Clinical commentary

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Extreme delta brush in a patient with anti-NMDAR encephalitis

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ABSTRACT – Anti-N-methyl-D-aspartate receptor encephalitis is a severe, potentially treatable, disorder and prognosis depends on early recognition and prompt immunotherapy. We report a case of anti-N-methyl-D-aspartate receptor encephalitis with atypical age and gender, and a characteristic electroencephalographic pattern that supported the diagnosis. A 66-year-old male presented with psychiatric disturbances and focal seizures with alteration of consciousness, and progressed to a state of akinetic mutism. Auxiliary tests were negative or non-specific for anti-NMDAR encephalitis. Electroencephalographic monitoring revealed a unique pattern; the extreme delta brush. The patient improved with immunotherapy and was asymptomatic at six months of follow-up. Ancillary testing was positive for anti-N-methyl-D-aspartate receptor antibodies. Extreme delta brush is a recently described electroencephalographic pattern presenting in only one third of patients with anti-N-methyl-D-aspartate receptor encephalitis. The identification of this pattern, as in our case, may guide early diagnosis and treatment of anti-N-methyl-D-aspartate receptor encephalitis.

Key words: autoimmune encephalitis, anti-NMDAR encephalitis, extreme delta brush, VEEG

Six years ago, a severe form of encephalitis, associated with antibodies against NR1-NR2 heteromers of the N-methyl-D-aspartate subtype of ionotropic glutamate receptors N-methyl-D-aspartate receptor (NMDAR), was identified (Dalmau *et al*., 2007). This encephalitis predominantly develops in young women with an underlying teratoma (Dalmau *et al*., 2008; Dalmau *et al*., 2007). However, almost half of the cases are non-paraneoplastic and this entity has also been recognised in men, children, and older patients (Irani *et al*., 2010). Anti-NMDAR

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encephalitis is a spectrum of clinical symptoms, characterised initially by a prodromal non-specific viral-like illness, followed by neuropsychiatric symptoms and memory deficits, decreased consciousness, seizures, dysautonomia with central hypoventilation, and, finally, movement disorders (Wandinger *et al*., 2011; Wingfield *et al*., 2011). Anti-NMDAR encephalitis belongs to the group of immune-mediated encephalitis associated with surface membrane antibodies. Recently proposed diagnostic criteria include: acute or subacute (<12 weeks) onset, exclusion of other causes, and evidence of CNS inflammation by either CSF, MRI or inflammatory neuropathology on biopsy (Zuliani *et al*., 2012).

Anti-NMDAR encephalitis remains a diagnostic challenge, especially in patients with atypical features and negative results in ancillary work-up. Since immunotherapy is highly effective, a correct and early identification of this disease is crucial. We present a case of anti-NMDAR encephalitis with a unique and recently described EEG pattern that guided us in the diagnosis.

