

Serial EEG findings in anti-NMDA receptor encephalitis: correlation between clinical course and EEG

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ABSTRACT – Anti-NMDA receptor encephalitis is a paraneoplastic encephalitis characterised by psychiatric features, involuntary movement, and autonomic instability. Various EEG findings in patients with anti-NMDA receptor encephalitis have been reported, however, the correlation between the EEG findings and clinical course of anti-NMDA receptor encephalitis remains unclear. We describe a patient with anti-NMDA receptor encephalitis with a focus on EEG findings, which included: status epilepticus, generalised rhythmic delta activity, excess beta activity, extreme delta brush, and paroxysmal alpha activity upon arousal from sleep, which we term “arousal alpha pattern”. Initially, status epilepticus was observed on the EEG when the patient was comatose with conjugate deviation. The EEG then indicated excess beta activity, followed by the emergence of continuous slow activity, including generalised rhythmic delta activity and extreme delta brush, in the most severe phase. Slow activity gradually faded in parallel with clinical amelioration. Excess beta activity persisted, even after the patient became almost independent in daily activities, and finally disappeared with full recovery. In summary, our patient with anti-NMDA receptor encephalitis demonstrated slow activity on the EEG, including extreme delta brush during the most severe phase, which gradually faded in parallel with clinical amelioration, with excess beta activity persisting into the recovery phase.

Key words: autoimmune encephalitis, extreme delta brush, N-methyl-D-aspartate receptor

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In 2007, Dalmau and colleagues reported anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, a limbic encephalitis with characteristic symptoms including psychiatric features, involuntary movement, and autonomic instability caused by antibodies to the NMDA receptor (Dalmau *et al.*, 2007). Following a report of “burst and slow complexes” (Ikeda *et al.*, 2006), various EEG findings in patients with anti-NMDA receptor encephalitis have been identified (Kirkpatrick *et al.*, 2011; Schmitt *et al.*, 2012; Veciana *et al.*, 2015), including extreme delta brush (EDB), generalised rhythmic delta activity (GRDA), and excess beta activity (EBA). However, the correlation between such EEG findings and the clinical course in patients with anti-NMDA receptor encephalitis remains unclear.

Here, we describe the clinical and EEG aspects of a patient with anti-NMDA receptor encephalitis. Close inspection of the EEG revealed EDB, GRDA, and EBA, and the correlation between these EEG findings and the clinical course of anti-NMDA receptor encephalitis is discussed.

Case study

Clinical course

The patient was a 22-year-old, right-handed, previously healthy woman. Disease onset was marked by amnesia and *déjà vu*, preceded by headache. She developed agitation, confusion, and bizarre behaviour, for which she was admitted to a care centre. Antipsychotic drugs did not resolve her symptoms, and abdominal computed tomography (CT) indicated an ovarian tumour. On Day 9, she was transferred to our medical centre due to convulsion and disturbance of consciousness. On arrival, the patient was febrile and comatose. She had conjugate deviation towards the right and autonomic instability, such as apnoea, hyperhidrosis, and paroxysmal bradycardia. An EEG demonstrated status epilepticus with left parietally dominant evolution. Lumbar puncture revealed 32 white blood cells/mm³ (including 100% mononuclear cells) and 12 mg/dl of protein. The oligoclonal band was positive, and the IgG index was 0.88. Bacterial, tuberculosis, and fungal cultures were negative. Polymerase chain reaction (PCR) for herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and parvovirus was negative. Anti-neuronal and onconeuronal antibodies were tested and included antibodies against Hu, Ma, collapsin response mediator protein 5 (CRMP5), glutamate decarboxylase 65 (GAD65), voltage-gated calcium channels, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and the potassium channel complex; all were negative. Results for antibodies to the NMDA receptor were obtained at a later stage. No abnormal signals were

observed on a brain MRI fluid-attenuated inversion recovery sequence. MRI of the pelvis revealed bilateral ovarian tumours. The patient was intubated and ventilated artificially due to apnoea, followed by tracheotomy after two weeks, and was admitted to the intensive care unit (ICU).

