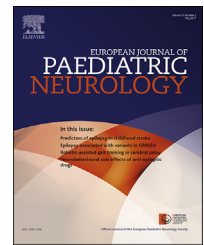




Official Journal of the European Paediatric Neurology Society



Original article

Epileptic phenotypes, electroclinical features and clinical characteristics in 17 children with anti-NMDAR encephalitis

E. Haberlandt ^{a,*}, M. Ensslen ^b, U. Gruber-Sedlmayr ^c, B. Plecko ^j,
M. Brunner-Krainz ^c, M. Schimmel ^d, S. Schubert-Bast ^e, U. Neirich ^f,
H. Philippi ^g, G. Kurleman ^h, M. Tardieu ⁱ, G. Wohlrab ^j, I. Borggraefe ^b,
K. Rostásy ^k

^a Clinical Department of Pediatrics I, Neuropediatrics, Medical University of Innsbruck, Innsbruck, Austria

^b Department of Pediatric Neurology and Developmental Medicine and Social Pediatrics, Dr. von Haunersches Children's Hospital, University of Munich, Munich, Germany

^c Department of Pediatrics, Medical University of Graz, Graz, Austria

^d Department of Pediatrics, Klinikum Augsburg, Augsburg, Germany

^e Department of Pediatric Neurology, University Children's Hospital Heidelberg, Heidelberg, Germany

^f Department of Pediatrics, Neurology, Stiftungskrankenhäuser Frankfurt am Main, Clementine Kinderhospital, Frankfurt am Main, Germany

^g Sozialpädiatrisches Zentrum Frankfurt Mitte, Frankfurt am Main, Germany

^h Department of General Pediatrics, Neuropediatrics, University Children's Hospital Münster, Münster, Germany

ⁱ Assistance publique hôpitaux de Paris, Hôpitaux universitaires Paris-Sud, Université Paris-Sud, Paris, France

^j Department of Neuropaediatrics and Neurophysiology, University Children's Hospital, Zuerich, Switzerland

^k Department of Pediatric Neurology, Children's Hospital Datteln, University Witten/Herdecke, Witten, Germany

ARTICLE INFO

Article history:

Received 27 October 2015

Received in revised form

3 September 2016

Accepted 25 November 2016

Keywords:

Anti-NMDAR encephalitis

Epilepsy

Children

Focal seizures

Generalized seizures

ABSTRACT

Background: Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a rare disorder characterized by seizures, neuropsychiatric symptoms, dyskinesia and autonomic instability.

Objective: Aim of the present study was to evaluate the seizure phenotypes and electroencephalogram (EEG) features in children with anti-NMDAR encephalitis.

Methods: Seizure types, electroclinical features and clinical characteristics of 17 children with anti-NMDAR encephalitis were analysed in a retrospective case series from nine centres in Europe.

Results: Nearly half (8/17) of the children presented with psychiatric symptoms, whereas in 4/17 patients seizures were the first symptom and in 5/17 both symptoms occurred at the same time. During the following course seizures were reported in 16/17 children. The first EEG detected generalized slowing in 11/17 patients, focal slowing in 3/17 and normal

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; EDB, extreme delta brush; NMDAR, anti N-methyl D-aspartate receptor.

* Corresponding author. Clinical Department of Pediatrics I, Neuropediatrics, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. Fax: +43 512 504 24904.

E-mail address: edda.haberlandt@tirol-kliniken.at (E. Haberlandt).

<http://dx.doi.org/10.1016/j.ejpn.2016.11.016>

1090-3798/© 2016 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.

Extreme
Delta brush

background activity in only 3/17 children. The extreme delta brush (EDB) pattern was detected in 9/17 (53%) patients.

Conclusion: In addition to psychiatric symptoms, children with anti-NMDAR encephalitis often show generalized slowing in EEG with or without seizures at initial presentation. EDB is present in half of all children and is potentially a helpful tool for early detection of this immune-mediated disease.

