RESEARCH PAPER

Predictive value of electroencephalography in anti-NMDA receptor encephalitis

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ABSTRACT

Objectives Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is a severe, but treatable disease. This study aims to give a detailed description of electroencephalogram (EEG) results in paediatric and adult patients to improve disease recognition, and analyses the predictive value of the first EEG for the final clinical outcome.

Methods This nationwide cohort study includes patients with N-methyl-D-aspartate receptor antibodies confirmed with cell-based assay and immunohistochemistry in serum and cerebrospinal fluid. EEG recordings were re-evaluated by two experienced neurophysiologists, mixed with control EEGs for blinding. Initial EEG as well as follow-up registrations were analysed.

Results 35 adults and 18 children were included. Only two patients (4%) had a normal EEG. During the first recording, the majority of the patients had normal posterior rhythm (71%), which was associated with better modified Rankin Scale at final outcome (OR 4.74; 95% CI 1.56 to 14.47; p=0.006). In addition, EEGs showed focal (73%) or diffuse (67%) slowing. The first EEG was severely abnormal in 26%. However, 8 of 14 patients with a severely abnormal first EEG still had a favourable outcome. During the course of the disease, extreme delta brushes (EDBs) were present in 6 of 53(11%)patients.

Conclusions The first EEG commonly shows normal posterior rhythm with focal or diffuse slowing. Although the sensitivity of an abnormal EEG is high (96%), normal EEG does not exclude anti-NMDARE. EDBs are only present in severely affected patients. The first EEG recording is predictive of the final clinical outcome.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is the most common antibody-mediated encephalitis. Patients develop subacute psychiatric symptoms, memory loss, movement disorders and seizures, often followed by intensive care unit (ICU) admission due to consciousness decline, autonomic dysfunction or hypoventilation.[1] The disease mostly affects women of childbearing age or children. Thirty-eight per cent of patients have a tumour, mainly ovarian teratoma. Antibodies are directed to the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAR), which is found across the brain. This explains why the disease is not restricted to the limbic area. MRI of the brain is often normal, but electroencephalogram (EEG) is useful to analyse the functional deficits caused by the NMDAR antibodies. EEG studies have reported diffuse slowing in a substantial part of the patients.[2 3] In a study of nine children, diffuse abnormalities with lack of normal posterior rhythm were associated with poor outcome,[4] but this has not been studied further. Most larger studies aim to give a description of all disease characteristics and therefore do not analyse or report detailed EEG data.[1 2 5–9] Also, questions remain regarding the occurrence of extreme delta brushes (EDBs). The pattern of EDB is pathognomonic for anti-NMDARE,[10 11] but incidence ranges from 0%to 100%, depending on patient selection, clinical situation and timing of EEG.[3 8 10 12] Our study aims to give a full description of the EEG results in an unselected group of paediatric and adult patients with anti-NMDARE. The first EEG as well as follow-up registrations are analysed, and the predictive value of EEG is discussed.

METHODS

Patients' accrual and laboratory testing

Samples had been sent for antibody testing to the laboratory of Medical Immunology of the Erasmus University Medical Center, Rotterdam. Samples were sent from July 2006 until July 2017. NMDAR antibodies were detected with cell-based assay (Euroimmun, Lübeck, Germany) and immunohistochemistry on rat brain,[13 14] in both serum and cerebrospinal fluid (CSF), if available. Patients were considered positive if at least two tests confirmed the presence of NMDAR antibodies. Both adult and paediatric (<18years at disease onset) patients were included in this study if at least one EEG recording was available for analysis. Patients were included in the longitudinal part of the study if EEG recordings from predefined stages of the disease were available: within 2weeks after disease onset, after 1month and after 3months (at least 2 out of 3).

Clinical information was obtained from medical records, and included demographic data, clinical symptoms, tumour presence, intensive care admissions and treatment. First-line immunotherapy included corticosteroids, intravenous immunoglobulin and/or plasma exchange. Second-line treatment included cyclophosphamide and/or rituximab. Disease severity and clinical outcome were measured with the modified Rankin Scale (mRS). Outcome was analysed if follow-up was at least

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6months after disease onset. Outcome mRS≤2 was considered favourable, as this reflects independency in daily life.

