Clinical Case Report

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Efficacy of perampanel for anti-*N*-methyl-D-aspartate receptor encephalitis

A case report

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Abstract

Rationale: We report this 1st case because perampanel may be effective against the seizures and abnormal behavior that occur in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.

Patient concerns: The patient was a healthy 26-year-old woman who suddenly developed seizures and exhibited abnormal behavior.

Diagnoses: NMDAR encephalitis was diagnosed based on positive NMDAR antibody on cerebrospinal fluid analysis.

Interventions: Treatment with anticonvulsants and sedatives was started immediately, along with steroid pulse therapy and plasmapheresis, but these measures did not adequately control the repeated seizures and abnormal behavior. However, with the addition of oral perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, the seizures and abnormal behavior promptly disappeared.

Outcomes: The patient was transferred to the rehabilitation hospital and returned to her job.

Lessons: It appears that perampanel rapidly eliminated these clinical features by inhibiting inflow of abnormal glutamic acid and attenuating nerve hyperexcitability by acting as a selective and noncompetitive antagonist of AMPA receptors that had increased in the postsynaptic membrane due to anti-NMDAR encephalitis. To the best of our knowledge, there are no other reports showing that perampanel was effective against anti-NMDAR encephalitis. This case suggests that perampanel may be effective against the seizures and abnormal behavior that occur in anti-NMDAR encephalitis.

Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CT = computed tomography, EEG = electroencephalography, MRI = magnetic resonance imaging, NMDAR = N-methyl-D-aspartate receptor.

Keywords: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, abnormal behavior, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, perampanel, seizures

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a form of acute autoimmune encephalitis that was 1st described in a case report of 4 young female patients by Vitalian et al in a 2005,[1] and was later found to be mediated by antibodies against extracellular components of NMDAR by Dalmau et al in 2007.[2] The initial clinical symptoms are nonspecific prodromal symptoms such as headache or symptoms of flu-like illness or a similar upper respiratory infection, followed by any of various serious symptoms including abnormal behavior, cognitive impairment, speech dysfunction, seizures, involuntary movements, reduced level of consciousness, autonomic nerve disorder, and hypoventilation. Although uncommon, sudden seizures can also occur as an initial symptom.[1–7] In the present case, we used the α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) antagonist perampanel to treat a patient with anti-NMDAR encephalitis presenting with sudden repeated seizures and abnormal behavior that were inadequately controlled by treatment with steroid pulse therapy and plasmapheresis, and the symptoms promptly disappeared. Perampanel possibly eliminated the seizures and abnormal behavior by acting as a selective and noncompetitive antagonist of AMPA receptors (AMPAR) that had increased in the postsynaptic membrane due to autoimmune anti-NMDAR encephalitis to attenuate nerve hyperexcitability

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Consent for publication: Informed consent was obtained from the patient for publication of this case report. A copy of the consent form is available for review by the journal editor.

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caused by glutamate. We report this 1st case because perampanel may be effective against the seizures and abnormal behavior that occur in anti-NMDAR encephalitis.

