Clinical Neurophysiology 124 (2013) 2354–2361

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children

Cyril Gitiaux [a,b,d,*], Hina Simonnet [a], Monika Eisermann [b,c], Dorothee Leunen [a,c], Olivier Dulac [a,c], Rima Nabbout [a,c,e], Mathilde Chevignard [f,g], Jerôme Honnorat [h], Svetlana Gataullina [a], Lucile Musset [i], Emmanuel Scalais [j], Agnès Gauthier [k], Marie Hully [a], Nathalie Boddaert [l,m], Mathieu Kuchenbuch [b], Isabelle Desguerre [a,d], Anna Kaminska [b,c]

[a] Service de neurologie pédiatrique et maladies métaboliques, hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[b] Service d'explorations fonctionnelles, laboratoire de neurophysiologie clinique, hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[c] INSERM U663, Université Paris-Descartes, Faculté de Médecine, Paris, France
[d] INSERM U1016-CNRS8104-Université Paris-Descartes, Faculté de Médecine, Paris, France
[e] Centre de référence épilepsies rares, hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[f] Service de rééducation des pathologies neurologiques acquises de l'enfant, Hôpitaux de Saint Maurice, Saint Maurice, France
[g] Er – 6 UPMC Paris 6, Hôpital de la Salpêtrière, Paris, France
[h] Hospices Civils de Lyon, Hôpital Neurologique, Centre de Référence Maladie Rare "Syndromes neurologiques Paranéoplasiques", Lyon Neuroscience Research Center INSERM U1028/CNRS UMR 5292, Université Claude Bernard Lyon 1, Lyon, France
[i] Département d'Immunologie, CHU Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France
[j] Service de neurologie pédiatrique, Centre Hospitalier de Luxembourg, Luxembourg
[k] Service de pédiatrie, centre hospitalier universitaire de Nantes, France
[l] INSERM U1000, Paris, France
[m] Service de Radiologie pédiatrique, hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

ARTICLE INFO

Article history:
Accepted 30 May 2013
Available online 2 July 2013

Keywords:
Anti-NMDA receptor encephalitis
Electroencephalogram
Outcome
Child

HIGHLIGHTS

- Abundant theta and alpha band rhythms in non-rapid eye movement (NREM) sleep represent a suggestive EEG pattern of anti-NMDA receptor encephalitis in pediatric patients.
- Preserved background activity over at least one hemisphere in the awake state and in sleep were correlated with milder clinical expression.
- The disruption of NMDA neurotransmission may lead to decrease of the slow waves component in the NREM sleep.

ABSTRACT

Objective: To describe initial and follow-up electroencephalographic (EEG) characteristics in anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.
Methods: Consecutive polygraphic video-EEG recordings were analyzed in nine pediatric patients with anti-NMDAR encephalitis at the initial stage of the disease and during the intermediate period until motor recovery. EEG characteristics in waking and sleep stages as well as EEG correlates of abnormal movements are described.
Results: In six of nine patients with anti-NMDAR encephalitis, the waking EEG showed preserved background activity and either focal or unilateral hemispheric slowing. During non-rapid eye movement (NREM) sleep, a decrease in the expected slow waves and unilateral or diffuse theta-alpha band rhythms were also observed in six of nine children. They all had more favorable outcome than the three children with diffuse slowing. Clinically, unilateral abnormal movements contra-lateral to hemispheric or focal slowing were also indicative of milder severity when compared to generalized abnormal movements and diffuse slowing.

* Corresponding author. Address: Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France. Tel.: +33 1 42 19 26 95; fax: +33 1 42 19 26 92.
E-mail address: cyril.gitiaux@nck.aphp.fr (C. Gitiaux).

http://dx.doi.org/10.1016/j.clinph.2013.05.023

Conclusions: In pediatric patients presenting behavioral disorders and abnormal movements, early EEG patterns may be suggestive of anti-NMDAR encephalitis. Moreover early electro-clinical presentation contributes to outcome prediction.
Significance: This case series demonstrates that early EEG patterns may be suggestive of anti-NMDAR encephalitis in pediatric patients with behavioral disorders and abnormal movements.

1. Introduction

Anti-N-methyl D-aspartate (NMDA) receptor encephalitis (NMDAR-encephalitis) is a severe neurological auto-immune disease first reported in four young women displaying a paraneoplasic neuropsychiatric disorder associated with ovarian teratoma (Vitaliani et al., 2005). NMDA receptors are glutamate-gated cation channels, assembled from NMDAR subunits 1 (NR1) and 2(NR2A, NR2B, NR2C, or NR2D). They have a fundamental role in cortical development, sensory transmission, and neurotoxicity (Haberny et al., 2002). Calcium flux through NMDAR is thought to be critical in synaptic plasticity, a cellular mechanism for learning and memory, inducing long-term potentiation (Hughes et al., 2010; Manto et al., 2010). In anti-NMDAR encephalitis, the extracellular domain of the NR1 subunit is directly targeted by the antibodies displacing NMDAR out of the synapses and completely blocking synaptic plasticity (Mikasova et al., 2012). The severity and outcome of anti-NMDAR encephalitis is related to antibody titers (Dalmau et al., 2011). Since the first description, an increasing number of cases have been reported as well as the key clinical features (Dalmau et al., 2008; Florance et al., 2009; Poloni et al., 2010; Dalmau et al., 2011; Titulaer et al., 2013). Typical clinical manifestations involve emotional and behavioral disturbances, seizures, language deterioration often associated to abnormal movements and autonomic dysregulation. Cognitive impairment, psychomotor regression, short term memory loss and amnesia are common features of the disease. An expanding spectrum, occurring in children, including milder or incomplete forms with isolated psychiatric symptoms, seizures or hemidystonia has been reported (Niehusmann et al., 2009; Rubio-Agustí et al.,2011). Previous reports of anti-NMDAR encephalitis focused on non-specific generalized or predominantly fronto-temporal slowing or disorganization occasionally incorrectly classified as non-convulsive status epilepticus (Bayreuther et al., 2009; Florance et al., 2009; Johnson et al., 2010; Gataullina et al., 2011). Recently, the EEG pattern of "extreme delta brush" was described in adults and in one child with anti-NMDAR encephalitis and was shown to be correlated to more prolonged illness (Schmitt et al., 2012; Armangue et al., 2013). The network mechanisms underlying these EEG changes remain unknown. With prompt adequate treatment, including immunotherapy, long term outcome is good (Titulaer et al., 2013). Reliable criteria for early diagnosis are therefore important to identify. The aim of this study is to describe the EEG characteristics in awake and sleep recordings at different stages of the disease and electro-clinical correlates of abnormal movements in nine consecutive pediatric patients with anti-NMDAR encephalitis.

