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PRACTICAL PEARL

Anti-N-Methyl-D-Aspartate Receptor Encephalitis with Favorable Outcome Despite Prolonged Status Epilepticus

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Abstract
Background To describe a case of auto-immune encephalitis in an adolescent with favorable outcome despite prolonged status epilepticus.
Methods A 17 year old Asian man without previous medical history developed alteration of consciousness and partial seizures. The diagnosis of anti-N-methyl-D-aspartate receptor encephalitis was confirmed by the detection of specific antibodies in both cerebrospinal fluid and serum.
Results The clinical course was complicated by prolonged status epilepticus which was refractory to a large number of antiepileptic drugs, including barbiturate coma. Immunomodulatory therapy included steroids, plasma exchanges, and intravenous immunoglobulins. After 86 days of intensive therapy, the patient regained consciousness progressively. Brain magnetic resonance imaging never demonstrated any lesion. Extensive search for a tumor was negative. At 12 month follow-up, the patient had made an excellent recovery.
Conclusion Auto-immune encephalitis is likely underdiagnosed in adolescents. In their most severe presentation, seizures may be resistant to a large number of anti-epileptic drugs, and the clinical improvement seems to be mainly because of the immunomodulatory therapy. Relapse is possible, as well as the delayed development of a teratoma or other tumor.

Keywords Encephalitis · Anti-NMDA receptor antibodies · Status epilepticus · Seizure management · Ketamine · Immunosuppressive therapy

Introduction

In children and adolescents, psychiatric disorders combined with epileptic seizures and altered consciousness of subacute onset are usually consistent with limbic encephalitis. Diagnostic priority is to exclude viral encephalitis, particularly because of herpes simplex virus. Recent publications suggest that auto-immune encephalitis is likely underdiagnosed [1]. Within this auto-immune disease group, anti-N-methyl-D-aspartate receptor (NMDAR) antibodies have been shown to induce a broad spectrum of neurologic disorders, ranging from memory deficits to coma and convulsions [2, 3]. We report a recent case with favorable outcome despite prolonged status epilepticus.

Case Report

A 17 year old Asian man without previous medical history complained for 2 days of intense fatigue and flulike

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symptoms. He was admitted to another hospital because of right focal epileptic seizures. Initial symptoms were repeated lateral rotations of the head to the right. The patient also complained from mild paresis and paresthesia in the right hand and foot. At the time of admission, he was fully alert with a glasgow coma score (GCS) of 15/15 and no motor deficit. No neck stiffness was noted at physical examination. Contrast-enhanced brain computed tomography did not reveal any specific lesion. Cerebrospinal fluid (CSF) analysis showed an increased white blood cell count (40/μl, 100 % lymphocytes), but concentrations of a normal glucose (77 mg/dL), proteins (17 mg/dL), and lactate (14.2 mg/dL). A few CSF-restricted oligoclonal IgG bands were detected. The first hypothesis was viral encephalitis complicated with partial seizures. Accordingly, the initial treatment included acyclovir and valproic acid. Levetiracetam was introduced on the second day, as seizures persisted. However, CSF culture remained negative as well as the polymerase chain reaction for Herpes simplex virus. This CSF sample was no longer available for further studies, but the paired serum sample was negative for anti-NMDAR, anti-LGI1, and anti-GABARb1 antibodies in an indirect immunofluorescence biochip mosaic assay (Biognost, Heule, Belgium). The patient's neurologic condition worsened over the next 12 days. He became confused and disorientated, with a stiff and painful neck, and was transferred to the intensive care unit (ICU). He presented right-sided partial complex seizures evolving to status epilepticus. Orotracheal intubation was required, and after failure of phenythoin therapy, barbiturate coma was started. The patient was referred to our university hospital on day 23. His GCS was 3/15 under barbiturate therapy. Valproic acid had been stopped because of hyperammoniemia. The electroencephalogram (EEG) performed upon admission revealed intermittent interictal epileptiform discharges in the left central and fronto-temporal areas. They rapidly disappeared following introduction of topiramate. The CSF collected on day 24 showed an increase in the number of oligoclonal IgG bands. Anti-NMDAR antibodies were detected in both CSF and serum samples, and this result was confirmed in another CSF sample collected on day 32. The diagnosis of anti-NMDAR encephalitis was made, and the patient was first treated with intravenous methylprednisolone, 1 g/day for 5 days with oral tapering, followed by five plasma exchanges, and finally with intravenous immunoglobulins, 0.4 g/kg day for 5 days. Orofacial dyskinesias were evident from day 26 without concomitant epileptiform discharges during continuous EEG monitoring (c-EEG). Thiopental infusion was gradually tapered down from day 30 and stopped on day 34. Eye opening was noted, not only with some motor response, but also with periods of agitation or prostration. The patient presented stereotypic movements with elevation of the legs (video). Hypertonia was noted in the four limbs. On day 40, generalized tonic–clonic seizures reappeared and marked dysautonomic symptoms were present (diaphoresis, tachycardia, hypertension, etc.). Thiopental was then reintroduced with lacosamide. Clinical seizures disappeared. In contrast, c-EEG documented recurrent electrical seizures, consisting of rhythmic epileptiform discharges beginning in the temporal regions, predominant on the left, followed occasionally by secondary generalization (Fig. 1). Seizures lasted between 10 and 650 s, and up to seven seizures per hour were noted. Some periods of electrical status epilepticus were recorded (Fig. 1). Ketamine was started on day 66, because of persistence of electrical seizures under barbiturate therapy, at a rate of 1 mg/kg h and gradually increased up to 3 mg/kg h. Thiopental was definitively stopped on day 70 and replaced by midazolam (10 mg/h). Seizure activity upon c-EEG gradually decreased and disappeared on day 76. Ketamine was administered for a total of 13 days, and midazolam infusion was progressively decreased and stopped on day 86. CSF anti-NMDAR antibodies were still present in the sample collected on day 62, but barely detectable on day 85. The patient gradually regained consciousness, with spontaneous eye opening and motor response. Neurologic examination was mainly characterized by extreme agitation and delirium alternating with prostration. When the patient was discharged from the ICU on day 93, he was awake, but completely mutic. Oral corticosteroids were definitely withdrawn after 6 months. Brain MRI did not demonstrate any focal abnormalities throughout the disease. Extensive search for a teratoma or other neoplasms was negative.