EEG analysis

EEG recordings were collected retrospectively. All recordings were based on the International 10–20 system, and the majority of the recordings were spot EEG. In the few cases with continuous registration, only the first 30 min were included in the analyses. EEG recordings were independently re-evaluated by two experienced neurophysiologists (DLJT, SA), mixed with control EEGs for blinding. If in disagreement, both neurophysiologists convened to achieve agreement. In all patients, the first available EEG was evaluated. If serial EEGs were recorded, the EEG at disease nadir was analysed as well. The following EEG characteristics were evaluated: posterior dominant rhythm, diffuse slowing (mild, moderate, severe), focal slowing, rhythmic delta activity, ictal and interictal epileptiform discharges, periodic discharges, and EDB. Status epilepticus was defined as the occurrence of virtually continuous or repetitive epileptiform seizure pattern in an EEG, whereas seizure pattern was defined as a phenomenon consisting of repetitive epileptiform EEG discharges at>2c/s and/or characteristic pattern with quasi-rhythmic spatiotemporal evolution (ie, gradual change in frequency, amplitude, morphology and location).[15] EEG findings were subdivided into four categories: (1) normal EEG, (2) normal posterior rhythm (reactive, posterior dominant rhythm with an age-appropriate frequency) with diffuse or focal abnormalities, (3) lack of normal posterior rhythm, with focal or diffuse abnormalities, and (4) severely abnormal EEG, defined as lack of normal posterior rhythm with (A) severe slowing or (B) periodic discharges or (C) status epilepticus (adjusted from Amodio *et al*).[16] EEGs showing status epilepticus were excluded for analysis of specific EEG characteristics.

Standard protocol approvals, registrations and patient consents

Informed consent was obtained in all patients.

Statistical analysis

Categorical data were analysed with Fisher-Freeman exact test. In the comparison between paediatric and adult patients, eight EEG characteristics are evaluated. According to Bonferroni, p values<0.00625 are considered significant. Kaplan-Meier analyses are used to calculate follow-up time, censoring deceased patients. Ordinal logistic regression was performed to analyse the association between the characteristics of the first EEG and the final mRS. Mann-Whitney U test was performed to analyse the relation between posterior rhythm and duration of hospital stay. These analyses are exploratory. Therefore, p values<0.05 are considered significant, but should be interpreted with caution. SPSS Statistics V.21 was used for analysis.

RESULTS

Patient and disease characteristics

Seventy adults and 35 children tested positive for NMDAR antibodies. EEG recordings were available in 53 patients (35 adults and 18 children), all included in the study (see figure 1 for EEG fragments). Of the adult patients, 30 of 35 were female and the median age was 26 years (range 18–74; table 1). Tumours were present in 10 of 28 female patients, including ovarian teratoma (n=8), small cell lung cancer (SCLC) (n=1) and Merkel cell carcinoma (n=1). All five male patientshad no tumour. All but three adult patients received immunotherapy. Two untreated patients

