Paroxysmal EEG pattern in a child with *N*-methyl-D-aspartate receptor antibody encephalitis

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ABBREVIATION
NMDAR *N*-methyl-D-aspartate receptor

A previously healthy 8-year-old male presented with cognitive regression, sleep disturbance, hallucinations, and severe attacks of agitation and oligoclonal bands in the cerebrospinal fluid. *N*-methyl-D-aspartate receptor (NMDAR) antibodies in serum and cerebrospinal fluid were detected 2 months after onset of symptoms. Bursts of agitation were initially considered to be epileptic leading to the administration of a high dose of benzodiazepines. Video-electroencephalography (EEG) failed to disclose any correlation between the episodes of agitation and paroxysmal rhythmic slow activity on EEG persisting throughout and after attacks of agitation. Clinical improvement and EEG normalization followed an initial plasma exchange performed 3 months after onset of disease. This particular paroxysmal EEG pattern in NMDAR antibody encephalitis suggests that it may result from the combination of reduced NMDAR function and major γ-aminobutyric acid (GABA)-ergic activation.

An 8-year-old male with an unremarkable history complained of difficulty in concentration and tiredness. A few days later he suddenly became anxious and experienced sleep disturbances consisting of frequent awakening and night terrors, and on sudden arousal he would shout, 'I will die'. He then started to experience visual hallucinations (e.g. seeing his mother's eyes in the middle of her front or believing that his trousers were on upside down) and episodes of micropsia. No abnormality was found on neurological examination. Gradually the child lost speech and exhibited cognitive regression, chewing movements, and athetoid movements in his left upper limb. There were frequent paroxysmal attacks of agitation and terror, often triggered or amplified by any attempt to control them, which lasted up to 1 hour and took the form of screaming, as if fighting against something or someone. These paroxysmal episodes were associated with autonomic manifestations including sweating and tachycardia, suggesting complex partial seizures. Valproate was administered without success, as were carbamazepine, topiramate, levetiracetam, and a ketogenic diet. The persistence of daily paroxysmal attacks of agitation led to the administration of midazolam in progressively increasing doses up to 900 μg/mL, resulting in the child becoming comatose while major pyramidal and extrapyramidal signs developed progressively. Parental consent was obtained to publish this report.

Analysis of the cerebrospinal fluid (CSF) revealed a lymphocyte count of 176/mm^3 (normal range 0–5/mm^3) with oligoclonal bands on electrophoresis, but extensive studies failed to disclose any virus. Three magnetic resonance images (MRI) showed a slightly high T2 periventricular signal, particularly in the trigone, which remained unchanged for more than 8 months. High titres of *N*-methyl-D-aspartate receptor (NMDAR) antibodies were identified in the CSF and serum (score 3 on a range of 0–4; normal value <1[1]) 2 months after onset of symptoms, consistent with the suspected NMDAR antibody encephalitis. Immunoglobulins were administered without any efficacy.

At this point, an electroencephalography (EEG) showed diffuse rhythmic delta waves with particularly sudden onset and cessation (Figs. 1 and 2) suggesting an ictal discharge which persisted throughout and after paroxysmal episodes of agitation. Between the sudden onset and cessation the frequency of the rhythmic activity did not change. Because of possible drug intoxication, all antiepileptic drugs, including midozalam, were gradually discontinued from day 63 of the illness. Consciousness improved after cessation of midozalam, but daily paroxysmal attacks of agitation, suggesting hallucinations, reappeared (Video S1, supporting material online) with no corresponding change on EEG: video-EEG failed to disclose any correlation between the episodes of agitation and the EEG discharges (Video S2, supporting material online). In addition, there was no improvement in cognition or in pyramidal and extrapyramidal symptoms. Antipsychotic drugs were administered but with no success.

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Ten weekly plasma exchanges were performed, starting 3 months after onset of the disease. The paroxysmal diffuse high-amplification, rhythmic, slow EEG activity disappeared completely following the first plasma exchange. After 10 plasma exchanges, CSF and serum NMDAR antibodies gradually decreased over time (titrated values are shown in Fig. 3). A significant improvement in motor and cognitive functions and a total recovery from pyramidal symptoms and gross motor deficit were seen. The child could sit, hold a pencil, and say a few words (Video S3, Supporting material online). Progressive return of walking and fine motor activity was observed following plasma exchanges without any other treatment.

