical industry. If the current clinical trial of arundic acid or ONO-2506 in neurodegenerative diseases and of VPA in cancer patients is successful, it may serve as a model and incentive for future research leading possibly to the utilization of AEDs or other VPA derivatives in the treatment of Parkinson's and Alzheimer's diseases. Thus, the design and development of broad spectrum AEDs will be more attractive to industry as their utilization in epilepsy may open doors for subsequent therapeutic use (following regulatory approval) in other nonepileptic CNS disorders.

UNCONTROLLED STUDIES: SOME THOUGHTS

S. Schwabe (Novartis Pharmaceuticals, USA)

The pharmaceutical industry, like many others, is adapting to a rapidly changing environment. This will necessitate the rethinking of many topics long considered to have been definitively dealt with, including the quality and type of data generated by development programs and used to obtain health authority approvals.

This presentation will look at some of the ways in which the data traditionally collected in drug development programs does, and does not, tie in with clinical reality when these drugs are used in real patients.

Long held beliefs will be discussed. These include issues around the use of highly complex and sometimes artificial trial designs to generate data on populations, whereas physicians have to use this data on individual patients.

Difficulties that can arise when scientific data is used as guidance for an art, such as medicine, will also be touched upon.

COLLABORATION WITH A LARGE PHARMA COMPANY AS A WAY FORWARD IN THE DEVELOPMENT OF NOVEL AEDs

R. Hill (Licensing and External Research, Europe, MSD Research, Harlow, UK)

Research on novel antiepileptic drugs has been most productive in the last 20 years and many new agents and mechanisms are at various stages of evaluation from early discovery research through to clinical trials. This is also a field where academic laboratories have been very active. There is therefore no shortage of opportunities for members of the pharmaceutical industry if they wish to set up a collaboration or to license an early stage project from workers in an academic laboratory. It is therefore necessary for academic scientists seeking a collaboration to make sure that they differentiate their project from the offerings of others so that the merits and advantages of their drug or strategy are clearly perceived as attractive by the licensing and scientific team from industry. A clear and concise, nonconfidential summary, making ownership of IP and the exact stage of the project evident, is essential to generate interest as most large companies review thousands of such proposals from academic laboratories each year and reject most of them. Broad spectrum agents with activity (or predicted activity) against, for example, bipolar disease and / or neuropathic pain will be more attractive than agents which are solely antiepileptic. Also, the more advanced a compound is in development the more attractive it will be with clinical proof of concept data conveying a

real advantage over projects where only preclinical data is available. The pharmaceutical industry needs the inspiration and inventiveness of the academic world to make sure that it stays at the cutting edge of research into diseases where there is a real medical need such as epilepsy. In turn, the experience and ability of industry to effectively perform late stage development and commercialization can provide an academic partner with the capacity to turn their novel science into a prescribed medicine.

A REGULATORY APPROACH TO ACADEMIA–INDUSTRY PARTNERSHIPS IN DEVELOPING NEW AEDs

R. Katz (FDA-Center For Drug Evaluation & Research, Neuropharmacology Division, USA)

No abstract received.

Wednesday July 5, 2006
15:00–17:00
Hall 5A
Discussion Group Session
Magnetoencephalography: its contribution for detection of epileptogenicity and functional important cortex

FAST (RIPPLE) ACTIVITY: A MARKER OF REGIONAL EPILEPTOGENICITY

S. Rampp (Epilepsycenter (ZEE)–Department of Neurology, University Erlangen-Nuremberg, Germany)

The detection of epileptiform discharges in electroencephalography recordings (EEG) is a crucial part in diagnosing epilepsy. Thorough electrophysiologic evaluation yields information that allows for tailored surgical therapy in many cases, and thus improves treatment outcome. In recent years, the existence of oscillations in frequency bands >60–80 Hz (ripple activity) has been demonstrated in the animal and human brain. It was shown that these high frequency oscillations are highly significant for epileptic network function. Analysis of high frequency activity might provide valuable information for localization of epileptic networks and understanding of their dynamics. While initial research concentrated on the investigation of these basic mechanisms, clinical applications, especially the diagnostic value beyond the information yielded by well-known patterns such as epileptic transients, are increasingly coming into focus.

While investigations regarding pathological high frequency activity have mostly been performed using intracerebral depth electrodes and subdural EEG, magnetoencephalography (MEG) and surface EEG might offer noninvasive alternatives. However, small and highly localized signal generating neuronal populations and consequently very low signal-to-noise ratios pose difficult problems for these modalities. Nevertheless, new methods for the analysis of oscillations, such as beamformer algorithms, are becoming available and might offer solutions.

An overview concering recent findings on high frequency activity and clinical applications is given. The use of MEG for noninvasive detection and analysis of high-frequency activity in patients with epilepsy is discussed, including methods, challenges and preliminary results.

ORGANISATION OF LANGUAGE SPECIFIC CORTEX

E. Pataraia (Medical University of Vienna, Department of Neurology, Austria)

Objective: Advanced knowledge of the language-specific zones can facilitate surgical planning and reduce the morbidity associated with resection of eloquent cortex, especially in cases of epilepsy surgery. In the present study the noninvasive neurophysiological method–magnetoencephalography (MEG) was used to examine brain activation profiles associated with receptive language in patients with left temporal lobe epilepsy (TLE) before and after an anterior temporal lobectomy as well as in patients suffering from focal lesions or mesial TLE in the left hemisphere. We evaluated which patients were most likely to show a change in the lateralization and localization of the mechanisms supporting receptive language.

Methods: Event related fields (ERFs) time-locked to abstract word stimuli were recorded in the context of a continuous word recognition task. The anatomical location of magnetic activity sources was determined by coregistering MEG coordinates onto the patients' structural MRI scans.

Results: The incidence of atypical lateralization of language-specific activity was higher among MTLE patients compared with lesional patients (43% vs. 13%, $p < 0.02$). The majority (78%) of patients with onset of seizures before the age of 5 years had atypical lateralization of language. The incidence of atypical localization of the receptive language-specific cortex in left-hemisphere dominant patients was higher in the lesional than in the MTLE group (30% vs. 14%, $p = 0.023$). Patients with atypical language lateralization on the Wada test were significantly more likely to show a shift in language representation toward greater right hemispheric activity after surgery. Patients with left hemispheric dominance preoperatively were more likely to show intrahemispheric changes involving a slight inferior shift of the putative location of Wernicke's area.

Conclusion: There is an increased risk of partial or total shift of language-specific brain functions to the right hemisphere in patients with MTLE. Focal lesions in the left temporal lobe typically result in an aberrant location of the language-specific cortex within the left hemisphere. Variables such as type and lesion location did not appear to play a role in the type of reorganization of receptive language functions. MEG can contribute significantly not only to the precise localization of Wernicke's area for presurgical planning, but is also an important tool for documenting postoperative language reorganization.

EPILEPTOGENICITY OF THE SYLVIAN REGION

R. Paetau (Hospital for Children and Adolescents, University of Helsinki, Finland)

Unilateral perisylvian spikes are common during childhood, and often give neither ictal nor developmental symptoms, while bilateral epileptic dysfunction of the sylvian region can cause serious permanent regression of the receptive and/or expressive language, and sometimes, a wider regression of communication skills. Bilateral perisylvian epileptogenesis is either due to bilateral independent foci or to bilateral synchrony secondary to a unilateral epileptogenic focus. Only the latter group may benefit from surgery. Simulateously recorded EEG and MEG may help to separate the two groups with diffferent treatment options.

Methods: We used MEG to record intrasylvian fissural cortex and simultaneous EEG to record the perisylvian convexity spike-waves under natural sleep or light thiopental anaesthesia, and determined small time lags between left and right sylvian sources, and between fissural and convexial sources to identify a pacemaker area, if present.

Results: One-third (32%) of CSWS patients showed a unilateral pacemaker allowing for surgical treatment with successful outcome. In occasional patients, separately recorded MEG and EEG suggested different hemispheres for surgery.

Conclusion: Simultaneous MEG and EEG recordings are crucial and very effective in determining, whether a patient with bilateral spike-waves and language regression is suitable to surgical treatment

FUNCTIONAL CORTEX, PATHWAYS AND EPILEPSY SURGERY

M. Buchfelder (Department of Neurosurgery, University of Erlangen-Nuremberg, Germany)

Current operative therapy of pharmacoresistant focal epilepsies is based on thorough preoperative diagnostic evaluation. To estimate the area of epileptogenic brain tissue precise morphological and functional

examination is necessary. Given that the anatomical localization of the suspected epilepsy focus and the topographic representation of various functional qualities are defined, the neurosurgical resection of epileptogenic brain tissue becomes possible.

Relatively recently presurgical diagnostic methods and new intraoperative techniques were developed allowing to diagnose and treat patients who were unsuitable candidates for epilepsy surgery several years before. Preoperatively collected structural and functional data are provided by advanced magnetic resonance imaging (MRI) and spectroscopy, functional MRI, MRI volumetry and tractography, nuclear medical imaging, magnetic source imaging (MSI) and magnetoencephalography (MEG). Pathological findings are matched with normal cerebral function in eloquent brain regions, e.g., the speech areas and the motor pathways. During surgery this information is integrated into the operative work flow allowing the resection of putative epileptogenic foci in the close vicinity of functionally significant eloquent brain areas.

Intraoperative imaging with a high-field MRI scanner offers the opportunity to evaluate the volume of resected tissue during surgery, the combination with a neuronavigation system allows to precisely approach epileptogenic foci and to spare functionally eloquent structures. Our experience with 86 patients operated on temporal or extratemporal focal epilepsy with intraoperative MR imaging and functional neuronavigation is promising, the combined use with intraoperative electrocorticography (ECoG) helps to add certainty to the definition of the suspected epileptogenic area.

The combination of intraoperative high-field MRI, electrocorticography and integration of functional data into a neuronavigation system is a novel approach to optimize the tailoring of epilepsy surgery close to eloquent cortical areas. Especially patients harboring lesional pathologies or suffering from critical neuropsychological backgrounds are good candidates to profit from this technological progress.

EPILEPTOGENICITY: DEPTH AND MEG RECORDINGS, PROS AND CONS

P. Chauvel (Hopital Timone Adultes, INSERM EMI 9926, Marseille, France)

No abstract received.

Wednesday July 5, 2006
15:00–17:00
Hall 5B
Discussion Group Session
Is low IQ a contraindication for resective epilepsy surgery?

COGNITIVE AND SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN CHILDREN WITH LOW IQ

H. Bjørnæs (The National Centre for Epilepsy, Norway)

There are relatively few studies regarding outcome following resective surgery for refractory focal epilepsy in children with low IQ. The obvious reason for this is that few of these children have been considered for surgery. As mental retardation is often associated with multifocality or diffuse lesions, the prognosis for becoming seizure free has not been considered good. There has also been a concern whether cognitive abilities in these children would be particularly vulnerable to surgery due to insufficient cognitive reserve capacity.

Outcome with respect to seizures seems indeed to be poorer in these children than in nonretarded children, although there are exceptions to these findings. Nevertheless, between 1/3 and 2/3 of surgically treated children with low IQ are reported to become seizure free, and a substantial additional proportion has significantly improved seizure frequency, results that may be considered good enough from a risk-benefit point of view. Predictors for success are not well known, but will probably show up to be the same as in nonretarded children.

Cognitive outcome has been reported in a few studies. Seemingly, cognitive levels do not change significantly in most patients, although the probability of an improved development is greater than for a cognitive decline. Predictors are largely unknown with the exception of duration of epilepsy: Early surgery is clearly enhancing the probability of an improvement, while late intervention is associated with a decline. The relation to seizure outcome is unclear.

We report on a small group of children with IQ $\leq$ 70 who were treated with epilepsy surgery. Seven out of eight patients (88%) became seizure free. On a group level, there were no significant changes in cognition, although many children improved their performance with more than one standard deviation compared to baseline on several test measures, and only a few declined.

COGNITIVE AND SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN ADULTS WITH LOW IQ

U. Gleissner (University of Bonn, Department of Epileptology, Germany)

Intellectual disability (ID, pragmatically defined as a measured IQ of more than 2 SD below the mean IQ $\leq$ 70) is more frequent in patients with medically intractable epilepsy than in the normal population ($\sim$35% for those patients with an early onset of epilepsy versus 2%–3% in the normal population). Patients with epilepsy and ID are often difficult to treat and drug resistance is frequent. On the other hand, bilateral or diffuse morphological brain damage is frequent thus increasing the probability of a multifocal epilepsy or diffuse epileptogenic regions. Therefore, a surgical treatment is often not considered as a possibility for patients with ID. Behavioral problems can further complicate the presurgical examination and the postoperative cognitive outcome could be unfavourable, since compensation of surgically induced deficits also depends on the integrity of the whole brain. My talk will give a survey of recent studies regarding the cognitive and seizure outcome after resective epilepsy surgery in adults with ID and I will present current data from our department. The available data allow the conclusion, that IQ alone is not a good predictor of the postoperative outcome. As with patients of normal intelligence, the decision to operate on patients with a low level of intelligence should depend on the results of the presurgical workup. However, all available studies are post hoc studies on the group of operated patients. Some information, necessary to estimate the percentage of good surgical candidates with ID, remains unclear (f.i., how many patients are a priori excluded from a presurgical workup because of ID; in how many patients with ID a presurgical workup indicated a multifocal epilepsy). Therefore, further research will be necessary.

IS THERE A RELATION BETWEEN IQ AND SEIZURE OUTCOME AFTER TEMPORAL LOBE RESECTIONS FOR EPILEPSY?

K. Malmgren (Institute of Neuroscience and Physiology, Epilepsy Research Group, Sahlgrenska Academy at Göteborg University, Sweden)

Temporal lobe resection (TLR) is the most common epilepsy surgery procedure. It has been assumed that low IQ indicates diffuse brain damage and hence less probability of good seizure outcome. Few investigations have, however, focused on the results of TLR in patients with IQ $<$ 70.