© 2016 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an immune-mediated disorder with a range of symptoms including seizures, neuropsychiatric symptoms, dyskinesia and autonomic instability.¹ Whereas it was first characterized in young women as a paraneoplastic entity with teratomas of the ovary, the number of patients diagnosed without teratoma is steadily increasing, particularly in pediatric case series. All patients have serum and/or cerebrospinal fluid antibodies against NMDAR, a ligand-gated cell surface cation channel with important functions in synaptic transmission and plasticity.²

Clinical symptoms usually start with psychiatric disturbances followed within weeks by encephalopathic changes, dyskinesias and autonomic instability. Seizures are present in the majority of patients. In one study of 44 patients with anti-NMDAR encephalitis including ten children, 16 had dyscognitive seizures, 12 had simple partial and 33 patients additionally had generalized seizures.³ Epileptic phenotypes with focal motor or complex seizures developing at early stages of the disease have also been described.⁴ Electroencephalographic (EEG) findings of non-specific, generalized slowing without epileptiform discharges dominate the clinical picture in adults.⁴ Schmitt et al. recently described “extreme delta brush pattern” as a novel EEG finding defined as delta activity with superimposed fast activity in the beta range predominately symmetric and synchronous, typically seen across all regions.⁵

We here describe the epileptic phenotypes, electroclinical features and clinical features of 17 children with anti-NMDAR encephalitis.

2. Methods

2.1. Patients

Seventeen children with anti-NMDAR encephalitis were retrospectively enrolled between 2002 and 2012 from nine different neuropediatric centres in Europe. All patients underwent extensive diagnostic studies including magnetic resonance imaging (MRI) of the brain, EEG, serum and cerebrospinal fluid (CSF) studies. The following demographic and clinical data were obtained: age, gender, presence of tumours, NMDAR antibody status in serum and/or CSF, clinical course

including symptoms (e.g. psychiatric, neurological signs), outcome, seizure semiology, treatment regimes and EEG findings. Medical information was made available by the treating physicians.

Outcome was measured with the modified Rankin Scale (mRS), ranking neurological recovery on a scale from 0 to 6. 2 mRS designates a slight disability, with the patient able to walk, being only slightly handicapped for everyday life. 3 mRS designates moderate disability with severe handicap for daily routine. Modified Rankin Scale 4–6 designates more severe motor disability.

Outcome of patients was scored as (1) full neurological recovery if they were able to return to all their daily activities without any sequelae; (2) substantial improvement if they returned to their homes with mild deficits but still improving; or (3) limited improvement if there was minimal change in the neurological status three months after initial presentation.

2.2. Seizures and EEG findings

Seizures were characterized as generalized (e.g. atonic seizures, generalized tonic clonic seizures) or focal (dyscognitive, focal motor seizures) with or without status epilepticus, seizure frequency <1/day (less than one seizure per day) or >1/day (more than one seizure per day) – with or without therapy resistance during the course of the disease according to the revised terminology for seizures reported by the International League against Epilepsy (ILAE) in 2010.⁶

The EEGs from initial presentation and the last available follow-up were evaluated by two pediatric neurologists as follows: presence of background activity changes (generalized slowing, focal slowing and extreme delta brushes (EDB)), presence of interictal epileptic paroxysms such as sharp waves, spike waves, polyspike waves or generalized discharges, focal interictal epileptic discharges, multifocal interictal epileptic discharges and electrographic seizures.

3. Results

3.1. Clinical characteristics and laboratory findings (Table 1)

Seventeen (5 male, 12 female) patients with a median age at disease onset of 8.7 (range: 1.8–17.3) years with antibody-confirmed anti-NMDAR encephalitis were enrolled. Median follow-up was 14 (range: 2–30) months. In 2/17 (12%) patients

Table 1 – Patient characteristics of 17 children presenting with anti-NMDAR encephalitis.

