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Case Report

Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis

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ABSTRACT

Anti-NMDA receptor antibody encephalitis is a limbic encephalitis with psychiatric manifestations, abnormal movements, coma, and seizures. The coma and abnormal movements are not typically attributed to seizure activity, and slow activity is the most common EEG finding. We report drug-resistant nonconvulsive status epilepticus as the basis for coma in a 19-year-old woman with anti-NMDA receptor antibodies and a mediastinal teratoma. The EEG showed generalized rhythmic delta activity, with evolution in morphology, frequency, and field typical of nonconvulsive status epilepticus. The status was refractory to antiepileptic drugs, repeated drug-induced coma, resection of the tumor, intravenous steroids, rituximab, and plasmapheresis. She awoke after the addition of felbamate, and the rhythmic delta activity ceased. The rhythmic delta activity described with coma in anti-NMDA receptor antibody encephalitis may represent a pattern of status epilepticus in some patients. Felbamate, which has NMDA receptor antagonist activity, should be studied as a therapeutic agent in this condition.

1. Introduction

Anti-NMDA receptor antibody-related limbic encephalitis is a relatively new entity [1]. In 2008, Dalmau et al. reported a case series of 100 patients with encephalitis and NMDA receptor antibodies [2]. All patients presented with psychiatric symptoms or memory problems. Various types of seizures occurred in 76%. Status epilepticus was reported in only 6%, whereas coma/unresponsiveness was reported in 80% of patients, attributed mostly to encephalitis rather than seizure activity. The EEG was reported to show delta or theta activity, generalized or in frontotemporal regions in 71%, and epileptic activity in only 21% of patients [2]. There have been only few reports of drug-resistant status epilepticus related to this condition [2,3]. We describe a case of anti-NMDA receptor antibody encephalitis with coma and EEG rhythmic delta activity that proved to be a pattern of nonconvulsive status epilepticus.

2. Case study

A 19-year old, right-handed, previously healthy woman initially complained of periods of amnesia and memory difficulties for 3 months. Pronounced behavioral problems were noted by her parents and college classmates after she watched the movie *Paranormal Activity*. Following the film, she was noted to be emotionally labile and to cry for 45 minutes. The following day she began to have religious verbalizations and auditory hallucinations in class. She also displayed personality changes and bizarre behaviors, responding to hallucinations and reacting aggressively. Her aberrant behaviors prompted her professor to call the campus police. The patient was not cooperative, which led to her arrest. She was taken to a local emergency room where she denied anything was wrong. When examined, she was amnestic to prior events. A head CT scan was unremarkable. She was documented to have slurred speech, delusions, flight of ideas, and visual and auditory hallucinations. She was admitted and treated with antipsychotics, initially ziprasidone, and benzodiazepines. She was then transferred to a secondary care center, where MRI of the brain with and without contrast showed a small area of encephalomalacia in the right centrum semiovale with surrounding T2 hyperintensity, which was thought to be incidental and related to an old ischemic insult. There was no restricted diffusion to suggest acute infarct. No other areas of abnormal parenchymal signal were present on FLAIR sequence and there was no contrast enhancement. Lumbar puncture showed no nucleated or red blood cells and was negative for herpes simplex by PCR. She was reported to have clinical seizures, but there were no detailed descriptions of the events. Because of recurrent seizures the patient was sedated and intubated, then transferred to our medical center. On arrival, she was sedated with a propofol infusion. This infusion was stopped for an initial examination and the patient was comatose with intact brainstem reflexes. She had a left beating nystagmus and lip smacking. Plantar

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responses were mute bilaterally. Continuous EEG monitoring showed almost continuous generalized rhythmic delta activity and absent posterior dominant rhythm (Fig. 1). The rhythmic delta activity had an evolution in voltage, frequency, and field consistent with nonconvulsive status epilepticus. This evolution of the EEG pattern became more apparent when the EEG was compressed (Fig. 2). She was treated aggressively with benzodiazepines (lorazepam, diazepam) and other antiepileptic drugs (phenytoin, levetiracetam, valproate) at high doses and with drug level monitoring. Another lumbar puncture was performed 1 week after admission to our ICU. The cell count was normal (5 white cells and 2 red cells per microliter). Glucose (62 mg/dL) and protein (18 mg/dL) were also normal. There were no oligoclonal bands. The gram stain was negative. She was started on prednisone for suspected steroid-responsive encephalopathy. Given that the patient remained in status, she was placed into a pentobarbital-induced coma to a burst suppression pattern. She had recurrence of nonconvulsive status epilepticus after pentobarbital withdrawal and repeatedly required resumption of drug-induced coma (up to 3 days each time), while we added oxcarbazepine, then phenobarbital, with no improvement. CT of the chest, abdomen, and pelvis revealed a 5.1 × 4-cm right anterior mediastinal mass. An extensive metabolic and immunological workup revealed anti-NMDA receptor antibodies. The mass was removed and pathology was consistent with a teratoma. Pentobarbital was stopped the day after surgery, but the patient remained unresponsive and lip smacking recurred with the EEG pattern of nonconvulsive status epilepticus. This persisted even after she was started on aggressive immunosuppression including rituximab, high-dose steroids, and repeat plasmapheresis. Four days after surgery, she was placed back in pentobarbital-induced coma. At the same time, felbamate was added at 3600 mg per day. After 2 days, pentobarbital was stopped, and for the first time the pattern of nonconvulsive status did not recur. This was followed by gradual clinical improvement. Six weeks after the initiation of this treatment the patient was able to communicate and follow commands. Following 3 months of rehabilitation, the patient improved dramatically to almost baseline cognitive function. Ten months after discharge, she reported only some residual memory difficulties and right lower extremity weakness. Formal neuropsychiatric testing was not performed. However, she is near her previous baseline, and back in college with a B average.