Chelune et al. (1998) studied TLR outcome in relation to preoperative IQ in 1034 adults. In the highest IQ category (110+) 83% of patients became seizure free versus 76% in the middle (76–109) and 67% in the lowest IQ category (50–75) ($p < 0.037$). The conclusion was, that IQ scores alone should not be used to exclude patients from surgery, but are useful for counseling. Interestingly, only 2.3% of the patients in this study had IQ $<$ 70.

To further study seizure outcome after TLR in relation to IQ, data from the population-based Swedish National Epilepsy Surgery Register 1990–99 were analysed. Outcome data at the two-year follow-up were related to preoperative IQ. Of 448 resective procedures 73% (N = 325) were TLR, 250 adults and 75 children. 8% of the adults and 27% of the children had IQ $<$ 70. 65% of those with IQ $>$ 70 became seizure-free compared to 42% of those with IQ 50–69 and only 13% of those with IQ $<$ 50 ($p < 0.001$), but a substantial proportion of low-IQ

patients obtained >75% reduction of seizure frequency (29% versus 38%).

Hence, there is a clear relation between IQ and seizure outcome after TLR with worse outcome in low-IQ patients. However, many patients with low IQ benefit from TLR, either by becoming seizure free or by obtaining a substantial reduction in seizure frequency. It may well be that TLR is an underutilised treatment for low IQ patients. Low IQ should not per se be an exclusion criterion for TLR in patients otherwise suitable for surgical treatment of their epilepsy.

ARE THERE LESSONS TO LEARN FROM THE PATHO-ANATOMICAL DIAGNOSES IN PATIENTS WITH LOW VERSUS NORMAL IQ?

B. Rydenhag (Institute of Neuroscience and Physiology, Epilepsy Research Group, Sweden)

Epilepsy surgery has been questioned for patients with low IQ. There are few studies of the underlying pathologies in these patients. Gleissner (1998) reported 16 patients with IQ < 85, 6 with lesions and 5 with mesial sclerosis. 14 of the patients had a one-year follow up, 64% were seizure-free. In a recent study by Gleissner et al. (2006) three IQ groups (IQ < 70, N = 21; IQ 70–85, N = 24 and IQ > 85, N = 21) were matched according to clinical and etiological criteria. 79% had mesial sclerosis, low-grade tumours or cortical malformations. Seizure outcome was shown not to depend on IQ level. Björnäs (2004) reported on 35 patients with IQ < 70: 8 posttraumatic, 1 tumour, 1 migration disorder, 4 other and 17 cryptogenic. In 52% of the temporal and 35% of the extratemporal resections the low-IQ patients became seizure free.

Data from The Swedish National Epilepsy Surgery Register 1990–99 were analysed with respect to resective epilepsy surgery, IQ and patho-anatomical diagnoses. In patients with IQ > 70 27% had a lesion (low-grade tumours and cavernomas), 14% had cortical malformations and 48% had gliosis. In patients with IQ < 70 the corresponding proportions were 8%, 20% and 51%.

Patients with IQ>70 became seizure free in 80% if the etiology was a lesion, in 62% if they had cortical malformations and in 53% when the diagnosis was gliosis. Corresponding proportions for IQ < 70 were 67%, 27% and 31%. The seizure outcome thus correlated to the patho-anatomical diagnosis in both IQ groups, but with better outcome in the patients with IQ>70.

These data support the notion that epilepsy surgery in patients with epileptogenic lesions is successful irrespective of IQ level. In the Swedish series there were remarkably few lesions in patients with IQ < 70, and one reason for this might be that low-IQ patients seldom get the opportunity to be evaluated for epilepsy surgery.

Wednesday July 5, 2006
15:00–17:00
Hall 5C
Discussion Group Session
Epilepsy and the emotional brain

NEURAL SYSTEMS MEDIATING HUMAN EMOTIONS

A. Papanicolaou (The University of Texas Medical School, USA)

Affective valence–specific spatiotemporal brain activation profiles: an MEG study

Regions of the brain involved in the generation of affect in response to picture sets rated as extremely unpleasant(disgusting and/or fearful), pleasant(sexually arousing), and affectively neutral, as well as the order of activation of each region, were investigated using magnetoencephalography (MEG) in a group of sixteen young normal adult male volunteers. We found spatiotemporal maps consisting of two basic components: An early one involving activation in the occipital and basal aspects of the temporal cortex, related to the perception of the stimuli was common to all three affect conditions. The second, later component, involving activation of the cingulate gyrus, the prefrontal cortex and the temporal lobes, differentiated the pleasant and unpleasant conditions, featuring more activity over right hemisphere structures during the unpleasant condition. These activation patterns are consistent with the notion of hemispheric specialization for affective valence and they demonstrate the utility of the MEG method in exploring both the structures involved in the generation of affective responses and the temporal order of their activation.

EMOTIONAL EXPRESSION AND BEHAVIOUR DURING EPILEPTIC SEIZURES

E. Gardella (Department of Neurosciences, Bellaria Hospital–University of Bologna, Italy)

Introduction: the extension of the emotional network and its relationships with neocortical frontotemporal structures suggest its probable significant contribute to frontotemporal ictal semiology. Steaming from this consideration, we aimed to analyze the spectrum of ictal emotional behaviors.

Methods: we reviewed video-EEG recordings of 477 seizures of 84 candidates to epilepsy surgery (45 temporal/39 frontal lobe), 51 studied with SEEG (epilepsy surgery centre "C. Munari," Milan). The clinical interpretation of emotion—including facial expression of emotion (FEE), motor and/or verbal behavior and coherent emotional experience—has been validated by psychological studies (F.A.C.S., spectrograms, body movements rating). We compared prevalence and features of the six basic emotions (fear, happiness, disgust, rage, sadness and surprise).

Results: in 66% of seizures we observed emotional manifestations, ranging from isolated FEE to complex motor/acoustic behaviors (21% of seizures); only in 13% of seizures the experience of emotion was referred. All the six basic emotions were represented; about 25% of FEE were morphed.

FEEs had similar prevalence in frontal and temporal lobe seizures and in both genders, but female more frequently shoved also an emotional behavior and/or referred an emotional feeling. Fear, disgust, rage, sadness were related with right ictal discharge. Fear and disgust were associated with oro-alimentary automatisms. The same patient expressed 1–3 types of ictal emotions (mean 1,6) and up to three different emotion could emerge in one single seizure (mean 1,3). Only 35% of patients presented the same type of emotion in all seizure, with variable latency.

Conclusions: Ictal emotional manifestations consisted in a spectrum of events, from isolated mimic modifications to complex motor/acoustic behaviors, that showed inter and intraindividual heterogeneity. The association of ictal display of emotions and complex eupraxic behavior support the hypothesis of the involvement of a wide physiological network including prefrontal, frontomesial and temporal limbic structures; the right prevalence of the ictal discharge confirm the hemispheric right specialization for emotions. Study of behavioral psychology have documented a prevalence of rage expression in males and happiness/sadness in females. This difference, as well as the female prevalence in reporting emotions, has been justified by the competitive social role of males and the nursing attitude of females. The sexual dimorphism in expressing ictal emotions suggest the involvement of "universal" cross-cultural mechanisms.

RECOGNITION AND MEMORY OF EMOTIONS IN EPILEPSY PATIENTS

E. Lehner-Baumgartner (Department of Neurology, Medical University of Vienna, Austria)

Mesial temporal lobe epilepsy (MTLE) affects key brain structures mediating emotions, namely the amygdala and the hippocampus. Therefore MTLE represents a unique model disease to study human emotions. Indeed, more than 50% of patients with MTLE suffer from serious emotional disturbances including depression and anxiety disorders. Moreover, MTLE offers the unique opportunity to assess the effect of selective removal of these brain structures in patients undergoing elective epilepsy surgery for medically refractory seizures. Recognition and memory for emotional faces offers a validated neuropsychological tool to study disturbances of emotion processing in patients with MTLE. Possible factors affecting the performance on emotion recognition and

memory tasks include (1) the lateralization and location of the epileptogenic zone, (2) epilepsy specific variables like age at seizure onset, disease duration and seizure frequency, (3) volumetric measurements of amygdala and hippocampus, (4) a comprehensive neuropsychological examination, (5) personality traits and psychopathological abnormalities, and (6) the lateralization and site of surgical resection. Concerning emotion recognition in right versus left temporal lobe epilepsy patients, most authors found an impairment of emotional recognition in patients with right TLE or after right temporal lobectomy, while one study reported an impaired emotional recognition in left TLE patients. No consistent findings were reported on emotion memory in right versus left TLE patients. Some authors proposed that reduced emotion recognition explained at least in part a reduced emotion memory. Study of emotion recognition and memory for emotional faces should provide new insights into the basis of human emotions and should open new therapeutic strategies for emotional disturbances in patients with temporal lobe epilepsy.

CLINICAL fMRI OF THE AMYGDALA IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

H. Jokeit (Swiss Epilepsy Center Zurich, Switzerland)

Rationale: Amygdalar and hippocampal sclerosis usually occur together in mesial temporal lobe epilepsy (MTLE), but the sclerosis may also be solely restricted to the hippocampus or amygdala. The surgical treatment of MTLE involves both structures. The amygdala is one of the key structures involved in emotional processing and social perception. Bilateral, and to some degree also unilateral, amygdala damage may lead to impairments in these functions. Current fMRI studies of MTLE exclusively focus on memory-related MTL structures. Our aim was to investigate whether fMRI of the amygdala could contribute to the presurgical evaluation of MTL structures in patients with refractory MTLE.

Methods: A fearful face fMRI paradigm using video sequences was developed and subsequently investigated in 17 patients with epilepsy (12 had MTLE [6 right- and 6 left-sided]) and 17 healthy control subjects. Reproducibility was demonstrated by reimaging 12 of the control subjects. In addition, parahippocampal activation was measured using Roland's Hometown Walking Task within the same session in all patients and in nine of the control subjects.

Results: A fearful face paradigm led to significant amygdala activation ($p < 0.001$) in all subjects. Amygdala activation was bilateral in control subjects and clearly lateralized in patients with MTLE. Dissociated amygdala and parahippocampal activation was found in three MTLE patients. A combination of results from both fMRI paradigms improved the identification of the laterality of seizure onset in patients with MTLE.

Conclusions: fMRI activation of the amygdala evoked by a fearful face video paradigm is strong, reproducible, and specific in individual subjects. The combination of the fearful face paradigm and Roland's Hometown Walking Task provides a more reliable presurgical mapping of mesial temporal lobe structures. First results on the relation between amygdalar fMRI activation and performance in tests of advanced social cognition will be presented.

THE AMYGDALA AND PSYCHOPATHOLOGY IN EPILEPSIES

M. Trimble (Institute of Neurology, London, UK)

No abstract received.

Wednesday July 5, 2006
15:00–17:00
Hall 3D
Discussion Group Session
Brain inflammation in temporal lobe epilepsy

THE CONTRIBUTION OF BRAIN INFLAMMATION TO INJURY AND RECOVERY IN EXPERIMENTAL MODELS OF TEMPORAL LOBE EPILEPSY

A. Vezzani (Department of Neuroscience, Mario Negri Inst for Pharmacol Res, Milano, Italy)

Innate inflammatory responses are triggered by experimentally-induced seizures in microglia, astrocytes and neurons. Interleukin (IL)-1□ is an early marker of brain inflammation which decreases seizure threshold, prolongs seizure duration and exacerbates neurodegeneration. In the acute phases (4–18h) of status epilepticus (SE), during the latency phase (3–7 days after SE) preceding the onset of spontaneous seizures, and in the chronic phase of spontaneous seizures (8 months after SE), IL-1β and its signaling receptor, IL-1R1, are both increased in glia in rat neocortical and limbic areas. Damaged Fluoro-Jade-positive neurons are observed 18h-7days after SE in the same brain regions where IL-1β was up-regulated. Blood–brain barrier (BBB) damage is evident 18-48h after SE concomitantly with IL-1β up-regulation and neurodegeneration. Monocytes (macrophages invade brain parenchyma from 18h after SE until spontaneous seizures occur while granulocytes appear transiently (18h-3 days) in areas of IL-1β over-expression. Markers of adaptive immunity such as B-, T-, NK-cells are scarse or absent during acute seizures, epileptogenesis and in chronic epileptic tissue.

In organotypic hippocampal slice cultures and primary cultures of hippocampal neurons IL-1β dose-dependently enhances NMDA-dependent Ca^{2+} influx and excitotoxic damage. These actions of IL-1β, together with effects on BBB permeability and immune cell brain infiltration, may promote hyperexcitability and excitotoxicity. However, IL-1β intrinsically contributes to the generation of the seizures in a rodent model of febrile seizures where seizures evoke epileptogenesis but not cell death. Thus, in this model the proepileptogenic actions of IL-1β may be dissociated from excitotoxicity. Finally, IL-1β and IL-1R1 can be expressed by surviving neurons and surrounding astrocytes in chronic epileptic tissue suggesting autocrine/paracrine neurotrophic actions. IL-1β actions on hyperexcitability, neuronal survival and epileptogenesis may involve different signaling cascades (direct actions on ion channels and neurotransmitter receptors or transcription-dependent enduring alterations in gene expression programs) and may significantly contribute to the pathophysiology of epilepsy.

INFLAMMATORY REACTIONS IN HUMAN TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

A. Crespel (CHU Gui De Chauliac, Montpellier, France)

Temporal lobe epilepsy (TLE) associated with hippocampal sclerosis has a well defined course: first, a complicated febrile seizure in early childhood and, several years later, occurrence of typical TLE seizures. Our knowledge about the events occuring during this silent period in Human is purely speculated on the basis of experimental models of TLE: neuronal loss, release of proinflammatory cytokines, microgliosis, astrogliosis, increased neurogenesis and synaptogenesis. All these processes participate in an intense tissue remodelling, which is assumed to support hyperexcitability and hypersynchronization.

Epilepsy surgery, a treatment proposed in refractory (TLE) allows the possibility to analyse directly the epilepsy focus. Looking for these changes in human chronic focus (analyzed after several years of refractory epilepsy), confirmed that most of TLE patients presented a hippocampal sclerosis (HS) and a dispersion of the dentate gyrus.