What this paper adds

- This case report shows that not all rhythmic activity is epileptic in individuals with NMDAR antibody encephalitis.
- It highlights the need to record paroxysmal events in order to correlate EEG features with clinical behaviour in affected individuals.
- Video-EEG is helpful in the clinical context.

Six months after the initial exchange, the child continued to have moderate language and cognitive dysfunction. He had word-finding problems, transient use of neologisms, and semantic paraphasia. The Wechsler Intelligence Scale for Children revealed better non-verbal performance than verbal ability, particularly for object assembly and block design. The

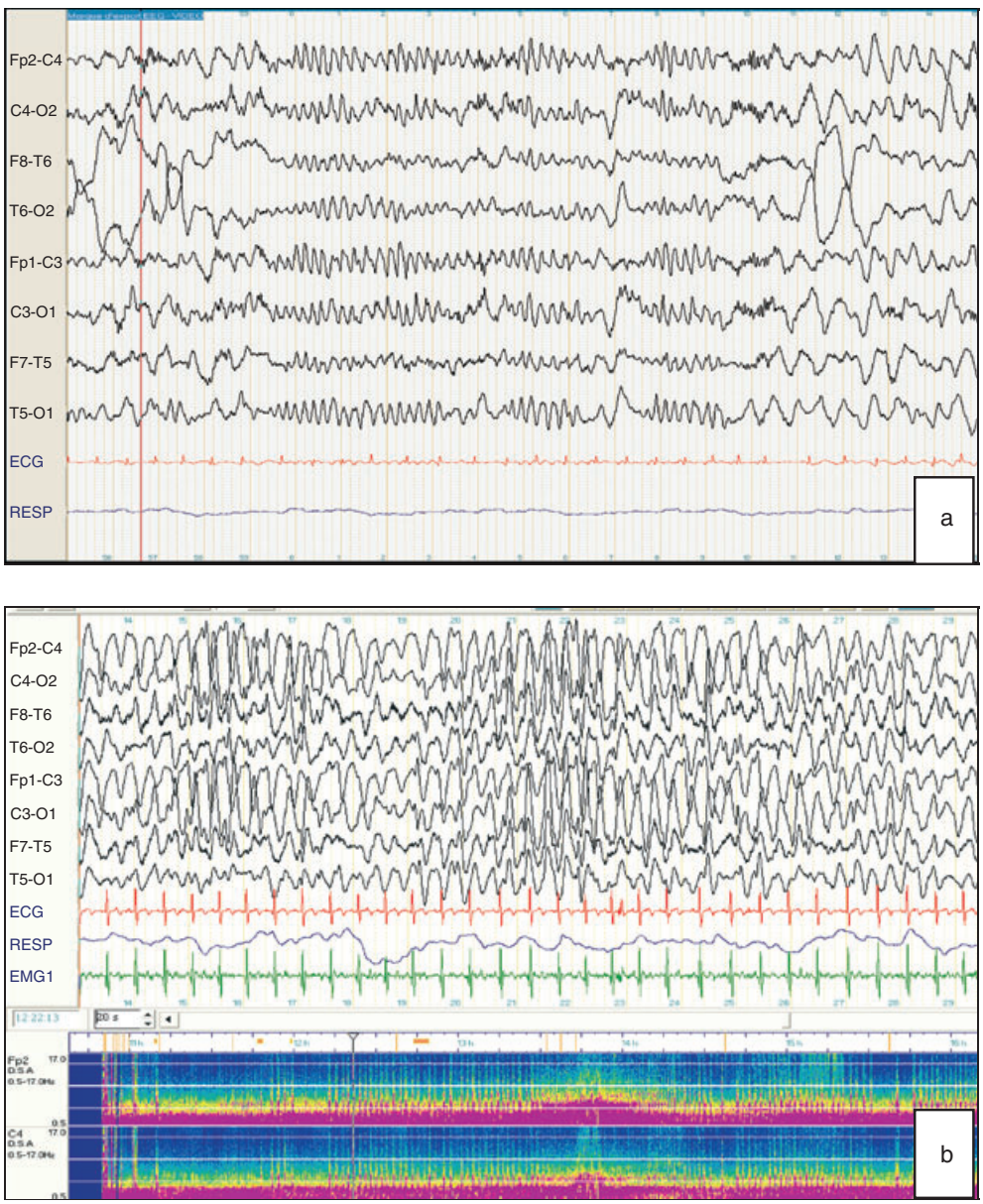

Figure 1: Electroencephalography (EEG; 10 μV/mm, 15mm/s), (a) 58 and (b) 64 days after onset of disease (with and without midozolam respectively) showed a paroxysmal pattern with repeat bursts of diffuse rhythmic theta activity. Each burst on EEG lasted about 10 seconds and corresponds to `bursts' on spectral EEG.

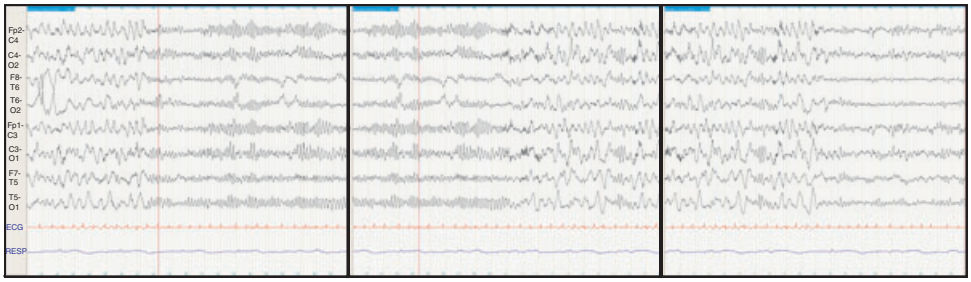

Figure 2: Electroencephalogram showing bursts of rhythmic activity.

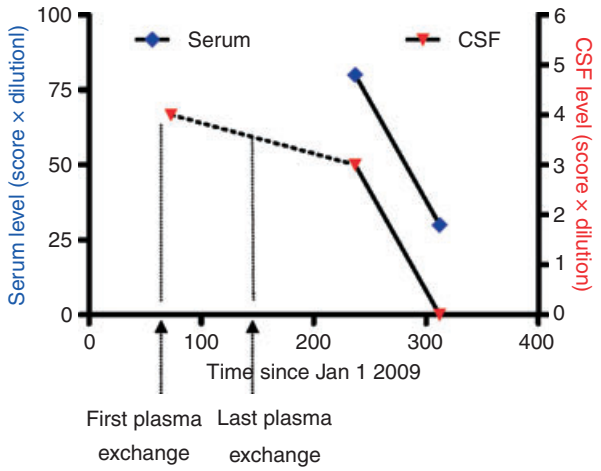

Figure 3: The results of serial estimations of *N*-methyl-D-aspartate receptor (NMDAR) antibodies over the course of the illness during which the child received 10 plasma exchanges. Three cerebrospinal fluid (CSF) and two serum samples were tested for binding to NMDARs expressed in HEK293 cells after serial dilutions to determine accurately the changes