

Focal EEG slowing and chorea: electroclinical clues to the diagnosis of anti-NMDAR encephalitis

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Received June 24, 2014; Accepted October 8, 2014

ABSTRACT – Variations in clinical presentation can lead to delays in the diagnosis and initiation of treatment of anti-N-methyl-D-aspartate receptor encephalitis. Most patients have an EEG study performed early in the course of their illness. Although not specific, there may be clues in the electroclinical features that should alert clinicians and electroencephalographers to the possibility of this diagnosis. This case is a reminder that anti-anti-N-methyl-D-aspartate receptor encephalitis may present initially with a movement disorder as the sole symptom, without features of an encephalopathy. In addition, it adds to the growing body of evidence that recognition of certain electroclinical clues may shorten the time to diagnosis. [*Published with video sequence*]

Key words: acute dyskinesia, anti-NMDAR encephalitis, chorea

While the fulminant syndrome of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis with personality changes and neurological decompensation is increasingly readily recognised, variations in the clinical presentation remain more challenging and continue to lead to delays in investigations and diagnosis. Children in particular may present initially with a movement disorder as the sole symptom, without features of an encephalopathy. This can lead to delay in making the diagnosis. Researchers have recently suggested that recognition of certain

electroclinical presentations may help to speed the diagnosis and may aid in the prediction of outcome (Schmitt *et al.*, 2012; Gitiaux *et al.*, 2013). Electroencephalographers may have a role in enabling a rapid diagnosis.

We present the details of a child diagnosed with anti-NMDAR encephalitis who presented with predominantly unilateral chorea and contralateral focal EEG slowing. She had no features of encephalopathy for several weeks. Recognition of her electroclinical presentation may have reduced delays in her diagnosis.



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Case study

A 6-year-old girl presented with a two-week history of increasing falls and an unsteady gait. Two days before presenting to hospital, she developed choreiform movements of her left arm and both lower limbs, left worse than right. Brain MRI was normal. An EEG recorded at this stage was asymmetric with focal polymorphic high-amplitude delta activity observed over the right hemisphere (*figure 1A*), particularly over the right sagittal row of electrodes. The slow waves did not have superimposed fast activity (Schmitt *et al.*, 2012). The posterior background rhythm was also mildly slowed on the right, but reactive to eye opening. The choreiform movements were not associated with ictal EEG activity and no epileptiform discharges were observed.

A diagnosis of Sydenham's chorea was made and she was treated with penicillin V, carbamazepine, and physiotherapy. She was thought to have made some improvement and was discharged. Three weeks later, she re-presented with behavioural changes and sleep disturbance. She was aggressive and tearful, throwing temper tantrums and experiencing visual hallucination. A repeat EEG at this stage showed worsening of the high-amplitude polymorphic delta slow wave abnormality over the right hemisphere. The posterior background rhythm on the right was now significantly abnormal (*figure 1B*), with no demonstrable alpha rhythm. There was no superimposed fast activity (Schmitt *et al.*, 2012). The behavioural changes were attributed to possible carbamazepine toxicity. The drug was stopped and she was discharged. A month later (seven weeks after her initial presentation), she was admitted to hospital again. She was mute, not eating, and incontinent of urine and faeces. At her worst, she was bed-bound with constant choreiform movements of all four limbs. A repeat MRI scan was normal. A third EEG study showed diffuse irregular delta waves without the extreme delta brush pattern. CSF analysis at this stage showed a pleocytosis, and was positive for oligoclonal bands and anti-NMDAR antibodies. A diagnosis of anti-NMDAR encephalitis was made.

Extensive metabolic investigations including plasma amino acids, urine organic acids, acylcarnitine, white cell enzymology, lead, zinc, copper, caeruloplasmin, trace elements, ferritin, vitamin A, E, and D, and urinary VMA were normal. Mycoplasma and viral serology were normal. Thyroglobulin antibodies were noted to be elevated. Other autoimmune antibodies, including anti-GAD, VGKC, and Hu/Ri/La, were negative.

Chest X-ray, ultrasound scans of her abdomen and pelvis, as well as MRI scans of her abdomen, pelvis and spine revealed no tumours.

She had a limited response to steroids and IVIg, but responded quickly to cyclophosphamide and tolerated it well. Her language skills improved and she started to speak in sentences. She also ate and drank safely, and regained the ability to walk independently. She continued to make a good recovery and her neurodevelopmental profile was age-appropriate ten months later.