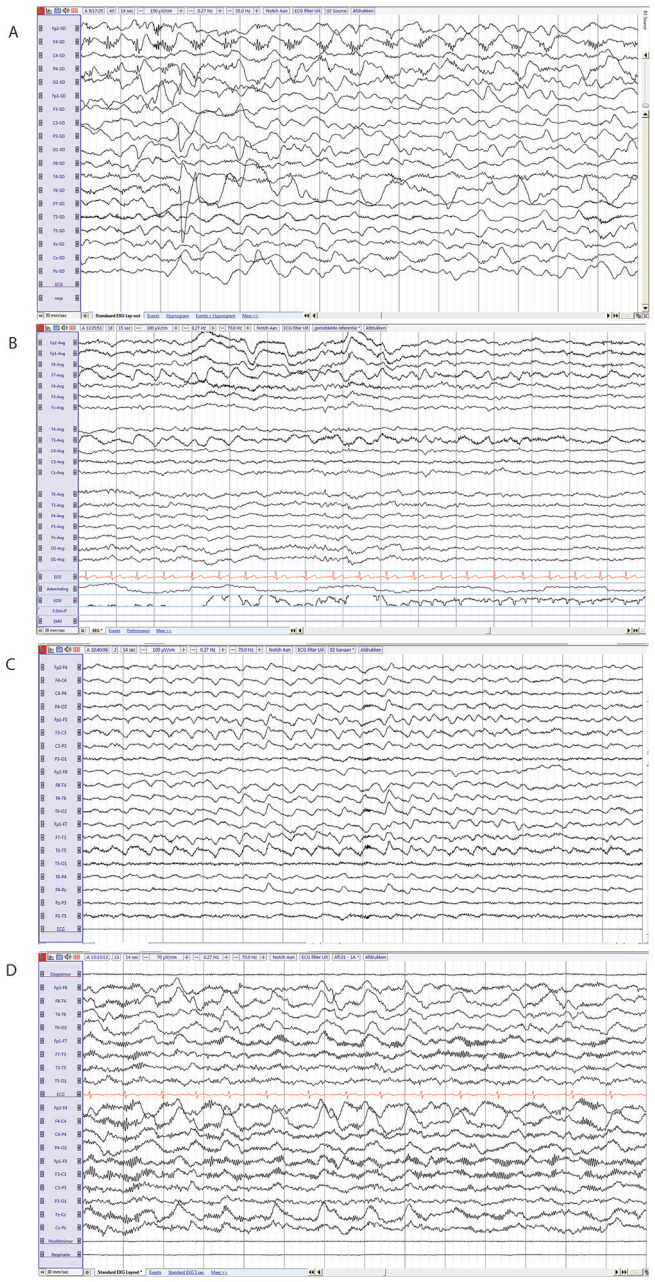

Figure 1 EEG fragments. (A) Rhythmic delta activity mixed with polyspikes over the left frontal region, consistent with a focal seizure (asymptomatic) (preschool child, EEG in source derivation, 150Hz/cm, high-pass filter 0.27Hz, low-pass filter 35Hz, notch filter on). (B) Rhythmic delta activity at 2Hz over the left (fronto)temporal region (adolescent, EEG in average reference montage, 100Hz/cm, high-pass filter 0.27Hz, low-pass filter 70Hz, notch filter off). (C) Generalised periodic discharges (adolescent, EEG in bipolar double banana, 70Hz/cm, high-pass filter 0.27Hz, low-pass filter 70Hz, notch filter on). (D) Left frontal rhythmic delta activity at 2Hz with superimposed burst of rhythmic 22Hz beta frequency, consistent with the pattern of extreme delta brush (adolescent, EEG in bipolar double banana montage, 70Hz/cm, high-pass filter 0.27Hz, low-pass filter 70Hz, notch filter on). EEG, electroencephalogram.

died; in both cases diagnosis was established post mortem. Eighteen paediatric patients were included in the analyses, of whom 14 were female.[17] Five children were younger than 12 years of age. Three children had an ovarian teratoma. These years were

Table 1 Patient characteristics

	Adults (n=35)	Children (n=18)
Female sex	30/35 (86%)	14/18 (78%)
Age at onset, median (IQR, range)	26 (21–48, 18–74)	14.5 (7–17, 3–17)
Clinical seizures	26/34 (76%)	15/18 (83%)
mRS at maximum disease severity		
1	–	–
2	1/35 (3%)	2/18 (11%)
3	15/35 (43%)	8/18 (44%)
4	2/35 (6%)	2/18 (11%)
5	17/35 (49%)	6/18 (33%)
Admission to the ICU	18/35 (51%)	6/18 (33%)
First-line immunotherapy	32/35 (91%)	18/18 (100%)
Second-line immunotherapy	14/35 (40%)	6/18 (33%)
Follow-up in months, median (IQR)	13 (9–18)	25 (14–46)
mRS at follow-up (> 6 months)		
0	5/35 (14%)	5/17 (29%)
1	13/35 (37%)	4/17 (24%)
2	9/35 (26%)	6/17 (35%)
3	2/35 (6%)	–
4	1/35 (3%)	2/17 (12%)
5	–	–
6	5/35 (14%)	–

ICU, intensive care unit; mRS, modified Rankin Scale.

13–17 years old at disease onset. All children were treated with immunotherapy, and all paediatric patients survived.

Adult patients: cross-sectional EEG analysis

The median time from disease onset to the first EEG recording was 19days (table 2). At the timing of the first EEG, only 3 of 34 patients were admitted to the ICU. Two-thirds of the patients had normal posterior rhythm, often with focal (65%) or diffuse (65%) slowing. Diffuse slowing was either mild (n=9), moderate (n=6) or severe (n=7). Epileptic discharges were present in 24% of the recordings. Two patients had EDB on their first recording. Their functional mRS scores were 4 and 5 during EEG, and one of them was admitted to the ICU. Two patients had normal EEG; no follow-up EEG was done, and both patients had a favourable outcome (mRS 0 and 1).