2. Case report

The patient was a 26-year-old female bank employee. Her chief complaints were repeated seizures and abnormal behavior, and she had no past medical history of note including seizures. She did not smoke or drink alcohol. She had been previously healthy and did not exhibit any flu-like prodromal symptoms such as fever or headache. However, while eating lunch with her mother at a restaurant at 2:00 PM on March 29, she developed sudden generalized tonic-clonic seizures with upward rolling of the eyes, limbs extended, teeth clenching, and altered consciousness (Fig. 1). The seizure had lasted for 5 min and her mother called an ambulance. Her consciousness level improved on the way to the hospital. Results of blood tests and head magnetic resonance imaging (MRI) performed on arrival at the hospital were unremarkable, so the patient was administered an intravenous drip of levetiracetam 1 g and sent home with no oral medications. She subsequently did not experience any more seizures, however, around dinner time on March 31, she suddenly had a repeated episode of abnormal behavior witnessed by her mother, whom she repeatedly asked meaningless questions such as "Write down these recent episodes, what is the current condition?" in a stronger tone of voice than usual. The following day on April 1, the patient went to a scheduled appointment with her previous doctor for electroencephalography (EEG). Although suspected rhythmic slow waves were detected in the left and right frontal regions of the head, there was no seizure spike wave. As this was the patient's 1st seizure, no oral anticonvulsant was prescribed and she was scheduled for outpatient follow-up. After returning home, she went to get a massage with her mother. The mother went to the bathroom and returned to find her lying down unconscious on the couch in the waiting room, so she called an ambulance. The patient was brought to the previous hospital but had regained consciousness upon arrival. Head computed tomography (CT) results were unremarkable, so she was sent home. On April 2, she visited another clinic out of concern. She was sent home wearing a Holter electrocardiography monitor. After she returned home, she started behaving abnormally again, repeating the same incoherent phrases over and over and trying to speak without any words coming out. Soon after that, she began having a tonic-clonic seizure with upward rolling of the eyes and limbs extended, and was brought to the previous hospital by ambulance and admitted (Fig. 1). On arrival, she had a fever in the range of 37°C. An intravenous drip of levetiracetam 1 g/day was started, but the patient continued to have speech dysfunction like aphasia and the abnormal behavior persisted, so encephalitis was considered to be the likely diagnosis. Therefore, cerebrospinal fluid was collected for analysis that same day. Opening pressure was 175 mm H_2O, cell count was 85 (lymphocytes 67), protein level was 24 mg/dL, and the glucose level was 64 mg/dL. Neither herpes simplex encephalitis nor autoimmune encephalitis could be ruled out, so the patient was started on an intravenous drip of acyclovir 750 mg/day and steroid pulse therapy 1 g/day. She still had occasional seizures after that point, so oral lamotrigine (25 mg once daily) was started on April 4. Nevertheless, she continued to exhibit abnormal behaviors such as gripping the bed railing and repeating the word "Okay?" over and over and lining up disposable chopsticks and glue stick on the table in a nonsensical manner. A repeat EEG showed intermittent irregular slow waves in the right frontal region, but no spike wave. Abdominal plain CT performed as part of a diagnostic workup showed suspected calcification in the ovaries, so the

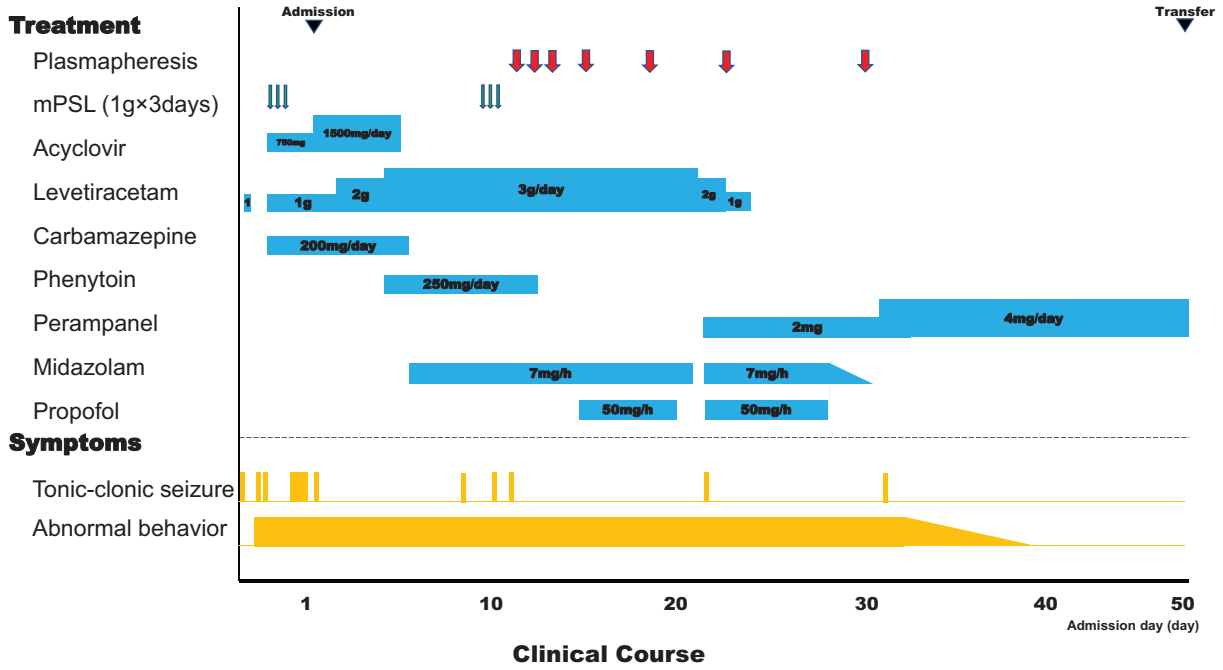

Figure 1. Clinical course. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis manifesting as seizures and abnormal behavior. Treatment with anticonvulsant and sedative drugs was started immediately along with steroid pulse therapy (a total of 2 cycles) and plasmapheresis (a total of 7 sessions). However, these treatments did not adequately control the repeated seizures and abnormal behavior. The seizures and abnormal behavior promptly disappeared with the addition of oral perampanel on day 22 of hospitalization. NMDAR = N-methyl-D-aspartate receptor.

