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Antiepileptic treatment for anti-NMDA receptor encephalitis: the need for video-EEG monitoring

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ABSTRACT – Anti-NMDA receptor encephalitis is a severe disorder characterised clinically by seizures, autonomic instability, and severe disturbances of memory, behaviour, and cognition. Due to the severity of symptoms, many patients are admitted to the intensive care unit. For some patients, the presence of various movement disorders and abnormal autonomic signs, as well as a history of seizures, lead to a false impression of status epilepticus, which is reported in 6% of the cases. Here, we present two young female patients, one of whom had ovarian teratoma. Both patients were referred to our neurological intensive care unit with a diagnosis of status epilepticus. However, prolonged video-EEG findings were compatible with encephalopathy. We avoided aggressive treatment with intravenous anaesthetics and both patients recovered after immunotherapy, one of whom received surgery. Physicians should be cautious in interpreting abnormal movements and autonomic signs in such patients and video-EEG monitoring is advised when status epilepticus is suspected. [*Published with video sequences*]

Key words: anti-NMDA receptor encephalitis, status epilepticus, video-EEG monitoring, intensive care unit

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Anti-NMDA receptor encephalitis (ANRE) is a severe disorder that has been described recently by Dalmau and colleagues (Dalmau *et al*., 2007). It occurs in association with the presence of antibodies directed to the NR1 subunit of the NMDA receptor and results in a specific syndrome, which is usually characterised by psychiatric symptoms, memory dysfunction, seizures, various movement disorders, and autoimmune instability (Dalmau *et al*., 2008). ANRE can occur in a paraneoplastic (usually ovarian teratoma in females) or non-paraneoplastic form. ANRE was reported in 1% of all young women admitted to the intensive care unit (ICU) with encephalitis of unclear aetiology (Prüss *et al*., 2010). Complex partial seizures (CPS)

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or generalised tonic-clonic seizures (GTCS) have been reported in many patients, however status epilepticus (SE) is rare (Dalmau *et al*., 2008). Seizures and SE are refractory to antiepileptic drugs (AEDs) and this may therefore lead to over-treatment (Florance *et al*., 2009). Patients usually benefit from surgical removal of the teratoma and intense immunosuppressive therapy. Unusual EEG findings and movement disorders resembling partial seizures may result in the false diagnosis of non-convulsive SE (NCSE), leading to an unnecessary increase in dose of *iv* anaesthetics and related morbidity. There are few reports in the literature of patients with ANRE who have been investigated using prolonged video-EEG monitoring in the ICU. Here, we present the clinical and electrophysiological findings in two female patients who underwent prolonged video-EEG monitoring in our neurological ICU.

Case reports

Case 1

A 25-year-old woman was admitted to a local hospital with acute-onset, psychiatric symptoms and secondary GTCS. She had fever and was encephalopathic during hospitalisation. Fourteen days after the onset of her symptoms, she was intubated because of intractable seizures and therapy was initiated with intravenous midazolam. Lymphocytosis was detected by analysis of cerebrospinal fluid (CSF), thus acyclovir was given empirically, but was ineffective. Repeated cranial MRI was reported to be normal. Phenytoin (DPH), levetiracetam (LEV), carbamazepine (CBZ), valproic acid (VPA), and zonisamide (ZNS) were added successively, however, she was still uncooperative and presented with bizarre movements in her face and extremities when midazolam infusion was stopped. Treatment with propofol, phentanyl, and thiopental infusion was also attempted but the movements reappeared each time these anaesthetics were tapered.

The patient was admitted to our hospital 45 days after the initiation of her symptoms. Besides midazolam infusion, she received CBZ, LEV, VPA, and ZNS. Neurological examination after discontinuation of midazolam showed orofacial dyskinesias, extreme hypersalivation, and episodes of hyperventilation, besides a lack of cooperation. Video-EEG monitoring was initiated due to suspected NCSE and continued for 11 days. EEG typically displayed diffuse, rhythmic, delta activity without any prominent epileptiform discharges (*figure 1*). Her autonomic symptoms or dyskinesias were not accompanied by alterations on the EEG. Altogether, these findings were not interpreted as NCSE, however, AEDs were continued because of a history of seizures at the onset of her symptoms. Attempts to taper midazolam resulted in increased autonomic instability and dyskinesias without ictal EEG patterns. Topiramate (TPM) was added and ZNS and VPA were discontinued. The patient had a history of oopherectomy for ovarian teratoma that was discovered during a Caesarean section. This, together with her clinical findings, suggested ANRE, which led to intensive radiological investigation of the pelvis after which another teratoma was detected in her remaining ovary. Her blood and CSF samples were positive for NMDA receptors (Prof Dalmau, Philadelphia, USA). Ten days after her admission to our ICU, the patient received plasma exchange five times, which was followed instantly by intravenous pulse steroid for five days. Immediately afterwards, the teratoma was surgically removed and she was also given intravenous immunoglobulin (IVIG) for five more days. The patient responded to these therapies within several days. Midazolam infusion was tapered and discontinued, and she was later taken off mechanical ventilation. CBZ and TPM were rapidly tapered. Dyskinesias decreased but persisted, therefore clonazepam (CLZ) was added and pulse steroid therapy was administered. The patient showed further improvement in the following weeks, thus CLZ and LEV were also discontinued. No epileptiform abnormalities were detected in the follow-up video EEG recordings. She was discharged six months after the onset of symptoms and has been living independently for a year with minimal cognitive impairment, based on her neuropsychological tests.

