First Reported Case of Anti-Ampa Receptor Encephalitis in a Vietnamese Adolescent

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ABSTRACT

INTRODUCTION: Autoimmune encephalitis refers to a group of diseases characterized by the presence of antibodies that directly attack receptors on the neuron surface and are associated with cognitive and behavioral disorders. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor autoimmune encephalitis is very rare and has been reported in only a few individual cases, with little clinical experience.

CASE REPORT: We describe the clinical manifestation and disease course of the first diagnosed case of anti-AMPA receptor encephalitis at the Neurology Department of Children's Hospital 2 in November 2020. A previously healthy 10-year-old presented with symptoms over 2 periods. During each period, the patient presented with multiple focal seizures, a cognitive-behavioral disorder, and amnesia. The brain magnetic resonance imaging (MRI) results were persistently normal. Electroencephalography (EEG) recorded many focal spikes and spike waves. Antibodies against N-methyl D-aspartate (NMDA) were not detected. Antibodies against AMPA receptors were detected in the serum and cerebrospinal fluid using an indirect fluorescent antibody test. This patient was treated with immunotherapy, including methylprednisolone and intravenous immunoglobulin (IVIG), and antiepileptic drugs, such as oxcarbazepine, topiramate, and levetiracetam. The seizures were controlled, but the cognitive-behavioral disorder was only partially resolved.

CONCLUSION: This case report contributes to the clinical understanding of anti-AMPA receptor encephalitis disease manifestation, the response to the immunotherapy, and relapse.

KEYWORDS: Neuroimmune disorders, autoimmune encephalitis, AMPA

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Introduction

Antibody-mediated encephalitis defines a class of diseases in which antibodies target surface receptors on neurons and are associated with behavioral and cognitive disturbances.[1] Autoimmune encephalitis has been increasingly recognized as an important and treatable cause of subacute encephalitis. The early recognition and prompt treatment of autoimmune encephalitis are important due to the good recovery prognosis associated with immunomodulatory drug treatment. Consequently, the clear identification of rare clinical autoimmune encephalitis manifestations is important for early recognition, which can minimize the morbidity and mortality associated with this group of pathologies.[1] The neurotransmitter glutamate can act on 2 receptor types in the brain: the N-methyl-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. The AMPA receptor (AMPAR), which is involved in memory, learning, and seizures, has been shown to be targeted by the glutelin type-A 1 (GluA1) and glutelin type-A 2 (GluA2) subunit antibodies, which were found to be associated with encephalitis for the first time in 2009, during a study of autoantibodies in borderline encephalitis.[2] This entity is exceptionally rare, and its clinical phenotype has been incompletely described. The increasing number of anti-AMPAR encephalitis reports have revealed diverse clinical presentations for this disease.[3] We present the findings associated with 1 case of anti-AMPAR encephalitis that exemplifies the variability of this disease spectrum and summarize the findings of published cases using a systematic literature review. Furthermore, we provide evidence to suggest neurological improvements following immunomodulatory therapy, which, combined with the outcomes reported in other cases, emphasizes the importance of testing for autoantibodies against neuronal surface proteins, including AMPAR, in patients with clinical and neuroimaging findings that suggest the presence of autoimmune encephalitis.