over time. The results are expressed as the binding score × the dilution of serum or CSF. Note the different axes for serum and CSF. Unfortunately, the second CSF assay was not performed until 5 months after the final plasma exchanges (dotted line); the effect of this treatment on the CSF levels of NMDAR antibodies cannot be inferred from these data, although a dramatic clinical response to this treatment was observed.

child's behaviour had also improved, although he was still not able to cope adequately with frustration. MRI following plasmapheresis remained unchanged 8 months after onset, and CSF showed mild pleocytosis (six lymphomonocytic cells) with persisting oligoclonal bands.

DISCUSSION

This child presented with a clinical picture comprising sleep disturbance, cognitive regression, visual hallucinations, extrapyramidal and pyramidal symptoms, and psychotic behaviour combined with oligoclonal bands in the CSF. Over 2 months elapsed before proper diagnosis and treatment was made possible by the identification of NMDAR antibodies in CSF and serum. Thus, the child had the features of NMDAR antibody encephalitis with no identified tumour. Such a presentation is increasingly common, particularly in children.[1–3]

The clinical picture was dominated by severe paroxysmal attacks of psychomotor agitation that were initially believed to be the result of epileptic seizures. This led to aggressive antiepileptic treatment that resulted only in major deficits in consciousness without any reduction in paroxysmal episodes.