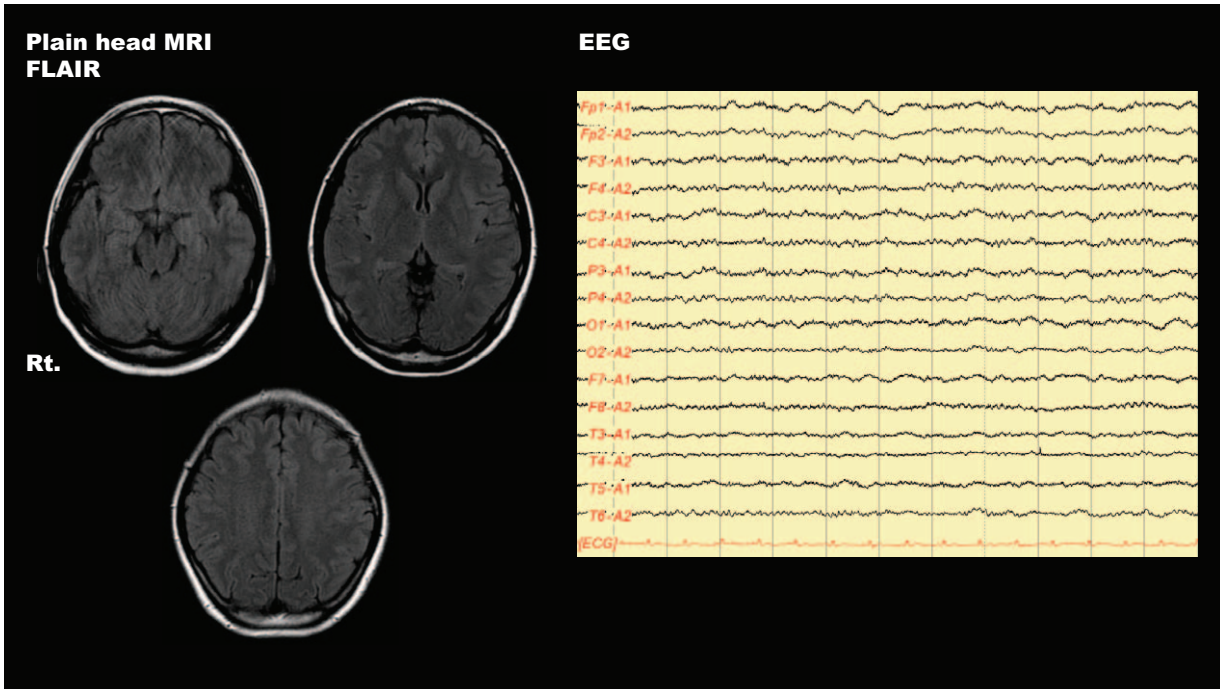

Figure 2. Brain MRI and EEG. Plain head MRI performed on day 2 of hospitalization was unremarkable, and no spike wave was detected on EEG on day 6. EEG = electroencephalography, FLAIR = fluid attenuated inversion recovery, MRI = magnetic resonance imaging, Rt. = right.

patient was transferred to our hospital on April 6 for further examination and treatment.

