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CASE REPORT

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Severe anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis with prolonged hyperammonemia: a case report

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Abstract

Background Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis (Anti-AMPAR-E) is a very rare subtype of autoimmune encephalitis, typically presenting with memory decline, seizures, and changes in psychosis and behavior. Anti-AMPAR-E is often associated with the presence of neoplasms and generally has a poor prognosis. Currently, cases of severe anti-AMPAR-E, particularly those accompanied by hyperammonemia, are exceedingly rare.

Case presentation A 66-year-old man was admitted to the hospital, complaining of deterioration in memory and confusion for at least 10 days and worsening for 3 days. The patient's condition rapidly progressed to coma, which persisted for 2 months, manifesting as a fulminant course. At that time, his Glasgow Coma Scale (GCS) score was 6, and AMPAR antibodies were strongly positive in both serum and cerebrospinal fluid (CSF). Additionally, his serum ammonia levels consistently exceeded reference values during his hospital stay. Consequently, he was diagnosed with severe anti-AMPAR-E with prolonged hyperammonemia and treated with intravenous methylprednisolone pulse (IVMP) therapy, intravenous immunoglobulin (IVIG), and rituximab therapy until he regained consciousness. However, 10 months after discharge, he was readmitted to the hospital due to seizures and subsequently diagnosed with lung cancer. The patient eventually passed away at home.

Conclusions Even if the short-term prognosis is good, regular tumor-related screening is essential for patients with severe anti-AMPAR-E to detect potential tumors early and improve long-term outcomes. Moreover, it is necessary to perform repeated ammonia level assessments and to adequately treat hyperammonemia.

Keywords Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis, Autoimmune encephalitis, Hyperammonemia

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Background

Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis (Anti-AMPAR-E) is a rare autoimmune encephalitis mediated by AMPAR antibodies, first reported by Lai et al. in 2009 [1]. Anti-AMPAR-E presents with diverse clinical manifestations and is often complicated by the presence of tumors. In recent years, as our understanding of autoimmune encephalitis deepens and diagnostic tools mature, reports of anti-AMPAR-E have increased rapidly. However, most cases exhibit relatively mild clinical symptoms, and instances of severe anti-AMPAR-E are rarely reported. Currently, there is no unified standard for diagnosing severe encephalitis; however, patients presenting with status epilepticus who require admission to the intensive care unit (ICU) for treatment are typically classified as severe encephalitis cases [2]. In this case illustration, we aim to report the clinical manifestations, diagnostic tests, treatment process, and prognosis of an adult patient with severe anti-AMPAR-E and prolonged hyperammonemia to raise awareness among neurologists.

Case presentation

A 66-year-old man suffered from perirhinal herpes for 10 days before his admission. As he was a country doctor, he self-treated with penicillin G and steroids. However, he gradually developed confusion, slight slowness in response, and memory decline after treatment. Throughout the course of his illness, he did not experience fever, headache, seizures, or paresthesia. His clinical symptoms worsened for 3 days prior to admission, characterized by significant memory decline, deteriorating slow responses, and occasional gibberish speech. The patient had a history of pulmonary heart disease and asthma for over 20 years, managed with Seretide. He denied any other medical conditions, including tumors, infections, or mental disorders. His vital signs were stable, and the general physical examination showed no obvious abnormalities. Examination of nervous system showed that the patient was male, conscious, slow in reaction, in poor mental state, occasionally disobeying orders, short-term memory loss, slight increase in muscle tension of limbs, slight stiffness of neck, and suspicious positive Keniger's sign. No other neurological signs were present. The patient's blood analysis revealed a white blood cell count of 9. 78 (reference range 4-9.5)×10^9/L, a neutrophil count of 6. 65 (reference range 2-6.5) × 10^9/L, and a mononuclear cell count of 0. 73 (reference range 0.12–0.8) × 10^9/L. Hepatic and renal function values, tumor marker values, and coagulation function values were all within the reference range. When lumbar puncture was performed, clear and colorless cerebrospinal fluid (CSF) flowed out, and the intracranial pressure was measured to be 350 mmH_2O (reference range 80–180 mmH_2O). The Pandy test was positive (+), with a white blood cell count of 87 (reference range 0–8) × 10^6/L and a leukocyte mononuclear ratio of 98. 8% (reference range 2–10%). Protein quantification in the CSF was 65. 8 mg/dL (reference range 15-45 mg/dl). Metagenomic next-generation sequencing (mNGS) of the DNA from the CSF sample was also conducted, but no pathogens (including viruses, bacteria, fungi, and parasites) were identified. Magnetic resonance imaging (MRI) showed multiple small ischemic lesions (Fig. 1). A computed tomography (CT) scan revealed bronchitis, emphysema, right upper lobe consolidation, and multiple nodules in both lungs (Fig. 2). The CT of the abdomen showed no abnormalities.