Laparoscopic enucleation of the ovarian tumours was performed on Day 9; the subsequent surgical pathology report identified a mature cystic teratoma. After the operation, the patient was sedated with propofol in the ICU. Intravenous phenobarbital (PB) was started on Day 9, and levetiracetam and valproic acid were added on Day 12 and Day 13, respectively, but were stopped on Day 15 due to elevated liver enzymes. High-dose intravenous corticosteroids and immunoglobulin were administered from Day 9 to 13, and oral corticosteroids were subsequently introduced, followed by additional intravenous corticosteroids from Day 20 to 22. Treatment with midazolam (MDZ) was introduced on Day 22 due to involuntary movement, and then reduced and terminated on Day 24. Despite treatment, the patient remained comatose and showed moderate involuntary movement, including orolingual dyskinesia, limb and truncal dystonia, and athetosis. Diazepam (DZP) and clonazepam (CZP) were added on Day 29 because of the deterioration of involuntary movement, including oral dyskinesia, dystonic posture, and bruxism, and MDZ was started again on Day 48. Plasmapheresis was performed three times a week from Day 34 to 46, due to her inability to follow commands and unresponsiveness to external stimuli that persisted with the deterioration of involuntary movement. At the time of admission to our centre, it was revealed that antibodies to the NMDA receptor were detected in her CSF; the antibody titre was 1:400.

Over the next four weeks, she awakened and was able to follow simple commands and shake her head in response to questions. A reduction in PB was started on Day 57. She was successfully weaned off artificial ventilation on Day 60 with improvement in involuntary movement. Propofol and MDZ were reduced and terminated on Day 62 and 69, respectively; reductions in DZP and CZP were initiated on Day 80.

During the following six weeks, she began to write, eat, walk unassisted, and speak, and she became almost independent in activities of daily living (ADL), however, severe attention disturbance and amnesia were present. Oral corticosteroids were reduced and terminated on Day 149. The CSF anti-NMDA receptor antibody titre decreased to 1:1 on Day 152 with resolution of fever and autonomic instability. She was discharged and moved to a rehabilitation centre on Day 154. Treatment with DZP and CZP was terminated on Day 221, and she was almost fully recovered with subtle attention disturbance and amnesia on Day 249.