2. Patients and methods

2.1. Patients

Between January 2009 and November 2011, nine previously healthy, unrelated children (6 females and 3 boys) aged 1.5–15 years (median 6.2) were hospitalized in the pediatric neurology department in Necker-Enfants Malades Hospital, and diagnosed with anti-NMDAR encephalitis (Table 1). Anti-NMDAR encephalitis was suspected because of a rapid change of behavior or psychosis associated with abnormal movements (orofacial and limb dyskinesia) and sleep disturbances. Analysis of the cerebrospinal fluid revealed an increased lymphocyte count (>10 cells) in five cases, hyperproteinorachia >0.4 g/l in two cases and oligoclonal bands on isoelectrofocusing in all cases. Anti-NMDAR antibodies, systematically screened in this clinical context, were disclosed in the CSF of all patients using cell based assay with HEK cells transfected with NR1 and NR2B subunits of NMDAR, as previously reported (Mikasova et al., 2012). In all patients brain MRI was performed within the first week after the onset of the first symptoms and it was considered normal in two cases. Abnormalities included uni or bilateral white matter hyperintensities (T2 or FLAIR), without specific localization ($n = 3$), additional brainstem and pallidal hyperintensities ($n = 1$); unilateral rolandic atrophy ($n = 1$) and cortical T2 hyperintensities ($n = 2$). Thoracic and abdominal scan and pelvic ultrasound to detect underlying tumor were negative in all patients. Eight children received immunosuppressive treatment within the first month post onset, whereas one patient started treatment three months after initial symptoms. All patients were treated with the same combination of first-line immunotherapy (steroids and intravenous immunoglobulin). To facilitate the description of electro-clinical features, we divided the clinical course of the disease in two stages: An "initial stage" (IS), ranging from onset to the maximum of neurological symptoms, and an "intermediate period" (IP) including the steady state and the improvement period until full recovery of motor functions and complete cessation of abnormal movements. Following full "motor recovery" (MR) most children still had cognitive, behavioral and language impairment. We categorized the clinical disability at the IS as follows: (i) Patients who did not lose the ability to walk and kept nearly normal or reduced social interaction were classified in the "mild severity" group. (ii) Patients who rapidly lost their communication skills and the ability to walk or to sit without support were classified in the "high severity" group. After MR, neurocognitive tests were performed using age-appropriate scales of cognitive abilities between six months and one year after the acute phase: The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) for children between 30 months and 6 years of age (Wechsler, 2002), and the Wechsler Intelligence Scale for Children (WISC-IV) for those aged 6–16 years (Wechsler, 2004).

2.2. EEG recordings

We reviewed forty-four polygraphic Video-EEG recordings including waking and sleep states and nine long duration polygraphic Video-EEG recordings comprising the whole night sleep (Table 1). In all children EEG was performed under spontaneous ventilation without sedative drugs during the initial stage. Electrodes were placed according to the 10/20 international system. Signal was acquired at 256 Hz sampling, amplified (1000 times), filtered with 0.01–97 Hz band and analyzed offline with the Coherence 3NT program (Deltamed, Paris, France). Polygraphic recordings systematically included electrocardiogram, abdominal respiration and surface electromyogram of deltoid muscles. Electro-oculogram was added for two long duration EEG video

Table 1
Electro-clinical features.