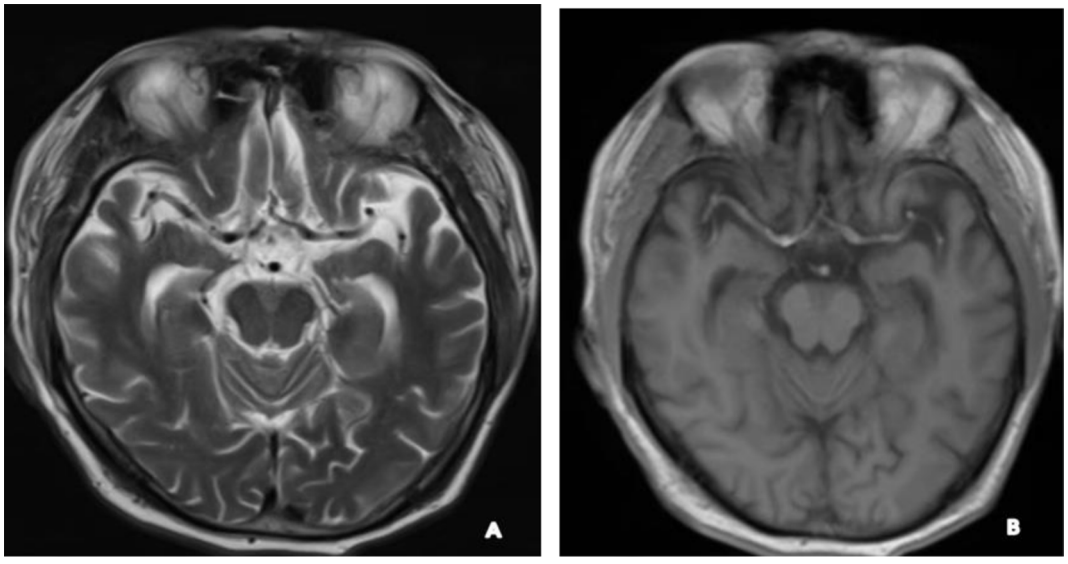

Fig. 1 Brain MRI reveals multiple small ischemic lesions

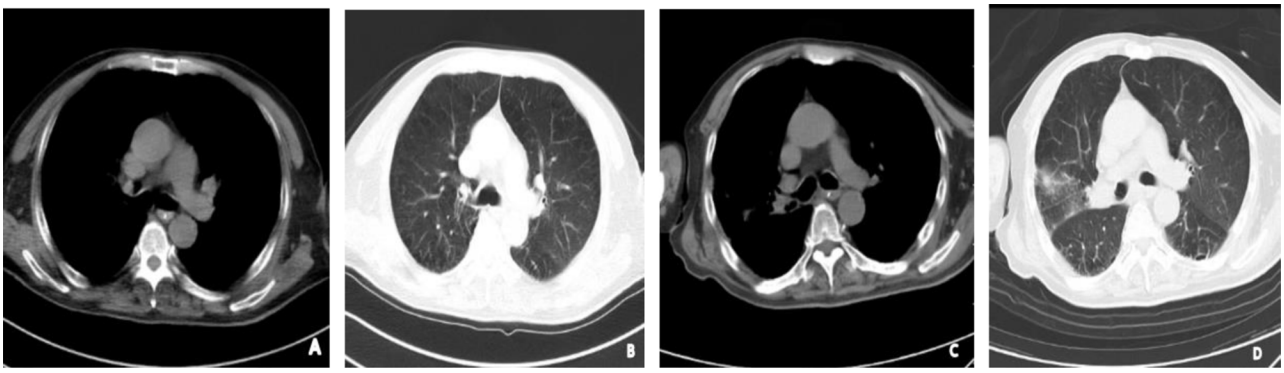

Fig. 2 (**A&B**): Upon the patient's initial admission, a CT scan revealed bronchitis, emphysema, right upper lobe consolidation, and multiple nodules in both lungs. (**C&D**): At the time of discharge, a follow-up CT scan showed exudative lesions in the lower lobes of both lungs and localized atelectasis in the upper lobe of the right lung

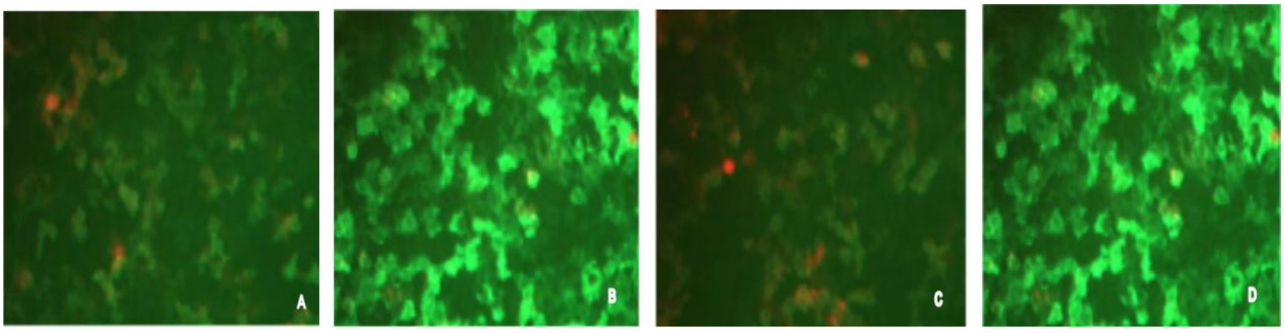

Fig. 3 (**A**): Anti-AMPAR antibodies in the serum were positive. (**B**): Positive control in the serum was also observed. (**C**): Anti-AMPAR antibodies in the cerebrospinal fluid (CSF) were positive. (**D**): Positive control in the CSF was also observed. The titers of antibodies in both the CSF and serum were measured at 1: 320 using an indirect immunofluorescence assay of cell-based transfection, with an original magnification of 100× (KingMed Diagnostics, Jinan, China)

Although no virus was found in the metagenomic next-generation sequencing (mNGS) of DNA, viral encephalitis was suspected due to the history of perirhinal herpes before the onset of the disease. Therefore, the patient was treated with the antiviral drug acyclovir. Three days after admission, antibodies against AMPAR were detected in both the serum and cerebrospinal fluid (CSF), with a titer of 1: 320 in both samples (KingMed Diagnostics, Jinan, China) (Fig. 3). Consequently, the diagnosis of anti-AMPAR encephalitis was confirmed. The patient was then treated with intravenous methylprednisolone at a dose of 1 g daily for 3 days, reduced to 500 mg daily for the next 3 days, and further reduced to 80 mg daily for 14 days, eventually maintaining at 30 mg daily. Additionally, he received intravenous immunoglobulin (IVIG) at a dose of 30 g daily (0. 