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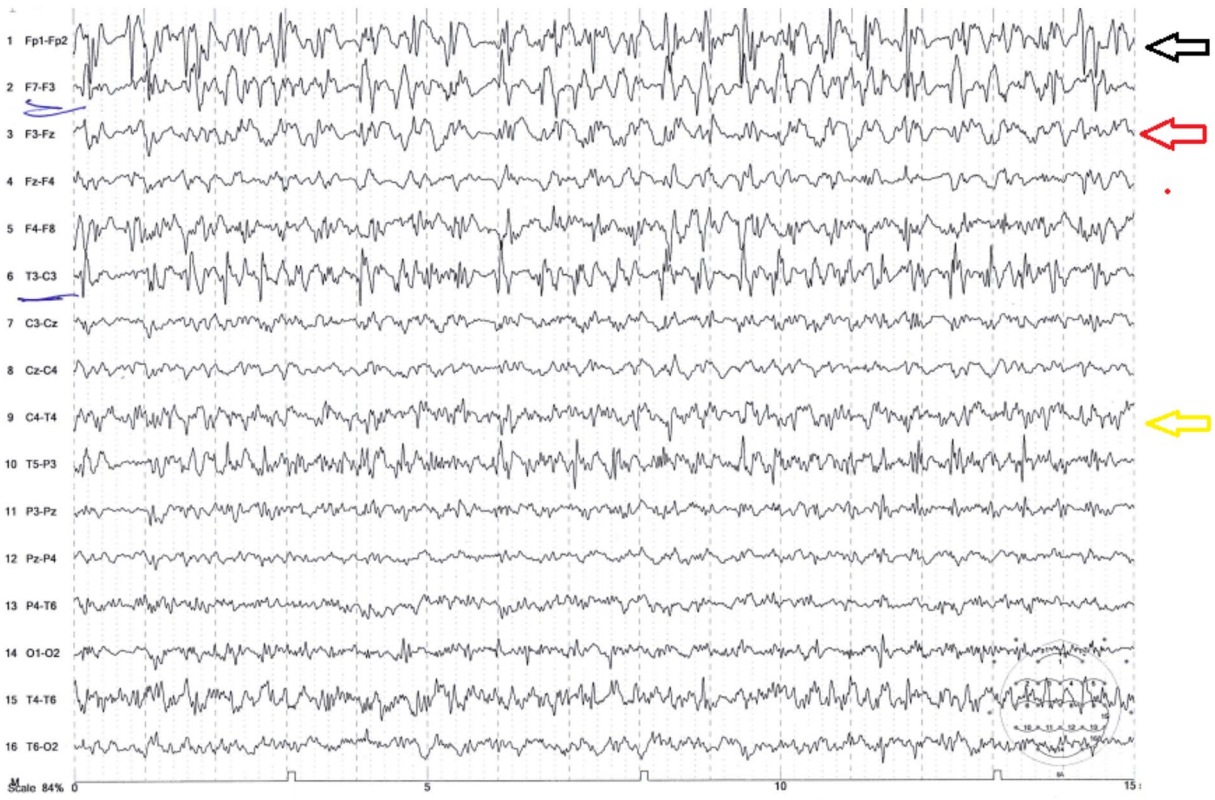

Figure 1. EEG recording, showing low-voltage background activity (black arrow), theta slow-wave (red arrow), and synchronized multi-spike activity predominately in the left hemisphere (yellow arrow).

Case Report

A 10-year-old male patient, weighing 35 kg, with a previously healthy medical history and normal psychomotor development, was in grade 5, with good academic performance. The disease progression was documented in 2 separate periods.

The First Period

The first period was characterized by the acute onset of fever (39.5°C) associated with an unknown infection for 3 days that resolved on its own, with no specific treatment. One day after the fever stopped, symptoms of poor communication, fatigue, lethargy, and drowsiness appeared. The onset of convulsions was marked by the rotation of the eyes in the direction of head motion, sometimes to the left and sometimes to the right, which developed into generalized convulsions, accompanied by a purple coloration, and the loss of consciousness. Each episode lasted 1 to 2 minutes, with urinary incontinence and lethargy after each episode.

The patient was admitted to the hospital with an early diagnosis of suspected herpes encephalitis, and acyclovir treatment was started. Cerebrospinal fluid (CSF) showed 0 cells/mm^3, and protein and glucose levels were within the normal range. Microbiological tests for herpes simplex virus, Japanese encephalitis virus, and bacteria cultures were performed and were negative. An anti-NMDAR autoantibody test performed on CSF was negative. Brain magnetic resonance imaging (MRI) results were normal. The antinuclear antibody test of the blood was negative. The patient was diagnosed with probable autoimmune encephalitis with negative anti-NMDAR antibodies. Acyclovir was discontinued after 3 days. Methylprednisolone 20 mg/kg/day was started in the second week of disease and last for 5 days. Oxcarbazepine was started at 600 mg/day. The following week, the patient was treated with 2 g/kg intravenous immunoglobulin (IVIG) for 5 days, and antiepileptic drugs (600 mg/day oxcarbazepine and 100 mg/day topiramate) and 1 mg/kg prednisone were taken daily for 6 weeks. Electroencephalography (EEG) results showed local onset paroxysmal activity in the left hemisphere with inhibited background activity (Figures 1 and 2). Many types of localized seizures were observed, accompanied by confusion, loss of time orientation, amnesia, insomnia, symptoms of hyperactivity disorder, irritability, and abnormal movement disorder included twisted mouth, no autonomic dysfunction, speech dysfunction. Maintenance IVIG therapy, at 0.4 mg/kg each week was administered for 5 consecutive weeks, and the doses of oxcarbazepine and topiramate were gradually increased to 1050 and 200 mg/day, respectively, and 1 mg haloperidol at night and 500 mg/day levetiracetam were added. Convulsions ceased after 14 days, stopped a few days, then relapsed with a frequency of 3 to 4 attacks/week. At sixth to ninth week, cancer screening tests, including computed tomography (CT) chest scan, were normal. Normal abdominal ultrasound. The patient showed improvement in cognitive-behavioral disorder symptoms and memory recovery but remained hyperactive and easily agitated. After 2 months of inpatient treatment, the patient was discharged from the hospital and continued