Patient/sex/age (years) (Follow-up, intermediate state duration, months)	Initial stage (First month of the disease)		Intermediate state		Motor recovery	
	EEG	Abnormal movements/ seizures Video-EEG	EEG	Abnormal movements/ Seizures, VEEG	EEG	Neuropsychological and neurological outcome
1/M/7.5 (48, 5)	A: Bi-frontal SW NREM sleep: right centro-temporal SW	Dystonia and myoclonic jerks of the left UL, attacks of terror and agitation	A: diffuse SW with frontal predominance; NREM: diffuse theta rhythmic sequences alternating with delta rhythmic SW and spike W	Rhythmic frontal-central spike W and SW discharges, asymptomatic or with increase of perioral clonic jerks and eyes upward	Normal	WISC-IV: VCI(82), PRI(73),WMI(70),PSI (100)
2/M/3 (24, 6)	A: left hemispheric SW. NREM sleep: left frontal-central theta rhythms	Dystonia myoclonic jerks of Right UL V-EEG: Subclinical rhythmic left SW discharges	A: bilateral frontal spike W and SW with left predominance	Persistent right UL myoclonic jerks and dystonia	A: left frontal-temporal theta rhythms NREM sleep: normal	WPPSI-III: (PI)98, (VI)90. Speech and language impairment, visuo-motor and graphic disorders, attentional fluctuations
3/F/5 (18, 8)	A: activity. Left central-temporal occipital, SW NREM sleep: activity, left frontal theta rhythms, bi-frontal rapid rhythms	Dystonia, of right UL attacks of terror and agitation V-EEG: subclinical rhythmic left frontal-temporal-occipital SW discharges	A: unchanged NREM sleep: unchanged	Persistent right UL dystonia, attacks of terror and agitation	A: left SW, left central-temporal-occipital spikes and spike W NREM: unchanged	WPPSI-III: (PI)82, VI(87) Speech and language impairment
4/F/8.5 (12, 2)	A: bilateral central parietal SW with right predominance NREM sleep: bilateral frontal central theta rhythms	Myoclonic jerks of left LL or abdominal complex movements V-EEG: rhythmic SW discharges subclinical or with increase of abnormal movements	A: unchanged NREM sleep, diffuse theta rhythms with frontal predominance	Persistent left LL jerks	Unchanged	WISC-IV: VCI(118), PRI(90),WMI(109),PSI(93). Full recovery
5/M/13.5 (11, 3)	A: diffuse SW with frontal predominance, pseudo periodic bi-frontal complex	Generalized fixed dystonia, parkinsonism, Tonico-clonic seizures, attacks of agitation	A: improved background activity bilateral frontal SW	Persistent parkinsonism	Unchanged	WISC-IV: VCI(72), PRI(73). Episodic and semantic memory deficits
6/F/15 (10, 3)	A: bilateral central parietal and vertex SW, NREM sleep: diffuse slowing	Tonic seizures of right LL V-EEG: rapid spikes discharges on CZ	Normal	V-EEG: dystonic movements of LL predominant on the right	Normal	WISC-IV: VCI (90), PRI (96). Full recovery
7/F/2 (30,9)	A: diffuse, high amplitude SW with right predominance. NREM sleep: diffuse theta rhythms,	Severe generalized mobile dystonia and chorea V-EEG: Rhythmic right spike W and SW discharges; subclinical or with increase of dystonic posturing	A: diffuse, high amplitude SW; NREM sleep diffuse SW mixed with multifocal spikes	V-EEG: Tonic and hypermotor frontal seizures with diffuse flattening and rapid rhythms, spasms	Subnormal, bi-frontal spikes	Not evaluable, speech and language impairment
8/F/1.5 (12, persistent)	A: diffuse, high amplitude SW with right predominance. Rhythmic right SW discharges without clinical correlate. NREM sleep: diffuse theta rhythms	Severe generalized, mobile dystonia and chorea V-EEG: no EEG correlate	A: unchanged NREM sleep: improved diffuse SW and bi-occipital spikes, polyspikes and spike W	Persistent generalized mobile dystonia	NA	Not evaluable Generalized mobile dystonia
9/F/6.5 (10, persistent)	A: diffuse high amplitude SW right W discharges without clinical correlate NREM sleep: diffuse, theta rhythms, Diffuse SW with beta rhythms	Severe generalized mobile dystonia and chorea V-EEG: no EEG correlate	Unchanged	Severe acute anoxic-hypoxic complication after sepsis and dysautonomic dysfunction at 4 months post onset	NA	Not evaluable Generalized mobile dystonia and pyramidal signs

A: awake state; V-EEG: Video-electro-encephalogram; LL: lower limb; NREM: non rapid eye movements sleep; W: Waves; SW: slow waves; UL: upper limb; WISC IV: The Wechsler Intelligence Scale for Children - Fourth Edition: Verbal Comprehension Index (VCI); Perceptual Reasoning Index (PRI), Working Memory Index (WMI), Processing Speed Index (PSI), WPPSI-III: Wechsler preschool and primary scale of intelligence: performance index (PI), verbal index (VI), total index (TI). NA: Not Applicable.

recordings. Sleep stages were defined according to the American Academy of Sleep Medicine recommendations (Novelli et al., 2010).

3. Results

3.1. Clinical findings

3.1.1. At the initial stage

The delay between the first symptoms and the first examination in our department was less than one month for eight children and three months for one. All children suffered cognitive regression and language deterioration, six had orofacial dyskinesias characterized by chewing and tongue thrusting and five exhibited emotional/behavioral and sleep disturbances. Six patients were classified in the "mild severity group" (patient 1–6; Table 1). Four of them had strictly unilateral abnormal movements: Upper and/or lower limb dystonia, or complex chewing and myoclonic jerks (patient 1–4). Two had additional attacks of agitation and terror associated with dysautonomic symptoms as sweating and tachycardia (patient 1, 5). One patient in the mild severity group had focal seizures of the right lower limb (patient 6) and one had diffuse akinetic-rigid parkinsonism (patient 5). The three patients in the "high severity group" (patients 7–9; Table 1) rapidly lost their communication skills and the ability to walk or to sit without support. Dystonia was a prominent part of a mixed movement disorder and was associated with chorea.

3.1.2. At the intermediate period and motor recovery

The nine patients were followed up for a median duration of 12 months (range 10 months to 5 years, SD 12.8 m). One child experienced an acute hypoxic-ischemic complication at four month of follow-up requiring hospitalization in the ICU and sedation with midazolam and fentanyl, which led to persistent neurological sequelae (patient 9). One patient did not recover her communication skills and abnormal movements persisted twelve months post-onset (patient 8). Seven children recovered from abnormal movements and motor deficit within two to nine months. For one of them, formal neuropsychological testing was not possible, due to severe speech and language impairment (patient 7). Among the six children who were able to undergo neuropsychological testing at the end of the follow-up period, four had sub-normal Full-Scale Intelligence Quotient (FSIQ), one child had low FSIQ and one child had dissociation between low Performance IQ and subnormal Verbal IQ (Table 1). These six children returned to school but three of them had to receive special education because of persistent semantic memory deficit (word retrieval difficulties) and visual episodic and working memory impairment.

3.2. Electro-clinical findings at the initial stage

Each patient underwent four to eleven routine Video EEG polygraphic recordings during the whole follow-up (mean: 5.8, SD: 2.5), and six children had one to two additional long duration Video-EEG recordings. All patients had at least one Video-EEG polygraphic recording including waking and sleep states within the first month of the disease. No child received sedative drugs, benzodiazepines nor phenobarbital at the initial stage. Two distinct electro-clinical patterns were observed:

3.2.1. Mild severity group (patients 1–6)

For these patients waking EEG showed unilateral, focal or hemispheric, or bilateral focal, continuous (0.5–3 Hz) slow waves (SW) (Fig. 1A). Normal or nearly normal background activity and physiological figures were however preserved on at least one hemisphere on waking and sleep EEG. In three patients we observed abnormal theta and alpha rhythms in N2 stage of NREM sleep that predominated in the fronto-central areas (Fig. 1B, Fig. 2). Four of these six patients had unilateral abnormal movements during video-EEG recording (Table 1), consisting in myoclonic jerks or dystonic postures contralateral to the focal or hemispheric unilateral SW activity. These abnormal movements either had no EEG correlate or were accompanied by an increase of the frequency of the SW, sometimes organized in rhythmic discharges. They disappeared in NREM and REM sleep. One patient had typical epileptic discharges with rapid rhythms and spikes recorded over the vertex concomitant to tonic seizures of the right lower limb (patient 6).