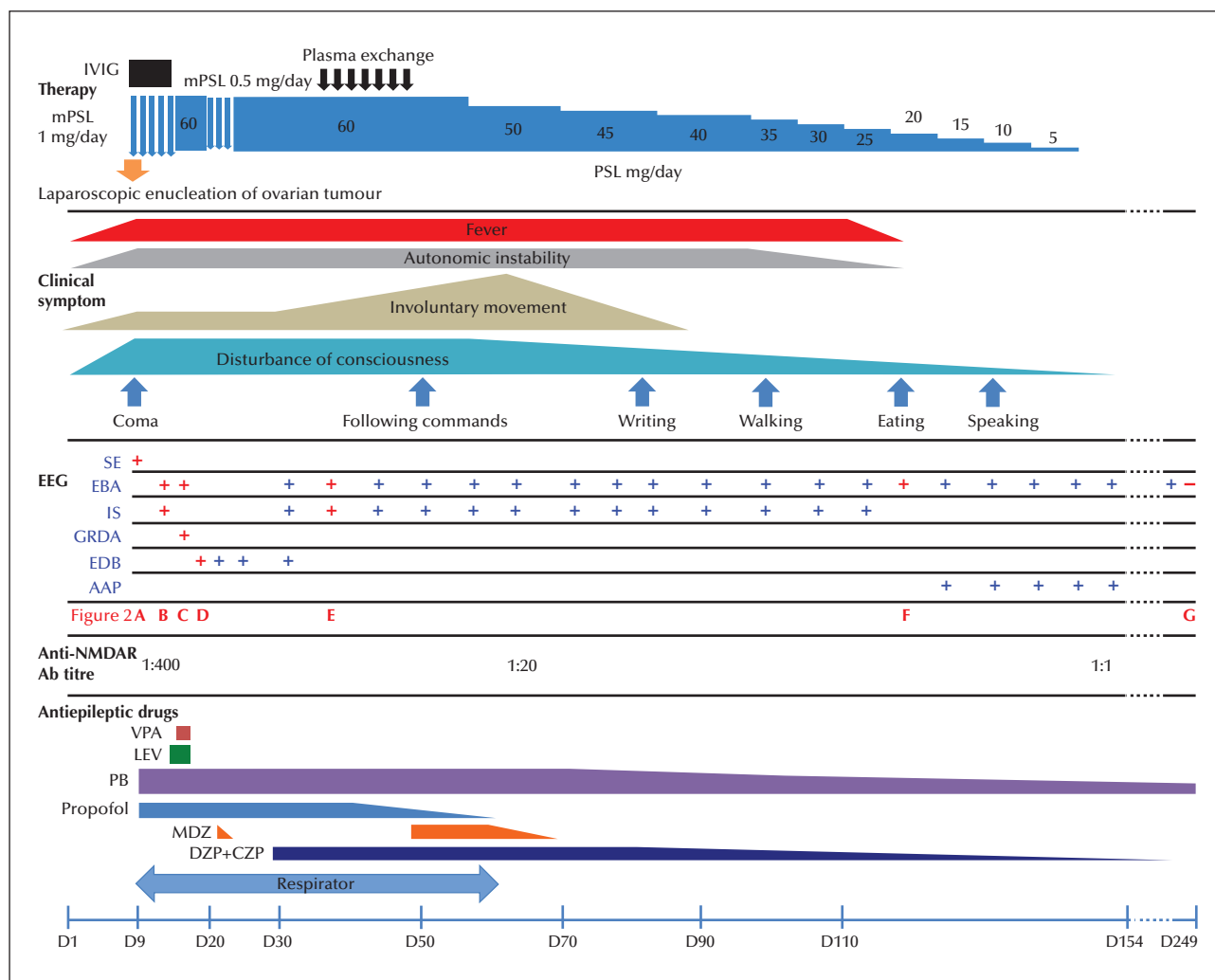


Figure 1. Clinical course and EEG findings. Laparoscopic enucleation of the ovarian tumours was performed and antiepileptic drugs were administered while the patient was sedated. Immunotherapy, including corticosteroids, intravenous immunoglobulin, and plasma exchange, was introduced. Gradual clinical improvement and a decrease in the CSF anti-N-methyl-D-aspartate (NMDA) receptor antibody titre were observed. Autonomic instability included hypersalivation, apnoea, tachycardia, bradycardia, and hyperhidrosis. Involuntary movement included orolingual dyskinesia, limb and truncal dystonia, and athetosis. (A-G) correspond to the EEG patterns in figure 2.

IVIG: intravenous immunoglobulin; mPSL: methylprednisolone; PSL: prednisolone; SE: status epilepticus; EBA: excessive beta activity; IS: intermittent slow activity; GRDA: generalised rhythmic delta activity; EDB: extreme delta brush; AAP: arousal alpha pattern; anti-NMDAR Ab titre: anti-NMDA receptor antibody titre; LEV: levetiracetam; VPA: sodium valproate; PB: phenobarbital; MDZ: midazolam; DZP: diazepam; CZP: clonazepam

EEG alterations

The clinical course and EEG findings are shown in figure 1. Continuous EEG monitoring was performed during the most severe phase, and other EEG recordings were performed once a week during the recovery phase, and once every two weeks after discharge.