3. Discussion

We described a patient with anti-NMDA receptor antibodies in whom coma was secondary to nonconvulsive status epilepticus. The EEG pattern of rhythmic delta activity would not have been diagnostic of nonconvulsive status without careful assessment of EEG evolution over time, facilitated by compression of the EEG time base. There are few reports of status epilepticus in association with anti-NMDA receptor antibody limbic encephalitis [3–5]. The largest series reports status epilepticus in only 6% of patients, yet decreased level of consciousness and unresponsiveness are described in 80% [2]. The EEG is reported to show delta or theta activity in the majority of patients. We propose that at least in some patients, delta activity may have been ictal in nature. The published ictal EEG shows delta activity in two case reports [3,4]. The notching, the evolution of frequency and morphology, and the response to therapy are clues to the ictal nature of the EEG pattern [6–8]. The main purpose of our case report is to increase the index of suspicion for nonconvulsive status epilepticus as an explanation for coma in anti-NMDA receptor antibody-related encephalitis and to emphasize the need for continuous or long-term EEG monitoring in this patient population.

Our patient presented with psychiatric manifestations, consistent with the majority of reported patients [2]. Psychosis has been linked to alteration of NMDA receptor activity. It is mostly hypoactivity of these receptors that is known to produce symptoms of psychosis [9,10]. The occurrence of seizures, abnormal movements, and decreased level of consciousness in a patient (particularly a young woman) with psychosis should prompt an investigation for anti-NMDA antibodies and associated neoplasm.

The most common neoplasm associated with anti-NMDA receptor encephalitis is an ovarian teratoma. However, the condition may be

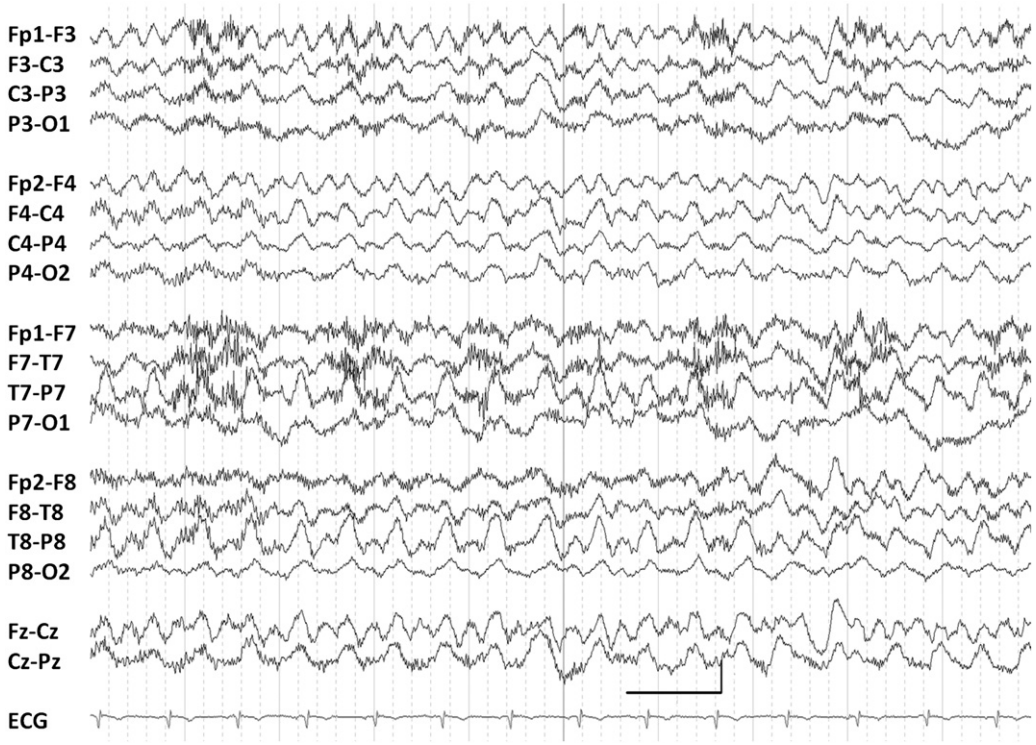

Fig. 1. EEG obtained 2 days after admission showing generalized rhythmic delta activity. The evolution of the EEG pattern is difficult to appreciate based on one 10-second epoch. The calibration mark represents 1 second and 50 μV.