3.2.2. High severity group (patients 7–9)

All patients lacked the physiological EEG figures of background activity during waking and sleep states. Waking EEG consisted in diffuse, high amplitude SW (Fig. 3A). In NREM sleep, all children presented high amplitude diffuse alpha-theta rhythms predominating over anterior areas, a decrease of normal SW activity and no identifiable stages of NREM sleep (Fig. 3B). In REM sleep, EEG showed diffuse SW activity similar to that recorded in the awake state. One child had additional diffuse high amplitude SW, superimposed with diffuse or unilateral rapid rhythms in the beta band (patient 9) (Fig. 4). Abnormal movements recorded on video-EEG in these children consisted of continuous, bilateral generalized mobile dystonia associated with choreo-athetosis and oro-facial

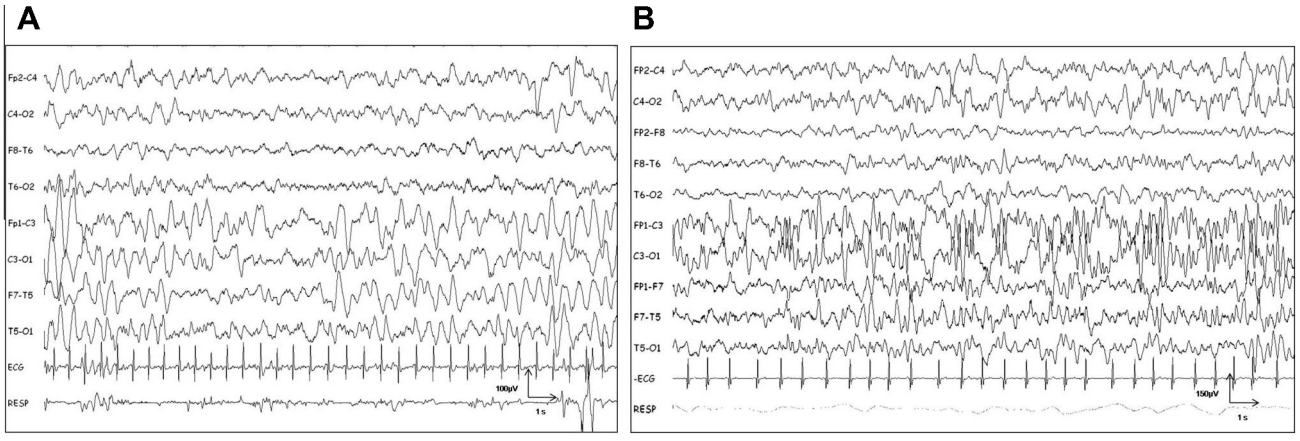

Fig. 1. (A) Patient 3. Awake state. Intermittent posterior alpha rhythms on the right hemishere. On the left hemisphere diffuse high amplitude slow delta activity. (B) Patient 2. Drowsiness. Left hemispheric high amplitude theta rhythms predominating on the central area.