After 1 year of rehabilitation, the patient was free of symptoms and could resume his high school education.

Discussion

Antibodies against the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptors have been reported in patients with encephalitis with an incidence that remains to be determined [2, 3]. The diagnosis can be specifically made by detecting intrathecal anti-NMDAR antibodies by immunofluorescence.

It affects preferentially women (80 %), with a clear association with ovarian teratoma [4, 5]. Only 5 % of male patients older than 18 years have an underlying tumor. With increased awareness of the disorder, recent series show that the disease may also occur in younger teenagers and children [1, 6].

Patients with anti-NMDAR encephalitis may present with only psychiatric disturbances and amnesia [7]. Severe forms are characterized by seizures, autonomic features, obtundation, orofacial dyskinesias, and intermittent jerking

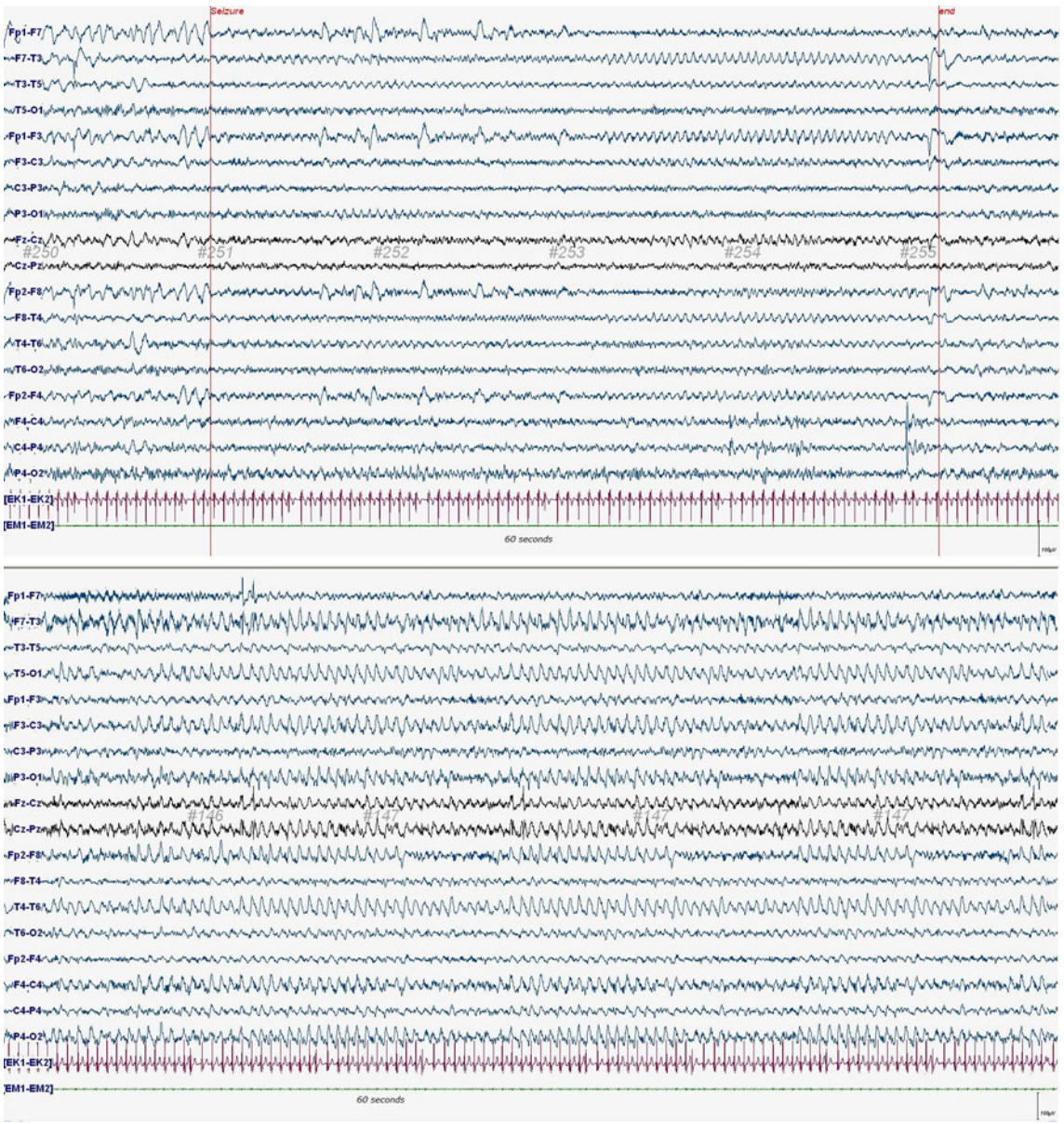

Fig. 1 EEG samples during the ICU monitoring. In the *upper part* of the figure, an illustrative pattern of an electroclinical seizure is shown, with rhythmical delta waves in the fronto-temporal areas occurring in association with orofacial dyskinesias (day 26). In the *lower part* of the figure, under barbiturate therapy after day 40, the same electrical pattern is observed in a continuous mode for several hours, corresponding to electrical status epilepticus without evidence of clinical manifestations

of the limbs and trunks. These abnormal movements combined with altered consciousness and hypoventilation are the primary indication for sedation and mechanical ventilation [8]. Motor or complex seizures develop at early stages of the disease [2, 3]. For the ICU physician, the differential diagnosis between abnormal movements and epileptic seizures is often difficult, with a risk of either under recognition of the seizures, or overtreatment of dyskinesias with antiepileptic drugs. Continuous EEG monitoring is therefore strongly recommended. Dysautonomic manifestations are also often very impressive (autonomic storms), and include hyperthermia and alternating brady-tachycardia and hypo-hypertension [3].