Case study

A 66-year-old Caucasian male with a medical history of hypertension, smoking, anxiety, and autoimmune thrombocytopenia was admitted to the emergency department following onset, during the previous week, of paranoid delusions and aggressive behaviour. His physical examination, including vital signs, was normal. Neurological examination revealed a disorientated, agitated, verborrheic, and delusional patient. Neither focal neurological signs, nor meningism were present. Complete blood count, metabolic panel, serology, immunology, and urine toxicology screening were normal. Initial head computed tomography revealed a left-frontal hyperdense subcortical lesion, suggestive of acute haemorrhage. One day after admission, fever was documented. A lumbar puncture was performed to rule out viral encephalitis and CSF showed mildly elevated protein, with normal glucose and cell count. He was empirically started on intravenous (IV) acyclovir, but this was subsequently discontinued because of impaired renal function and the low probability of herpes simplex virus encephalitis. Brain MRI showed a left frontal cavernoma, without temporal lobe abnormalities. Over the first days after admission, the patient fluctuated between episodes of normal lucidity and episodes of unresponsiveness and stereotyped movements. These episodes were interpreted as complex partial seizures and antiepileptic treatment began (carbamazepine at 400 mg every 8 hours and levetiracetam at 1,000 mg every 12 hours). Despite this, over the next days, the patient went on to develop a state of akinetic mutism with catatonic posturing. An autoimmune encephalitis was suspected and samples were obtained in order to evaluate reactivity with paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ri, anti-Ma, anti-CRMP5, and anti-amphiphysin) and anti-NMDAR and anti-voltage-gated potassium channel antibodies. In the catatonic stage, 15 days after clinical onset, a three-hour video-VEEG was performed. The VEEG showed diffuse background slowing and continuous rhythmic delta activity at 1-2 Hz with superimposed bursts of rhythmic beta frequency activity on each delta wave in the left temporal region (*figure 1*). The patient was not receiving treatment with barbiturates or benzodiazepines, thus the beta activity could not be attributed to these medications. During the recording, the patient displayed episodes of unresponsiveness, stereotyped movements, and catatonic posturing which did not modify the occurrence of the EEG pattern. This pattern was also independent of external stimulation. These characteristic EEG alterations suggested the possibility of anti-NMDAR encephalitis. Treatment with prednisone at 60 mg/day, followed by two cycles of a five-day course of immunoglobulin and methylprednisolone, was ineffective. Fourteen plasmapheresis sessions only partially improved symptoms. An aggressive immunotherapy with cyclophosphamide (1,500 mg/m^2) and rituximab (750 mg once weekly) was introduced with marked improvement of symptoms. Brain MRI, one month after onset, was unchanged, and testicle ultrasound and whole-body PET were normal. Anti-NMDAR antibodies in spinal fluid were positive five weeks into admission. The positive reactivity of the antibodies was determined in rat brain with the avidin-biotin-peroxidase technique and confirmed in a cell-based assay of human embryonic kidney 293 cells expressing the NR1 and NR2 subunits of NMDAR.

The patient was discharged five months after admission. After six months of follow-up, symptoms had completely resolved and he was seizure-free. The patient reported only persisting amnesia of the entire period of hospitalisation.

Discussion

We present a case of anti-NMDAR encephalitis in which a highly characteristic EEG pattern observed upon VEEG monitoring pointed towards this entity.

Anti-NMDAR encephalitis prognosis depends on early recognition and prompt immunomodulatory therapy (Titulaer *et al*., 2013). Not all patients present with the classic clinical picture and early features can be difficult to identify. In addition, this encephalitis is