4 g/kg × 75 kg) for 5 days [3]. Despite this treatment, his symptoms continued to gradually worsen. Four days after admission, he suddenly experienced unconsciousness, accompanied by gnathospasm, staring eyes, limb convulsions, and fecal incontinence. However, he remained in a coma (GCS score of 6) even after the epileptic symptoms were managed with diazepam and valproate, necessitating transfer to the neurology intensive care unit (ICU). There, a dynamic video-electroencephalogram (EEG) revealed a state of burst suppression, and the titer of anti-AMPAR antibodies in serum remained at 1: 320. Rituximab treatment was initiated, consisting of 100 mg on the first day and 500 mg on the second day, followed by three cycles of IVIG over the next three months [3]. During this period, the percentage and absolute count of CD19 + B Cells in peripheral blood gradually decreased to 0. Dynamic video-EEGs were repeatedly performed, showing low-voltage EEG activity across all leads, but with minimal waveform changes (Table 1). An MRI of the patient's head was re-examined, yielding results consistent with previous findings. Starting from the 65th day after admission, the patient's symptoms began to improve, presenting with eye-tracking movements, slight head turning, and mild limb movements. The titer of anti-AMPAR antibodies in serum was rechecked and found to be 1: 100. On the 107th day after admission, there was significant relief in the patient's symptoms; he regained consciousness and could move his limbs autonomously and raise them as instructed. Consequently, he was permitted to be discharged, with his serum anti-AMPAR antibody titer decreasing to 1: 10 (Table 2) at that time. Oral corticosteroid treatment was continued after discharge.