Seventeen patients had follow-up EEG at maximum disease severity. Ten patients were admitted to the ICU. Two patients (12%) had status epilepticus. Fourteen out of 15 (93%) had diffuse slowing. EDBs were present in 3 of 15 patients. They had an mRS score of 4 (n=2) or 5 (n=1), and one of them was in the ICU at that time. Six out of 15 (40%) patients still had normal posterior rhythm.

Paediatric patients: cross-sectional EEG analysis

The median time from disease onset to the first EEG recording was 8 days (table 2). There were no normal EEGs. However, 14 of 18 patients had normal posterior rhythm. Focal slowing (89%) and diffuse slowing (72%) were common. One child had EDB on his first EEG (mRS=5), and he was the only paediatric patient admitted to the ICU during the first recording.

Nine paediatric patients had follow-up EEG at maximum disease severity, of whom three were admitted to the ICU. Three out of nine (33%) children still had normal posterior rhythm. Focal slowing (89%), diffuse slowing (89%) and intermittent rhythmic delta activity (78%) were common.

There was a trend towards more rhythmic delta activity in paediatric EEGs compared with adult patients, but differences between the populations were not significant (table 2).

Table 2 Cross-sectional EEG results

	Adults (n=35)	Children (n=18)	P values
First EEG			
Time to first EEG in days, median (range)	19 (0–125)	8 (1–105)	0.61
Status epilepticus	1/35 (3%)	0/17 (0%)	1.00
EEG patterns			
Normal posterior rhythm	21/33 (64%)	14/18 (78%)	0.53
Diffuse slowing	22/34 (65%)	13/18 (72%)	0.76
Focal slowing	22/34 (65%)	16/18 (89%)	0.10
Rhythmic delta activity	14/34 (41%, 7 FIRDA, 7 TIRDA)	14/18 (78%, 4 FIRDA, 8 TIRDA, 2 OIRDA)	0.02
Interictal epileptic discharges	6/34 (18%)	3/18 (17%)	1.00
Ictal epileptic discharges	2/33 (6%)	2/18 (11%)	0.61
Periodic discharges	6/34 (18%)	2/18 (11%)	0.70
EDB	2/34 (6%)	1/18 (6%)	1.00
Normal EEG	2/35 (6%)	0/18 (0%)	0.54
Follow-up EEG (disease nadir)*			
Status epilepticus	2/17 (12%)	0/9 (0%)	0.53
EEG patterns			
Normal posterior rhythm/reactivity	7/15 (47%)/6/7 (86%)	4/9 (44%) / 3/4 (75%)	1.00
Diffuse slowing	14/15 (93%)	8/9 (89%)	1.00
Focal slowing	7/15 (47%)	8/9 (89%)	0.08
Rhythmic delta activity	7/15 (47%, 4× FIRDA, 2× TIRDA, 1× OIRDA)	7/9 (78%, 3× FIRDA, 1× TIRDA, 1× OIRDA, 2× GRDA)	0.21
Interictal epileptic discharges	2/15 (13%)	1/9 (11%)	1.00
Ictal epileptic discharges	2/15 (13%)	4/9 (44%)	0.15
Periodic discharges	2/15 (13%)	4/9 (44%)	0.15
EDB	3/15 (20%)	0/9 (0%)	0.27
Normal EEG	0/17	0/9	1.00

P values<0.00625 are considered significant (Bonferroni).
*Median time between first EEG and follow-up EEG was 21days (IQR 11.5–36).
EDB, extreme delta brush; EEG, electroencephalogram; FIRDA, frontal intermittent rhythmic delta activity; GRDA, generalised rhythmic delta activity; OIRDA, occipital intermittent rhythmic delta activity; TIRDA, temporal intermittent rhythmic delta activity.

Predictive value of the first EEG recording

The predictive value of normal posterior rhythm on the first EEG recording could be analysed in 52 patients (figures 2 and 3A). Thirty-five patients had normal posterior rhythm, of whom 32 had a favourable outcome (91%). Seventeen patients had no normal posterior rhythm, of whom only 10 patients had a favourable outcome (59%). Ordinal logistic regression shows that the presence of a normal posterior rhythm was associated with lower mRS at final follow-up (OR 4.74; 95% CI 1.56 to 14.47; p=0.006). To explore whether limited disease was a confounding variable for both good EEG result and good clinical outcome, we restricted the analyses to the 40 patients with mRS