n	Sex/Age at onset	Observ period	Aetiology Tumour	CSF pleocytosis	NMDAR Abs serum	NMDAR Abs CSF	cMRI	Immunomodulatory therapy
1	f 6.4 y	24 mo	–	–	+	nd	Normal	HD cortisone IVIG, PLPH, MycoM
2	f 8.6 y	24 mo	–	–	+	nd	Normal	HD cortisone IVIG
3	f 14.7 y	18 mo	+	+	+	+	Normal	HD cortisone PLPH, IAD, Ritux
4	f 6.8 y	38 mo	–	–	+	nd	Normal	HD cortisone PLPH
5	f 16.6 y	12 mo	–	+	+	nd	Normal	HD cortisone IVIG, PLPH
6	f 2.6 y	5 mo	–	+	+	+	Normal	HD cortisone IVIG, Ritux
7	f 5.7 y	2 mo	–	+	+	–	Normal	HD cortisone IVIG
8	f 16.5 y	5 mo	–	+	+	+	Normal	HD cortisone IVIG, PLPH
9	f 13.3 y	5 mo	–	+	–	+	Normal	HD cortisone
10	m 7 4/12 y	5 mo	–	+	–	+	Normal	HD cortisone IVIG
11	m 3.3 y	14 mo	+	–	+	–	Normal	nd
12	m 4.3 y	18 mo	–	+	+	+	Normal	HD cortisone IVIG, Ritux
13	f 17.3 y	14 mo	–	+	–	+	Normal	nd
14	f 3.9 y	20 mo	–	–	+	–	Normal	HD cortisone IVIG, MycoM
15	m 1.8 y	16 mo	–	+	–	+	Normal	HD cortisone IVIG, PLPH, MycoM,
16	m 1.9 y	9 mo	–	+	+	+	Normal	HD cortisone IVIG, Cycloph, MycoM, Ritux
17	f 14 y	27 mo	–	+	+	+	Normal	HD cortisone IVIG

Abbreviations in alphabetical order: +, positive; –, negative; **Abs**, autoantibodies; **cMRI**, cerebral magnetic resonance imaging; **CSF**, cerebrospinal fluid; **Cycloph**, cyclophosphamide; **f**, female; **HD cortisone**, High-dose cortisone; **IAD**, immunoadsorption; **IVIG**, intravenous immunoglobulins; **m**, male; **mo**, months; **MycoM**, mycophenolate-mofetil; **nd**, not done; **n**, number; **nephroblast**, nephroblastoma; **Observ**, observational; **olig**, oligoclonal; **ovary terat**, ovary teratoma, PLPH, plasmapheresis; **Ritux**, rituximab; **y**, years.

an ovary teratoma and nephroblastoma were detected. Cerebral MRI was normal in all children. CSF pleocytosis defined as ≥ 5 cells/ μ l was detected in 12/17 (70%) of patients. Oligoclonal bands were found in 7/17 (41%) patients. NMDAR autoantibodies in serum were positive in 13/17 (76%) children and in 10/17 (59%) children in CSF. In three patients NMDAR autoantibodies were found only in serum, but not in CSF. In four cases NMDAR autoantibodies were detectable only in CSF. In our cohort 2/17 (12%) children with anti-NMDAR encephalitis had a spontaneous recovery. All other children were treated with various immunomodulatory therapies (Table 1). None of the children suffered a relapse.

Nearly half of our children, namely 8/17 (47%), presented with psychiatric symptoms, seizures 4/17 (23%) or both 5/17 (29%) (Table 2). Nearly all 16/17 (94%) study patients subsequently developed clinical symptoms of encephalopathy and seizures. Bulbar symptoms were present in 12/17 (70%) children, followed by dyskinetic movements in 9/17 (53%), other neurologic problems in 8/17 (47%) and autonomic dysfunction in 13/17 (77%) of our cases.

Full neurological recovery was observed in 7/17 (35%) cases (0 mRS), substantial improvement in 8/17 (47%) (3 mRS) and limited improvement in 2/17 (12%) (2 mRS).

3.2. Seizure types and treatment (Table 3)

Generalized seizures were described in 5/16 (31%) and focal seizures in 4/16 (25%) patients. In our cohort 7/16 (44%) patients had generalized and focal seizures. Only one child had no seizures. No child was in status epilepticus in the initial stage. Seizure frequency was <1 seizure per day in 9/16 (56%) children. No patient with low seizure frequency had seizures at the end of follow-up; 8/16 (50%) children had frequent seizures (>1 seizure/day). Three of the eight children in this subgroup had ongoing epilepsy at the end of the study period.