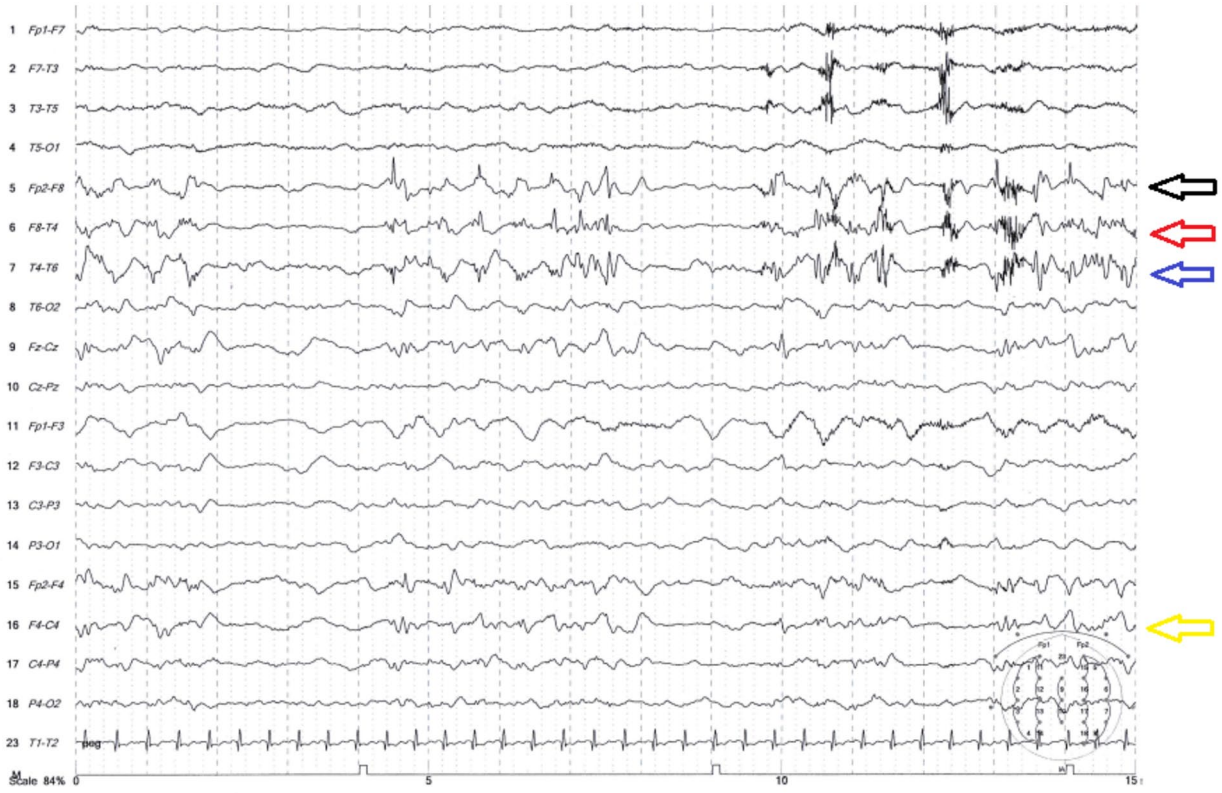

Figure 2. EEG, showing background activity abnormality (black arrow), theta slow-wave, diffuse delta wave (blue arrow), and right hemisphere-dominant multi-spike activity (yellow arrow).

outpatient treatment with antiepileptic drugs, including oxcarbazepine, topiramate, levetiracetam, and haloperidol.

At thirrd month, re-examination, and re-assessment, the patient continued to experience 1 to 2 seizure episodes/month, returned to school, played chess, and performed math. The patient scored 125 points (high IQ) on the Raven's Progressive Matrices intelligence quotient (IQ) test; 7/9 on the hyperactivity and 4/9 on the attention reduction scales of the Vanderbilt ADHD Diagnostic Rating Scale; and 2/8 on the impulsivity, and displayed significantly reduced behavioral disturbances. The second brain MRI did not show any abnormalities. The symptoms, laboratory data, and treatment modalities for this period lasted for 19 weeks and are presented in Table 1.