Table 1 The findings from the dynamic EEG improved in accordance with the patient's condition

Date	The results of dynamic-EEG
2022–9–6	The electroencephalogram (EEG) demonstrated a burst-suppression pattern. The burst segments were predominantly located on the left side, featuring slightly more medium amplitude sharp waves and sharp slow waves that were differently scattered in the frontal pole, as well as in the frontal, central, and parietal regions.
2022-9-14	A low-voltage trend was observed in the full leads, with the majority of leads showing this trend in VI-b and a minority of leads in VI-a.
2022–9–30	A low-voltage trend was observed in the full leads (with the majority of leads being VI-b and a minority being VI-a). There has not been much change, although there is a slightly increased presence of paroxysmal medium-amplitude slow waves (20–40 μV) compared to the last EEG.
2022–10–11	A low-voltage trend was observed in the full leads (with the majority of leads being VI-a and right occipital leads VI-b). Compared to the last EEG, there is slight improvement: there is increased low-amplitude fast wave activity with the eyes open and a slightly greater presence of low-amplitude spindle activity during sleep, particularly on the right side.
2022–11–5	A low-voltage trend was observed in the full leads. A few delta waves were sporadically present in the bilateral frontopolar, frontal, and anterior temporal regions during sleep, particularly on the left side. Frequent abnormal movements were detected; however, the EEG showed no abnormal waves (non-epileptic) during the same period. Therefore, subcortical tonic movements were considered.

Table 2 The titer of AMPAR antibodies gradually decreased as the patient's condition improved

Date	The titer of AMPAR antibody	
	CSF	Serum
2022-9-1	1: 320	1: 320
2022-9-17	1: 100	1: 320
2022-9-28		1: 320
2022-10-27		1: 320
2022-11-11		1: 100
2022-12-13		1: 10

Throughout the course of the disease, the patient's pulmonary infection fluctuated from mild to severe, necessitating multiple adjustments to antibiotic therapy based on drug susceptibility results. The antibiotics used included mezlocillin, cefoperazone/sulbactam, amikacin, and others. Additionally, he received treatments aimed at reducing phlegm, nutritional support, and other symptomatic therapies, as well as invasive procedures such as endotracheal intubation, bronchoalveolar lavage, and tracheotomy. During this period, chest CT scans were performed multiple times, which showed no signs of tumors, but did reveal inflammatory changes.

Amazingly, we found that the patient's serum ammonia level was 70 μmol/L (reference range: 9–30 μmol/L) upon admission and remained elevated even after ammonia-lowering therapy, fluctuating between 45 and 159 μmol/L. Additionally, after receiving sodium valproate, his blood concentration was measured at 52. 74 μg/mL (reference range: 50–100 μg/mL).

Half a year after discharge, the patient was able to resume all his activities of daily living, although he continued to experience slow reaction times and memory decline.

In July 2023, the patient was readmitted to the hospital due to unconsciousness and twitching. At that time, the AMPAR antibody titer in serum was tested and found to be 1: 1000. Paraneoplastic syndrome test values in the serum were within the reference range. Tumor marker testing indicated a neuron-specific enolase level of 40. 91 ng/mL (reference range: 0–35 ng/mL). A repeat brain MRI yielded results consistent with previous examinations. An enhanced CT scan revealed neoplasms in the right hilum and right upper lobe, accompanied by mediastinal lymph node metastasis (Fig. 4). However, his family refused further evaluation and treatment, and he ultimately passed away at home approximately 20 days later.