Of the study patients 15/17 (88%) received antiepileptic drugs; 3/15 (20%) patients were given monotherapy and 12/15 (80%) patients received up to eight antiepileptic drugs in various combinations (Table 3).

Table 2 – Clinical symptoms of 17 children presenting with anti-NMDAR encephalitis.

n	Presenting symptoms	Psychiatric symptoms	Mental status change	Seizures	Bulbar symptoms	Dyskinetic Mov Dis	Other neurological symptoms	Autonomic dysfunction	Neurol. outcome (mRS) Observ. time
1	Psychiatric	Change behaviour Psychosis	Encephalopathy	+	–	–	–	+	Full (0) 24 months
2	Psychiatric	Change behaviour	Encephalopathy	+	–	–	–	+	Full (0) 24 months
3	Psychiatric	Change behaviour Psychosis	Encephalopathy	+	+	+	+	+	Limited (2) 18 months
4	Psychiatric Seizure	Change behaviour Psychosis	Encephalopathy	+	+	+	+	+	Full (0) 30 months
5	Psychiatric	Change behaviour Psychosis	Encephalopathy	+	+	+	+	+	Full (0) 12 months
6	Psychiatric Seizure	Change behaviour	Encephalopathy	+	+	–	–	+	Full (0) 12 months
7	Psychiatric	Change behaviour	Encephalopathy	+	+	+	+	+	Full (0) 5 months
8	Psychiatric	Change behaviour Psychosis	Encephalopathy	–	+	+	–	+	Substantial (3) 2 months
9	Psychiatric seizure	Change behaviour Psychosis	Encephalopathy	+	+	–	+	–	Substantial (3) 5 months
10	Psychiatric	Change behaviour	Encephalopathy	+	–	+	+	–	Substantial (3) 5 months
11	Seizure	Change behaviour	Encephalopathy	+	+	+	–	+	Substantial (3) 5 months
12	Psychiatric Seizure	Change behaviour Psychosis	Encephalopathy	+	–	–	–	+	Substantial (3) 14 months
13	Seizure	Change behaviour	Encephalopathy	+	+	+	+	+	Substantial (3) 18 months
14	Psychiatric	Change behaviour Psychosis	Encephalopathy	+	+	+	–	+	substantial (3) 14 months
15	Seizure	–	–	+	+	–	–	–	Substantial (3) 20 months
16	Psychiatric Seizure Seizure	Change Behaviour	Encephalopathy	+	+	–	+	+	Limited (2) 16 months
		–	Encephalopathy	+	–	–	–	–	Full (0) 14 months

Abbreviations in alphabetical order: +, positive; –, negative; **dyskinetic mov dis**, dyskinetic movement disorder; **full**, full recovery; **limited**, limited recovery; **mRS**, modified Rankin Scale; **neurol**, neurological, observ., observational; **psychiatric**, psychiatric symptoms; **substantial**, substantial recovery.

Table 3 – Seizures and EEG characteristics of 17 children presenting with anti-NMDA-R encephalitis.