In these tissues, we reported that reactive astrocytes, few surviving pyramidal neurons of the injuried areas and numerous dentate granule cells over-expressed NFkappaB-p65, a transcription factor which up-regulates genes related to the inflammatory and immunological responses. The overexpression of this marker in all foci of TLE with HS suggests either a chronic inflammatory state or frequent acute reactions to recurrent seizures. Many target genes activated by NFkappaB participate in secondary epileptogenesis by worsening excitability or neuronal death (IL-1beta, TNFalpha). Moreover, proliferative cytokines (M-CSF, GM-CSF) and adhesion molecules (VCAM, ICAM), also upregulated by NF?B, may play a pivotal role in neurogenesis and tissue remodeling.

In connection with this, we described in human TLE with HS large quantitites of neural progenitors in the subgranular layer and the peri-ventricular zone (both known neurogenic areas) as well as in the fissura hippocampi. The quantity of progenitors seems to be related to

the extent of lesions. However, this abundant population shows a phenotype of immature astrocytes which never differentiate in mature neurons. More, in the zones of dentate gyrus dispersion, progenitor cells resemble to radial glia, building a scaffold for granule cell migration. We hypothesize that the excessive proliferation of progenitors and their differentiation in glial cells is due to inflammatory conditions.

Finally, we recently brought evidence for of vascular reorganization in TLE foci, showing the presence of endothelial progenitors and immature microvessels in neurogenic areas. This putative angiogenesis is probably related to the strong and persistent expression of VEGF by neurons and glia. VEGF is a pleiotropic factor, able to increase inflammation by stimulating progenitor proliferation and by disrupting the blood brain barrier.

It seems therefore that, in the focus of human TLE, inflammatory reactions are chronically active and involve a vicious circle of redundant neuro-glio-vascular interactions.

FROM FEBRILE SEIZURES TO TEMPORAL LOBE EPILEPSY—THE PUTATIVE ROLE OF INTERLEUKINS

J. Peltola (Tampere University Hospital, Department of Neurology, Tampere, Finland)

No abstract received.

IMMUNOGETICS OF TEMPORAL LOBE EPILEPSY

C. Ozkara (Univesity of Istanbul, Cerrapasa Medical School, Istanbul, Turkey)

Immunological mechanisms have been implicated in the pathogenesis of epilepsy although their role still remains hypothetical despite some evidence obtained from animal and human studies. Several proinflammatory signals are found to be induced during a seizure. In brain tissue of patients who undergone to epilepsy surgery, an overexpression of such molecules in neurons and glia was demonstrated. These inflammatory responses are regulated by different genetic programs especially, the homozygosity in allele variants of the IL-1 ß gene promotes enhanced cytokine production. Recent genetic studies shown that a polymorphism in the promotor region at position −511 of the IL-1 ß gene is associated in temporal lobe epilepsy (TLE) and hipocampal sclerosis (HS) and in children with febrile seizures (FS). However, this Japanese study was not confirmed with other studies from different countries which may raise the issue of ethnicity. The preliminary results of ongoing study which investigate the association between the gene polymorphisms of different cytokines (IL-10, IL-6, TNF-α, TGF-β1b, IFN-γ) in Turkish population showed a slight difference in TGF- β 1b expression the patients and control group.

Human leukocyte antigens (HLA) located on chromosome 6p is genetically controlled part of immune system. Several studies in different epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastout syndrome demonstrated some correlation with various HLA subgroups. Class II antigens namely DQ2–DR4 and DR7 were found to be more frequent in patients with TLE-HS in one study which may implicate a possible impact on epileptogenesis. An association between HLA system and FS was also investigated but results were usually failed to show any relationship. However, in one study an increased frequency of HLA-B5 was demonstrated in Egyptian children with FS where in another study HLA-A11 was significantly increased in children with previous cytomegalovirus infection and FS.

In conclusion, current evidence related to the role of immunogetics in epilepsy is yet inadequate to establish definite correlations which necessitates further studies.

Wednesday July 5, 2006
15:00–17:00
Ballroom 1
Discussion Group Session
The occipital lobe and how to see it

DEVELOPMENT AND PATHOPHYSIOLOGY OF THE VISUAL PATHWAY

S. Seri (Birmingham Children's Hospital, Birmingham, UK)

No abstract received.

ELECTROENCEPHALOGRAPHIC MANIFESTATIONS

G. Rubboli (Department of Neurosciences, Bellaria Hospital, Bologna, Italy)

Several epileptic conditions affecting occipital lobe can display photosensitivity. Photosensitivity is an abnormal sensitivity to visual stimuli, that can be investigated in the EEG laboratory with different techniques. The most common procedure is intermittent photic stimulation (IPS). Although IPS is a widespread and routinely used procedure in the EEG laboratories, only recently standardized protocols (including characteristics of photostimulators, protocol of investigation) have been proposed (Kasteleijn-Nolst Trenité et al., 1999; Rubboli et al., 2004). IPS can elicit several types of EEG responses, with different clinical significance. A recent classification (Kasteleijn-Nolst Trenité et al., 2001) has identified the following types: a*) photic following*: a normal response that ends with termination of the stimulus train; b) *orbitofrontal photomyoclonus*, represented by an essentially electromyographic (although a frontal cortical component has been hypothesized) response at the flash frequency, terminating at the end of stimulation; c) *posterior stimulus-dependent response,* that is a particular type of EEG reaction that can be observed in neuronal ceroid lipofuscinosis or after suppression of IPS-induced generalized epileptiform activity because of medication; d) *posterior stimulus-independent response*, that is characterized by a theta-delta activity and overt epileptiform patterns, not related to the flash frequency or its harmonics; this type of response can stop at the end of stimulation or outlast it, in this latter case evolving eventually in an overt seizure; e) *generalized photoparoxysmal response (PPR)*, represented by multiple spikes or by spike-wave complexes, apparently generalized, with anterior predominance. This response can be related to the stimulus train or be self sustaining, continuing after the end of stimulation. This latter type of response has been demonstrated to be related to epilepsy and visually induced seizures; f) *activation of preexisting epileptogenic areas* is the triggering, rarely occurring, of a spontaneously, posteriorly located, epileptogenic cortex; its relationships with PPR is still unclear.

CLINICAL VARIABILITY AND IMPACT ON GENETIC RESEARCH

D. Kasteleijn-Nolst Trenité (University La Sapienza (Rome), Italy and University of Utrecht, The Netherlands)

Occipital seizures are by definition seizures, that start in the occipital cortex. Patterns of spreading of the epileptiform discharges to other brain areas as well as the velocity of spreading determine the eventual clinical picture. Therefore a rather broad variability in semiology can be found ranging from subjective complaints like visual auras to objective signs like loss of consciousness and a generalised tonic clonic seizure. Most typical are the seizures without loss of consciousness in which the epileptiform discharges last for about a minute and remain limited to the occipital lobe with a visual aura as the only clinical manifestation. Differentiation with migraine might be difficult since both have visual aura and headache as symptoms and sometimes even a combination of the two occurs in the same patient or family. The occipital seizures can be spontaneous or evoked by visual stimuli. Sometimes a anatomical lesion is found, in most cases however no underlying cause can be detected. Patients with these seizures can thus be found among those with an symptomatic, idiopathic or cryptogenic epilepsy. More precise phenotyping helps genetic research. Examples of seizure typing and genetic research will be given.

Conclusion: Information about the variety of symptomatology of occipital seizures within the various syndromes will be given and its importance for genetic research explained.

Grant: European Cie–Marie Curie Actions

PSYCHOLOGICAL MANIFESTATIONS

K. Eriksson (Pediatric Research Centre, Medical School, University of Tampere and Department of Pediatric Neurology, Tampere University Hospital, Finland)

There is more known about the occipital lobes than any other region of the brain, probably because of the importance of vision for humans and the interest in how the brain processes visual information. Case studies reported in the literature have demonstrated the clinical symptomatology related to dysfunctioning of occipital lobes which include distinct syndromes of visual disturbance, dissociation between vision for guiding movements and recognizing objects.

One of the main dysfunction of occipital lobes is visual agnosia, i.e., inability to recognize objects without impairment of visual acuity or general intelligence. Agnosias are classified in object agnosias and other agnosias. Object agnosias can be either apperceptive or associative whereas other agnosias include prosopagnosia (i.e., inability to recognise familiar, even own, faces), alexia (inability to read) and visuospatial agnosia (disorder of spatial perception and orientation). The most commonly involved anatomical region related to visual agnosias is the occipitotemporal boarder, a part of the ventral visual system.

The occipital epilepsy syndromes (idiopathic photosensitive occipital lobe epilepsy, Landau syndrome, Panayiotopoulos syndrome) manifest as seizures related to elementary visual hallucinations, ictal blindness or severe blurring of vision, epigastric discomfort, emesis/vomiting, tonic deviation of the eyes, eyelid fluttering or repetitive eye closures, and unresponsiveness with hemiconvulsions or generalized convulsions. However, relatively little is know about those structural and neuropsychological abnormalities which relate to electrophysiological abnormalities of occipital lobes in persons without observable seizures.

Single case report of long-term follow-up of neuropsychological functions in a patient diagnosed with occipitotemporal continuous epileptiform activity during sleep (CSWS) and severe visual agnosia (ventral simultanagnosia) has been published. This follow-up study suggests that the general intellectual measurement (IQ) is not enough and more precise assessment of neuropsychological functioning and description of academic skills are needed in patients with CSWS–even after the disappearance of the electrophysiological phenomena.

Thursday July 6, 2006

Thursday July 6, 2006
7:30–9:00
Hall 5A
Teaching Session
Epilepsy surgery in infancy and childhood

PRESURGICAL EVALUATION OF EPILEPSY

I. Tuxhorn (Epilepsy Center Bethel, Germany)

Epilepsy surgery is no longer a treatment of last resort for children with drug resistant focal epilepsy. It should be considered early to reduce the negative impact of epilepsy on developmental and social outcome.

The spectrum of surgically remediable epilepsy syndromes of childhood has expanded in recent years to include 1) patients with tuberous sclerosis who have a leading resectable focus, 2) infantile spasms or Lennox-Gastaut syndrome (or other age specific epileptic encephalopathies) secondary to a resectable epileptogenic zone and 3) formerly "cryptogenic" cases with very subtle cortical dysplasias.

The goal of the presurgical evaluation is to identify patients who have surgically treatable epilepsy by assessing the risk benefit scenario of surgical intervention.

The accepted standards of evaluation include seizure analysis with video monitoring and scalp recording of the interictal and ictal EEG, high resolution MRI, neuropsychology, WADA test for assessing laterality of mnestic and language functions. Functional imaging including PET, ictal SPECT, postprocessing MRI techniques and fMRI are important techniques to evaluate difficult extratemporal cases.

The role of invasive neurophysiology with subdural, epidural and intracerebral recordings is changing since the advent of functional imaging of the epileptogenic region e.g., EEG triggered MRI and methods outlined above.

Patients with a focal electroclinical syndrome and a congruent MRI lesion are excellent candidates for selection and the seizure outcome prognosis may be considered high if the epileptogenic zone is completely resectable.

In pediatric epilepsy early patient referral for presurgical evaluation should be considered in specific syndromes—catastrophic focal epilepsy, hemispheric syndromes, Sturge Weber syndrome, and well localized symptomatic epilepsies.

SURGICAL PROCEDURES AND COMPLICATIONS

W. Harkness (UK)

No abstract received.

RESULTS OF EPILEPSY SURGERY

H. Cross (Great Ormond Street Hosp. NHS Trust, UK)

Advances in presurgical evaluation and neurosurgical techniques have resulted in an increased number of children being selected for epilepsy surgery. Data now accumulating on outcome show considerable benefits. Seizure outcome is clearly important but other aspects such as psychosocial, functional and cognitive outcome are also significant determinants of surgical success.

Seizure outcome depends on underlying causative pathology as well as the degree of resection based on electrical or structural studies. This will also be determined by surgical procedure but limited series suggest it is not influenced by age of surgery. Data on children undergoing temporal lobe resection suggest less chance of seizure freedom in children with associated comorbidities, but is not predicted by IQ. Despite the emphasis on reduction in AEDs postoperatively, there is little data to guide in whom this will be possible.

The rate of cognitive dysfunction in those coming to surgery is high. Although many consider that seizure control will lead to improved developmental progress, this is difficult to evaluate objectively and longitudinal studies are required. There is also a high rate of psychopathology in children coming to epilepsy surgery, but it is difficult to predict those in whom this is likely to improve and this should be incorporated into preoperative counselling.

It remains important to assess each individual with regard to all components of likely outcome preoperatively, and to discuss this at length with the family. Primary outcome aims may differ between patients; this should be documented and reviewed postoperatively.

EFFECTS OF EPILEPSY SURGERY ON COGNITION AND BEHAVIOUR

M. Korkman (Psychology, Åbo Akademi University, Finland)

Effects of pediatric epilepsy surgery on cognitive development

Most studies on cognitive effects of pediatric epilepsy surgery have concerned temporal lobe resections. In general, no postsurgical decline in general intelligence has been reported. Some studies have reported a decline of verbal memory after left temporal resection whereas other studies have not found effects. Visual memory seems to be relatively robust.

Few studies have been undertaken on cognitive development after extratemporal resections. This group of patients is very heterogeneous and the results of follow-up studies have been varied. Children who undergo hemispherotomy usually have a compromised cognitive capacity presurgically. In general, the surgery has not added to the impairment.

Factors that may influence postsurgical cognitive development other than site and size of surgery include gender, age at surgery, medication, and seizure control. The results are relatively contradictory. Taken together, the results concerning the cognitive effects of pediatric epilepsy surgery are varied and individual variation is great.

Another factor that increases the variability in cognitive findings is variation in methods. Not many studies have applied comprehensive neuropsychological assessments. On an individual level problems with attention and executive functions as well as language and learning disorders are common in children with epilepsy. Manual and constructional functions, visuospatial perception, and different types of memory and learning may be affected as well. It would be important to follow the development in these domains after surgery.