The timeline of the case is summarized in Fig. 5.

Discussion and conclusion

Anti-AMPAR-E is a recently discovered autoimmune encephalitis characterized by acute or subacute onset. The age of onset for anti-AMPAR-E ranges from 14 to 92 years, with the highest prevalence in middle-aged individuals and no significant gender distribution [4]. The clinical manifestations of anti-AMPAR-E are varied and primarily include short-term memory deficits, confusion, seizures, and other mental symptoms [5–7]. Due to the low incidence of anti-AMPAR-E, its pathogenesis remains largely undefined. However, previous studies have confirmed that AMPARs, which belong to a class of chemically gated ion channel receptors and that are tetramers composed of GluR1-GluR4 subunits and several auxiliary subunits, is a transmembrane ionic glutamate receptor, mediating most fast excitatory neurotransmission in the brain [8, 9]. AMPARs are highly concentrated in the central nervous system, particularly in the hippocampus, cortex, and cerebellum [5, 9, 10], as well as in the peripheral nervous system [11]. Current research indicates that AMPAR antibodies can lead to a selective decrease in the total surface area and synaptic localization of AMPARs, disrupt neuronal activation of the classical complement cascade response, and ultimately cause damage to the corresponding brain areas, resulting in a series of clinical symptoms such as memory loss,

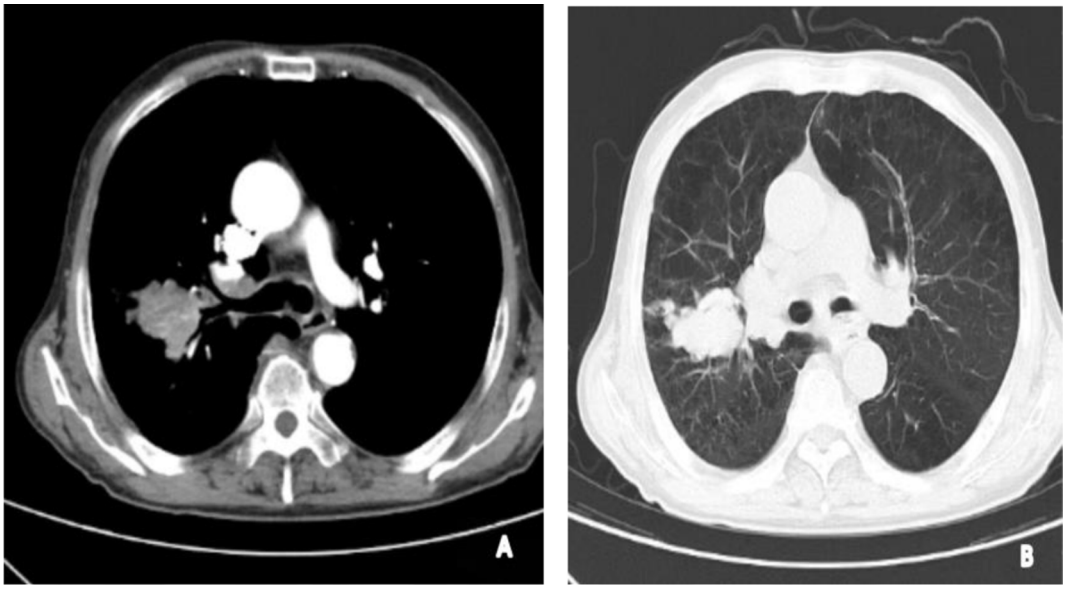

Fig. 4 The enhanced CT scan revealed neoplasms in the right hilum and right upper lobe, accompanied by mediastinal lymph node metastasis