Case 2

A 26-year-old woman was admitted to hospital because of acute psychiatric symptoms. She was confused, disoriented, and had fever. Three days later, she had two partial seizures with oral automatisms. Phenytoin and LEV were started but she presented with episodes of unresponsiveness and severe tachycardia. It was assumed that she had SE and was admitted to the medical ICU, intubated, and was given intravenous midazolam infusion. Six days after the onset of her symptoms, she was transferred to our neurological ICU. In order to better characterise the clinical signs, midazolam was withdrawn and continuous video-EEG monitoring was performed for more than four days (*video sequences 1 and 2*). Background EEG activity was consistent with generalised, diffuse slowing-down in the theta-delta range, sometimes accompanied by rhythmic, delta waves and without epileptiform activity, similar to that shown in *figure 1*. Stereotypic rotatory movements involving her head and extremities, frequent blinking, and paroxysmal attacks of severe dysautonomia were recorded, but there were no ictal EEG changes. Midazolam was not

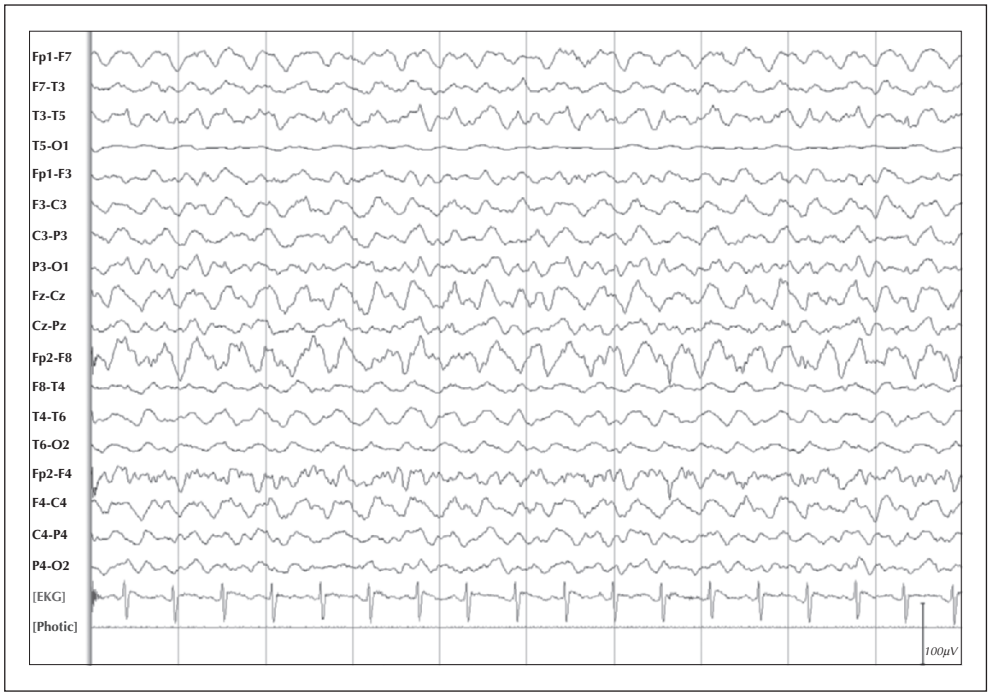

Figure 1. The most characteristic findings of continuous EEG recordings were rhythmic, 2-3-Hz, moderate, high-amplitude delta activity in Case 1.

re-introduced and she was extubated. As her clinical findings suggested ANRE, blood and CSF samples were examined for the presence of NMDA receptor antibodies, which were found to be positive (Prof Dalmau, Philadelphia, USA). Exhaustive radiological investigations failed to detect a tumour. Fifteen days after admission to our ICU, the patient received IVIG for five days which was repeated after three weeks. She responded well to this treatment within 1-2 weeks. Phenytoin was withdrawn and LEV was tapered over two weeks, however, she had a secondary generalised tonic-clonic seizure shortly afterwards, thus treatment was re-initiated. EEG monitoring as an outpatient revealed mild, diffuse slowing-down of background activity and sharp-wave activity over the left temporal lobe. Further clinical improvement was seen with repeated IVIG treatment once every three weeks. At the last follow-up visit, almost one year after discharge, she was clinically symptom-free with normal neuropsychological test results.