The Second Period

Five months after the disease onset, the recurrence of multiple seizures was observed, and the patient presented to the Children's Hospital 2. The results of CSF analysis showed 8 white blood cells/mm^3 and normal protein and glucose levels. CSF and blood were examined using indirect immunofluorescence to detect 5 antibodies known to cause autoimmune encephalitis, including those against NMDAR, leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), gamma-aminobutyric acid B receptor ($GABA_BR$), and AMPAR (Figure 3). The result was positive for the AMPAR antibody. The brain MRI was normal. EEG showed generalized paroxysmal epileptic activity in the left temporal lobe with abnormal slow-wave background activity. Cancer screening tests, including a computed tomography (CT) scan of the chest and an ultrasound of the abdomen, were normal. The patient was diagnosed with anti-AMPAR encephalitis. Autoimmune-induced local epilepsy was treated with 30 mg/kg/day methylprednisolone for 5 days, and the antiepileptic drug treatment was adjusted (increase oxcarbazepine to 1800 mg/day, reduced levetiracetam to 3000 mg/day, and maintained topiramate at 300 mg/day). The patient responded with a significant reduction in seizure frequency, experiencing occasional short seizures lasting for a few seconds, with no purpleness and improved behavioral disturbances. Test Raven IQ again showed high IQ (110 points). This progression lasted from weeks 20 to 30 (Table 1).

Discussion

Autoimmune encephalitis is increasingly diagnosed in children and has become an important cause of encephalitis, in addition to infections.[1] A number of autoimmune encephalitis-causing autoantibodies have been identified, including the NMDAR antibody, but the clinical cases associated with other antibodies have been reported sporadically.[1] Autoantibodies against AMPAR act on the glutamate receptor 1 (GluR1) and glutamate receptor 2 (GluR2) subunits, resulting in glutamate-stimulating messenger overactivation, which causes neuronal damage.[4] Clinical manifestations include behavioral disorders, characterized by psychiatric, cognitive, and memory impairments, and convulsions.[3]

Table 1. Case progression.

	CLINICAL SIGNS	INVESTIGATION	TREATMENT
W1	High fever, 39.5°C to 40°C, headache, fatigue, lethargy, drowsiness, but do exactly as required.	None	Fever reduction, rehydration
W2	First focal seizure, repetitive attention, increased fatigue, drowsiness, hospitalization	CSF: no cells; Protein: 0.38 g/L; Pandy (+); Clo:124 mmol/L; Glucose: 4.0 g/L; HSV (–); JEV (–) The first brain MRI: normal ANA (–); C3: 1.69 g/L (0.85-1.42 g/L); C4: 0.37 g/L (0.12-0.4 g/L); Routine EEG: slowing background, multifocal spikes, and wave-like epileptic discharges	The first MethylPred 20 mg/kg/day for 5 days. AEDs: OXC 600 mg/day.
W3	Focal seizures, amnesia (unable to determine space and time, only recognizing acquaintances without remembering his name or the name of his parents), poor sleep, imbalance.	NMDAR antibody (–)	IVIG: 2 g/kg dose divided across 5 days. Pred: 1 mg/kg/day Maintain of OXC 600 mg/day Add on TPM 100 mg/day
W4–5	Seizures ceased for 2 weeks		IVIG: 0.4 g/kg/d every week for. Maintain: OXC and TPM
W6–9	Memory improved gradually, concentration was poor, thinking better, could perform math, could play chess; limbs recovered well, was able to walk, run, and eat well, take care of himself, mild excitement. Some disturbing behaviors (profanity, swearing, teasing others) still occasionally happened 3 to 4 times/day. Discharged from hospital	Cancer screening tests, including computed tomography (CT) chest scan, were normal. Normal abdominal ultrasound.	IVIG: 0.4 g/kg/day every week (for 5 weeks) Optimization: OXC (1050 mg/days) and TPM (200 mg/day) Add on Haloperidol (1 mg/day) and LEV (500 mg/day)
W10–19	At home, seizures occurred occasionally, 1 to 2 times/month. Weight gain of 10 kg/2 months (35-45 kg). The patient did not sweat; therefore, during exercise or play, the heart rate increased, and the body temperature increased as high as 38°C. Raven IQ: 125 points Vanderbilt scale: decreased attention 4/9, increased activity 7/9 pulse 2/8, behavior disorder, and anxiety (–).	The second brain MRI was normal	Maintain OXC, TPM, LEV, and haloperidol, with doses as above
W20–23	Seizures occurred 3 to 4 times/week, and some days featured 4 seizures/day. The patient displayed reduced thinking ability, more behavioral disorders, more playfulness, mania (speaking out of turn, swearing, teasing others, argumentative, hitting, lazy movement, lazy thinking, difficulty of expression). Test Raven IQ (second time): 110, distracted, teased, difficult to manage behavior.	Routine EEG: slowing background, multifocal spikes, and wave-like, continuous, partial epileptic discharges	Optimization OXC (1800 mg/day), TPM (300 mg/days), Haloperidol (1 mg/day), and LEV (3000 mg/day)
W24	Occasional seizures, drowsiness for a few seconds. Slow thinking, more inactive, not absorbing new knowledge, difficulty learning, losing track of time, simple calculations were difficult, sometimes forgetting how to write words, and how to read. Poor memory Loss of ability to express meaning to others Aggravated behavior (irritable, easily agitated, smashing, throwing things, swearing when angry, touching breasts and sensitive parts of relatives and strangers, taking off pants in public).	The second CSF test showed 8 white blood cells/mm^3 and normal protein and glucose level Tested for 5 antibodies known to cause autoimmune encephalitis using the indirect immunofluorescence method, including NMDAR, LGI1, CASPR2, $GABA_BR$, and AMPAR. The result was positive for the AMPAR antibody The third brain MRI: normal Routine EEG: slowing background, multifocal spikes, and wave-like epileptic discharges	The second MethylPred 30 mg/kg/day for 5 days. Maintain: OXC, TPM, and LEV with dose as above
W25-30	Improved behavior and improved memory. Improved language. Good muscle power Still no sweating, slightly high body temperature, continued touching of sensitive parts of relatives and strangers 1 to 2 mild focal seizures per month	Routine EEG: abnormal background for age, no epileptic discharge	Maintain Pred for 6 weeks Maintain OXC, TPM, and LEV with dose as above