Comprehensive neuropsychological assessments are recommended both for studies and in individual patients. Individual assessments are best carried out using comprehensive, standardized sets of tests; studies may alternatively employ control groups. Tests should cover a broad age range to permit follow-up over several years and assessment of children of various ages and cognitive levels. Ideally, base rates or norms concerning developmental changes and repeated assessments should be collected.

Thursday July 6, 2006
9:15–11:00
Hall 1
European Epileptology Award Symposium
Bridging basic with clinical epileptology

PROGRESSIVE MYOCLONUS EPILEPSY EPM1: A MODEL FOR GENETICALLY DETERMINED SUSCEPTIBILITY TO SEIZURE-INDUCED NEURODEGENERATION

A. Lehesjoki (Folkhälsan Institute of Genetics and Neuroscience Center, University of Helsinki, Finland)

Progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1) is characterized by the age of onset at 5–16 years, stimulus-sensitive myoclonus, tonic–clonic seizures and progressive ataxia. Mutations in the gene encoding cystatin B (CSTB), an inhibitor of lysosomal cysteine proteases, cathepsins, underlie EPM1. The majority of patients are homozygous for a dodecamer repeat expansion in the *CSTB* promoter. In cells of the patients significantly reduced cystatin inhibitory activity

correlates with significantly increased cathepsin activity suggesting that cathepsins contribute to the EPM1 pathogenesis. CSTB is a multicompartment protein being mainly lysosomal and nuclear in dividing cells and mainly cytoplasmic in differentiated cells. Missense mutant proteins representing patient mutations fail to associate with lysosomes, implying a critical lysosome-associated physiological function for CSTB. A mouse model for EPM1 has been created by targeted disruption of the mouse *Cstb* gene. The *Cstb*−/− mice show progressive ataxia and myoclonic seizures. Loss of cerebellar granule cells by apoptosis and less marked neuronal apoptosis, neuronal atrophy and gliosis in the cerebrum are characteristic neuropathological findings in the mice. The uneven distribution of neuropathological changes in the mice suggests differential neuronal sensitivity to CSTB deficiency. The changes are similar in both seizure-prone and seizure-resistant genetic backgrounds indicating that CSTB deficiency causes neuronal degeneration independent of seizure events. However, initial data suggest that kainate-induced seizures evoke greater hippocampal neuronal damage in *Cstb*−/− than control mice implying that neurodegeneration in EPM1 can be enhanced by recurrent seizures or myoclonic jerks. Studies of mice double mutant for the *Cstb* and *Cathepsin B* genes show that cathepsin B contributes to cerebellar phenotype, but not to the abnormal EEG or to ataxia phenotypes suggesting that CSTB has other functions than preventing cell death. Despite these advances, the molecular pathogenesis of EPM1 and the physiological function of CSTB remain to be elucidated.

PATHOPHYSIOLOGICAL MECHANISMS OF ABSENCE SEIZURES

V. Crunelli (School of Biosciences, Cardiff University, UK)

Typical absence seizures of idiopathic generalized epilepsies are characterized by brief loss of consciousness and the appearance of 3Hz spike-and-waves discharges (SWDs) in the EEG, that involve paroxysmal firing in thalamic and cortical networks. Whereas molecular-genetic analyses of affected individuals and families have led to important breakthroughs in the identification of candidate genes for the simple mendelian types of idiopathic generalized epilepsies, the genetics and pathophysiological mechanisms of typical absence seizures are still not fully understood. During my presentation, I will critically review data from the last ten years of experimental work in thalamus and cortex, and highlight how the use of inappropriate models has often led to unsatisfactory views on the intrinsic and network mechanisms of SWD generation. In addition, I will present some of our recent data showing abnormalities both in phasic and tonic GABAergic inhibition in a well established genetic model of typical absence seizures, the Genetic Epilepsy Rats from Strasbourg (GAERS). The phasic GABAergic abnormalities include a 40% faster decay of the IPSCs, a reduced $GABA_B$ autoreceptor sensitivity (58% with 1mM baclofen) and a 45% smaller paired-pulse depression, compared to Non-Epileptic Control (NEC) rats: all these differences are area-selective, being present in neurons of the thalamic reticular nucleus but absent in thalamocortical and cortical neurones. Tonic GABAergic inhibition is stronger in thalamocortical neurones of GAERS, and is likely to represent the mechanism underlying the tonic hyperpolarization that is present in these neurones during spontaneous SWDs.

UPDATE ON BASIC MECHANISMS OF TEMPORAL LOBE EPILEPSY

J. Engel Jr (UCLA, USA)

Because mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) can be successfully treated surgically, it is often the subject of invasive research into basic mechanisms. In vivo studies can be carried out during intracranial EEG evaluations, and in vitro studies can be performed on resected tissue. Consequently, more is known about the fundamental neuronal disturbances underlying epileptogenesis in MTLE with HS than about any other form of human epilepsy. Basic research on MTLE with HS is augmented by numerous excellent animal models of this condition induced with excitotoxic agents such as kainic acid and pilocarpine, or prolonged hippocampal stimulation. Reiterative parallel investigations using patients and animals indicate that epileptogenesis in HS is initiated by specific types of cell loss and neuronal reorganization, which results not only in enhanced excitation, but also enhanced inhibition, predisposing to hypersynchronization. Even within this single, well-studied epileptic disorder, however, there is evidence for more than one type of ictal onset, and multiple mechanisms responsible for ictal propagation and termination, as well as enduring interictal disturbances. The most common ictal onset pattern consists of hypersynchronous discharges, which are usually associated with the aura, or no clinical signs or symptoms. Transition to a low-voltage fast ictal pattern results in contralateral propagation and the behavioral complex partial seizure. Some seizures, however, begin with low-voltage fast activity. Novel high frequency (200–500 Hz) oscillations, termed Fast Ripples (FR), characterize the primary epileptogenic region, and may reflect the principal epileptogenic dysfunction. FR-generating neurons are not homogeneously distributed throughout mesial temporal structures, but are located within small neuronal clusters. An increase in the size of, and synchronization among these clusters could be mechanisms of seizure initiation. Fundamental neuronal mechanisms underlying these abnormal high-frequency oscillations, and factors that modulate their temporospatial relationships, could elucidate important substrates of epileptogenesis and epileptogenicity.

WHAT CAN WE LEARN FROM HUMAN TISSUE STUDIES ON MECHANISMS OF PHARMACORESISTANCE?

U. Heinemann (Institute Neurophysiology, Charité Universitätsmedizin Berlin, Humboldt Universität, Germany)

We have used surgical specimen from patients with TLE to study mechanism of pharmacoresistance. Two hypotheses try to explain this feature. The transporter hypothesis suggests that drug resistance is due to upregulation of multidrug transporters in the blood brain barrier and in the tissue preventing sufficient drug levels in the tissue. The target hypothesis contends that tissue alterations account for drug resistance. We were able to induce different forms of epileptiform activity in the human hippocampus by elevating extracellular potassium concentration. In most specimen from pharmacoresistant patients the evoked activity was insensitive to carbamazepine and valproate. By contrast, in slices from patients suffering from tumours the evoked activity was suppressed by carbamazepine or valproate. Application of inhibitors of drug transporters (probenecide combined with verapamil) had usually no beneficial effect. However. in a minority of specimen inhibition of drug transporters was able to suppress epileptiform activity. The findings suggest that drug resistance can only in a minority of patients be explained by upregulation of multi drug transporters. It is likely due to alterations in tissue properties on a cellular and or on a network level.

Thursday July 6, 2006
11:30–13:30
Hall 1
Discussion Group Session
Chronic epilepsy: a development retarding or progressively dementing disease?

EVIDENCE FROM LONGITUDINAL EVALUATION OF CHILDREN VERSUS ADULTS WITH CHRONIC EPILEPSY

H. Bjørnæs (The National Centre for Epilepsy, Norway)

Several longitudinal studies have revealed a cognitive/intellectual decline in children with refractory seizures, whereas cognitive functioning in adults seems to be more resistant. Whether this may be due to more severe or progressive epilepsy on part of the selected children compared to the adults is not clear, as no direct comparisons of the seizure condition in the respective groups have previously been performed.

In the present study, we wanted to assess longitudinally the effects of refractory seizures on intelligence in children and adults, taking seizure severity and possible changes in the condition into consideration.

Seventeen children and 17 adults were tested twice with the age-appropriate version of Wechsler's Intelligence Scales. Mean test-retest

interval in the two groups was 3.5 and 6.0 years, respectively. There were no statistically significant differences between the groups with respect to severity of the epilepsy at Test 1, as indicated by retrospective assessments of seizure severity, interictal EEG pathology, and number of antiepileptic drugs received per patient. Assessments of changes in these variables during the test-retest interval did not indicate different courses of the disease in the two groups. Despite these similarities, a statistically significant difference was found between the children and the adults regarding changes in intellectual functioning. In the children, there was a decline in mean IQ scores during the test-retest interval, while the IQ scores increased in the adult group. As an explanation of these differences we proposed a development retarding model, as none of the children actually regressed in sum of raw scores. The gain in IQ scores in the adults might have been caused by improved AED treatment with respect to side effects.

Results in 15 children who were re-tested on average 11 years later as adults paralleled the findings in the former group of children.

EVIDENCE FROM CROSS-SECTIONAL AND LONGITUDINAL QUANTITATIVE MRI ANALYSIS

R. Liu (UCL Institute of Neurology, UK)

Chronic epilepsy: a development retarding or progressively dementing disease?

Chronic epilepsy is associated with widespread structural change and functional cognitive deficits. This presentation focuses on MRI evidence for seizure-related damage and whether a greater understanding of the timing and pathogenesis of these changes can contribute towards a model of how cognitive impairment develops in chronic epilepsy.

Cross-sectional and longitudinal quantitative MRI studies focus primarily on the hippocampus in patients with recent-onset and chronic temporal lobe epilepsy (TLE). Hippocampal volumes are easily and reproducibly quantified and the correlation between hippocampal atrophy and pathological hippocampal sclerosis is well-recognised. Besides the hippocampal changes in chronic TLE, cross-sectional studies report widespread extrahippocampal changes which may correlate with epilepsy duration. Literature on the cross-sectional relationship between seizures, epilepsy duration and hippocampal atrophy in TLE is reviewed.

Inherent limitations of cross-sectional studies have led to the development of longitudinal quantitative MRI studies. These MRI studies focus primarily on the evolution and progression of hippocampal atrophy in TLE. Single case studies and small patient series suggest that hippocampal atrophy may develop over years or even months following recurrent seizures or an episode of status epilepticus, although larger patient series have produced disparate findings possibly relating to methodological differences.Our results in a large population-based longitudinal MRI study show that hippocampal atrophy develops in some patients but is not common and that seizure-induced damage is likely to be influenced by individual susceptibility factors. Our findings are consistent with the concept that hippocampal and neocortical atrophy in chronic epilepsy is primarily the result of normal aging processes superimposed on a brain primed by preexisting damage.

EVIDENCE FROM ANIMAL MODELS

A. Nehlig (INSERM U 666, Faculty of Medicine, Strasbourg, France)

The lesions and plasticity phenomena induced by pilocarpine or kainate status epilepticus (SE) and leading to circuit reorganization and epileptogenesis induce behavioral and cognitive deficits in rodents. The nature and severity of the long-term consequences of SE depends on the nature of the structures undergoing neuronal loss during SE and also on the age of the animals at the time of SE. Adult rats undergoing SE develop behavioral impairment, mainly in spatial memory tasks, visuo-spatial learning and memory retention, reflecting mainly the disruption of the hippocampal-entorhinal cortex pathway. Disturbances in emotional behavior, reduced anxiety, hyperactivity and disinhibition were also reported. The disruption of hippocampal/entorhinal cortex/amygdala circuits occurring after SE might lead to misevaluation of threatening situations and hence enhanced activity and decreased anxiety. Conversely, when rats are subjected to SE earlier around PN10–PN14, most often there is only limited long-term impairment in spatial memory and sometimes enhanced anxiety and fear. Likewise, the repetition of seizures in very young animals (PN0–PN5 or PN7–PN9) leads to learning impairment, impaired visuospatial learning and decreased activity levels when rats are tested as adults. Full kindling in adult rats which does not lead to marked damage but rather to plastic changes also induces disrupted memory retention and increases anxiety. Finally, in genetic absence epilepsy models in which there are no lesions, the rats perform better than controls. Thus, it appears that the pattern of behavioral impairment corresponds to the distribution of lesions but also to plastic molecular changes. However, since the panel of testing paradigms is quite limited in rodents and since there are no available studies that performed temporal follow-up of the behavioral disturbances in animals rendered epileptic, the available experimental evidence does not allow to conclude whether epilepsy is developmentally retarding or progressively dementing.

EVIDENCE FROM LONGITUDINAL DATA FROM CHILDREN WITH IDIOPATHIC OR CRYPTOGENIC EPILEPSY

K. Oostrom (University Medical Center Utrecht, Wilhelmina Children's Hospital, Departments of Neuropsychology and Child Neurology, Utrecht, The Netherlands)

Background: We examined the course of early instability in cognitive and behavioural functioning of children with 'epilepsy only' (EO) and evaluated the importance of illness-related and contextual variables during the first few years after diagnosis.

Methods: We used a multicenter, prospective, controlled, initially one-year follow-up study of cognition and behaviour in 69 outpatient schoolchildren with newly diagnosed idiopathic or cryptogenic epilepsy. Using a call-back procedure to which 42 children with EO and 30 controls responded favourably, the follow-up was extended to 3.5 years after diagnosis. Three sources of information were used: 1) comprehensive neuropsychological assessments covering major domains of cognition, mental and motor speed and academic language skills, 2) behavioural checklists completed by parents and teachers, 3) semi-structured interviews of patients' parents inventorying contextual adversity. Contextual and illness data (aetiological classification, AED-use, seizure remission) were used as between subject factors in general linear model repeated measures analyses of variance with neuropsychological and behavioural scores as outcome measures. School delay was controlled for and taken into consideration in the study.