Discussion

ANRE is a severe disorder characterised clinically by seizures, autonomic instability, and severe disturbances of memory, behaviour, and cognition (Dalmau *et al*., 2008). The exact frequency is unknown, however, the rapidly growing number of recent publications demonstrates increasing awareness since its first description in 2007 (Dalmau *et al*., 2007). ANRE is usually seen in young females and is associated with a tumour, most commonly ovarian teratoma. The frequency of teratoma varies with age and is detected in almost 60% of females >18 years old, but 9% in girls ≤14 years old (Florance *et al*., 2009). Cranial MRI is normal in about half of the cases and various abnormal findings are observed in the other cases. Encephalitis usually progresses rapidly, necessitating prolonged ICU care for many patients. Better outcome and fewer relapses have been reported in patients who receive early tumour treatment, usually with immunotherapy. Recovery is typically slow and the rate of severe morbidity or mortality is about 25% (Dalmau *et al*., 2008).

For 76% of patients, seizures are often described as CPS or GTCS. In general, the frequency and intensity of the seizures decrease as the disease evolves. In accordance with this observation, epileptiform discharges were reported on EEG in 20% of patients early during the course of the disorder, but a generalised slowing-down in the theta-delta range was found later in 80% patients. Status epilepticus was reported in 6% of patients (Dalmau *et al*., 2008).

Seizures were one of the presenting symptoms for both of our patients. Although no EEG data were provided, the first patient was probably initially in SE and was treated with AEDs and intravenous anaesthetics. She was thought to have drug-resistant

NCSE and received aggressive SE treatment for six weeks. However, the findings based on prolonged video-EEG monitoring in our ICU were compatible with encephalopathy, thus aggressive treatment with various intravenous anaesthetics was avoided. Midazolam could not be withdrawn because each time the dose was tapered, dyskinesias and hyperventilation increased (Vural *et al*., 2012). AEDs did not alter the clinical findings but were administered, largely to prevent the recurrence of seizures that had occurred previously. The patient began to improve only after surgical removal of the tumour and intensive immunotherapy. The second patient was intubated and followed with midazolam in the medical ICU, since she was thought to have SE at the onset of her symptoms. Her abnormal movements and history of complex partial seizures were most probably misleading. Again, prolonged video-EEG recordings demonstrated only generalised slowing-down of background activity, without any clear ictal changes. Midazolam was withdrawn without any further clinical change. She only received AEDs based on a history of CPS. Similar to the first patient, this patient also improved only after immunotherapy.

Both of these cases demonstrate the diagnostic utility of prolonged video-EEG monitoring for patients with ANRE who are suspected to have SE, either convulsive or non-convulsive. There are few publications related to findings associated with video-EEG monitoring in these patients, most of which are case studies (Johnson *et al*., 2010; Goldberg *et al*., 2011; Kirkpatrick *et al*., 2011). Based on a very recent multicentre study of continuous video-EEG monitoring of 23 cases, the frequency of electrographic seizures was reported to be 60% (Schmitt *et al*., 2012). Ictal transformation, characterised by evolution of EEG patterns over time, has otherwise been reported in rare case studies (Chan *et al*., 2010; Kirkpatrick *et al*., 2011; Bayreuther *et al*., 2009; Johnson *et al*., 2010; Goldberg *et al*., 2011). The most characteristic EEG finding in our patients was diffuse, rhythmic, delta activity that lacked clear-cut evolution of waveforms. Rhythmic, delta activity may be detected in up to 17.4% in this group of patients (Schmitt *et al*., 2012) and should therefore be interpreted with caution.

The treatment of ANRE has been investigated using many different AEDs, without clear success. Although a patient was reported to respond to felbamate (Kirkpatrick *et al*., 2011), magnesium, ketamine and other NMDA receptor blockers did not lead to dramatic improvement in another patient (Davies *et al*., 2010). The most effective way to control both encephalopathy and seizures is aggressive immunotherapy, and surgery in relevant cases. Before attributing any improvement to AEDs, it should be kept in mind that recovery may take time after surgery or immunotherapy. Moreover, attempts to wean patients off sedation may result in increased respiratory difficulties, dyskinesias, hypoventilation or hypersalivation, *etc*. Physicians should be cautious in interpreting these signs as seizures and prolonged video-EEG monitoring may help to establish a correct diagnosis. □

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Legends for video sequences

Video sequence 1

High-amplitude, tremor-like, bilateral upper extremity movements (Case 2). EEG findings are obscured by movement artefact.

Video sequence 2

Right-to-left, high-frequency movement of the head (Case 2). EEG findings are again obscured by movement artefact.

Key words for video research on *www.epilepticdisorders.com*

Syndrome: non epileptic paroxysmal disorder
Etiology: Encephalitis (anti-NMDA receptor)
Phenomenology:
status epilepticus (non convulsive);
nonepileptic paroxysmal event;
behavior (altered)
Localization: not applicable

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