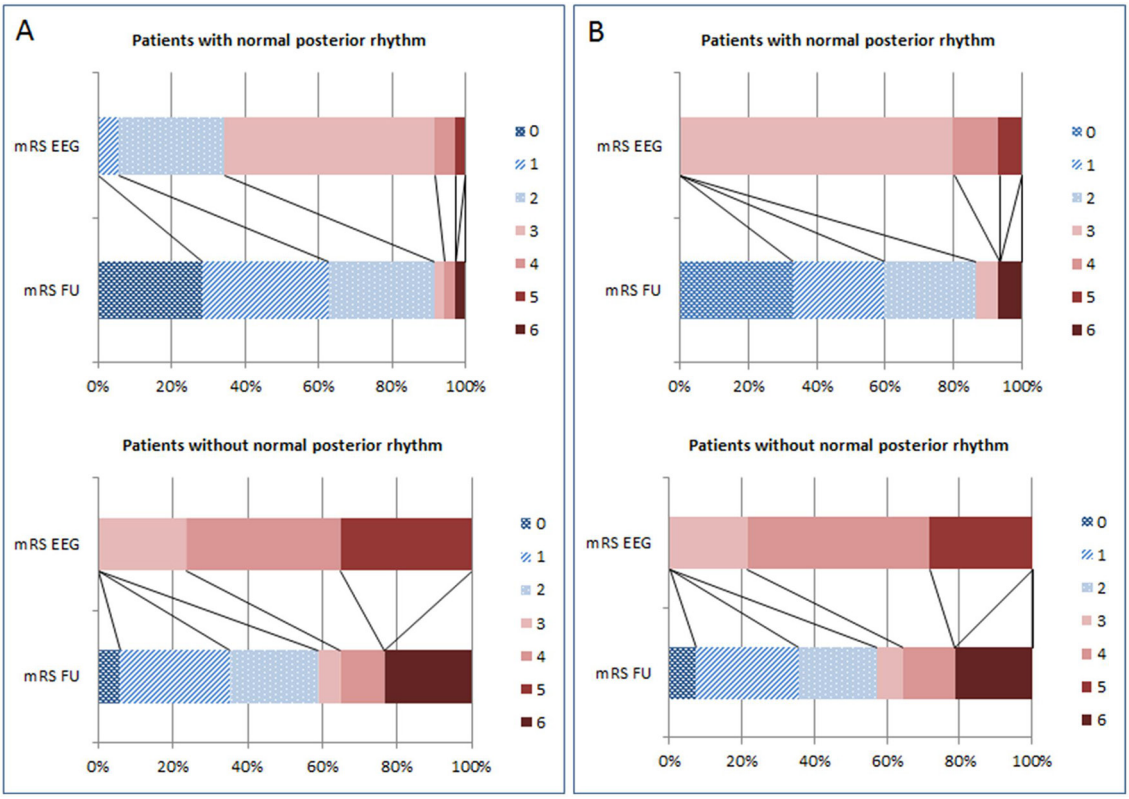

Figure 2 Predictive value of a normal posterior rhythm on first EEG recordings. The figure shows functional status measured with mRS during the first EEG and at final follow-up, comparing patients with and without normal posterior rhythm. (A) Unselected population (n=52), (B) subgroup of patients with severe disease (mRS≥3) and early EEG (within 30days) (n=29). EEG, electroencephalogram; FU, follow-up; mRS, modified Rankin Scale.

≥3 during the first recording. The association between normal posterior rhythm and better clinical outcome remained (OR 4.28; 95%CI 1.29 to 14.25; p=0.018). To mimic the clinical setting, we further narrowed the analyses to those with mRS≥3 during the first EEG within 30days after onset. With these test limitations, 29 patients could be included. Fifteen patients had normal posterior rhythm, of whom 13 patients had a favourable outcome (87%). Fourteen patients had no normal posterior rhythm, of whom eight patients had a favourable outcome (57%). Time since disease onset was not significantly different between patients with and without normal posterior rhythm. Although the frequencies of good outcome were similar, the association was no longer significant (OR 3.95; 95% CI 1.00 to 15.64; p=0.051), due to smaller sample size.

The presence of normal posterior rhythm on the first EEG was also associated with shorter hospital stay, which probably reflects early recovery. Patients who had died during hospital stay were excluded. Data were available in 45 patients. Thirty-two patients had a normal posterior rhythm with a median hospital stay of 35.5 days (range 0–338). Thirteen patients did not have a normal posterior rhythm, and their median hospital stay was 67 days (range 31–551, p=0.003). Looking from the other perspective, a severely abnormal first EEG was associated with higher final mRS (OR 0.23; 95% CI 0.07 to 0.74; p=0.014). However, more interestingly, 8 of 14 patients with a severely abnormal first EEG still had a favourable outcome in the end.