Results: 1) Group-wise, cognitive and behavioural differences between children with EO and healthy classmates existed but did not change. 2) Instability in performances was characteristic of children with EO. 3) 'Persistent' cognitive deficits, over-represented in children with EO (19 *vs* 3% in controls) concerned children with contextual adversity.

Conclusion: In the first three to four years after diagnosis EO cannot be considered to cause cognitive or behavioural deterioration. Individual deficits pertained to instability of performance, i.e., processing aspects that could be best understood by contextual adversity (difficulties in adjustment to the diagnosis by parents and by the children themselves, and—even prior family problems).

EVIDENCE FROM CROSS-SECTIONAL AND LONGITUDINAL EVALUATION OF PATIENTS WITH TEMPORAL LOBE EPILEPSY

C. Helmstaedter (University Clinic of Epileptology Bonn, Germany)

Recent studies on the impact of chronic epilepsy on brain and brain-function give rise to propose a model which takes into consideration the age at which epilepsy hits the brain, where epilepsy hits the brain, and whether damage and dysfunction are transient or persistent. Seizures, interictual epileptic dysfunction, as well as unwanted negative side effects of medical or surgical treatment can add to cognitive impairment. Thus, lesions and more or less controllable and reversible epileptic dysfunction may interfere with brain and cognitive development. Accumulation of damage in the course of epilepsy appears an individual rather than a systematic aspect of chronic epilepsy. Finally, accelerated mental decline

can be assumed as a consequence of the interaction of physiological or pathological mental aging with preexisting damage. This proposition of a model of cognitive development in chronic epilepsy will be outlined on the basis of recent cross sectional and longitudinal studies in patients with temporal lobe epilepsy in particular.

Thursday July 6, 2006
11:30–13:30
Hall 5A
Discussion Group Session
What future for radiosurgery in epilepsy surgery?

WHAT HAVE WE LEARNED FROM EXPERIMENTAL STUDIES?

A. Gil-Nagel (Hospital Ruber Internacional, Madrid, Spain)

The goal of stereotactic radiosurgery is the precise delivery of a single high dose of radiation to an area of pathological tissue of the brain with minimal effect on normal tissue. Tolerance of normal tissues to radiation depends on total dose, time of exposure, volume radiated, radiation quality, and adjunctive treatments. Mathematical models have been devised to predict a 5% to 50% probability of injury at 5 years (T-D 5/5); according to these models, 50 ± 10 Gy is the T-D 5/5 for the whole brain, and 60 ± 10 Gy is the T-D 5/5 for a limited volume of the brain. The effect of radiation in non-neoplastic brain tissue has been analyzed in the rat frontal lobe model. These studies have demonstrated that radiosurgery produces predictable histological changes: edema within the treatment volume at 14 days, circumscribed cerebral necrosis at 21 days, and complete destruction within the treatment volume later in time. Information on the mechanism of action of radiosurgery in non-neoplastic brain tissue in humans is less abundant. Series on gamma-knife therapy in the treatment of epilepsy have demonstrated some relevant aspects: (1) delayed onset of its effect is probably related to the time mitotic cycles occur in susceptible tissues, such as the endothelium of small vessels and capillaries, and astrocytes; (2) occurrence of an increased frequency of brief simple partial seizures is common at the time of tissue changes seen in brain MRI, and this is probably related to earlier involvement of white matter pathways, those that participate in seizure propagation; (3) differences in individual susceptibility to radiation may explain failure of treatment in some patients, and indicate the existence of a higher risk of radiation necrosis in some individuals. Assays have been devised to quantify individual susceptibility to radiation; however, information on their predictive value is still inconclusive and their use in the analysis of patients with lower sensitivity to radiation has not been explored.

RATIONALE FOR RADIOSURGERY IN MESIAL TEMPORAL LOBE EPILEPSY

F. Brunnhuber (King's College Hospital, UK)

The fundamental reason and logical basis for resective epilepsy surgery is rooted in Lueder's concept that the removal or resection of the epileptogenic zone leads to partial or complete seizure control with minimal or at least acceptable risks and side effects. Resective surgery in Mesial temporal lobe epilepsy (MTLE), which is one of the best-studied epileptic conditions, yields very favourable results and thus makes it the treatment of first choice if intractability has been demonstrated (1).

Whereas radiosurgery complies with Lueders concept of the epileptogenic zone as treatment target, it does not aim at its removal or destruction but rather its irradiation, thus leading to partial or complete seizure control with minimal or at least acceptable risks and side effects.

Three strands of rationale provide justification for its clinical use and development:

Firstly, irradiation has been shown to have antiseizure properties and can lead to seizure control in humans (2, 3, 4, 6).

Secondly, animal models with hippocampal epilepsy have demonstrated that seizure control can be achieved with nondestructive radiation doses. These experiments have also found a dose response relationship and proved the anatomical accuracy of the radiosurgical procedure. One study has reported clear seizure control with no neuropsychological or behavioural deterioration (5, 7, 8, 9, 10, 11). Thirdly, clinical studies have shown that the noninvasive radiosurgical approach can yield similar results as a well-established resective approach, the selective amygdalohippocampectomy in MTLE. (12, 14)

However, in order to secure a place in the treatment arena of intractable MTLE, radiosurgery will have to demonstrate superiority or a potential advantage over the established treatment in at least one of the following clinical or public health outcomes: patient selection, peri-operative risks, side effects, seizure outcome or socioeconomic benefit.

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RESULTS OF THE U.S. PROSPECTIVE TRIAL

N. Barbaro (University of California, San Francisco Medical Center, San Francisco, CA, USA)

Patients with pharmacoresistant temporal lobe epilepsy are frequently referred for possible surgical management, and approximately half of them are found to be candidates for surgical resection of their seizure focus. The most common type of surgery performed is anterior temporal lobectomy. Data from contemporary surgical series indicate that for patients with well-defined medial temporal foci, that the seizure-free rate following surgical treatment is approximately 80%. The most common pathologic finding in tissue removed during these procedures is mesial temporal sclerosis. We are in the process of completing a multicenter pilot clinical trial investigating the effectiveness of radiosurgical treatment of temporal lobe epilepsy. A recently completed European multicenter trial showed that approximately 65% of patients became seizure-free following Gamma Knife radiosurgery to the medial temporal lobe. We randomly assigned patients into two dosage groups (20 Gy and 24 Gy) Preliminary data indicate that there is a significant reduction of seizures in these patients with approximately 80% of the patients in the 24 Gy group becoming seizure-free. Approximately 60% of patients in the 20 Gy group are seizure-free. One patient in the high-dose group required surgical treatment for radiation-induced brain swelling with the neuropathological findings consistent with radiation necrosis. No patients in the European trial required surgery for acute radiation changes. Thus preliminary data indicate that radiosurgical treatment has a clear biological effect on seizures and that seizure-free rates are comparable with open temporal lobectomy.

Patients who undergo open temporal resections for epilepsy in the dominant hemisphere show measurable changes in language approximately 30% of the time and may have significant problems with psychosocial adjustment following their operations (irrespective of seizure outcomes). Patients treated for dominant hemisphere seizures seem not to develop significant reductions in verbal memory at the time of maximal radiation change (one year), and two-year data confirm this lack of deficits. Likewise, patients treated with radiosurgery seem not to develop significant depression or other reductions in quality of life measures seen soon after temporal lobe surgery. Thus, there may be an advantage of radiosurgery over temporal lobectomy in this select patient population.

When all outcome aspects are considered, there is equipoise that justifies a direct comparison between these two forms of treatment for patients with refractory seizures. A prospective, multicenter U.S. Trial is being planned to compare temporal lobectomy with radiosurgery for well-defined temporal lobe epilepsy patients.

LONG-TERM CLINICAL RESULTS OF RADIOSURGERY IN MTLE AND NEUROPSYCHOLOGICAL OUTCOME

J. Régis, M. Tamura, F. Bartolomei, and P. Chauvel (Hôpital D'adulte De La Timone, Marseille, France)

Radiosurgery in mesial temporal lobe epilepsy: long-term outcome

Objective: The short-term safety efficacy of Gamma knife surgery (GKS), using 24 Gy, in patients presenting with mesial temporal lobe epilepsies (MTLE) have been demonstrated by several teams. However, till now no long-term follow-up was available.

Methods: Since march 1993, 53 patients presenting with MTLE have been operated in Marseille University Timone Hospital. A total of 38 patients with unilateral MTLE have been operated more than 4 years ago. Among these patients a follow up longer thant 4 years is available for 17 patients operated by GKS at the state of the art including 9 females for 8 males. The marginal dose at the 50% was 24 Gy. The target was essentially including the anterior parahippocampal cortex the ventral part of the amygdaloid nucleus and hippocampus (head and body).

Results: The median age was 34 years (mean 35, min 22, max 46) and the median age at the onset of the epilepsy was 10,5 years (mean 8,5, min 1 & max 27). The MTLE was on the dominant side in 9 cases (53%). The median follow up is 8 years (mean 7,7, min 4, max 10). At the last follow up 12 were still seizure free (70,5%) one have been operated on due to a failure. Seizures have stopped with a median delay of 14 months (mean 13, min 1 and max 19). A visual field have revealed a deficit in 8 patients (47%). Neuropsychological testing have failed to identify any deficit and specially no verbal memory deficit when the MTLE was on the dominant side.

Conclusion: Long term results of GKS in MTLE are confirming the very good safety efficacy observed on the short term. Memory sparing on the long term seems to be a major advantage over microsurgical resection.

Thursday July 6, 2006
11:30–13:30
Hall 5B
Discussion Group Session
Focal drug and gene delivery for refractory epilepsy: fantasy or clinical reality?

SCIENTIFIC RATIONALE: OVERVIEW OF FOCAL DRUG DELIVERY STUDIES IN VITRO AND IN VIVO

H. Cock (St Georges, University of London, UK)

Refractory epilepsy remains a significant clinical problem, on which the availability of new antiepileptic drugs has had little impact. For the large number of patients for whom resective surgery is not an option, novel treatment approaches are urgently required. Systemic drug delivery is inevitably limited by the potential for unwanted side effects, due to actions both outside the CNS and in nonepileptic brain regions. There is now a considerable body of work in which a range of established and putative antiepileptic agents applied directly to the brain (most commonly the seizure focus) have proven efficacy in reducing/aborting seizure activity both in brain slices, and in vivo. The commonest approach has been to infuse or apply GABAergic agents such as diazepam direct to the seizure focus, although other agents including glutamate antagonists and sodium channel blockers have also been used. Other sites, such as the substantia nigra, potentially important in seizure propagation, have also been used, with some benefits at least in terms of reducing seizure severity, but usually with unacceptable side effects, even in the short term. Until recently most studies have been in acute seizure provocation models (rather than epilepsy), and in models known to be essentially drug sensitive. However in a model of cortical epilepsy which has been well characterized, including frequent spontaneous seizures and which is known to be refractory to systemic AEDs, it has recently been demonstrated that a focal drug delivery approach offers clear benefits in terms of efficacy and tolerability, at least in the short term. A focal approach also offers the potential for using novel agents that would be considered too toxic systemically (e.g., gap junction blockers). If longer term benefits can be established, this offers a real hope for patients with refractory cortical epilepsy who are not suitable for surgery.

VIRAL VECTORS AND GENE THERAPY IN EPILEPSY

A. Vezzani (Department of Neuroscience, Mario Negri Inst for Pharmacol Res, Milano, Italy)

Gene therapy techniques may provide a realistic therapeutic approach for intractable focal epilepsies not responding to conventional antiepileptic drugs. These techniques involve the transfer and expression of a "therapeutic" gene into the ictogenic brain area(s), thus permitting long-term CNS expression of molecules with potential anticonvulsive and antiepileptogenic properties. The success of a gene therapy approach is largely dependent on the selection of the "therapeutic" gene and the methods of gene delivery. There are mainly two approaches to deliver genes to CNS: ex vivo—gene transfer is performed in cultured cells which are subsequently transplanted; in vivo—the gene is delivered to the subject to transduce target cells directly. The in vivo gene delivery approach includes nonviral (naked DNA, liposomes, polymers) and viral (retrovirus, HSV, AAV, lentivirus) approaches. Neurotropic AAV represent the most often used tool for gene delivery in experimental models of epilepsy. Therapeutic strategies have been focused mainly on modulating signaling mediated by excitatory neurotransmitters (NMDA receptors), or enhancing the release of neuroactive peptides (galanin, neuropeptide Y). Enzyme replacement has also been addressed, i.e., in a model of Canavan Disease. Gene therapy studies have been carried

out using experimental models of focally induced acute seizures, with or without secondarily generalization, and in some instances models of primary generalized, genetically determined seizures. Preclinical studies are now focusing on the efficacy of gene therapy in rats with spontaneous recurrent seizures. Thus, chronic epileptic tissue is often characterized by neuropathological features which may affect the targets of the therapeutic genes and impair their efficacy. Regulation of gene expression and possible host tissue reactions to these transgenes or side effects are under evaluation in experimental models since they are instrumental for establishing a proof-of-principle of the applicability of gene transfer technologies in epilepsy.

IN VIVO EXPERIENCE WITH ADENOSINE IN EPILEPSY: POLYMERS VERSUS NEURONAL GRAFTING

D. Boison (R.S. Dow Neurobiology Laboratories, Legacy Research, Portland, Oregon, USA)

Adenosine is a neuromodulator with antiepileptic and neuroprotective properties. The adult brain is normally kept under tonic adenosinergic control by low levels of adenosine kinase (ADK), the key enzyme of adenosine metabolism, which, in most brain regions, is restricted to expression in astrocytes. Recently, dysfunction of the adenosine system, in particular upregulation of ADK as a consequence of astrogliosis, was shown to contribute to epileptogenesis and to cause seizures. Therefore, restoration of adenosinergic neuromodulation is a rational treatment approach for epilepsy. Although pharmacological activation of the adenosine system prevents pharmacoresistant seizures, systemic application of such agents is precluded by cardiovascular and sedative side effects. We therefore explored three strategies for focal adenosine delivery in the rat hippocampal kindling model: (i) Intraventricular implants of synthetic polymers releasing adenosine provided transient seizure protection, thus demonstrating that a local source of adenosine is sufficient to suppress seizures. (ii) A more long-term solution was achieved by engineering fibroblasts and myoblasts to release adenosine based on a disruption of their *Adk* genes. To study selectively paracrine effects, these cells were encapsulated into semipermeable polymer membranes. Intraventricular release of adenosine from encapsulated cells provided seizure protection for up to 8 weeks, without sedative side effects. (iii) To assess a combination of paracrine adenosine release and network effects on epileptogenesis, embryonic stem cells were engineered to lack both alleles of ADK and differentiated into neural precursors and adenosine releasing neurons. ADK deficient neural precursors were transplanted into hippocampi of rats one week before initiation of kindling. Rats with ADK deficient implants were characterized by a significant delay in kindling acquisition and failed to develop generalized seizures during 48 stimulations. In contrast, wild-type implant or sham treated animals consistently developed generalized seizures after 40 stimulations. Thus, focal cell mediated adenosine release might have an antiepileptogenic potential.