N	Age at onset	Seizure type	Seizure frequency	AED therapy	Therapy outcome	Epilepsy outcome	First EEG Background	First EEG IEP	Electroenc seizure	Last EEG Background observ. time	Last EEG IEP	EDB
1	6 5/12 y	Generalized Focal + SE	>1/d	CLB, ESM, LEV, MDZ, STM, TPM, PB, VPA	th-resistant	+	Generalized Slowing	Generalized	+	Generalized Slowing 24 months	–	–
2	8 7/12 y	Generalized Focal + SE	>1/d	LEV, LTG, MDZ, OXCZB, PB, TPM, VPA	th-resistant	+	Normal	Generalized	+	Generalized Slowing 24 months	Generalized	–
3	14 8/12 y	Generalized focal + SE	>1/d	CBZ, CLB, LEV TPM, VPA	th-resistant	–	Generalized Slowing	Generalized	+	Generalized Slowing 18 months	–	+
4	6 10/12 y	Generalized Focal	>1/d	–	th-resistant	–	Normal	–	–	– 30 months	–	+
5	16 7/12 y	Generalized	<1/d	–	–	–	Generalized Slowing	–	–	– 12 months	–	–
6	2 7/12 y	Focal + SE	<1/d	CLB, LEV, STM	–	–	Generalized Slowing	Multifocal	–	Generalized Slowing 12 months	–	+
7	5 8/12 y	Focal	>1/d	CBZ, PB, LEV	th-resistant	–	Generalized Slowing	–	–	– 5 months	–	+
8	16 6/12 y	Generalized	<1/d	CLN, LEV, LZP, PB	–	–	Generalized Slowing	–	–	Generalized Slowing 2 months	–	–
9	13 3/12 y	Generalized Focal	>1/d	CLB, LTG, MDZ, OXCZB, PB	th-resistant	–	Generalized Slowing	–	+	– 5 months	Generalized Focal	–
10	7 4/12 y	Focal	<1/d	CBZ, LEV, PB	–	–	Focal Slowing	–	–	– 5 months	–	–
11	3 3/12 y	Generalized	<1/d	PB, RVT, VPA	–	–	Generalized Slowing	–	–	Generalized Slowing 5 months	–	+
12	4 4/12 y	Generalized	<1/d	PHT	–	–	Generalized Slowing	–	–	– 14 months	–	+
13	17 3/12 y	Generalized Focal	<1/d	LEV, LTG	–	–	Normal	–	–	– 18 months	Multifocal	–
14	3 11/12 y	–	–	VPA	–	–	Generalized Slowing	Focal	–	– 14 months	Generalized	–
15	1 9/12 y	Generalized	>1/d	VPA	th-resistant	–	Generalized Slowing	Focal	–	Generalized Slowing 20 months	Generalized	+
16	1 11/12 y	Generalized Focal	>1/d	LCS, LEV, OXCZB TPM	th-resistant	+	Focal Slowing	Focal	–	Generalized Slowing 16 months	Generalized	+
17	14 y	Focal	<1/d	LCS, LEV, LTG, VPA	–	–	Focal Slowing	–	+	– 12 months	–	+

Abbreviations in alphabetical order: +, positive; –, negative; AED, antiepileptic drugs; background, background activity; CLB, clobazam; CLN, clonazepam; electroenc, electroencephalographic; EDB, extreme delta brush; EEG, electroencephalogram; ESM, ethosuximide; f, female; IEP, interictal epileptic paroxysms; LCS, lacosamide; LEV, levetiracetam; LZP, lorazepam; LTG, lamotrigine; m, male; MDZ, midazolam; n, number; OXCZB, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; RVT, rivotril; SE, status epilepticus; STM, sultiamine, th-resistant, therapy-resistant; ton, tonic; TPM, topiramate; VPA, valproic acid; y, years.

3.3. EEG findings (Table 3)

Background activity in the first available EEG was normal in only 3/17 (18%) cases. Generalized slowing was seen in 11/17 (65%) patients and focal slowing in 3/17 (18%) (Fig. 1). Epileptic paroxysms at the beginning of the disease were detected in 7/17 (41%) cases. Of these seven patients three presented with generalized, three with focal and one patient with multifocal paroxysms. Electroencephalographic seizures were detected in 5/17 (29%) patients, and EDB in 9/17 (53%) children (Fig. 2). EDB activity with superimposed fast activity in the beta range was predominately symmetric and synchronous and typically seen across all regions. During the course of the disease and follow-up EEGs this pattern disappeared; it was mainly seen in the severe course of the disease with substantial and limited outcome. When EEG examinations were videotaped, movement artefacts could be ruled out. EEG at last follow-up still showed generalized slowing in 8/17 (47%) cases and generalized epileptic paroxysms in 4/17 (23%) patients. Only in 1/17 (6%) patients were multifocal epileptic paroxysms present, and in one other patient focal and generalized epileptic paroxysms were equally distributed.

4. Discussion

Anti-NMDAR encephalitis is increasingly recognized in persons of all ages. However, seizure semiology and EEG changes have not been studied in detail in children to date. We here describe the clinical course, seizure history of and EEG changes in 17 children with anti-NMDAR encephalitis.