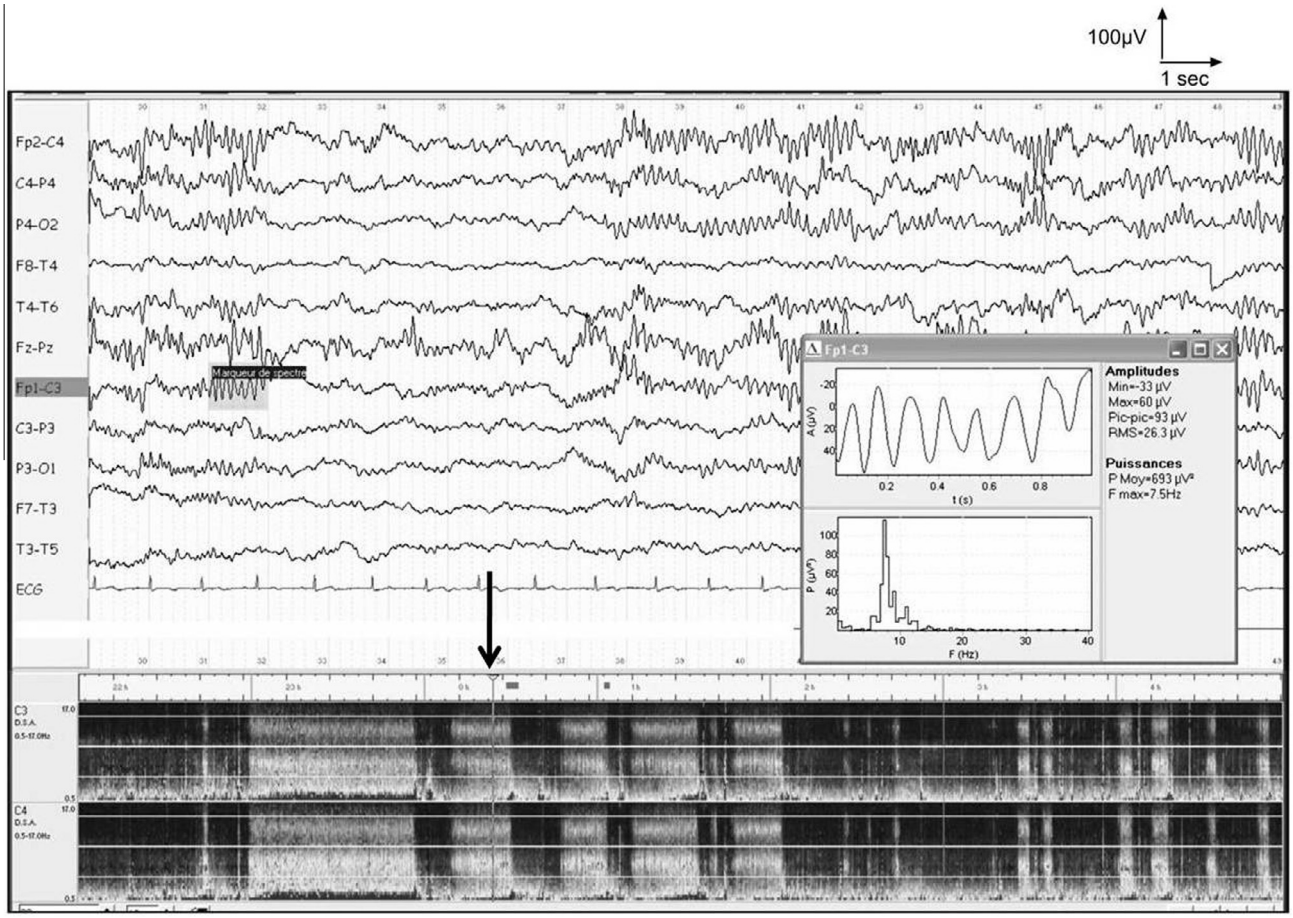

Fig. 2. Patient 4. Long duration Video EEG.7 h night sleep from 22 to 05 h presented as Density spectral array (DSA) of central derivations C3 and C4. Above: 20 s EEG sample in NREM sleep (at the time indicated by the arrow). DSA and EEG show abnormal, diffuse rhythms in theta and alpha frequency bands predominating on the frontal-central areas, during the whole NREM sleep periods.

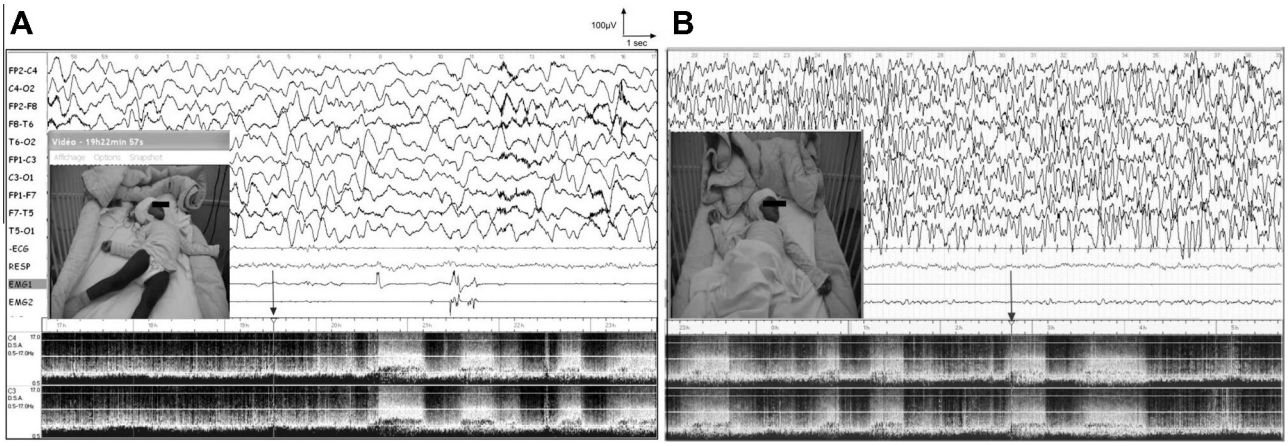

Fig. 3. Patient 8. Polygraphic long duration Video EEG (ECG, respiration, right deltoid [EMG1], left deltoid [EMG2]). DSA. (A) Above: 20 s EEG sample in the awake state indicated by the arrow showing high amplitude diffuse SW. (B) 20 s EEG sample in NREM sleep indicated by the arrow, showing high amplitude, diffuse theta and alpha rhythms without normal sleep figures.

dyskinesia, with no EEG correlate during the awake state. These movements disappeared in NREM sleep.

Focal rhythmic SW discharges intermixed or not with rhythmic spikes or spike-waves, lasting up to a few minutes were observed in both groups (five children in the "mild severity" and three in "high severity" group) (Fig. 5). Although SW and spike-wave discharges were sometimes associated with an increase of the contralateral movements, their semiology was not typical for epileptic seizures (Table 1).

3.3. Electro-clinicalfindings at the intermediate period and motor recovery

3.3.1. Mild severity group (patients 1–6)

EEG did not improve in four of the six patients in this group during the 2–8 months of the IP (Table 1). One patient developed a spike and spike-wave focus in the area of the initial SW focus (Fig. 6). In patient 1, who did not receive immunosuppressive treatment in the first month, attacks of agitation and terror