PRECLINICAL AND CLINICAL EXPERIENCE OF FOCAL DRUG DELIVERY FROM NEUROONCOLOGY AND NEURODEGENERATION: PROSPECTS AND PITFALLS

J. Benoit (INSERM U 646, France)

Drug delivery to the central nervous system remains a challenging area of investigation for both basic and clinical neuroscientists. Numerous drugs are generally excluded from blood to brain transfer due to the negligible permeability of the brain capillary endothelial wall, which makes up the blood brain barrier in vivo. For several years, we have explored the potential applications of the microencapsulation of therapeutic agents to provide local controlled drug release in the central nervous system. Due to their size, these microparticles can be easily implanted by stereotaxy in discreet, precise and functional areas of the brain without damaging the surrounding tissue. This type of implantation avoids the inconvenient insertion of large implants by open surgery and can be repeated if necessary. We have established the compatibility of poly(lactide-co-glycolide) microspheres with brain tissues. Presently, the most developed applications concern Neurology and Neurooncology, with local delivery of neurotrophic factors and antimitotic drugs into neurodegenerative lesions and brain tumours, respectively. The drugs that had been encapsulated by our group included nerve growth factor (NGF), glial-cell derived neurotrophic factor (GDNF), 5-fluorouracil (5-FU) and BCNU. Preclinical studies have been performed with each drug. Studies with NGF and GDNF are reported as examples. A phase IIb clinical trial has been carried out in patients with newly diagnosed glioblastomas to assess the potentialities of 5-FU-loaded microspheres when intracranially implanted.

Menei P, Capelle L, Guyotat J, Fuentes S, assaker R, Bataille B, Francois P, Dorwling-Carter D, Paquis P, Bauchet L, Parker F, Sabatier J, Faisant N, Benoit JP

Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of malignant glioma: a randomized phase II trial

Neurosurgery, 2005, 56, 2, 1–6.

Thursday July 6, 2006
11:30–13:30
Hall 5C
Discussion Group Session
Non–age-related familial focal epilepsies: genotype-phenotype correlations

AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY: GENOTYPE-PHENOTYPE CORRELATIONS

A. Gambardella (Università Magna Graecia, Italy)

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a recently identified partial epilepsy, which is characterized by brief frontal-lobe motor seizures occurring mostly during light sleep. The age of onset is usually infancy and adolescence, although seizures may start in adult life. Inheritance is autosomal dominant with 70% penetrance. The clinical picture of ADNFLE is relatively homogeneous, even if a broad range of severity has been observed even among affected members of the same pedigree. The interictal EEG is usually normal but ictal recordings show that these events are epileptic and appear to arise from the frontal lobes. Misdiagnosis as nightmares, night terrors, other parasomnias or even hysteria is common if clinicians are unaware of ADNFLE.

So far, ADNFLE has been associated with mutations affecting two genes coding for alfa4 and beta2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR), which are located on chromosome 20q and chromosome 1 respectively. Moreover, although the gene has not yet been identified, another ADNFLE locus has been mapped to chromosome 15q24. More recently, there has been evidence that variations in the promoter of the corticotropic-releasing hormone gene may be also associated with ADNFLE. Nonetheless, the underlying gene has not yet been found in most ADNFLE families. Overall, these data support the pathogenic role of the cholinergic system in ADNFLE, even if its etiology appears to be the result of a variety of molecular defects despite the relative homogeneity of the clinical manifestations.

FAMILIAL MESIAL TEMPORAL LOBE EPILEPSIES: THE CLINICAL SPECTRUM AND GENETICS IMPLICATIONS

F. Picard (Department of Neurology, University Hospital of Geneva, Switzerland)

Familial mesial temporal lobe epilepsy (FMTLE) corresponds to an heterogeneous entity with syndromes of different severity.

FMTLE was first described as a benign autosomal dominant syndrome with onset in early adulthood, no temporal lobe or hippocampal abnormalities on MRI and no association with febrile seizures. Simple partial seizures comprise psychic (especially *déjà vu*) or autonomic symptoms, or special sensory components. Interictal EEG abnormalities are rare. A genetic locus has just been identified in a family with a classical form of FMTLE (with no hippocampal sclerosis) on chromosome 4q, but no gene has been identified yet.

Subsequently, families with more severe syndromes were described, especially FMTLE with frequent hippocampal sclerosis and a variable association with febrile seizures. Epilepsy begins in the first to third decade of life. Interictal EEGs show frequent temporal discharges. Patients are often pharmacoresistant. In these more severe forms, there is accumulating evidence for a genetic predisposition for the development of hippocampal sclerosis, but no linkages or genes have been identified yet.

Finally, a few families with individuals with both febrile seizures and temporal lobe seizures, but without hippocampal abnormalities on MRI, have also been reported. A common genetic susceptibility to both types of seizures is likely in these families.

AUTOSOMAL DOMINANT LATERAL TEMPORAL LOBE EPILEPSY AND THE SPORADIC FORM WITH AUDITORY FEATURES

R. Michelucci (Department of Neurosciences, Bellaria Hospital, Bologna, Italy)

Autosomal dominant lateral temporal epilepsy (ADLTE) otherwise reported as autosomal dominant partial epilepsy with auditory features (ADPEAF) is a recently recognised epileptic condition characterized by autosomal dominant transmission, non-age related onset, focal and secondary generalized tonic–clonic seizures with typical auditory auras and/or symptoms suggesting a lateral temporal onset, absence of neurological or mental impairment, mild and inconstant temporal EEG abnormalities, normal MRI findings, and benign evolution with rare and drug-responsive seizures. Since the first description by Ottman et al. in 1995, this condition was found to be linked to a locus on chromosome 10q24. Recently, the disease-causing gene for ADLTE has been identified: it is the leucine-rich, glioma inactivated 1 (LGI1) gene, now also named Epitempin, whose mutations often introduce premature stop codons, thus preventing the production of the full-length protein from the affected allele. The predicted protein structure of LGI1 consists, in the N-terminal portion, of three leucine-rich repeats (LRRs) flanked by typical cysteine-rich repeat sequences and, in the C-terminal portion, of seven newly identified repeats of about 50 aminoacids. LRRs are widespread among different classes of intra- and extracellular proteins and may be involved in ligand binding or protein-protein interaction. Although the function of Lgi1 is largely unknown, recent proteomic analysis data suggest that Lgi1 is tightly associated with Kv1.1-containing channel complexes and may promote epileptic activity by changes in inactivation gating of presynaptic A-type K channels.

Up to now it is clear that less than 50% of ADLTE families carry the LGI1 mutations; phenotypically, no differences may be observed between mutated and non-mutated families. Studies aimed to identify other putative loci or genes, including the structurally similar genes LGI2, LGI3 and LGI4, have not produced positive results.

The relevance of this gene has been also investigated in sporadic, "idiopathic" cases exhibiting a phenotype similar to ADLTE. One out of 100 patients has been shown to bear a de novo LGI1 mutation, suggesting that this gene plays a minor role in non familial cases.

OTHER FAMILIAL FOCAL EPILEPSIES AND THE FUTURE STRATEGIES OF CLINICAL AND GENETIC RESEARCH

O. Steinlein (Institute of Human Genetics, University of Munich, Germany)

Genetic factors play a major role not only in generalized epilepsy but also in partial epilepsies. During the last decade most known epilepsy genes were first located within the genome by linkage analysis and than finally cloned either by looking for the most promising candidate genes in the region of interest or by systematically sequencing every gene in this particular region. This approaches led to the successful cloning of several genes for generalized but also for some focal epilepsies, some of the latter have already been discussed in the previous talks of this session. However, the linkage approach requires large families or samples of many smaller families that are often difficult and time consuming to collect. Furthermore, it is of limited usefulness in epilepsies with an oligogenic rather than monogenic mode of inheritance. Thus, in the future other strategies will have to be used for the successful cloning of epilepsy genes. Examples for such strategies will be discussed in this presentation, like the identification of new candidate genes by phylogenetic and functional motif analysis of known epilepsy genes, the search for genes involved in epileptogenetic pathways by siRNA and morpholino knock down experiments as well as the introduction of animal models for epilepsy.

Thursday July 6, 2006
11:30–13:30
Hall 3A
Discussion Group Session
Further understanding of the pathophysiological mechanisms involved in Landau-Kleffener and related syndromes

THE CLINICAL SPECTRUM

U. Stefani (Klinik fur Neuropadiatrie Der Universitat Kiel, Germany)

No abstract received.

FROM ANATOMICAL TO FUNCTIONAL NEUROIMAGING

P. Van Bogaert (Université Libre de Bruxelles, Hôpital Erasme, Belgium)

The pathophysiological mechanisms underlying the EEG phenomenon of continuous spike-waves during sleep (CSWS) and related cognitive and behavioral deficits remain poorly understood. It is now admitted that diffusion of the epileptiform discharges during NREM sleep is related to a mechanism of secondary bilateral synchrony from a focal cortical onset. It is probable that thalamic nuclei play an important role in this phenomenon, presumably through a development of the physiological slow-sleep oscillation into diffuse slow waves because of the lack of inhibitory constraint. This hypothesis is supported by experimental CSWS-like pattern obtained in cats following unilateral thalamic ablation. The role of the thalamus in the generation of the CSWS phenomenon was recently emphasized by reports of patients showing thalamic clastic lesions on MRI. Studies performed using PET with 18F-fluorodeoxyglucose (FDG) by our group and by others in children with CSWS and normal MRI have failed to show consistent thalamic abnormalities, but data analysis is complicated by the fact that physiological metabolic changes occur in the thalamus during brain development. Indeed, the metabolic activity of the thalamus adjusted for global metabolism increases significantly during childhood. On the other hand, numerous studies have shown that cortical metabolic abnormalities are frequently found in epileptic children with CSWS. The latter consist in either focal hypermetabolism or focal hypometabolism. The analysis of our FDG-PET data led to the following conclusions: (1) The hypermetabolic zone is the ictal onset zone; (2) Hypermetabolic areas are usually associated with distinct cortical hypometabolic areas, probably as a result of either loss of functional connectivity or inhibition mechanism; (3) Both hypermetabolic and hypometabolic areas tend to decrease or even disappear at the recovery phase of CSWS; and (4) Similar types of metabolic patterns and evolution may be seen in children with CSWS associated with polymicrogyric-like lesions.

WHAT DO WE LEARN FROM RECENT ADVANCES IN NEUROPHYSIOLOGY?

E. Hirsch (Department of Neurology, Strasbourg, France)

In 1992, Landau hopes that medical community achieved collective agreement about Landau-Kleffner syndrome (LKS), diagnosis criteria, etiology, pathophysiology, rational therapy. Since 1992, neurophysiological recording (High resolution EEG, MEG, depths) correlated to neuroimaging studies and long term follow up studies, lead to the view

that LKS is an acquired aphasia, secondary to an epileptic disturbance affecting a cortical area involved in verbal processing. This view fits with the hypothesis of a "functional ablation" caused by epileptic activity "interictal spike-waves." Epileptic aphasia would then be a subgroup of the CSWS syndrome in which epileptic discharges arise from temporal cortex. Genetic predisposition could be derive from hyperexcitability and synchronization of interneurons within perisylvian cortices who are responsible for spike-waves generation. Major spike-waves activation during NREM sleep, following thalamocortical uncoupling, lead to an alteration of blood brain barrier who provokes an autoimmune system reaction. Interneurons hyperactivity might have an antiepileptic protective effect, associated with an inhibition of specific function. Long-term consequence of spike-waves might be associated with focal atrophy. This morphological defect might explain the poor verbal outcome in some cases of LKS.

FROM RATIONALE FOR EXISTING TREATMENT TO CONTROL STUDY?

E. Roulet Perez (CHUV, Lausanne, Switzerland)

No abstract received.

Thursday July 6, 2006
11:30–13:30
Hall 3D
Discussion Group Session
Glutamate and epilepsy: from molecules to molecular imaging

PHYSIOLOGY AND PHARMACOLOGY OF GLUTAMATE NEUROTRANSMISSION

N. Bowery (PsyCEDD, GSK Medicines Research Centre, Verona, Italy)

Glutamate plays a fundamental role in the mammalian CNS as an excitatory neurotransmitter. It can be synthesised in nerve terminals from α-ketoglutarate or glutamine and is accumulated in synaptic vesicles. Depolarisation of the nerve terminal releases the amino acid into the synaptic cleft from where it activates membrane receptors. It is removed to a large extent from the extracellular space by transport into glial cells where it is converted to glutamine. This is then transported back into the nerve terminal where it is reconverted to glutamate to replenish the neurotransmitter levels.