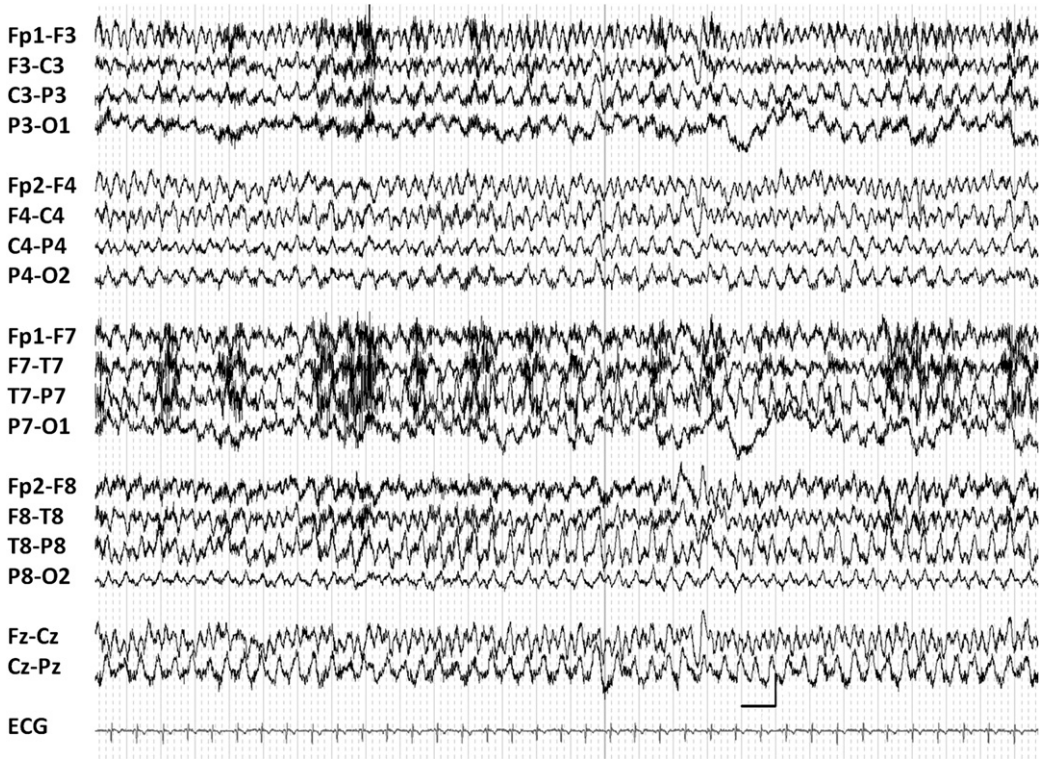

Fig. 2. EEG from one 30-second epoch including the 10-second period represented in Fig. 1, demonstrating evolution of the ictal pattern over time. The calibration mark represents 1 second and 50 μV.

associated with teratomas in other locations and even with other tumors. The present case report is, to the best of our knowledge, the second report of teratoma located in the mediastinum causing anti-NMDA receptor encephalitis. Anti-NMDA receptor antibodies have also been reported with Hodgkin's disease [11], a sex-cord stromal tumor, and a neuroendocrine tumor [2].

Status epilepticus in our patient was highly resistant to anti-epileptic drugs, and responded only after the addition of felbamate, which was chosen for its NMDA receptor antagonist effect. It is possible that felbamate is an effective treatment in this condition, even though we cannot exclude that there was also a delayed response from immunotherapy or resection of the teratoma. Felbamate's NMDA receptor antagonist activity was reported to be selective for the NR2B subunit of the NMDA receptor [12,13], and anti-NMDA antibody binding was reported to co-localize with the NR2B subunit of the NMDA receptor, which is preferentially expressed in the hippocampus and forebrain [1]. Felbamate has been associated with aplastic anemia and liver failure in a small percentage of treated patients. These serious idiosyncratic adverse effects usually do not occur before several weeks of treatment; felbamate can be discontinued after status is controlled, thus markedly reducing the risk of these idiosyncratic reactions. The possible role of felbamate as a specific treatment for status epilepticus related to anti-NMDA receptor encephalitis should be investigated further.

Continuous EEG monitoring was crucial to the diagnosis of nonconvulsive status epilepticus in this patient, and this case emphasizes the importance of continuous EEG monitoring in this subset of patients. Continuous EEG recordings increase the ability to identify evolution of the EEG pattern over time for the diagnosis of nonconvulsive status epilepticus, and allow monitoring of the effect of various treatments on these EEG patterns. It is likely that recognition and aggressive treatment of nonconvulsive status epilepticus will improve outcome in patients with anti-NMDA receptor antibody encephalitis.

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