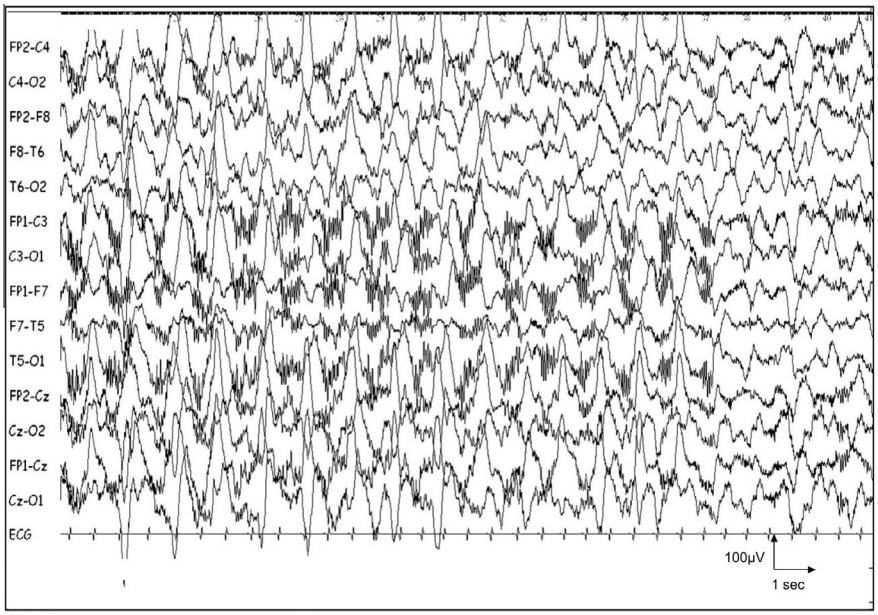

Fig. 4. Patient 9. Sleep. High amplitude diffuse SW superimposed or intermingeled with rapid rhythms predominating on anterior areas and the left hemisphere ressembling the ''extreme delta-brush'' pattern.

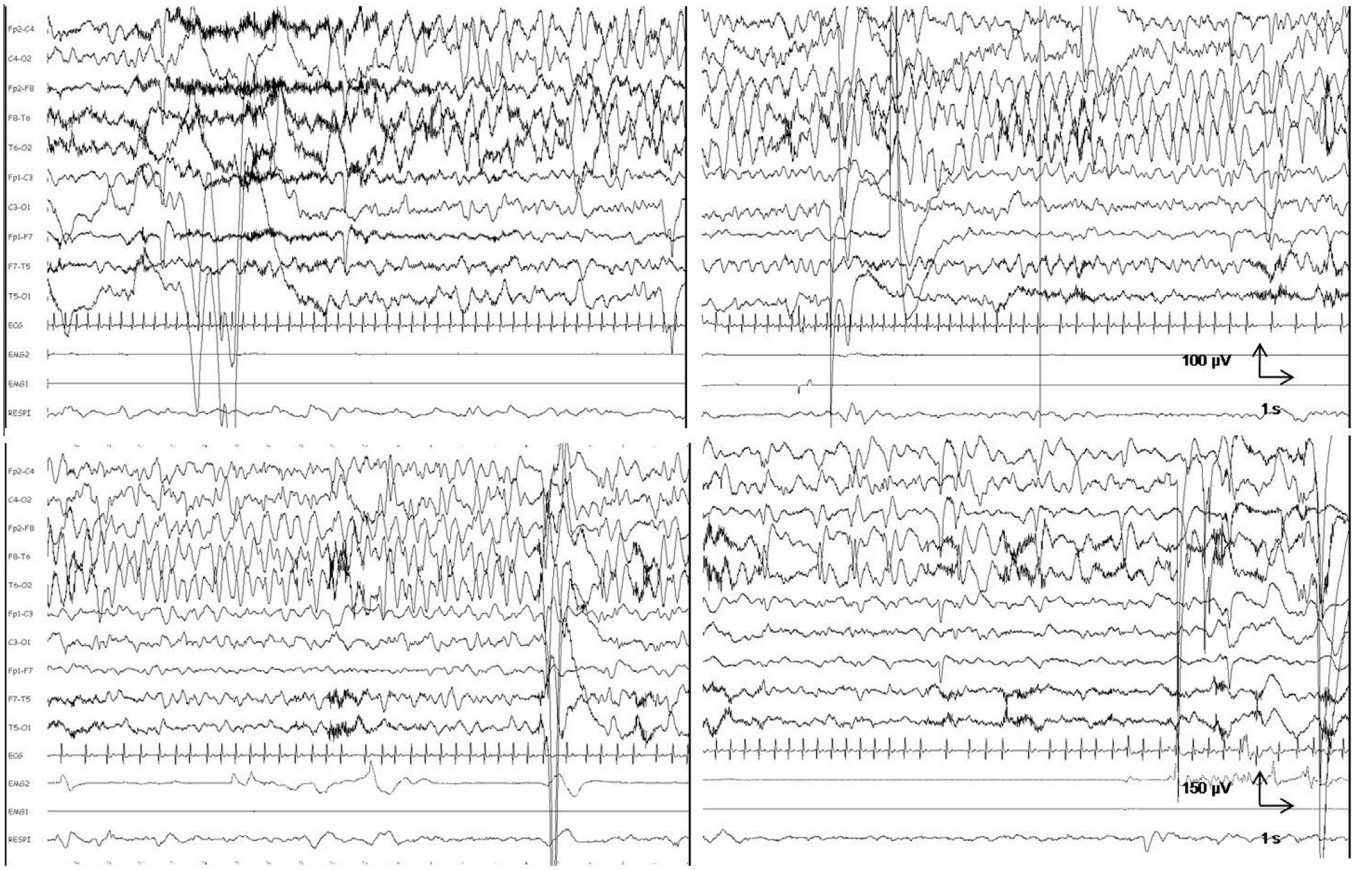

Fig. 5. Patient 8. Awake state. 80 s polygraphic EEG (ECG, respiration, right deltoid [EMG1], left deltoid [EMG2]). Sample showing a right hemispheric rhythmic SW with rare spikes discharge lasting 140 s, without clinical correlate.

dramatically increased. Long duration Video EEG at three months failed to show normal background activity neither in awake state nor in sleep with sub-continuous fronto-central high amplitude SW and spike waves discharges, mostly without clinical correlate or accompanied with peri-oral myoclonic jerks or upward eye deviation. This led to introduce antiepileptic treatment which resulted in major deficits in consciousness without any reduction of the paroxysmal events. The normalization of background