Glutamate can activate both ionotropic and metabotropic receptors which are located primarily at postsynaptic sites but they are also present, particularly metabotropic receptors, on presynaptic terminals. The ionotropic receptors have been classified broadly on the basis of selective agonists, namely NMDA, AMPA and Kainate. NMDA and AMPA receptors are widely distributed in the brain and coexist at the same synapses. Kainate receptors have a much more restricted distribution. AMPA and NMDA receptors exist as tetramers (GLU1-4) and (NR1+NR2[A-D]+NR3A+NR3B) respectively. Both of these receptors are permeable to Na^+ but NMDA also has a high Ca^{2+} permeability. Kainate receptors have a tetrameric structure comprising a combination of subunits from GLU5-7, KA1 and KA2. Multiple binding sites for coligands are present on NMDA receptors and the channel associated with this receptor is blocked at resting membrane potentials by magnesium ions. Occupation of the coligand site with glycine plus membrane depolarisation (by e.g. AMPA) is obligatory to obtain a response to NMDA activation. Metabotropic receptors for glutamate, of which there are eight, all belong to group 3 GPCRs. The eight mGluRs can be separated into 3 groups, Gp I ($mGluR_{1\&5}$), Gp II ($mGluR_{2\&3}$) and Gp III ($mGluR_{4,7,\&8}$) with Gp I signalling being mediated via inositol phospholipid breakdown and Gps II and III via modulation of adenylyl cyclase. All mGluRs are widely distributed throughout the brain at postsynaptic sites and on nerve terminals where they modify transmitter release.

IMAGING GLUTAMATE SIGNALLING AT THE SYNAPTIC LEVEL

D. Rusakov (Institute of Neurology, University College London, UK)

Information processing in the brain relies in large part on rapid activation of postsynaptic receptors by the excitatory neurotransmitter glutamate. In parallel, modulation of axonal excitability and neurotransmitter release by presynaptic glutamate receptors impinges on the susceptibility of cortical networks to seizures. The latter phenomenon is classically associated with the hippocampal mossy fibre system where presynaptic kainate receptors have long been implicated in the initiation and maintenance of epileptiform activity. Do these receptors change in number, do they redistribute or do they exert a 'pathologically' altered action after status epilepticus? To approach these questions, experimental probing of presynaptic receptor function at the level of single synapses is required.

We therefore combine single-cell electrophysiology with two-photon microscopy to investigate the role of kainate receptors in modulating presynaptic Ca^{2+} signalling at individual mossy fibre synapses in the hippocampus. Our pilot results indicate that presynaptic kainate receptors (a) may act as autoreceptors activated by a single glutamate discharge from a single giant mossy fibre bouton, (b) enhance the action potential evoked presynaptic Ca^{2+} transient, in a use-dependent manner, by involving Ca^{2+} release from presynaptic Ca^{2+} stores, and (c) are functionally expressed in a cell-target dependent manner. These data shed light on the principles of synapse-specific actions regulating neurotransmitter release through presynaptic glutamatergic signalling. Whether these actions undergo significant modifications associated with epilepsy is currently under study.

IMAGING GLUTAMATE USING MAGNETIC RESONANCE SPECTROSCOPY

M. Guye (INSERM U 751 & CNRS UMR 6612, Faculte de Medecine de Marseille, France)

Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) is a metabolic imaging technique providing totally noninvasive in vivo quantification of brain metabolites. Using acquisition sequences with short echo time, this technique may identify in the resulting spectra, a signal at the resonance frequency of 2.29 ppm corresponding to glutamate (Glu) and/or its degradation product glutamine (Gln). Differentiation between these two metabolites is difficult at 1.5T; therefore, the term glutamine-glutamate (Glx) concentration is usually used. Identification of Glx concentrations changes in brain areas in partial epilepsies and idiopathic generalized epilepsies have provided not only new insight, but also new questions about the biochemical alterations associated to these different forms of epilepsy, at a macroscopic scale. Technical issues and interpretation of findings will be discussed. Use of high fields scanners (>3T) and new techniques such as ^{13}C-MRS allowing better Glu quantification will also be presented.

IMAGING GLUTAMATE NEUROTRANSMISSION USING PET AND SPECT

A. Hammers (Imperial College London, UK)

Glutamate is the most important neurotransmitter, and its role in epilepsy is well recognized. Imaging glutamatergic neurotransmission has long been an elusive goal. While basic science has progressed enormously over the past decade, imaging has so far been lagging behind, with no successful PET/SPECT ligands for excitatory amino acids available.

Substituted methylguanidines are a comparatively new group of uncompetitive NMDA channel blockers. Three candidates from this group are currently being evaluated; [^{11}C]GMOM and [^{11}C]CNS 5161 as PET tracers and [^{123}I]CNS 1261 as a SPECT tracer. I will discuss the results so far and the difficulties in evaluating tracers for biological systems that are difficult to fully block in vivo.

Satellite Symposia

Sunday July 2, 2006
14:30-16:00
Hall 1
Merritt-Putnam Symposium
Preventing epilepsy—a realistic goal?

PREVENTABLE CAUSES OF EPILEPSY

L. Forsgren (Professor of Neurology, Department of Neurology, Umeå University Hospital, Umeå, Sweden)

Purpose: To give an overview of the most common causes of epilepsy, with special emphasis on causes that are potentially preventable.

Methods: Survey of population-based epidemiological studies of epilepsy from high- and low-income countries.

Results: In population-based studies of epilepsy, presumed causes are identified in a minority–between 30 and 50%. The most common potentially preventable causes are infectious (e.g., neurocysticercosis, meningitis/encephalitis), stroke, head trauma, and perinatal/early brain damage events. Neurocysticercosis is caused by ingestion of eggs discharged from humans with intestinal infection of the adult worm. The disease is common in many low-income countries. The proportion of epilepsy caused by neurocysticercosis is unknown. However, if 10% of epilepsies in endemic countries are assumed to be due to neurocysticercosis, this would account for around three million people. The proportion of epilepsies caused by meningitis/encephalitis is difficult to estimate due to variability of the causative microbial agents by time and place. It is likely that more than 100,000 people worldwide develop post-infectious epilepsy annually.

Studies show that 3–4 % of a stroke population develops epilepsy. Based on a stroke incidence of 250 per 100,000 in ages 25 years and above, and a 30% one-month mortality, it can be estimated that around 200,000 new cases with epilepsy are seen annually. In most studies, stroke is the most commonly identified cause of epilepsy, and it is estimated that 4–9 million people worldwide suffer from post-stroke epilepsy.

Traumatic Brain Injury (TBI)–both moderate and severe–accounts for 3–5% of all epilepsies, i.e., 1.5–2.5 million patients globally.

Conclusions: Reduction of poverty, improved sanitation, mass vaccination, treatment of hypertension and proper use of intoxicating agents would prevent many from developing epilepsy.

Suggested reading

Annegers JF, Hauser WA, Beghi E et al. The risk of unprovoked seizures after encephalitis and meningitis. *Neurology* 1988;38:1407–10

Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998;338:20–4

Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004;35:1769–75

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D'Ambrosio R, Perucca E. Epilepsy after head injury. *Curr Opin Neurol* 2004;17:731–5

Forsgren L, Edvinsson SO, Blomquist HK et al. Epilepsy in a population of mentally retarded children and adults. *Epilepsy Res* 1990;6:234–48

Garcia HH, Del Brutto OH; Cysticercosis Working Group in Peru. Neurocysticercosis: updated concepts about an old disease. *Lancet Neurol* 2005;4:653–61

PREVENTING EPILEPTOGENESIS–EXPERIMENTAL EVIDENCE AND CANDIDATE TARGETS

A. Pitkänen (A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland)

Epileptogenesis refers to abnormal neuronal reorganisation occurring over a long period of time following a specific cerebral insult leading to the occurrence of spontaneous seizures. Attempts to prevent epileptogenesis in experimental models have used status epilepticus (SE) as an epileptogenic brain insult and antiepileptic drugs (AEDs) as candidate antiepileptogenic compounds. So far, there is no hard evidence that any of these compounds is antiepileptogenic. Some positive effects that have been found have been difficult to distinguish from the suppressing effects of AEDs on the severity of SE itself (Pitkänen A, Kubova H. Antiepileptic drugs in neuroprotection. *Expert Opin Pharmacother* 2004;5(4):777–98). There are several recent developments in the field of epileptogenesis that will undoubtedly advance future research. These include enlargement of the armamentarium of animal models from SE-induced epileptogenesis to epilepsy that is triggered by traumatic brain injury (TBI) or stroke (Karhunen H, Jolkkonen J, Sivenius J, Pitkänen A. Epileptogenesis after experimental focal cerebral ischemia. *Neurochem Res* 2005;30(12):1529–42); (Pitkänen A, McIntosh TK. Animal models of post-traumatic epilepsy. *J Neurotrauma* 2006;23(2):241–61). Mouse models under development will provide tools to investigate the contribution of risk genes to epileptogenesis. Availability of long-term video-EEG monitoring and magnetic resonance imaging will advance the selection and follow-up of animals in a clinically relevant manner so as to minimise the possibility of false negative or positive findings in preclinical studies. Recently, experimental studies provided proof-of-principle evidence that epileptogenesis can be modified by pharmacological treatment. It was shown that chronic administration of the proconvulsant α_2-adrenergic antagonist, atipamezole, started one week after SE did not prevent the development of epilepsy but had a clear disease-modifying effect, i.e., seizure frequency was substantially lower than in the vehicle group (Pitkänen A, Narkilahti S, Bezvenyuk Z, et al. Atipamezole, an α_2-adrenoceptor antagonist, has disease modifying effects on epileptogenesis in rats. *Epilepsy Res* 2004;61:119–40). Recent molecular studies have elucidated the mechanisms that regulate various components of circuitry reorganisation including cell death, axonal and dendritic plasticity, neurogenesis, gliosis, angiogenesis, reorganisation of the extracellular matrix, and alterations in cellular membranes that eventually lead to change in network excitability and seizure generation [5]. Bioinformatic analysis has suggested that there are some similarities in the expression patterns of different functional gene groups after various epileptogenic brain insults such as SE, TBI and stroke, including genes contributing to inflammatory reactions. It remains to be explored if modification of inflammatory cascades will affect the risk of epileptogenesis in various aetiologies (Lukasiuk K, Dabrowski M, Adach A, Pitkänen A. Epileptogenesis-related genes revisited. *Prog Brain Res* 2006; in press). Future studies will determine whether treatments enhancing somatosensory or cognitive recovery after TBI or stroke will also improve epilepsy outcome.

PREVENTION OF EPILEPSY–TRANSLATING EXPERIMENTAL EVIDENCE TO CLINICAL TRIALS

G. Holmes (Professor of Neurology & Pediatrics, Neuroscience Center at Dartmouth, Dartmouth Medical School, Lebanon, New Hampshire, USA)

While there has been a multitude of pharmacological agents reported to have antiepileptogenic properties in preclinical studies, results from animal models have yet to be validated by clinical research. To date, no drug has been shown to have disease-modifying properties in epilepsy. Although kindling has been widely considered to be a model of epileptogenesis, agents that reduce kindling rate in animals have not been demonstrated to alter epileptogenesis in humans. The ideal antiepileptogenic agent is likely to be one that prevents the development of spontaneous seizures in rats with either acquired lesions or genetic abnormalities. Further studies in animals exploring the processes resulting from an insult to the brain to spontaneous seizures are needed. Determining which of the many biological changes that occur in the brain following an insult that should be a target for intervention remains a major challenge. In addition to not having validated animal models, clinical investigations may fail because of inappropriate study populations, inadequate outcome measures, or insufficient power. Proper studies of antiepileptogenic agents in patients are lengthy and costly, and surrogate markers

of epileptogenesis are urgently needed. Studies have indicated that both MRI and electroencephalographic features have potential as surrogate markers. Studies of MRI changes following prolonged febrile seizures as a predictor of epilepsy are ongoing and there is considerable interest in determining whether high-frequency oscillations following brain insults contribute to epileptogenesis. Before becoming clinically relevant, surrogate markers will require validation in human epilepsy. Trial methodology that bridges the gap from the experimental drug candidate to the clinical arena requires a novel approach to study design combining scientific rigour with economic practicalities. Despite our current failure in finding a drug or device that prevents epilepsy, increasing knowledge of the pathophysiological basis of epilepsy offers considerable hope that novel targets can be developed.

Suggested reading

Bragin A, Azizyan A, Almajano J, et al. Analysis of chronic seizure onsets after intrahippocampal kainic acid injection in freely moving rats. *Epilepsia* 2005;46:1592–8.

Bragin A, Wilson CL, Almajano J, et al. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. *Epilepsia* 2004;45:1017–23.

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Dube C, Yu H, Nalcioglu O, Baram TZ. Serial MRI after experimental febrile seizures: altered T2 signal without neuronal death. *Ann Neurol* 2004;56:709–14.

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Temkin NR, Dikmen SS, Winn HR. Clinical trials for seizure prevention. *Adv Neurol* 1998;76:179–88.

Monday July 3, 2006
17:30–19:00
Hall 1
Pfizer Inc. Satellite Symposium
An age-old challenge—epilepsy in the elderly

OLDER BUT ANY WISER? ARE WE MEETING THE CHALLENGE OF EPILEPSY IN OLDER PEOPLE?

R. Tallis (Emeritus Professor of Geriatric Medicine, University of Manchester, Manchester, UK)

Older adults are now the largest group of individuals presenting with epilepsy (Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998;352:1970–3) which affects over 1% of people over 65 years of age (Purcell B, Gaitatzis A, Sander JW, Majeed A. Epilepsy prevalence and prescribing patterns in England and Wales, Office of National Statistics. *Health Statistics Quarterly* 2002;15:23–30). The impact of seizures, their misdiagnosis, or their mismanagement, on an elderly person cannot be exaggerated. It is a matter of the greatest concern, therefore, that seizures in old age are comparatively neglected both in the scientific literature and in clinical practice (Tallis RC. 'Epilepsy'. In: Tallis RC, Fillit H (eds) *Textbook of Geriatric Medicine and Gerontology.* 6th ed. Edinburgh: (Churchill Livingstone, 2003;549–572). A recent survey in the United Kingdom showed a lack of training in the diagnosis and management of epilepsy by geriatricians (Epilepsy Action: Survey of Geriatricians in the United Kingdom, 2005 [http://www.epilepsy.org.uk/press/releases/2005/epilepsyaction_pr_epilepsyweek2005_medical.pdf]).