Abbreviations: AEDs, antiepileptic drugs; CSF, cerebral spinal fluid; EEG, electroencephalography; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; JEV, Japanese encephalitis virus; LEV, levetiracetam; MethylPred, methylprednisolone; MRI, magnetic resonance imaging; OXC, oxcarbazepine; Pred, prednisone; TPM, topiramate; W, week.

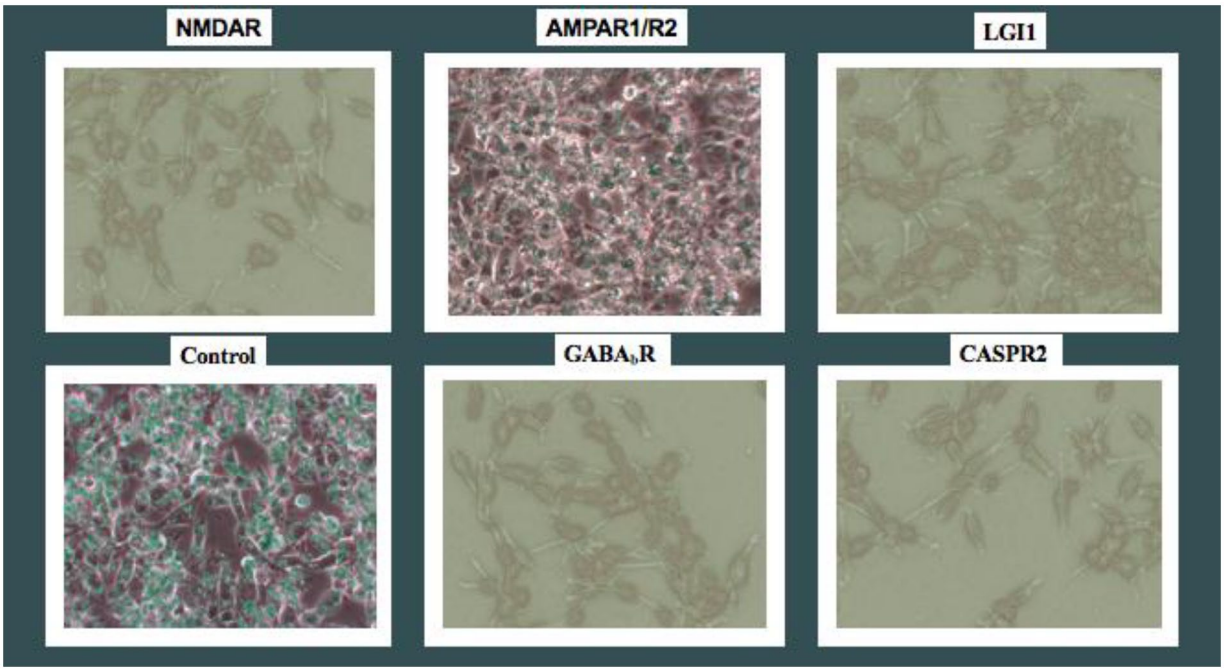

Figure 3. Results of fluorescent staining showed positivity to AMPAR antibodies, with negative results for antibodies against NMDAR, LGI1, GABA$_B$R, and CASPR2 (Control: control sample).

The incidence of anti-AMPAR encephalitis is relatively low.[4] Since 2009, only a few single cases or larger adult cohorts have been described; however, cases in children have been reported even less frequently. Therefore, the current understanding of this pathology is not clear.[2]

Hoftberger et al[5] described the clinical characteristics and prognosis of 22 patients in 2015, with ages ranging from 23 to 81 years. The majority of patients presented with hemorrhagic encephalitis (55%) or borderline dysfunction, with multifocal or diffuse encephalopathy (36%). Research has shown that cases associated with comorbid tumors (64%) and paracellular antibodies have a worse prognosis and higher mortality than other cases.[5]

Graus et al[6] introduced diagnostic criteria for autoimmune encephalitis, contour systemic encephalitis, and anti-NMDAR encephalitis. These diagnostic criteria enable doctors to initiate immunotherapy in patients with limbic encephalitis before identifying the pathogenic autoantibodies, including antibodies against AMPAR.

The study by Laurido-Soto et al[1] in 2018 reviewed the literature, including 81 patients diagnosed with anti-AMPAR encephalitis; however, only 53 patients were identified in the literature with sufficient clinical data, in addition to 2 cases identified by the author, resulting in a total cohort of 55 patients aged 14 to 92 years. The study concluded that anti-AMPAR encephalitis has a diverse clinical profile, a good treatment response, and an overall good prognosis. However, patients with psychotic symptoms at onset were often associated with worse outcomes and were associated with tumors.[1]