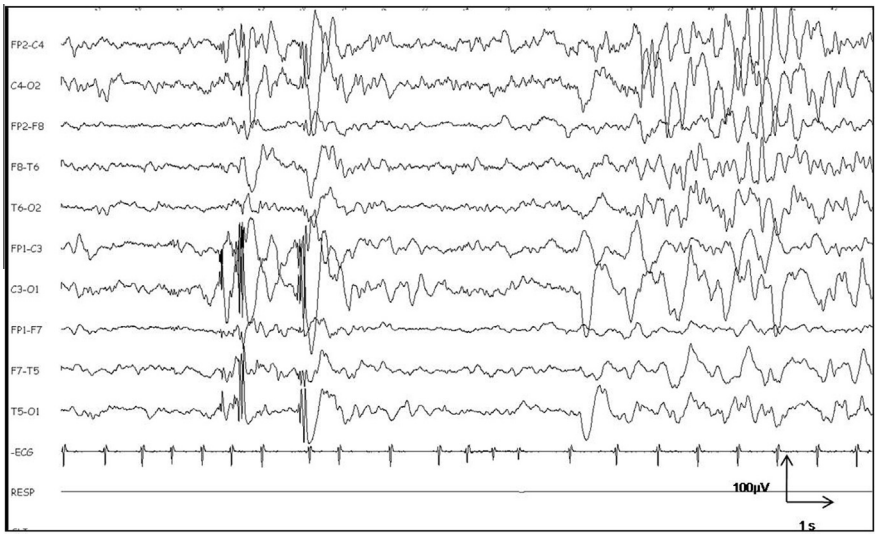

Fig. 6. Patient 3. Sleep stage N1. Left centro-temporal high amplitude polyspikes.

activity followed the first plasma exchange (Gataullina et al., 2011). At the MR stage that occurred within 3–8 months, complete normalization of the EEG was observed in only two patients. For the remaining four patients focal abnormalities such as SW, spikes, polyspikes or spike-waves persisted, usually in the same topography as the initial SW focus.

3.3.2. High severity group (patients 7–9)

Two of the three patients (patients 8, 9) showed modifications of NREM sleep background activity: the initial diffuse theta rhythms were replaced by diffuse SW and multifocal spikes and spike-waves with frontal or occipital predominance. Tonic and hypermotor epileptic seizures were recorded in one of these two children five months after disease onset, and disappeared within three months without antiepileptic medication. For the patient who suffered a severe anoxic hypoxic complication the background EEG activity became of very low voltage with persistence of unusual diffuse rapid rhythms.

4. Discussion

We report initial electro-clinical features and their evolution over time in nine children aged 1.5–15 years diagnosed with anti-NMDAR encephalitis. Two main electro-clinical presentations were correlated with outcome: Unilateral or focal abnormalities with persistence of normal physiological background activity on at least one hemisphere were associated with unilateral abnormal movements, moderate severity and better outcome, whereas diffuse abnormalities with lack of physiological background activity were associated with severe neurological impairment and poor outcome. Unilateral abnormal movements contra-lateral to focal MRI lesions or to variable positron emission tomography findings (hypo- or hypermetabolism) had also been reported in patients with anti-NMDAR encephalitis (Pillai et al., 2010; Consoli et al., 2011). Although it is striking that a systemic, auto-immune antibody mediated process can induce unilateral abnormal movements, focal clinical signs are also present in other auto-immune encephalopathies such neurolupus, post-streptococcic (PANDAS) and Hashimoto encephalitis (Luyendijk et al., 2011). The severity and outcome of NMDAR encephalitis are related to the antibody titers, and elimination of NMDAR-antibodies efficiently cures the disease (Dalmau et al., 2011). Our findings suggest that the extent of EEG abnormalities correlates with clinical severity in anti-NMDAR encephalitis.

While the role of anti-NMDAR antibodies in the EEG alterations associated with the encephalitis seems to be clear, the network mechanisms underlying EEG changes is unknown. In our patients, diffuse high amplitude SW in awake state were associated with severe neurological and cognitive impairment. These EEG changes may be related to the role of NMDAR in the maintenance of the active cortical state, which is largely supported by glutamatergic intracortical connections (Wang, 1999).

Interestingly, pharmacological suppression of NMDAR, e.g. by the open channel blocker ketamine or phencyclidine induces behavioral, cognitive and EEG changes recapitulating some of the features observed in anti-NMDAR encephalitis. At low doses ketamine, used in general anesthesia or analgesia in emergency medicine, causes psychosis, agitation, memory disturbance, and decreased responsiveness to pain. At higher doses it leads to catatonia, amnesia and analgesia, called dissociative anesthesia resembling the severe "catatonic" forms of the anti-NMDAR encephalitis (Dalmau et al., 2011). Studies on the effect of ketamine at anesthetic levels on EEG in humans reported an increase in the power spectrum of theta, fast theta, alpha, and slow beta frequency bands. Furthermore, visual analysis of the EEG signal revealed abundant fast gamma spindles (Maksimow et al., 2006).In six of the nine patients in both severity groups we found a characteristic EEG aspect in NREM sleep: a decrease of the physiological SW rhythms as well as an abnormal activity of diffuse or lateralized alpha-theta rhythms absent in the control group. This EEG pattern was not related to any treatment since no patient received sedative drugs, benzodiazepines or phenobarbital during the initial stage of the disease.

The second characteristic finding in our patients was the decrease of the SW component in the NREM sleep. The basic circuitry that generates slow-sleep oscillations in NREM sleep includes glutamatergic neocortical neurons with intracortical and thalamic projections, GABAergic nucleus reticularis neurons and glutamatergic thalamocortical neurons (Timofeev and Chauvette, 2011). NMDAR may play a role in at least two of these mechanisms: in cortically generated slow wave oscillation and in induction and synchronization of thalamic slow delta waves by the cortical slow oscillation (Bazhenov et al., 2002; Hughes et al., 2010).