There are many challenges facing a physician who wishes to provide good care for people with late-onset seizures: diagnosis; education and support to minimise the psycho-social impact of seizures; rational decisions about the use of antiepileptic drugs; the management of co-morbid conditions; and long-term monitoring of seizure control and the effects of medication.

Diagnosis often presents the most difficult challenge (Rowan AJ. 'Paroxysmal disturbances resembling seizures in the elderly'. In Kaplan PW, Fisher RS (eds) *Imitators of Epilepsy.* New York: Demos, 2005;111–119). The range of differential diagnoses is extensive and accurate diagnosis is often made more difficult by the lack of a detailed history. The most important differential diagnosis is syncope and physicians dealing with 'blackouts' in older people should provide, or have ready access to, a service for diagnosing and managing this very common condition. Diagnosis should include identification of the underlying cause. The close relationship between elderly-onset seizures and cerebrovascular disease is now more fully understood (Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. *Lancet* 2004;363:1184–6) and detection and treatment of cardiovascular risk factors should be a routine part of the service.

At present, we are a long way off meeting the challenge of epilepsy in older adults.

DOUBLE TROUBLE! THE IMPACT OF COMORBIDITY ON TREATMENT STRATEGIES

A. Kanner (Professor of Neurological Sciences & Psychiatry, Rush Medical College, Director, Laboratory of EEG and Video-EEG-Telemetry, Rush University Medical Center, Chicago, Illinois, USA)

Today, the choice of antiepileptic drug (AED) for the treatment of epilepsy is not only based on the type of epileptic syndrome and/or seizure, but on the presence of comorbid disorders and concomitant medications. Implementation of this principle is especially relevant in elderly people with epilepsy (EPWE), as they are more likely to suffer from a variety of comorbid neurological, psychiatric, cognitive and medical disorders than younger patients (Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64(11):1868–74). Furthermore, EPWE living in a nursing home have been found to be taking an average of five concomitant medications in addition to their AED (Lackner TE, Cloyd JC, Thomas LW, Leppik IE. Antiepileptic drug use in nursing home residents: effect of age, gender, and comedication on patterns of use. *Epilepsia* 1998;39:1083–7).

For example, in the selection of an AED to treat a seizure disorder caused by stroke, clinicians must factor-in: (i) a potential negative impact on the course of likely comorbid disorders such as dyslipidaemia, hypertension, large and small vessel disease of the brain, coronary artery disease and diabetes; (ii) the AED's potential pharmacokinetic and pharmacodynamic interaction with the concomitant medications used for the treatment of these conditions; (iii) a 30 to 50% risk of post-stroke depression that is often associated with comorbid generalized anxiety disorder, both of which are likely to limit the recovery of neurological deficits (including activities of daily living) and increase mortality risk (Beekman AT, de Beurs E, van Balkom AJ, et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am J Psychiatry* 2000;157:89–95; Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. *Biol Psychiatry* 2003;54:376–87).

The most frequently prescribed AEDs in most countries are enzyme-inducing AEDs (i.e., carbamazepine, phenytoin and phenobarbital). These drugs have a potentially negative impact on these comorbid disorders for the following reasons: (i) they may potentially worsen the course of the concomitant cerebrovascular disease and dementing disorders since they are associated with an increase of serum homocysteine concentrations (Apeland T, Mansoor MA, Strandjord RE, Kristensen O. Homocysteine concentrations and methionine loading in patients on antiepileptic drugs. *Acta Neurol Scand* 2000,101:217–23); and (ii) they limit the efficacy of concomitant medications by increasing their clearance (Ucar M, Neuvonen M, Luurila H *et al*. Carbamazepine markedly reduces serum concentrations of simvastatin and simvastatin acid. *Eur J Clin Pharmacol* 2004;59:879–82; (Faught E. Pharmacokinetic considerations in prescribing antiepileptic drugs. *Epilepsia* 2001;42(Suppl 4):19–23). This presentation will review practical strategies in the selection of AEDs for the treatment of EPWE taking into consideration some of the frequent comorbid medical and psychiatric disorders.

INTO A NEW AGE—CLINICAL TRIALS OF AEDS IN THE ELDERLY

E. Perucca (Clinical Pharmacology Unit, University of Pavia and Institute of Neurology IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy)

The incidence of epilepsy peaks in old age, and the number of persons with epilepsy in the over 65 age group is increasing exponentially due to improved life expectancy and higher rates of survival following epileptogenic insults such as cerebrovascular accidents. This epidemiological dimension contrasts with the paucity of well-conducted comparative trials of antiepileptic drug (AED) treatment in old age. This is regrettable since treatment outcome data in younger age groups cannot be readily extrapolated to the elderly, due to age-related differences in pharmacokinetics and pharmacodynamics. A few randomised trials have been completed in recent years, but interpretation of results is made difficult by methodological shortcomings in some of the studies. These include relatively small sample sizes; suboptimal inclusion criteria; relatively short duration of follow-up; and suboptimal dose titration rates, target dosages or dosing schedules. In most trials, carbamazepine was found to have inferior tolerability compared with some newer generation AEDs, particularly lamotrigine, but use of suboptimal (immediate-release) formulations and dosing schedules may have contributed to the differences in outcome between treatment groups. More studies with improved methodology are necessary before a fully evidence-based approach can be applied to the treatment of epilepsy with onset in old age.

Suggested Reading

Brodie MJ, Kwan P. Epilepsy in elderly people. *Br Med J* 2005;331:1317–22.

Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsy Res* 1999;37:81–7.

Craig I, Tallis R. Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study. *Epilepsia* 1994;35(2):381–90.

Perucca E, Berlowitz D, Birnbaum A, et al. Pharmacological and clinical aspects of antiepileptic drugs use in the elderly. *Epilepsy Res* 2006;68(Suppl. 1):49–63.

Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64(11):1868–73.

Saetre ER, Perucca E, Isojarvi J, et al. An international multicenter double-blind randomized comparative trial of lamotrigine and slow release carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsia* 2005;46 (Suppl. 8):216.

Monday July 3, 2006
19:30–21:00
Hall 1
Sanofi-Aventis Satellite Symposium
Management of epilepsy across the ages

IDIOPATHIC GENERALISED EPILEPSIES IN CHILDREN: TREATMENT AND CARE

A. Arzimanoglou (University Hospital Robert Debré, Paris, France)

Idiopathic Generalised Epilepsies (IGE) account for nearly one third of all epilepsies and the majority of cases have an onset in childhood or adolescence. When treated with the appropriate AEDs the majority of IGE patients will become seizure-free and will benefit from fully normal schooling and societal life. Consequently, individual tolerance of the chosen drug is of primary importance. Age-related and gender issues must also be taken into consideration. Whenever possible, drugs with an eventual impact on learning and language abilities or behaviour should be avoided. Drugs like carbamazepine, oxcarbazepine, vigabatrin, gabapentine and pregabalin must be avoided as they can aggravate, or sometimes even induce, myoclonic seizures and cannot control absence seizures.

Some of the IGE syndromes, like childhood absence epilepsy, will definitely resolve by adolescence, resulting in AED discontinuation. For patients with photosensitive epilepsies, treatment with AEDs is not always necessary as measures to avoid environmental stimuli may be sufficient. Juvenile myoclonic epilepsy is one of the most AED-dependent syndromes since discontinuation of all AEDs usually leads to recurrence of seizures.

Valproate is the only AED available that has the potential to control all three types of seizures encountered in the category of idiopathic generalized epilepsies (typical absences, myoclonias and generalized tonic–clonic seizures). Ethosuximide can be active for the control of typical absences and sometimes myoclonias. From the newer AEDs only levetiracetam, topiramate and lamotrigine can be used. Combination of two drugs may prove to be very useful in intractable cases or when a smaller dose is needed to avoid an undesirable effect.

MANAGING EPILEPSY IN WOMEN OF CHILD-BEARING POTENTIAL: HOW CAN WE BALANCE THE RISK-BENEFIT RATIO?

T. Tomson (Karolinska Institutet, Stockholm, Sweden)

The majority of women with epilepsy who become pregnant will have uncomplicated pregnancies and give birth to perfectly normal children. Nevertheless, the risk that seizures and antiepileptic drugs (AEDs) may harm the unborn child is a major concern. Potential adverse effects of AEDs need to be weighed against the fetal and maternal risks associated with uncontrolled seizures during pregnancy. The general strategy in pregnant women has been to use monotherapy with an AED suited to the type of epilepsy, at the lowest effective dose to maintain seizure control. In some recent studies the use of valproate has been associated with a particularly high risk of congenital malformations and a lower verbal IQ in the offspring. These potential adverse effects appear to be dose-related with higher risks at doses above 800–1000 mg/day. Whether lower doses of valproate are associated with higher risks than with other AEDs is unclear. Although further studies are needed, a conservative approach to the use of valproate in women of child-bearing potential is recommended. Thus, alternative AEDs should be proposed to those planning pregnancies wherever satisfactory seizure control can thereby be maintained. The importance of seizure control during pregnancy should not be neglected and any major treatment changes should be completed before conception. In cases where valproate is used during pregnancy, either because the pregnancy was unplanned or because alternative treatment options of equivalent efficacy are unavailable, appropriate counselling, precautionary measures and monitoring should be provided.

SPECIFIC ASPECTS OF ANTIEPILEPTIC DRUG TOXICITY IN THE ELDERLY: PREVENTION, DETECTION, AND MANAGEMENT

A. Aldenkamp (Epilepsy Centre Kempenhaeghe, Heeze & Department of Neurology, Maastricht University Hospital, The Netherlands)

Epilepsy affects around 1% of elderly people. Several studies have shown a linear increase in the incidence of epilepsy for each decade after the age of 60 years. The aetiology and manifestations of epilepsies in the elderly are complex due to comorbidities and other common underlying risk factors such as concomitant cerebrovascular, neurodegenerative, or neoplasic diseases. Elderly people are generally more susceptible than younger adults to antiepileptic drugs (AEDs) adverse effects such as sedation, cognitive side effects, and osteoporosis. For these reasons, elderly people should be treated with low starting doses of AEDs that should be titrated slowly according to clinical response. Drug-drug interactions should be given special consideration. The pharmacokinetics of all AEDs are altered in the elderly; the most significant change common to all AEDs is a moderate reduction in renal and metabolic clearance. Predicting pharmacokinetic changes in the individual, however, can be very difficult because multiple factors contribute to a high inter-patient variability. Moreover elderly patients are often taking other drugs which can influence pharmacodynamics. Seizures can sometimes

be severely disabling in an elderly person, though in many cases appropriate management can avoid this. The nature of the disease is poorly understood and minor seizures are often overlooked. An increase in the frequency of seizures may severely affect quality of life, particularly with regard to the resultant loss of independence. Elderly patients may become more isolated and reclusive. The psychosocial impact of the diagnosis of epilepsy in the elderly can cause anxiety due to memories of a remote past in which seizures were poorly controlled, as well as fear of social stigma.

A REAPPRAISAL OF THE PLACE OF VALPROATE TODAY IN THE TREATMENT OF EPILEPSY ACROSS THE AGES

G. Krämer (Zürich, Switzerland)

Although a lack of data prevents a comparison of the relative efficacies of traditional and 'new generation' antiepileptic drugs, 40 years of clinical experience have provided substantial evidence (level II & III ILAE) supporting the use of valproate in the treatment of many epilepsy syndromes across the ages. The clinical experience of drugs such as lamotrigine, levetiracetam and zonisamide is much less extensive. Valproate monotherapy has proven effectiveness in the treatment of focal epilepsy, generalised tonic–clonic seizures and partial onset seizures. For the same reason valproate may be prescribed to newly diagnosed patients in whom, pending identification of the specific epilepsy type, a conservative treatment option is recommended. Findings from open, uncontrolled studies also support a role for valproate in the treatment of idiopathic generalised epilepsies with multiple seizure types. Unlike other antiepileptic drugs (AEDs) that may aggravate seizures, valproate has been successfully used in clinical series to treat juvenile myoclonic epilepsy. In addition, other studies have concluded that valproate may be effective as an 'add on' treatment, acting synergistically when used in conjunction with lamotrigine. Insufficient evidence prevents the evaluation of valproate relative to other drugs such as lamotrigine, levetiracetam and topiramate in the treatment of absence epilepsies. With a proven track-record in safety and effectiveness, valproate is today a first-line treatment of choice for a broad spectrum of epilepsy syndromes in patients of all ages.

Wednesday July 5, 2006
17:30–19:00
Hall 1
Schwarz Pharma & Valeant Pharmaceuticals International Satellite Symposium
What's around the corner: AEDs in late development

LACOSAMIDE—EFFICACY AND TOLERABILITY

E. Ben-Menachem (Neurologkliniken, Sahlgrenska Universitetssjukhuset, Goteberg, Sweden)

Lacosamide is in Phase 3 of clinical development for the adjunctive treatment of epilepsy and neuropathic pain. Currently the mode of action (MOA) is under investigation since it has been previously demonstrated that lacosamide does not share a MOA with other currently marketed antiepileptic drugs (AEDs). The drug can be administered orally or intravenously. Results from pharmacokinetic studies suggest that lacosamide has a low potential for drug-drug interactions, and it appears that lacosamide has a minimal risk for affecting the pharmacokinetics of commonly prescribed concomitant AEDs for the treatment of epilepsy.

In a double-blind, randomized, placebo-controlled, multicenter trial for the treatment of partial seizures (SP667), lacosamide was administered orally in doses of 200 mg, 400 mg and 600 mg divided in 2 daily doses. In this trial, lacosamide demonstrated a statistically significant reduction in seizure frequency over placebo. Moreover, the 50% responder rate (defined as patients with at least a 50% reduction in seizure frequency) was statistically significant.

A further trial (SP616) investigated the safety, tolerability and pharmacokinetics of IV lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. The nature of AEs reported following 60- and 30 minute infusions of lacosamide was consistent with AEs reported following oral administration of lacosamide.

Dose-related adverse events include dizziness, nausea, fatigue, ataxia, vision abnormal, diplopia, and nystagmus.

The currently available results justify the further development of lacosamide for the treatment of epilepsy.