EEG on admission (Day 9) revealed status epilepticus (figure 2A), with a left parietally dominant evolution. Continuous EEG monitoring on Day 10 showed beta

activity and intermittent slow activity without evolution. The EEG demonstrated excessive *beta* activity with intermittent slow activity (figure 2B) on Day 11, generalized rhythmic *delta* activity on Day 13 (figure 2C), which was unresponsive to diazepam, and extreme *delta* brush on Day 15 (figure 2D). From Day 11 to 15, the patient remained comatose with moderate involuntary movement. The EDB gradually faded, and finally changed to excessive *beta* activity with intermittent slow activity on Day 36 (figure 2D), when the patient occasionally awakened

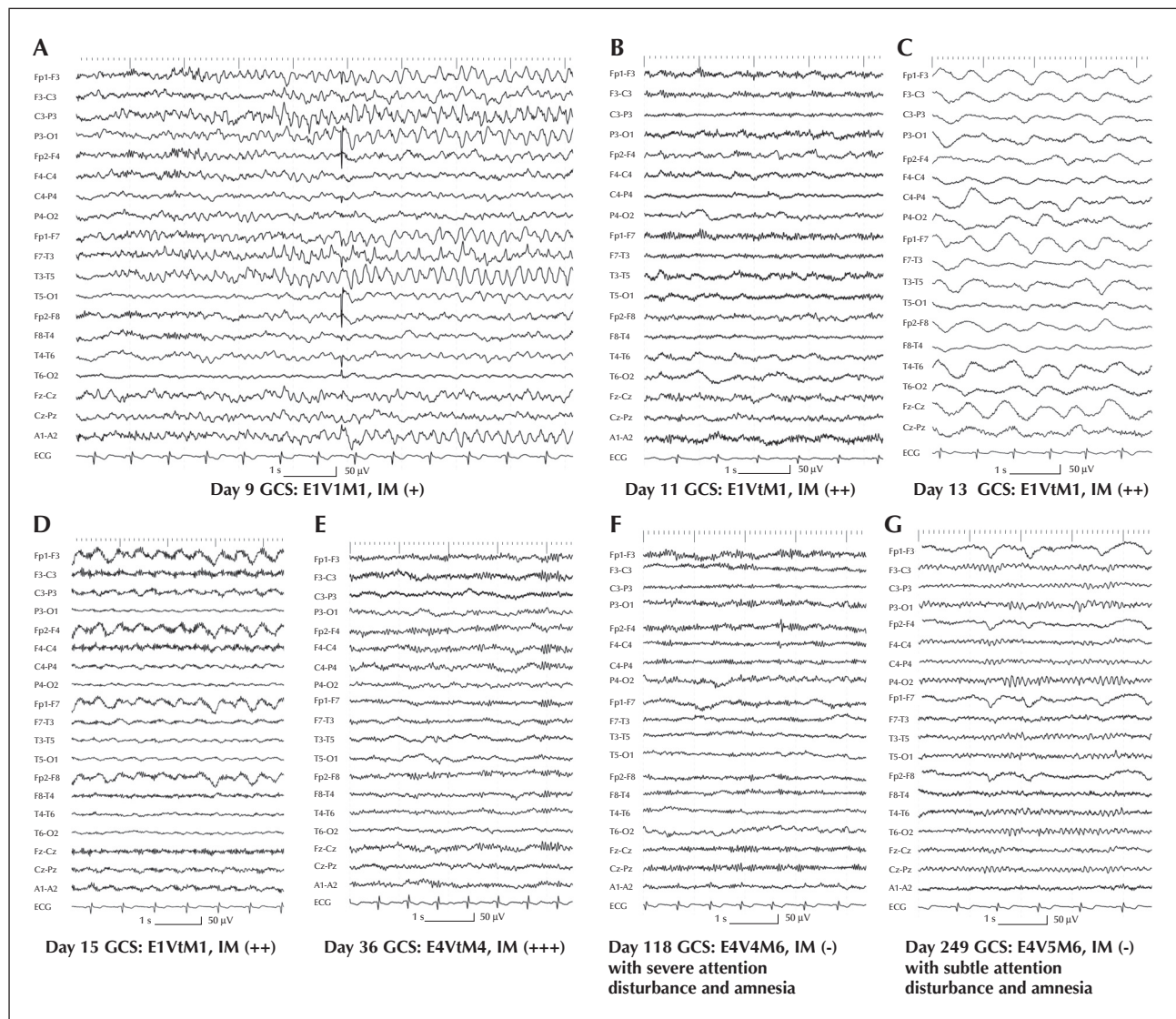


Figure 2. EEG findings. (A) EEG on Day 9 showing status epilepticus with a left parietally dominant evolution; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (B) EEG on Day 11 showing excess beta activity; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (C) EEG on Day 13 dominated by generalised rhythmic delta activity; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (D) EEG on Day 16 revealing generalised rhythmic delta activity at 2-3 Hz with superimposed frontally predominant bursts of beta activity, extreme delta brush; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (E) EEG on Day 36 demonstrating excess beta activity with intermittent slow activity; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (F) EEG on Day 118 showing excess beta activity without intermittent slow activity; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz. (G) EEG on Day 249 showing that excess beta activity was replaced by a posterior-dominant rhythm; high-pass filter: 0.5 Hz; low-pass filter: 70 Hz.

GCS: Glasgow Coma Scale; IM: involuntary movement: (-): involuntary movement was not seen; (+): involuntary movement was seen, but sedation was not needed; (++): involuntary movement was seen, and one sedative drug was needed; (+++): involuntary movement was seen, and more than two sedative drugs were needed.

but remained unable to follow any simple commands, and exhibited severe involuntary movement. Intermittent slow activity faded gradually in parallel with clinical improvement, and finally disappeared on Day 118 when the tracheotomy tube was removed and the patient was almost independent in ADL, however, severe attention disturbance and amnesia were present (figure 2F). EEGs after Day 126 showed parox-