In our cohort psychiatric symptoms were reported in nearly half of all children at disease onset and were associated with seizures in only one-third of these cases. No child was in status epilepticus in the initial stage. Seizures as the sole manifestation occurred in only 23% of our children, which is

in contrast to adults in whom seizures are the main presenting symptom in anti-NMDAR encephalitis.³

A cohort of 262 encephalitis patients registered in a database of the Tokai Pediatric Neurology Society between 2005 and 2012 included 44 patients with acute seizures, only ten of whom (23%) had postencephalitic epilepsy.⁷ These results resemble our low frequency of epilepsy after NMDAR encephalitis in children. Furthermore, prognostic factors of childhood postencephalitic epilepsy in children were clarified by Chen et al. Of 798 treated patients with encephalitis 44 patients presented with postencephalitic epilepsy. Relevant factors indicating a poor prognosis for these patients during the acute phase of encephalitis were status epilepticus occurring as the first seizure, slow background activity and multifocal spike discharges on EEG. These findings support our data that only patients with status epilepticus and multifocal spikes on EEG during acute encephalitis have an increased risk for developing intractable epilepsy.⁸ In a recent study Pillai et al. defined risk factors for postencephalitic epilepsy and drug-resistant epilepsy in a group of 164 children with acute encephalitis of various etiologies including patients with NMDAR encephalitis. Drug-resistant epilepsy was absent in NMDAR encephalitis. Status epilepticus, focal seizures and EEG epileptiform discharges during the acute encephalitis episode were identified as risk factors for drug resistant epilepsy. Again this confirms our data, as no child in our cohort presented status epilepticus in the initial stage, generalized seizures seemed to be the dominant seizure type and only 3/17 (18%) of our patients continued to have seizures at the end of follow-up.⁹

Forty-four patients (20 boys and 24 girls; age range: 21 months to 17 years, mean age 8.1 ± 4.6 years) with post-encephalitic epilepsy were selected from the 798 epileptic children treated and followed-up at our hospital between 1993 and 2003. Their clinical data included clinical features, electroencephalograms (EEGs), and neuroimages, all retrospectively reviewed and analysed. Based on their post-treatment

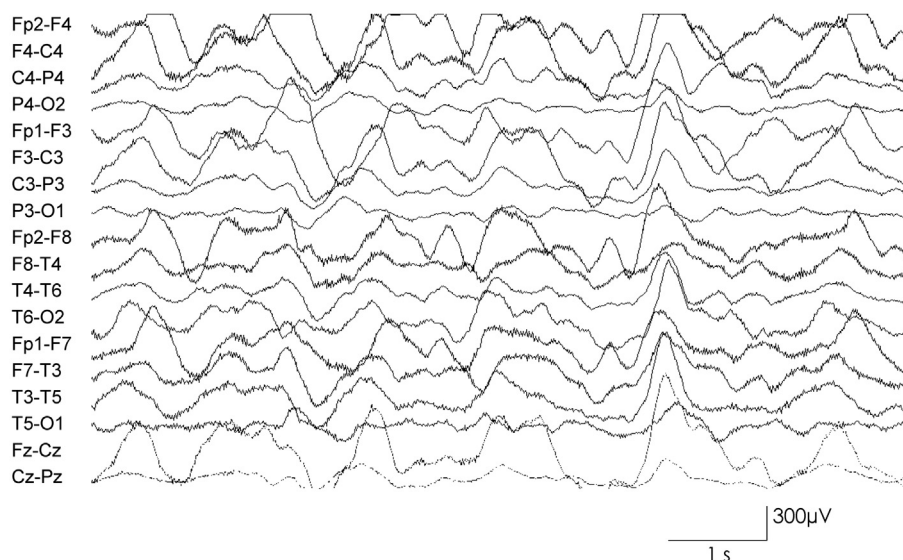


Fig. 1 – EEG with generalized slowing in a 14 year old patient with anti-NMDAR encephalitis (10 s/page, sensitivity 15 μ V/mm, filter: LF 0.5/HF 70, Notch 50 Hz).