Upon arrival at our hospital, vital signs were as follows: blood pressure 129/67 mm Hg, pulse 78 bpm, body temperature 36.6°C, respiratory rate 14/min, SpO_2 98% (room air). General physical findings were unremarkable. On neurological examination, consciousness level was E4V4-5M6 on the Glasgow Coma Scale, the patient was not responsive to verbal commands, she did not speak coherently, and she kept repeating the same meaningless phrases such as "I don't understand, I don't understand" and "food, food". There were no cranial nerve, motor system, reflex, sensory system, or co-ordination abnormalities, and no meningeal signs. Blood tests on admission showed that although the white blood cell count was 14300/μL, C-reactive protein was 0.05 mg/dL, hepatic and renal function were normal, and other parameters such as electrolytes and blood glucose were normal. On cerebrospinal fluid analysis, the cell count was 40 (mononuclear cells 37, segmented neutrophils 3), protein level was 20 mg/dL, glucose level was 95 mg/dL, and occult blood was not detected. Results of electrocardiography, plain chest X-ray, and head plain CT were also unremarkable; the only notable finding on chest and abdominal plain CT was suspected calcification near the right ovary. After transfer, administration of acyclovir and levetiracetam 1 g/day by intravenous drip was continued, and lamotrigine was switched to oral carbamazepine (Fig. 1). On day 2 after admission, the patient exhibited the following: repeated involuntary flexing and extending of the right arm for no clear purpose and other abnormal behaviors that were difficult to distinguish as voluntary or involuntary movements; restless behavior such as repeatedly sitting up; and communication disturbance. These occurred several times that day, so on day 3, the dose of intravenous levetiracetam was increased to 2 g/day and diazepam injection 5 mg was administered as needed. The abnormal behavior and impaired consciousness temporarily diminished with these treatment changes. Plain head MRI performed that day was unremarkable (Fig. 2), and plain pelvic MRI performed on day 3 showed no ovarian tumors or lymph node swelling. Nevertheless, the abnormal behavior, involuntary movements, restlessness, and communication disorder persisted, so the dose of intravenous levetiracetam was increased to 3 g/day on day 5, and continuous infusion of phenytoin was started as well. Another EEG performed on day 6 still showed no spike wave (Fig. 2), but the patient's previous doctor reported that cerebrospinal fluid had tested positive for anti-NMDAR antibody. Therefore, acyclovir was discontinued that day, and an intravenous infusion of midazolam was started to treat the persistent abnormal behavior, involuntary movements, and restlessness. With midazolam, involuntary movements such as thrashing of the feet and bowing forward disappeared, but the patient continued to repeat the same words in conversation over and over. In another cerebrospinal fluid analysis performed on day 8, cell count was 5 (mononuclear 5), protein level was 31.5 mg/dL, and glucose level was 69 mg/dL. Consequently, a 3-day steroid pulse therapy regimen (1000 mg over 3 days) was started on day 9. However, the patient continued to repeatedly exhibit various abnormal behaviors and involuntary movements such as making chewing motions, gesturing like she was going to spit out food, thrashing her feet alternating from left to right, suddenly bursting into laughter, thrusting out her arms, throwing back her arms and legs at the same time, and trying to go over the bed railings, and she still had speech dysfunction. On the morning of day 12, she had a sudden generalized tonic seizure with upward rolling of the eyes. Single filtration plasmapheresis was started that day. Even after starting plasmapheresis, the patient remained unresponsive and aphasic. She would laugh on occasion, with involuntary movements of the right leg. Communication would temporarily improve after administration of intravenous midazolam, and she

would become able to converse casually. Phenytoin was discontinued on day 13 as it was judged ineffective. The EEG performed on day 15 still showed no spikes, so intravenous propofol infusion was added and plasmapheresis was continued to treat the abnormal behavior. Plain head MRI performed that day and plain head CT performed on day 22 were both unremarkable. The abnormal behavior and seizures persisted even during plasmapheresis, so midazolam 7 mg/h and continuous infusion of propofol were continued. Reduction of the midazolam dose triggered the typical generalized tonic-clonic seizures, so oral perampanel 2 mg/day was added on day 22. When the dose was increased to 4 mg/day on day 31, the generalized tonic-clonic seizures, abnormal behavior, and involuntary movements disappeared, and the patient was able to communicate well. It was then possible to taper off intravenous midazolam. The patient was transferred to another institution on day 49 for rehabilitation to address residual impairment of higher brain functions. It should be noted that plain head MRI and abdominal contrast CT performed on day 32 and EEG and a brain I-123 Iofetamine single-photon emission CT scan performed on day 42 were also unremarkable. Based on these results, perampanel was reduced from 4 mg to 2 mg/day at the time of discharge, and discontinued 3 months later. Also, no additional antiepileptic drugs were prescribed even after transferred to the rehabilitation hospital. Thereafter, no seizures and abnormal behavior occurred. The patient was discharged from the rehabilitation hospital in June of the same year and returned to her job at the bank in September. Plain head MRI performed on December 27 was also unremarkable. On day 7 after admission, the patient tested negative for antibodies related to paraneoplastic neurological syndromes such as amphiphysin, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr. Blood and cerebrospinal fluid were not tested for anti-AMPA antibody.