ysmal alpha activity upon arousal from sleep, which we refer to as an "arousal alpha pattern" (AAP) (see *supplementary figure 1*). The EBA and AAP persisted until discharge (Day 154), however, on Day 249, when the patient was almost fully recovered with subtle attention disturbance and amnesia, the EBA and AAP disappeared and were replaced by a posterior-dominant rhythm (figure 2G).

Discussion

In patients with anti-NMDA receptor encephalitis, abnormal EEG findings, such as diffuse or focal slow activity, epileptic discharges, polymorphic delta rhythm, diffuse beta activities, and EDB, have been recorded at various stages (Zhang *et al.*, 2017). Our patient showed various abnormal EEG findings, which altered in association with the clinical course. The first EEG finding was status epilepticus, followed by EBA, and then an emergence of continuous slow activity, including GRDA and EDB. In parallel with clinical amelioration, slow activity became intermittent and gradually faded. The EBA persisted even after the patient became almost independent in ADL, but disappeared with full recovery. The AAP appeared in the middle of the recovery phase, lasted for a month, and disappeared with full recovery.

In animal studies, the neuronal cell firing mode in the nucleus reticularis of the thalamus changed to rhythmic delta burst when NMDA receptor was inhibited (Zhang *et al.*, 2009). This indicates that GRDA represents NMDA receptor dysfunction in the nucleus reticularis of the thalamus. GRDA was observed when our patient was comatose, supporting the association between GRDA and dysfunction in the nucleus reticularis of the thalamus. Whether GRDA is ictal or not is controversial, however, some reports indicate that GRDA without a progressive pattern does not respond to benzodiazepines, and it is emphasised that GRDA should not be interpreted as an epileptic discharge in anti-NMDA receptor encephalitis (Kirkpatrick *et al.*, 2011). We could not determine whether GRDA was ictal in our patient because of its characteristics, such as the slower frequency (1–1.5 Hz), the lack of evolution and fluctuation, and unresponsiveness to benzodiazepines (Trinka and Leitinger, 2015).