Despite prolonged ICU stay, even due to status epilepticus, the prognosis of anti-NMDAR encephalitis is good with an estimated mortality of 4 %, and about 75 % of patients recover or have mild sequelae [2]. The final outcome is almost the same in patients with or without tumor.

The treatment of severe forms of NMDAR encephalitis mainly relies on immunomodulatory therapy and tumor removal, when identified [3]. As first-line of immunotherapy, most patients receive corticosteroids, intravenous

immunoglobulins (IVIg), or plasma exchange [9]. The first-line treatment seems more effective when a tumor is found and removed. In patients without a tumor or with delayed diagnosis, second-line immunotherapy with rituximab or cyclophosphamide is usually required. Because relapse is possible in 20 % of patients (mainly in those without teratoma), immunosuppression with mycophenolate mofetil or azathioprine should be continued for at least 1 year. As for seizure management, classical antiepileptic drugs may certainly be proposed, but seizures are also influenced by the natural history of the disease and by the immunomodulatory therapy. While it appears that the frequency and intensity of the seizures decrease as the disease evolves, seizures and status epilepticus can recur at any time of the illness, particularly during the weaning of the patients from sedation, as illustrated by the present observation. In refractory cases, the possible antiepileptic activity of NMDAR antagonists, like ketamine or magnesium, can be discussed. There is a limited clinical experience suggesting that ketamine may be useful at a late stage for termination of status epilepticus [10].

Conclusions

Anti-NMDAR encephalitis in male teenagers is an unusual and often misdiagnosed entity that is usually not associated with a tumor. Despite delayed diagnosis and prolonged epileptic manifestations, the final outcome may be excellent, but relapse is possible. Seizures are often refractory to the most commonly used antiepileptic drugs, but are likely better influenced by the immunomodulatory therapy. They should be clearly distinguished from dyskinesias and stereotypic movements.

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