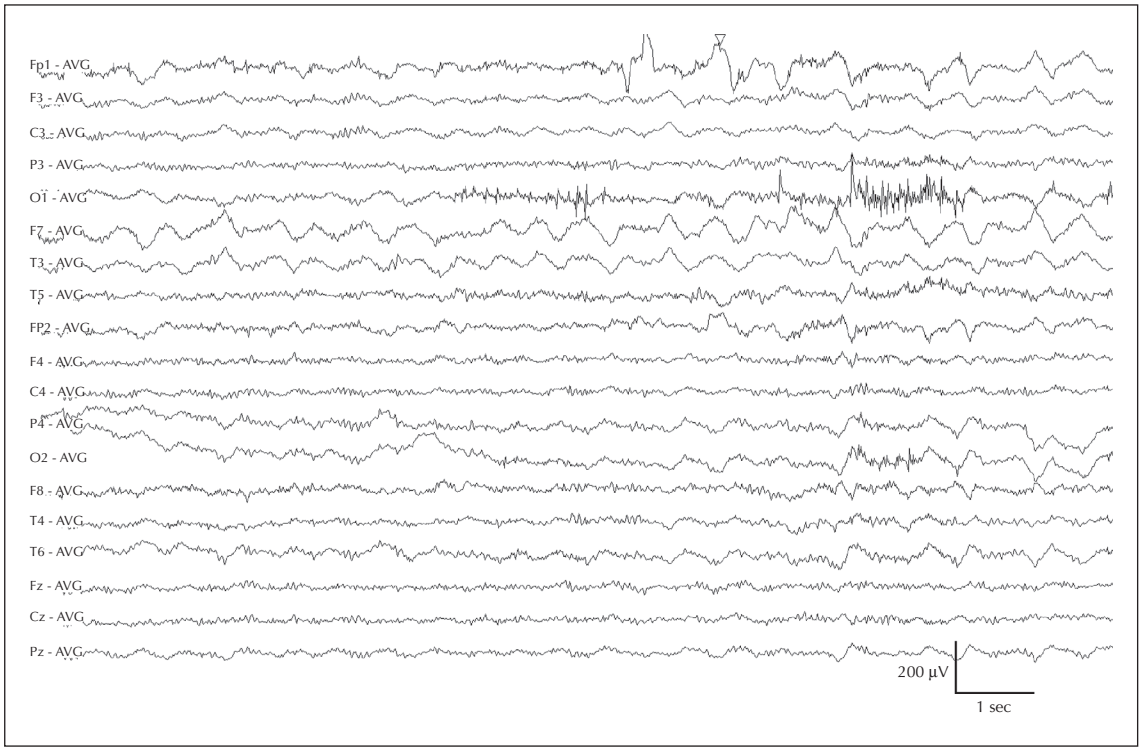

Figure 1. Electroencephalogram with interictal rhythmic continued delta activity with superimposed beta activity riding on each delta wave. Low and high frequency filters were set at 1 and 70, respectively.

associated with non-specific findings based on brain MRI and CSF analysis, and initial brain imaging can be normal in 89% of the patients and remain normal in a high percentage of cases (Irani *et al*., 2010). Confirmation of NMDAR antibodies takes several weeks. All these factors can delay the diagnosis and consequently affect the prognosis, which is otherwise good with prompt treatment.

EEG monitoring in anti-NMDAR encephalitis typically shows diffuse background slowing or focal slow waves in fronto-temporal regions (Dalmau *et al*., 2008; Irani *et al*., 2010). These patterns are frequent, but not specific to anti-NMDAR encephalitis. However, our patient had a unique and recently described pattern; the "extreme delta brush" (EDB) (Schmitt *et al*., 2012).

EDB is characterised by rhythmic continued delta activity with superimposed beta activity riding on each delta wave (*figure 1*). The aetiology of EDB is undetermined, but a plausible hypothesis is that delta activity is a reflection of focal dysfunction and the superimposed beta activity is the consequence of altered glutamatergic activity.

A similar EEG pattern to EDB has previously been described in non-convulsive status epilepticus (NCSE) in anti-NMDAR encephalitis (Ikeda *et al*., 2006; Kirkpatrick *et al*., 2011). In our patient, EDB was not modified after two IV boluses of 1,000 mg levetiracetam, nor did it evolve during the recording, thus it did not appear to correspond to NCSE.

Schmitt *et al*. (2012) suggested that this unique pattern may have prognostic implications, with patients with EDB demonstrating more prolonged periods of hospitalisation and worse outcomes. If this were the case, in the future, the presence of EDB might guide therapeutic decisions. The long-term prognosis of our patient was good, with symptoms resolving within six months, however, he only improved after aggressive immunotherapy had begun and required prolonged hospitalisation.

Further particularities of this case are the age at onset and gender, both of which are atypical, as well as the findings revealed during complementary work-up. EDB on EEG is observed in only 30% of patients with anti-NMDAR encephalitis. Although patient specificity of EDB is yet to be determined, evidence suggests that it is highly indicative of NMDAR-encephalitis. Since prompt diagnosis is crucial, we recommend VEEG monitoring in all patients with a suspicion of autoimmune encephalitis. □

Disclosures.
None of the authors has any conflicts of interests to disclose.

References

Dalmau J, Tüzün E, Wu H, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61: 25-36.

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.

Ikeda A, Matsui M, Hase Y, *et al*. Burst and slow complexes" in nonconvulsive epileptic status. *Epileptic Disord* 2006; 8: 61-4.

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: 1655-67.

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.

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.

Titulaer MJ, McCracken L, Gabilondo 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.

Wandinger K-P, Saschenbrecker S, Stoecker W, Dalmau J. Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. *J Neuroimmunol* 2011; 231: 86-91.

Wingfield T, McHugh C, Vas A, *et al*. Autoimmune encephalitis: a case series and comprehensive review of the literature. *QJM* 2011; 104: 921-31.

Zuliani L, Graus F, Giometto B, *et al*. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. *J Neurol Neurosurg Psychiatr* 2012; 83: 638-45.