Discussion

Most children diagnosed with anti-NMDAR encephalitis present with behavioural or personality change, or seizures (Florance *et al.*, 2009). It is increasingly recognised that movement disorders may be the sole presenting symptom. In our patient, there were no reported psychiatric or behavioural symptoms at the onset. The movement disorder remained the only symptom until four weeks into the illness.

Sydenham's chorea remains the commonest cause of chorea in childhood in the developed as well as the developing world (Kirkham *et al.*, 2011). However, this case illustrates the need to consider the possibility of anti-NMDAR encephalitis in a child presenting with chorea, even without features of an encephalopathy. Most patients with anti-NMDAR encephalitis will have undergone an EEG study. Whereas the return of antibody testing results from clinical laboratories may take weeks, EEG abnormalities that might be specific to the illness, detected at the time of presentation, can possibly improve the speed of discovery of associated teratomas and reduce delays in diagnosis and treatment. Most reports in the past have described non-specific EEG abnormalities (Florance *et al.*, 2009; Dalmau *et al.*, 2011). A number of recent studies, however, have attempted to systematically characterise the pattern of EEG abnormalities in both adults and children during wakefulness and sleep. In the right clinical context, certain EEG patterns should arouse suspicion of anti-NMDAR encephalitis as a possible diagnosis. As reported separately by Gitiaux *et al.* (2013) and by ourselves in this present case report, the electroclinical presentation of predominantly unilateral involuntary movements, associated with contralateral focal EEG polymorphic delta activity, particularly with normal or non-specific MRI abnormalities, may be a clue that the patient may have anti-NMDAR encephalitis. This electroclinical presentation is, however, not specific to anti-NMDAR encephalitis. Maegaki *et al.* (2000) described a patient with unilateral chorea and contralateral high-voltage slow wave activity on the EEG, associated with streptococcal infection. The authors suggested that the pathophysiology of the involuntary movements may be associated with sensorimotor cortex hyperexcitability.