Previous studies have not described cases of autoimmune encephalitis in young children. A recent November 2020 Chinese case report described the clinical manifestations, treatment, and 4-year follow-up of a 32-month-old boy diagnosed with anti-AMPAR encephalitis.[7] This patient had many similarities with our patient: onset characterized by the prominent symptom of convulsions; slow exposure and lethargy; normal CSF puncture and brain MRI results; EEG diagram showing slow-wave spikes; and no tumor. Both patients were treated with high-dose methylprednisolone combined with IVIG and the anti-epilepsy drug levetiracetam. The patient described in the previous paper responded with stabilized seizures and improved cognitive impairments, and the child developed normal mental and physical strength over the next 4 years. The course of the disease did not recur in this patient, unlike in our patient.

To date, no specific treatment regimen has been established for anti-AMPAR encephalitis, and typical treatment is similar to that used to treat other forms of autoimmune encephalitis, including immunotherapy, such as high-dose methylprednisolone, IVIG, and plasma exchange, depending on the clinical severity.[8] In patients with comorbid tumors, surgery is the first-line treatment, if possible. Most patients respond to treatment, but the response may be incomplete, or patients may be unresponsive to immunotherapy. However, some cases have been reported to relapse after treatment. In our patient, after the first round of treatment, the patient recovered well, with reduced seizures, allowing the patient to return to school. However, after 5 months, the patient showed signs of relapse and received high doses of corticosteroids, which improved the convulsions and cognitive-behavioral disorders, although not completely.

Currently, long-term immunosuppressive therapies have not been clearly demonstrated to prevent or reduce the risk of autoimmune encephalopathy recurrence.[8]

Conclusion

Anti-AMPAR encephalitis is a rare form of autoimmune encephalitis caused by antibodies against AMPARs expressed on the surfaces of neurons, especially in children. Anti-AMPAR encephalitis can present with diverse clinical manifestations, making diagnosis difficult. However, the early diagnosis and prompt treatment with immunotherapies can have significant implications for long-term results. This case report contributes to the understanding of the clinical and subclinical symptoms, treatment response, and recurrence associated with anti-AMPAR encephalitis in children.

Author Contributions

Nguyen-Le TH and Nguyen MD contributed equally to this article as co-first authors. All authors read and approved the final manuscript.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the legal guardian of patient for publication of this case report and accompanying images.

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