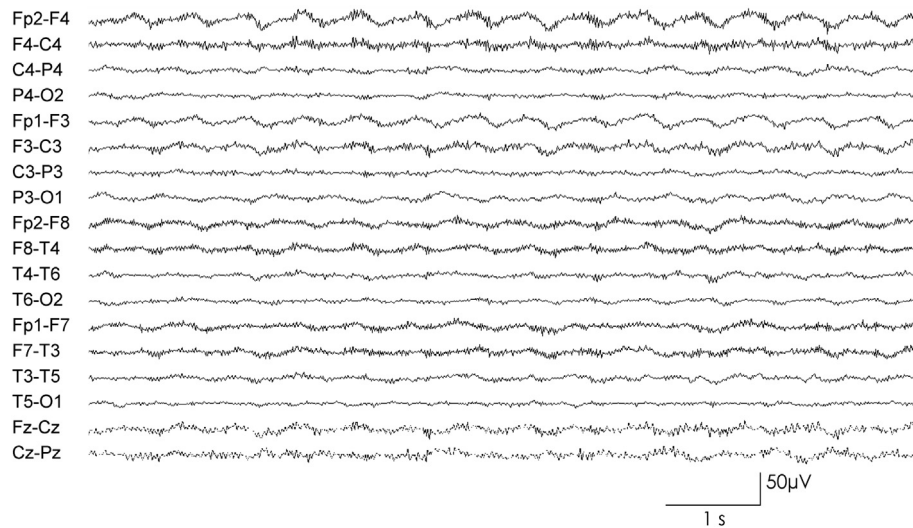


Fig. 2 – EEG with Extreme Delta Brushes in a 14 year old patient with anti-NMDAR encephalitis (10 s/page, sensitivity 15 μ V/mm, filter: LF 0.5/HF 70, Notch 50 Hz).

seizure outcomes, the children were divided into favourable ($n = 20$) and poor outcome groups ($n = 24$). Between the two groups, age at encephalitis, cerebrospinal fluid findings, and seizure type were comparable. Factors indicating poor prognosis for these patients during the acute phase of encephalitis were (1) status epilepticus occurring as the first seizure ($P < .005$), (2) slow background activity ($P < .001$) and multifocal spike discharges on EEGs ($P < .01$), and (3) herpes simplex viral encephalitis ($P < .01$). Our findings indicated that patients with status epilepticus and multifocal spikes on EEG during acute encephalitis have an increased risk for developing intractable epilepsy. To improve the outcome of postencephalitic epilepsy, intervention must occur earlier in the encephalitis stage.

With ongoing duration seizures were present in all but one patient. Seizure types with generalized and focal seizures were equally distributed; nearly half of all children presented both seizure types. At the end of follow-up only 3/17 (18%) patients continued to have seizures. According to the literature, adult patients seem to have focal seizures more often initially, whereas in children generalized seizures regularly occur and over the course of the disease seem to develop into the dominant seizure type.³

The initial EEG revealed in 65% of our cohort generalized, in 18% focal slowing and in 18% normal background activity. Generalized slowing as the predominant EEG pattern in the children with anti-NMDAR encephalitis has already been reported.^{10,11} Adults with anti-NMDAR encephalitis also show generalized or predominantly frontotemporal slowing.⁴ A recent study described focal slowing with preserved background activity over one hemisphere with milder clinical expression in children.¹² Similarly, around 40% of the children in our case series initially presented with epileptic discharges, whereas at the end of the observation period only 35% of the children continued to have epileptic paroxysms with only three patients having ongoing epilepsy. In 20–50% of adult patients epileptiform discharges can also be found during the early phase of the disease combined with generalized

slowing.⁴ On the other hand, two case series suggest that spike discharges are not commonly seen in routine EEG in adults.^{10,11}

In more than half of all our children EDB – an EEG pattern recently described in adult patients – was detected in the first EEGs, which appears to be associated with a more prolonged disease course.⁵ The EDB pattern appeared as a continuous combination of delta activity with superimposed fast activity in the beta range, which was most often symmetric and synchronous, across all head regions. In all patients studied to date, the delta brush pattern was continuously present in the initial EEGs, not varying with sleep–wake cycles or with level of arousal. This pattern does not represent movement artefacts, as it occurred independently of episodes of dystonia, choreoathetosis, and orofacial dyskinesia. Schmitt et al. also state that it is unlikely that it is caused by superimposed benzodiazepine- or barbiturate-induced beta activity, because in their study two patients had this pattern on the initial EEG before receiving benzodiazepines. Although the specificity of this pattern remains to be determined, its presence should raise the possibility of the diagnosis of anti-NMDAR encephalitis.