Longitudinal EEG analysis

EEG recordings from 13 patients (6 children and 7 adults) were available for inclusion in the longitudinal analysis (figure 3B). Initially, eight patients had a normal posterior rhythm with focal or diffuse abnormalities (category 2). EEG worsened (to category 4) in three patients. EEG remained only slightly abnormal in the other five patients, also including patients with severe disease (mRS 4 or 5). Three patients had a severely abnormal EEG at weeks 1–2. Their EEG recordings had not improved at 1 and 3months into the disease. However, one of these patients finally improved well (mRS=1). All patients with a severely affected EEG during the course of the disease had an mRS of 5 at nadir.

DISCUSSION

We report an extensive analysis including systemic re-evaluation of EEG data in over 50 patients with anti-NMDARE. The following are the most relevant findings: (1) first EEG recordings have a predictive value for clinical outcome; (2) diffuse and focal slowing are the most common EEG findings; (3) normal EEG does not exclude anti-NMDARE; (4) EDBs are only present in severely affected patients but not necessarily admitted to the ICU; and (5) long-term severe electrographic abnormalities can be followed by good clinical outcome. Electrographic abnormalities in the paediatric and adult population were comparable.

The first EEG recording has a predictive value for the final clinical outcome. The relation between mild disease, normal posterior rhythm and better outcome has been reported earlier in a study of nine paediatric cases.[4] In our large unselected cohort, we have shown that a normal posterior rhythm on the first recording predicts a favourable clinical outcome, while a severely abnormal EEG is associated with poor outcome. To analyse whether the EEG adds information to the clinical findings, we restricted our subsequent analyses to patients with mRS≥3. The association between normal posterior rhythm and better clinical outcome remained, showing that normal posterior