The EBA, a high-amplitude fast wave, has also been identified in anti-NMDA receptor encephalitis (Veciana *et al.*, 2015). The aetiology of EBA remains unknown, but the source of beta-range activity is recognised to be the cerebral cortex (Hari and Salmelin, 1997). Furthermore, blockage of the anti-NMDA receptor causes disinhibition of glutamatergic neurons in the cerebral cortex (Stone *et al.*, 2007). Therefore, we suggest that the EBA may reflect the hyperexcitability of the cerebral cortex caused by the anti-NMDA receptor antibody. In our patient, EBA persisted long after the patient became almost independent in ADL. Persistent EBA in anti-NMDA receptor encephalitis has not been reported; we suggest that this indicates persistent hyperexcitability of the cerebral cortex even during the recovery phase in patients with anti-NMDA receptor encephalitis. Although the EBA in our patient may have been drug induced due to benzodiazepine and barbiturate treatment, the effects

of such drugs are likely negligible because the EBA disappeared without interrupting barbiturate treatment. In 2012, Schmitt *et al.* reported that generalised rhythmic delta activity with superimposed beta activity (*i.e.* EDB) was characteristic of anti-NMDA receptor encephalitis (Schmitt *et al.*, 2012). The anti-NMDA receptor antibody internalises the NMDA receptor of gamma-aminobutyric acid (GABA)ergic interneurons and disinhibits dopaminergic and glutamatergic neurons (Iizuka and Sakai, 2008; Hughes *et al.*, 2010; Lazarewicz *et al.*, 2010). However, the aetiology of EDB remains unknown. EDB is observed in 30.4% of patients, and is specific to anti-NMDA receptor encephalitis (Schmitt *et al.*, 2012). In some cases, EDB was observed in the absence of benzodiazepine or barbiturate treatment, suggesting a difference between EDB and a drug-induced fast wave (Schmitt *et al.*, 2012; Di Capua *et al.*, 2013). EDB is associated with status epilepticus and severe cases that require more aggressive therapy, such as intubation and transfer to the ICU (Schmitt *et al.*, 2012; Di Capua *et al.*, 2013; Veciana *et al.*, 2015).

The first EEG finding in our patient was status epilepticus; subsequently, the EEG indicated EBA, and then became dominated by continuous slow activity, including GRDA and EDB, during the most severe phase of anti-NMDA receptor encephalitis. Thereafter, the slow activity became intermittent, gradually faded in parallel with clinical amelioration, and finally disappeared when the patient became independent in ADL. EBA persisted even after the slow activity disappeared, but finally changed to a posterior-dominant rhythm upon full recovery. The clinical and EEG observations indicate that the EEG findings in anti-NMDA receptor encephalitis correlate with the clinical course; slow activities, in particular, change in parallel with clinical amelioration. In addition, persistent EBA in the recovery phase may suggest that internalisation of the NMDA receptor in the cerebral cortex persists during the clinical course of anti-NMDA receptor encephalitis.

Here, we refer to the paroxysmal alpha activity observed upon arousal from sleep as the AAP. The AAP is clearly different from the normal posterior-dominant rhythm or activation of the reference electrode. The AAP may share features of alpha-delta sleep (the intrusion of prominent alpha activity on delta waves in sleep) and is found in various diseases, such as fibromyalgia (Moldofsky *et al.*, 1975). However, the AAP in this case was not seen during sleep but upon arousal from sleep, without delta waves. Furthermore, it appeared in the middle of the recovery phase and disappeared with full recovery. Although the AAP could be included in non-specific arousal responses, it may be correlated with anti-NMDA receptor encephalitis.

Conclusion

We conclude that close EEG observation in our patient with anti-NMDA receptor encephalitis revealed slow activities, including EDB during the most severe phase of anti-NMDA receptor encephalitis, that gradually faded in parallel with clinical amelioration, as well as EBA that persisted even into the recovery phase. More detailed clinical analyses and a greater number of cases are necessary to elucidate the correlation between the EEG findings, clinical course, and pathology of anti-NMDA receptor encephalitis. □

Supplementary data.

Supplementary figure is available on the www.epilepticdisorders.com website.

Disclosures.

Our patient provided informed consent. None of the authors have any conflict of interest to declare.

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TEST YOURSELF



- (1) What are the characteristic EEG findings in anti-NMDA receptor encephalitis?
- (2) How were EEG findings correlated with the clinical course of anti-NMDA receptor encephalitis in our patient?
- (3) Extreme delta brush is not associated with either status epilepticus or disease severity. Is this statement correct?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".