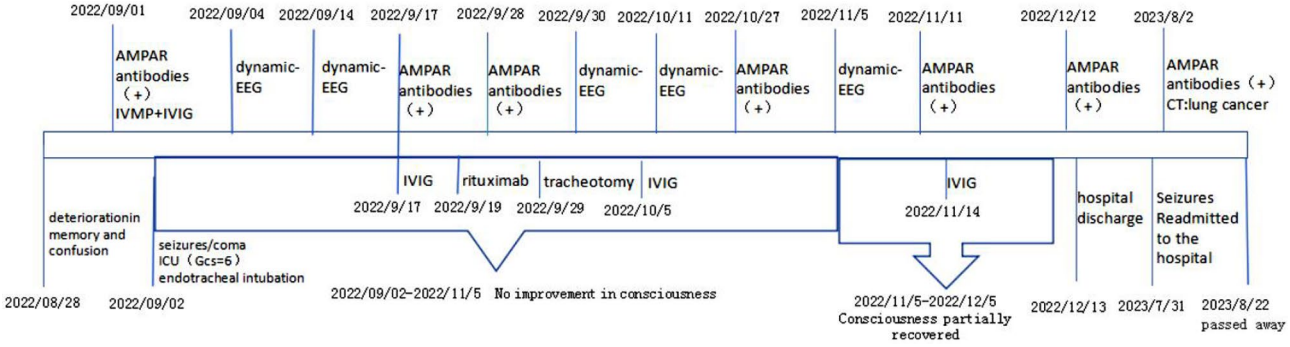

Fig. 5 Timeline of the case progression

epileptic seizures, and mental disorders [9, 12]. In line with previous studies, the patient described in this case was an elderly male whose primary clinical manifestations included short-term memory loss, confusion, and seizures. Both cerebrospinal fluid (CSF) and serum tested positive for AMPAR antibodies, confirming the diagnosis of anti-AMPAR-E. A notable difference in our patient's case is that he rapidly progressed to a coma (GCS score of 6), which lasted for 2 months and presented as fulminant severe encephalitis accompanied by hyperammonemia throughout the course of the disease. Fortunately, the patient's condition gradually improved following treatment, and his short-term prognosis was good.

At present, the results of auxiliary examinations for anti-AMPAR-E remain inconsistent, as most reports consist of individual case studies. In particular, our case involved a severe anti-AMPAR-E patient whose auxiliary examination results differ significantly from those previously reported. Some studies have indicated that the EEG findings in patients with anti-AMPAR-E are mainly characterized by non-specific slow waves, spike-wave patterns, or normal activity [13]. This discrepancy may be related to the milder conditions observed in earlier cases. However, the EEG of the patient in this study showed burst suppression and low-voltage activity, reflecting severe widespread impairment across the cortex. This suggests serious brain function damage and predicts an unfavorable neurological outcome [14], indicating that our patient's condition was more serious. Additionally, we noted that the patient's clinical symptoms improved alongside the EEG findings, with the latter showing significant improvement earlier than the former. This suggests that improvements in EEG findings could serve as an early indicator of treatment efficacy. Therefore, if the conditions of patients with severe anti-AMPAR-E allow, real-time EEG monitoring should be performed to guide treatment. Other studies have shown that up to 86% of patients with anti-AMPAR-E exhibit brain MRI abnormalities, primarily high signals on fluid-attenuated inversion recovery (FLAIR)/T2 sequences, predominantly

in the limbic lobe or temporal lobe [5, 15]. However, repeated brain MRI examinations in our patient consistently showed ischemic changes without other abnormal signal changes throughout the disease course. This suggests that even in critical cases of anti-AMPAR-E, brain MRI findings may still be negative. Currently, it is widely accepted that AMPAR antibodies in cerebrospinal fluid (CSF) have high sensitivity and specificity for diagnosing anti-AMPAR-E. Nevertheless, Zhe et al. [16] found that the positive rate of GluR2 antibodies in serum is higher than that in CSF. Coincidentally, our patient tested positive for GluR2 antibodies; thus, we opted to measure only the AMPAR antibody titer in serum at later stages, considering the cost and invasiveness of lumbar puncture. We also observed that the serum AMPAR antibody titer remained elevated while the patient was in a coma but gradually decreased as his clinical symptoms improved. This leads us to suspect a potential negative correlation between antibody titers and disease severity. Moreover, some studies have indicated that the AMPAR antibody titer in the CSF of anti-AMPAR-E patients who received immunosuppressive therapy decreased progressively as clinical symptoms improved [17], which is consistent with our findings.