The significance of the EEG discharges was the most challenging issue. They consisted of diffuse rhythmic theta–delta activity. The lack of frontal predominance permitted the exclusion of frontal intermittent rhythmic delta activity.[4] The paroxysmal nature of the disturbance enabled it to be distinguished from the non-convulsive status epilepticus reported in adults.[5] On the other hand, the frequency of rhythmic activity did not change along the discharge as is the case during an epileptic discharge. Furthermore, video-EEG revealed no evidence of a link between clinical and EEG paroxysms that would confirm epileptic seizures.

In NMDAR antibody encephalitis a prolonged hyperkinetic phase typically follows the prodromal phase, and comprises prominent psychiatric symptoms including anxiety, agitation, strange behaviour, delusional or paranoid thoughts, and visual or auditory hallucinations that may be paroxysmal.[1,3,6] Periods of akinesia alternate with agitation, and some individuals mumble unintelligible words and exhibit echolalia. Blurred consciousness may progress to a catatonic-like state in which eye contact and visual tracking are inconsistent. Orofacial dyskinesias or autonomic instability often develop. Seizures are mentioned as a common feature but no detailed description has been reported, and this raises the issue of their relationship with the episode of agitation. In a series of 100 individuals with NMDAR antibody encephalitis, EEG was reported to show generalized or predominantly frontotemporal slow or disorganized activity (delta–theta) in 77% without epileptic discharges.[2] This challenging difficulty was clearly reported by Bayreuther et al.[7] Our observation suggests that paroxysmal events need to be recorded by video-EEG in order that they are not mistakenly diagnosed as seizures.

The EEG tracing that we report, characterized by a sudden onset and cessation pattern of diffuse rhythmic delta activity, was misleading, and was first considered to be epileptic, despite the fact that there was no clinical counterpart and that recordings failed to show either repetitive spikes or low-amplitude fast activity, which are the usual characteristics of ictal

pattern. This pattern was recorded after the administration of a high dose of benzodiazepines. The normalization of background activity following the first plasma exchange indicates a significant role of NMDAR antibodies in the generation of abnormal rhythmic activity. The necessary combination of these two factors could explain why such a pattern has not been reported previously in the same aetiological context.

ACKNOWLEDGEMENTS

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ONLINE MATERIAL/SUPPORTING INFORMATION

Additional video material for this article may be found online.

REFERENCES

1. 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.
2. Dalmau J, Gleichman Ami J, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; **7:** 1091–8.
3. Florance NR, Davis RL, Lam C, et al. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; **66:** 11–8.
4. Watemberg N, Alehan F, Dabby R, Lerman-Sagie T, Pavot P, Towne A. Clinical and radiologic correlates of frontal intermittent rhythmic delta activity. *J Clin Neurophysiol* 2002; **19:** 535–9.
5. Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* 2010; **75:** 1480–2.
6. Iizuka T, Hara A. Anti-NMDA receptor antibody-mediated encephalitis/encephalopathy. *Rinsho Byori* 2009; **57:** 252–61.
7. Bayreuther C, Bourg V, Dallamonica J, Borg M, Bernardin G, Thomas P. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. *Epileptic Disord* 2009; **11:** 261–5.

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Reference

1. Johanna Darrah, Mary C Law, Nancy Pollock, Brenda Wilson, Dianne J Russell, Stephen D Walter, Peter Rosenbaum and Barb Galuppi. Context therapy: a new intervention approach for children with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 615–20.

We apologise for this error.

In the following article [1], the author's name was spelled incorrectly. Michelle M Mezey should be Michelle M Mezei.

Reference

1. Clara D M Van Karnebeek, Paula J Waters, Michael A Sargent, Michelle M Mezey, Lee-Jun Wong, Jing Wang and Sylvia Stöckler-Ipsiroglu. Expanding the clinical phenotype of the mitochondrial m.13513G>A mutation with the first report of a fatal neonatal presentation. *Dev Med Child Neurol* 2011; **53**: 565–68.

We apologise for this error.