In five patients, unilateral paroxysmal manifestations at the initial stage were considered as epileptic but only one had typical

focal epileptic seizures recorded at that time. Eight children in our series presented rhythmic, focal or hemispheric SW or spike-wave discharges, which were either subclinical, or accompanied by an increase of dystonic or myoclonic movements, without clear electro-clinical correlation, raising the question of their epileptic or sub-cortical origin. Similar discrepancies were reported in previous descriptions of children with anti-NMDAR encephalitis: Ictal discharges were also often described as sub-clinical and abnormal movements suspected to be seizures had no EEG correlate (Florance et al., 2009). While the pathophysiology of these discharges remains unclear, they are usually considered as epileptic, including non convulsive status epilepticus, and treated as such (Kirkpatrick et al., 2011, Gataullina et al., 2011). Rhythmic SW activity was reported to be frequent in severe, catatonic-like forms; this activity was not associated with abnormal movements and did not respond to antiepileptic drugs (Dalmau et al., 2011). The sites of action of ketamine and its EEG correlates were studied in the central nervous system using intracerebral recordings in cat. During the cataleptic anesthetic state induced by ketamine, recordings showed an alternating pattern of hypersynchronous delta wave bursts observed prominently in the thalamus and in the caudate nucleus and low voltage and fast wave activity in the neocortex and thalamus. Paradoxically, the hippocampus showed theta "arousal" waves (Miyasaka and Domino, 1968). In humans, the increase of glucose metabolic rate of the thalamus only and the increase of blood flow of the entire brain during ketamine anesthesia support the role of thalamus or thalamo-cortical loops in the generation of these abnormal EEG activities (Långsjö et al., 2005). Therefore, epilepsy seems to have been overestimated in previous reports, and long duration video-EEG monitoring is important to distinguish epileptic seizures from non epileptic abnormal movements.

This study is retrospective and qualitative since the group of pediatric patients with anti-NMDAR encephalitis is small and heterogeneous in terms of age which limits the power of findings and the possibility of inference. Our findings should be confirmed by further studies using long lasting Video-EEG recording focusing more precisely on EEG modification according to the different vigilance states.

Conflict of interest

None of the authors has any conflict of interest to disclose.

Acknowledgments

The authors wish to thank Dr Rustem Khazipov for the instructive comments on network mechanisms underlying EEG changes, Dr Nadia Bahi Buisson, Dr Christine Barnerias, Dr Nicole Chemaly, Dr Manoelle Kossorotoff for their contributions to care of these patients.

References

Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Spanish anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis work group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850–6.

Bayreuther C, Bourg V, Dellamonica J, Borg M, Bernardin G, Thomas P. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord 2009;11:261–5.

Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ. Model of thalamocortical slow-wave sleep oscillations and transitions to activated States. J Neurosci 2002;22:8691–704.

Consoli A, Ronen K, An-Gourfinkel I, Barbeau M, Marra D, Costedoat-Chalumeau N, et al. Malignant catatonia due to anti-NMDA-receptor encephalitis in a 17-year-old girl: case report. Child Adolesc Psychiatry Ment Health 2011;5:15.

Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.

Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.

Gataullina S, Plouin P, Vincent A, Scalais E, Nuttin C, Dulac O. Paroxysmal EEG pattern in a child with N-methyl-D-aspartate receptor antibody encephalitis. Dev Med Child Neurol 2011;53:764–7.

Haberny KA, Paule MG, Scallet AC, Sistare FD, Lester DS, Hanig JP, et al. Ontogeny of the N-methyl-D-aspartate (NMDA) receptor system and susceptibility to neurotoxicity. Toxicol Sci 2002;68:9–17.

Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010;30:5866–75.

Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology 2010;75:1480–2.

Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. Epilepsy Behav 2011;20:392–4.

Långsjö JW, Maksimow A, Salmi E, Kaisti K, Aalto S, Oikonen V, et al. S-ketamineanesthesia increases cerebral blood flow in excess of the metabolic needs in humans. Anesthesiology 2005;103:258–68.

Luyendijk J, Steens SC, Ouwendijk WJ, Steup-Beekman GM, Bollen EL, van der Grond J, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011;63:722–32.

Maksimow A, Särkelä M, Långsjö JW, Salmi E, Kaisti KK, Yli-Hankala A, et al. Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. Clin Neurophysiol 2006;117:1660–8.

Manto M, Dalmau J, Didelot A, Rogemond V, Honnorat J. In vivo effects of antibodies from patients with anti-NMDA receptor encephalitis: further evidence of synaptic glutamatergic dysfunction. Orphanet J Rare Dis 2010;5:31.

Mikasova L, De Rossi P, Bouchet D, Georges F, Rogemond V, Didelot A, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2receptors in anti-NMDA encephalitis. Brain 2012;135:1606–21.

Miyasaka M, Domino EF. Neural mechanisms of ketamine-induced anesthesia. Int J Neuropharmacol 1968;7:557–73.

Niehusmann P, Dalmau J, Rudlowski C, Vincent A, Elger CE, Rossi JE, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. Arch Neurol 2009;66:458–64.

Novelli L, Ferri R, Bruni O. Sleep classification according to AASM and Rechtschaffen and Kales: effects on sleep scoring parameters of children and adolescents. J Sleep Res 2010;19:238–47.

Pillai SC, Gill D, Webster R, Howman-Giles R, Dale RC. Cortical hypometabolism demonstrated by PET in relapsing NMDA receptor encephalitis. Pediatr Neurol 2010;43:217–20.

Poloni C, Korff CM, Ricotti V, King MD, Perez ER, Mayor-Dubois C, et al. Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: evidence for anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol 2010;52:78–82.

Rubio-Agustí I, Dalmau J, Sevilla T, Burgal M, Beltrán E, Bataller L. Isolated hemidystonia associated with NMDA receptor antibodies. Mov Disord 2011;26:351–2.

Schmitt SE, Pargeon K, Frechette ES, Hirsh LJ, Dalmau J, Friedman D. Extreme delta brush. A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1094–100.

Timofeev I, Chauvette S. Thalamocortical oscillations: local control of EEG slow waves. Curr Top Med Chem 2011;11:2457–71.

Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.

Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005;58:594–604.

Wang XJ. Synaptic basis of cortical persistent activity: the importance of NMDA receptors to working memory. J Neurosci 1999;19:9587–603.

Wechsler D. Wechsler preschool and primary scale of intelligence. 3rd ed. London: Pearson Assessment; 2002.

Wechsler D. Wechsler intelligence scale for children. 4th ed. London: Pearson Assessment; 2004.