Interestingly, in a recent Italian study of five children with NMDAR encephalitis four electroencephalographic phases over time were identified, consisting of an early phase with normal background activity and intermixed nonreactive slow waves. In the second or florid phase, background activity deteriorated with the appearance of sequences of peculiar rhythmic theta and/or delta activity unrelated to clinical changes. In the recovery phase, these sequences decreased and reactive posterior rhythm re-emerged followed by a normal EEG two to five months after onset.¹²

The 50% EDB in our cohort by contrast to the 30% reported by Schmitt et al. might be due to the immature brain with more obvious electroencephalographic phenomena, as often seen in children.⁵ Furthermore, there might also be a difference in the duration of recordings in the various study groups.^{11,12} With shorter EEG recordings this phenomenon

can be missed. All patients with EDB were in a comatose state, so no relationship to different vigilance states could be detected.

EDB was seen in only half of the cases in severe course of the disease, thus meaning that EDB does not predict poorer outcome in children than in adults.⁵

Electroencephalographic seizures in anti-NMDAR encephalitis were present in only 4/17 of the patients in our cohort. Generalized status onset and rhythmic delta activity representing a form of non-convulsive status in anti-NMDAR encephalitis has already been described in patients with anti-NMDAR encephalitis.^{13,14}

Similar to previous reports, only in two children was a tumour detected.¹⁰ Cerebral MRI was unremarkable in all children, also confirming recent reports that found only mild, non-specific, sometimes reversible brain lesions predominantly in the hippocampi/temporal lobes, but also in the cortical and subcortical region of patients with anti-NMDAR encephalitis.^{4,10}

In four children serum autoantibodies were negative but present in CSF, underscoring the importance of simultaneous measurement of NMDAR autoantibodies, as suggested previously.¹⁵

The main limitation of the current study is that it was based solely on retrospective data.

5. Conclusion

Our findings show that in children presenting with psychiatric symptoms combined with generalized slowing in EEG with or without seizures the diagnosis of anti-NMDAR encephalitis should be considered. The presence of EDB in half of the patients studied appears to be a helpful tool for early detection of this immune-mediated disease, as early administration of immunomodulatory therapy may influence outcome.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

We wish to thank all parents and patients as well as the colleagues involved in the medical care of our patients.

REFERENCES

1. 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.
2. Armangué 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.
3. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;133:1655–67.
4. 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.
5. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094–100.
6. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51(4):676–85.
7. Ito Y, Natsume J, Kidokoro H, Ishihara N, Azuma Y, Tsuji T, et al. Seizure characteristics of epilepsy in childhood after acute encephalopathy with biphasic seizures and late reduced diffusion. *Epilepsia* 2015 Aug;56(8):1286–93. <http://dx.doi.org/10.1111/epi.13068> [Epub 2015 Jun 29].
8. Chen YJ, Fang PC, Chow JC. Clinical characteristics and prognostic factors of postencephalitic epilepsy in children. *J Child Neurol* 2006 Dec;21(12):1047–51.
9. Pillai SC, Mohammad SS, Hachohen Y, Tantsis E, Prelog K, Barnes EH, et al. Postencephalitic epilepsy and drug-resistant epilepsy after infectious and antibody encephalitis in childhood: clinical and etiological risk factors. *Epilepsia* 2016;57(1):e7–11.
10. 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.
11. Gitiaux C, Simonnet H, Eisermann M, Leunen D, Dulac O, Nabbout R, et al. Early electro-clinical features may contribute to diagnosis of the anti-NMDAR encephalitis in children. *Clin Neurophysiol* 2013;124:2354–61.
12. Nosadini M1, Boniver C2, Zuliani L, et al. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. *J Child Neurol* 2015;30:238–45.
13. Kirkpatrick MP, Clarke CD, Sonmez Turk 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.
14. Nolan B, Plenck K, Carr D. Anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis presenting to the emergency department with status epilepticus. *CJEM* 2014;16:425–8.
15. 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.

1. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and