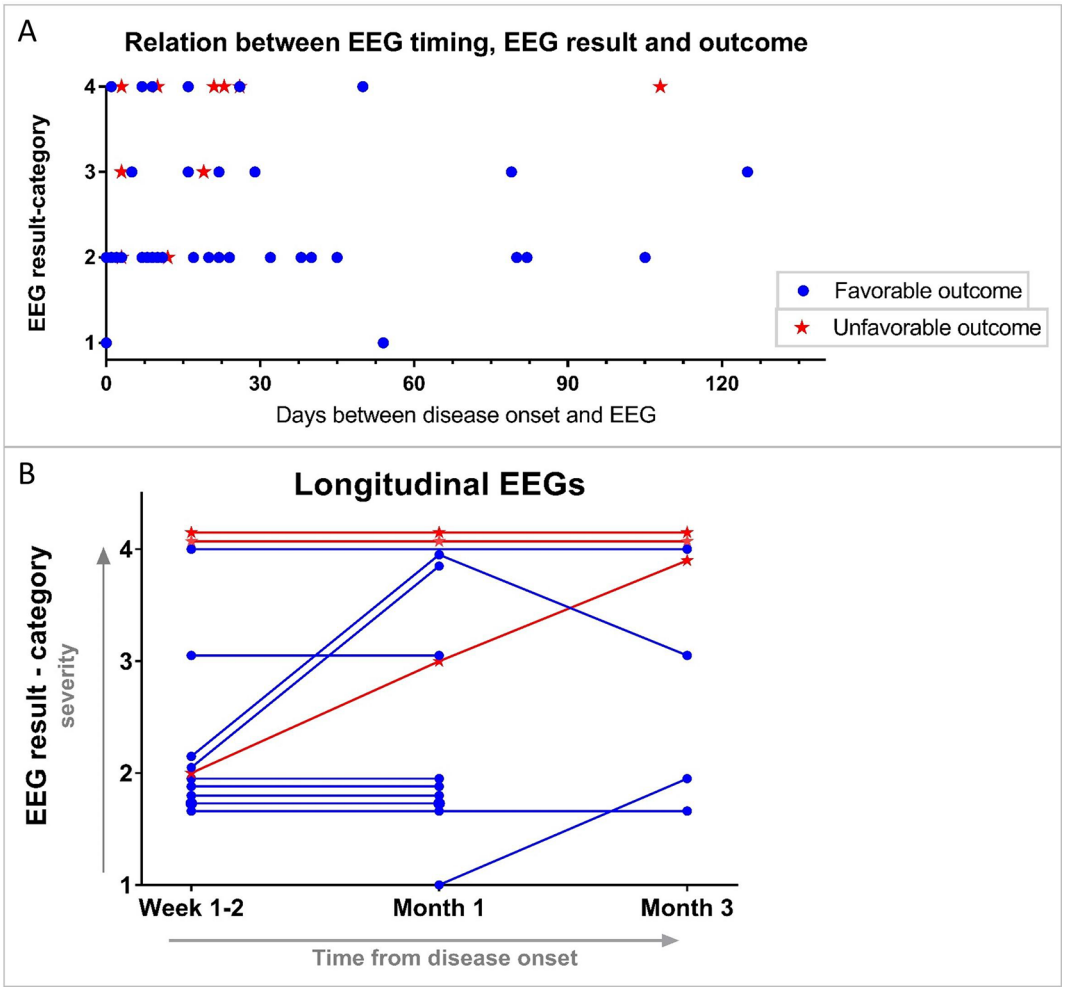

Figure 3 (A) Relation between timing of the first EEG, EEG category and final clinical outcome in 52 patients. (B) Longitudinal EEG analyses in 13 patients. Patients with favourable clinical outcome are marked in blue (dots), and patients with unfavourable outcome are marked red (stars). EEG categories: 1: normal EEG; 2: normal posterior rhythm with diffuse or focal abnormalities; 3: lack of normal posterior rhythm, with focal or diffuse abnormalities; 4: severely abnormal EEG (lack of normal posterior rhythm with severe slowing or periodic discharges or status epilepticus. EEG, electroencephalogram.

rhythm also in patients with clinically severe disease predicts a better outcome. Only a trend towards significance (p=0.051) is found if analysis is restricted to patients with mRS≥3 during the first EEG recorded within 30days after onset. This is probably due to the limited number of patients in the latter analysis, as the differences between groups (frequencies of good outcome and OR) remained similar.

EEG is abnormal in the vast majority of patients with anti-NMDARE, but we have shown that a normal EEG registration does not exclude the diagnosis. Unremarkable EEG was seen in 4% of our patients, compared with 0%–10% in earlier reports.[1–3 7 18 19] In our study, EEG has a sensitivity for anti-NMDARE of 96%, which is higher than the sensitivity of MRI brain (33%) or serum antibody analysis (87%).[1 13]

Schmitt *et al*[10] were the first to report the pattern of EDB in anti-NMDARE in 2012. Their study analysed patients in a tertiary neuro-ICU with continuous EEG registrations and found EDB in 7 of 23 (30%) patients. Since then, several studies described EDB in subgroups: EDBs were present in 9 of 17 (53%) paediatric patients and in 16% of children and adult patients at the peak stage of the disease.[3 20] A meta-analysis in paediatric anti-NMDARE calculated an incidence in EDB of 16%.[21] In our unselected group, EDBs were present in only 6 of 53 (11%) patients, either at first EEG registration (n=3) or only at follow-up EEG (n=3). All six patients had mRS ≥4 when EDBs were present, and three patients were admitted to the ICU. The estimated overall incidence of EDB in anti-NMDARE is 10%–15%, and this unique pattern only occurs during severe illness.

Longitudinal analyses of EEG recordings showed that EEG in the course of the first month remained stable or worsened. Lack of improvement of EEG is consistent with the earlier clinical observation that anti-NMDARE progresses over the first weeks of disease.[1] We did not identify EEG patterns related to specific stages of disease, as reported earlier in five paediatric cases.[22] Severely abnormal EEG was only seen in patients with severe clinical disease, while slightly abnormal EEGs were present in patients with either mild or severe disease. Long-term severe electrographic abnormalities can be followed by good clinical outcome, which is important in clinical decision making.

Due to the retrospective nature of our study, we were not able to collect EEG registrations on predefined stages of the disease. Therefore, the availability of follow-up EEGs was likely subject to selection bias. We analysed the EEGs from the begin stage and during maximum disease severity (if available) to obtain the clinically most relevant data. In addition, the retrospective design

made it impossible to perform structured cognitive assessment during the disease. The advantage of the retrospective study design is the opportunity to include over 50 patients. The most reliable data were obtained by independent re-evaluation of all registrations by two experienced neurophysiologists.

We have shown that the sensitivity of an abnormal EEG is high, but normal EEG does not exclude the diagnosis of anti-NMDAR encephalitis. EDBs are only present in severely affected patients. Most importantly, the first EEG recording has a predictive value for clinical outcome. A normal posterior rhythm on first recording predicts a favourable clinical outcome, while a severely abnormal EEG is associated with poor outcome.