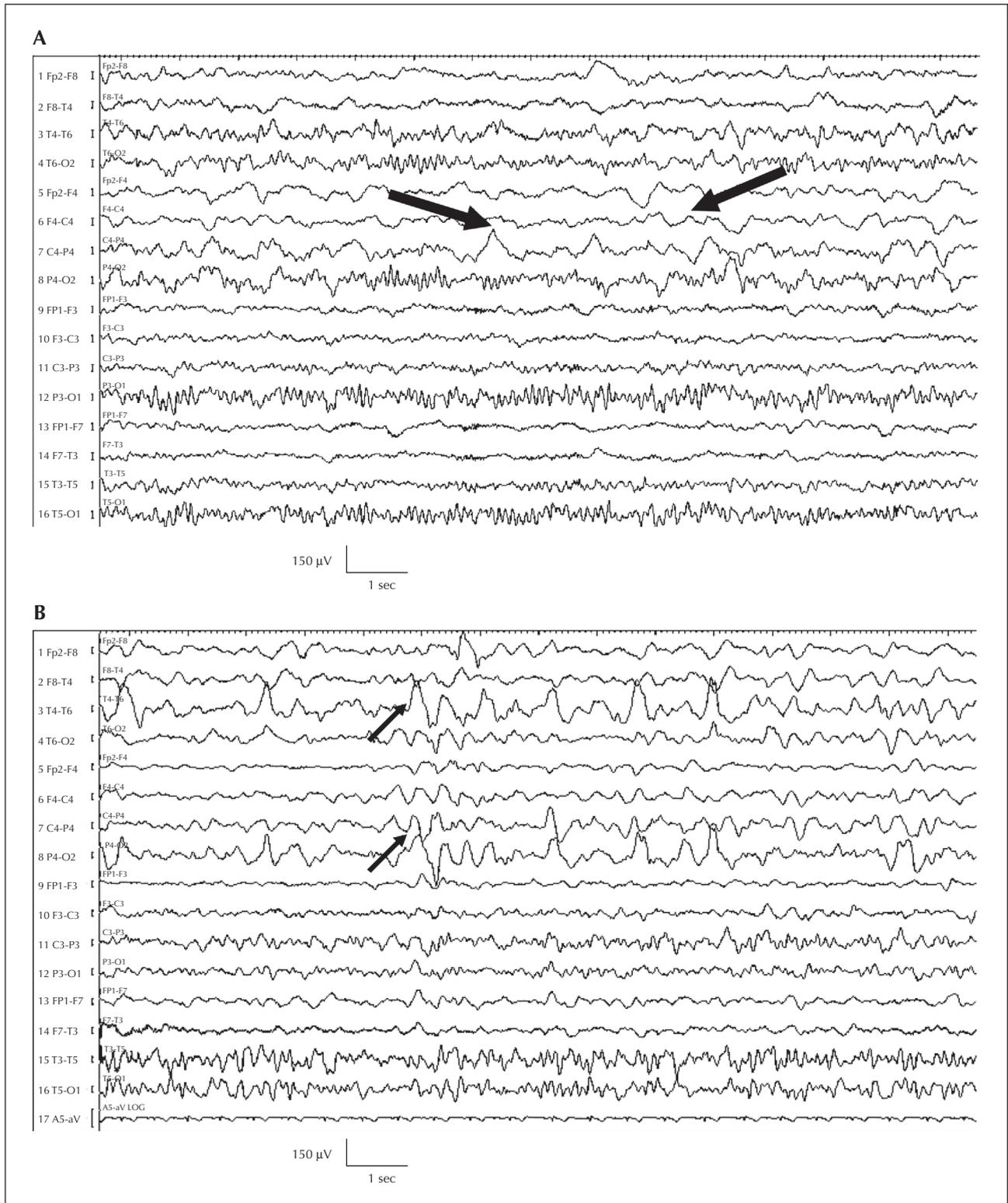


Figure 1. EEG recorded while awake during the initial stages of illness. Irregular delta slow wave activity is observed over the right hemisphere, particularly over the parasagittal row of electrodes (arrow). Clinically, the patient had chorea of her left upper limb and both lower limbs (A). A second EEG recorded four weeks into her illness. There is more marked slow wave activity over the entire right hemisphere (arrows) (B).

The recently described extreme delta brush EEG pattern may be unique to anti-NMDAR encephalitis (Schmitt *et al.*, 2012). The presence of bursts of fast (30-Hz) activity superimposed on the slow wave abnormality may be a distinctive feature. Our patient's EEG records did not demonstrate this pattern.

Apart from revealing clues to the diagnosis, the EEG findings may also correlate with clinical severity and may be useful in predicting outcome. The extreme delta brush pattern, for example, is thought to be associated with a more severe illness and a worse outcome (Schmitt *et al.*, 2012). The subset of Gitiaux *et al.* (2013) patients, who had unilateral or focal EEG abnormalities, were shown to have a milder illness and a better outcome than those with diffuse EEG abnormalities (Gitiaux *et al.*, 2013).

Dalmau *et al.* (2011) have previously reported that in patients with an underlying tumour, in whom the tumour was removed, first-line therapy (steroids and IVIg) is effective. In patients without a tumour or with a delayed diagnosis, additional treatment with second-line immunotherapy (rituximab or cyclophosphamide, or both) is usually needed (Titulaer *et al.*, 2013; Kashyape *et al.*, 2012). Our experience with this patient would support these findings. The patient had a limited response to steroids and IVIg, but responded quickly to cyclophosphamide and tolerated it well.

In conclusion, patients with anti-NMDAR encephalitis may not develop the full spectrum of symptoms or exhibit the typical multistage process in the accepted order; the hyperkinetic or movement disorder phase might precede the psychiatric phase. Clinicians and electroencephalographers need to be reminded of these variations during the disease course. Specifically, this case adds to the growing body of evidence that anti-NMDAR encephalitis may present in children with chorea as the only or predominant symptom, and precede the encephalopathic stage by several weeks. This possibility must be considered in patients presenting acutely with chorea. Although not specific, the electroclinical presentation of predominantly unilateral chorea with contralateral focal EEG slowing, with or without encephalopathy, in a child should raise the possibility of anti-NMDAR encephalitis. □

Acknowledgements and disclosures.

The authors have no conflicts of interests to disclose.

Legend for video sequence

The footage shows chorea (without encephalopathy) predominantly involving the left upper limb and both lower limbs in a patient later confirmed to have anti-NMDAR encephalitis.

Key words for video research on www.epilepticdisorders.com

Syndrome: not applicable

Etiology: Encephalitis (anti-NMDA receptor)

Phenomenology: nonepileptic paroxysmal event

Localization: not applicable

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