3. Discussion

Anti-NMDAR encephalitis is a form of acute autoimmune encephalitis 1st described by Vitalian et al in 2005, and later described as a paraneoplastic neurological syndrome associated with ovarian teratoma by Dalmau et al in 2007.[1,2] It tends to occur in young women, and in typical cases, nonspecific flu-like prodromal symptoms appear as the initial symptoms, followed by prominent and rapidly progressing neurologic manifestations, with rapid onset of unresponsiveness and impairment of consciousness. Progressive impairment of consciousness can lead to hypoventilation or apnea, and many patients require ventilation. During that period, despite unresponsiveness and apnea, patients exhibit various involuntary movements and autonomic nerve symptoms that are often difficult to differentiate from various seizure-like episodes and complex partial seizures. If treated in the acute phase by performing early tumor resection for tumor-associated cases or immunotherapy such as steroid pulse therapy, intravenous immunoglobulin, plasmapheresis, and in some cases, high-dose intravenous rituximab and cyclophosphamide, the prognosis is relatively good, and patients can recover gradually over a period of several years.[1–7]

Although the mechanisms behind these neurologic manifestations and abnormal movements in anti-NMDAR encephalitis are unclear, the current explanation is that anti-NMDAR antibodies specifically and reversibly inhibit formation of synaptic NMDAR clusters, which reduces the number of synaptic NMDAR clusters and consequently reduces the functioning of NMDAR.[3,5,6,8] It is believed that this ultimately results in disinhibition of glutamatergic and dopaminergic neurons, and that the symptoms occur due to loss of regulation of normally tightly regulated motor pathways.[9] Furthermore, 1 study found that this decrease in NMDAR functioning may also trigger a corresponding relative increase in AMPAR function.[10] In studies on mechanisms of onset of postencephalitic epilepsy, Bernadino et al and Stellwagen et al found that increased levels of cytokines in blood and cerebrospinal fluid, for example, matrix metalloproteinase-9 (a factor that disrupts the blood-brain barrier) and TNFα in cerebrospinal fluid, causes release of glutamate from glia, neuronal cell death, and a decrease in $GABA_A$ receptor, as well as an increase in AMPAR, and these lead to reduced inhibitory neuron function and increased nerve excitation, which triggers seizures.[11–13]

The AMPA receptor antagonist perampanel used in this case is an anticonvulsant that suppresses seizures by acting as a selective and noncompetitive antagonist of AMPAR to directly attenuate nerve hyperexcitability caused by glutamate but has no action in NMDAR.[14,15] This is why there have been no previous reports showing perampanel was effective against anti-NMDAR encephalitis. However, perampanel has been reported effective against refractory Rasmussen encephalitis and Rasmussen-like encephalitis, which are other conditions in which autoantibodies such as anti-AMPAR antibody and anti-NMDAR antibody are detected, though it is uncertain whether its effects are primary or secondary.[16–18] From the above evidence, a possible explanation for the effectiveness of perampanel here is that anti-NMDAR antibody produced due to the primary anti-NMDAR encephalitis cross-linked with NMDAR in the postsynaptic membrane. This caused internalization of NMDAR, and consequently a decrease in the number of receptors as well as an increase in AMPAR. Perampanel then worked to relieve the seizures and abnormal behavior by acting as a selective and noncompetitive antagonist of AMPAR to attenuate nerve hyperexcitability caused by glutamate.

Limitations of this case report are that there was only 1 patient due to the rare nature of anti-NMDAR encephalitis, and that sedatives such as propofol and midazolam were administered along with perampanel, making it unclear whether the effects observed were attributable to perampanel alone or to the combination of these agents. Furthermore, there were no other previous study that the AMPA receptor antagonist perampanel may be effective against the seizures and abnormal behavior that occur in anti-NMDAR encephalitis. A large-scale study will be necessary to establish the clinical effectiveness of perampanel in anti-NMDAR encephalitis.

Author contributions

HA and RS examined the patient. HA drafted the manuscript, and created the figures. YH helped draft the manuscript. All authors read and approved the final manuscript.
Conceptualization: Hisanao Akiyama.
Data curation: Hisanao Akiyama.
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Supervision: Yasuhiro Hasegawa.
Writing – original draft: Hisanao Akiyama.
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