Contributors AvS: study design, acquisition of data, statistical analysis, interpretation of data, draft of the manuscript. SA: study design, acquisition of data, interpretation of data, revision of manuscript for content. DLJT: study design, acquisition of data, interpretation of data, revision of manuscript for content. AEMB: acquisition of data, revision of manuscript for content. MAAMdB: acquisition of data, revision of manuscript for content. MWJS: acquisition of data, revision of manuscript for content. PAESS: study design, revision of manuscript for content. MJT: study design, statistical analysis, interpretation of data, revision of manuscript for content.

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Competing interests PAESS holds a patent for the detection of anti-DNER and received research support from Euroimmun. MJT received research funds for serving on a scientific advisory board of MedImmune, for consultation at Guidepoint Global, an unrestricted research grant from Euroimmun AG and a travel grant for lecturing in India from Sun Pharma, India. Erasmus University Medical Center has filed a patent for methods for typing neurological disorders and cancer, and devices for use therein.

Patient consent Not required.

Ethics approval The study was approved by the Institutional Review Board of the Erasmus University Medical Center, Rotterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Titulaer MJ, McCracken L, Gabilondo I, Gabilondo Cuellar I, *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.
2 Veciana M, Becerra JL, Fossas P, *et al*. EEG extreme delta brush: An ictal pattern in patients with anti-NMDA receptor encephalitis. *Epilepsy Behav* 2015;49:280–5.
3 Zhang Y, Liu G, Jiang MD, *et al*. Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China. *Clin Neurophysiol* 2017;128:1227–33.
4 Gitiaux C, Simonnet H, Eisermann M, *et al*. Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children. *Clin Neurophysiol* 2013;124:2354–61.
5 Irani SR, Bera K, Waters P, *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(Pt 6):1655–67.
6 Dalmau J, Lancaster E, Martinez-Hernandez E, *et al*. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
7 Florance NR, Davis RL, Lam C, *et al*. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11–18.
8 Huang Q, Wu Y, Qin R, *et al*. Clinical characteristics and outcomes between children and adults with anti-N-Methyl-D-Aspartate receptor encephalitis. *J Neurol* 2016;263:2446–55.
9 Viaccoz A, Desestret V, Ducray F, *et al*. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology* 2014;82:556–63.
10 Schmitt SE, Pargeon K, Frechette ES, *et al*. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094–100.
11 Armangue T, Titulaer MJ, Málaga I, *et al*. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162:850-856.e2.
12 Foff EP, Taplinger D, Suski J, *et al*. EEG Findings May Serve as a Potential Biomarker for Anti-NMDA Receptor Encephalitis. *Clin EEG Neurosci* 2017;48:48–53.
13 Gresa-Arribas N, Titulaer MJ, Torrents A, *et al*. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167-77.
14 van Sonderen A, Schreurs MW, de Bruijn MA, *et al*. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. *Neurology* 2016;86:1692–9.
15 Kane N, Acharya J, Benickzy S, *et al*. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clin Neurophysiol Pract* 2017;2(170-185):170–85.
16 Amodio P, Marchetti P, Del Piccolo F, *et al*. Spectral versus visual EEG analysis in mild hepatic encephalopathy. *Clin Neurophysiol* 1999;110:1334–44.
17 De Bruijn MAAM. Epilepsy in anti-GABABR, anti-LGI1, and anti-NMDAR encephalitis: the effect of antiepileptic drugs and immunotherapy. 2018. Submitted.
18 Dalmau J, Gleichman AJ, Hughes EG, *et al*. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–8.
19 Yildirim M, Konuskan B, Yalnizoglu D, *et al*. Electroencephalographic findings in anti-N-methyl-d-aspartate receptor encephalitis in children: A series of 12 patients. *Epilepsy Behav* 2018;78:118–23.
20 Haberlandt E, Ensslen M, Gruber-Sedlmayr U, *et al*. Epileptic phenotypes, electroclinical features and clinical characteristics in 17 children with anti-NMDAR encephalitis. *Eur J Paediatr Neurol* 2017;21:457–64.
21 Mohammad SS, Dale RC. EEG background activity and extreme delta brush in children with anti-NMDAR encephalitis. *Eur J Paediatr Neurol* 2018;22:207–8.
22 Nosadini M, Boniver C, 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.