It is worth noting that the case involved prolonged hyperammonemia without any abnormalities in liver function. However, the etiology of hyperammonemia and its potential relationship with the duration of illness remain unclear. Previous studies have shown that the causes of hyperammonemia can be classified into hepatic (acute or chronic) and non-hepatic conditions. Non-hepatic hyperammonemia may result from disorders not directly involving hepatic pathways and could be related to inadequate dietary intake or protein supplementation in ICU patients [18]. Other studies suggest that the etiopathogenesis of non-hepatic hyperammonemia may involve inappropriate dietary intake in ICU patients, leading to muscle injury and the subsequent release of amino acids into a gluconeogenesis cycle and substrates for ammonia production, thereby resulting in hyperammonemia [19]. In our case, the patient remained in a coma and was provided with short-peptide-based enteral nutrition via continuous nasal feeding due to hypoalbuminemia during the course of the disease. Therefore, we speculate that hyperammonemia may be associated with nutritional feeding; however, further research is needed. Additionally, a study has demonstrated that valproate (VPA)-associated hyperammonemia can occur even if the dose is within the reference range, without accompanying liver dysfunction [20]. In our patient's case, elevated blood ammonia levels were detected before the administration of VPA, and these levels remained higher than the reference values even after discontinuing sodium valproate and continuing ammonia-lowering therapy. Consequently, we believe that the hyperammonemia observed in this patient is not related to the application of VPA. Rajesh Verma et al. [21] reported a case of an anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis patient with prolonged hyperammonemia who did not respond well to immunosuppressive therapy but recovered quickly following ammonia-lowering treatment. This suggests that long-term hyperammonemia may exacerbate clinical symptoms and prolong the duration of the disease. Some studies have also indicated that acute hyperammonemia can increase extracellular glutamate levels in the brain, activating NMDARs, which leads to ATP consumption and ammonia-mediated toxicity, contributing to epilepsy, cognitive dysfunction, and mental illness [22]. Considering that both AMPAR and NMDAR are subtypes of glutamate receptors, we postulate that a similar mechanism may be present in anti-AMPAR-E patients with prolonged hyperammonemia. In other words, chronic hyperammonemia in our case may have exacerbated the underlying condition, contributing to a longer illness duration. We consistently provided aggressive ammonia-lowering therapy throughout the course of treatment, which may have played a positive role in the patient's recovery. This highlights the importance of managing non-hepatic hyperammonemia during the treatment of patients with severe anti-AMPAR-E to achieve better clinical outcomes.

It is well-known that anti-AMPAR-E responds favorably to immunotherapy, including first-line and second-line treatments. However, treatment options can be non-uniform. A multi-institutional observational study found that patients who did not improve with first-line treatment benefited from second-line immunotherapy, achieving better outcomes than those who did not receive it [23]. Additionally, other studies have indicated that second-line therapy should be initiated promptly for patients who do not respond to first-line treatment [4]. In our case, the patient suffered from severe anti-AMPAR-E and was initially treated with intravenous methylprednisolone (IVMP) alongside intravenous immunoglobulin (IVIG) therapy. However, the patient did not respond to this first-line treatment. Subsequently, we administered second-line therapy with rituximab within two weeks of starting first-line treatment, in combination with multiple rounds of IVIG to enhance the effects of the initial immunotherapy. Ultimately, we achieved favorable clinical results. This case suggests that various treatment strategies should be considered for patients with severe anti-AMPAR-E, including timely initiation of second-line therapy, combination immunosuppressant therapy, or repeated administration of the same immunosuppressant, to achieve better clinical outcomes.

In this study, the patient experienced seizures 11 months after the onset of the disease. At that time, he

underwent an AMPAR antibody titer test in the serum, which was found to be 1: 1000, indicating a recurrence of the disease. Some studies have shown that the recurrence rate of anti-AMPAR-E is approximately 23. 8% [24], but the mechanisms inducing clinical recurrence remain unknown. Some researchers have found that GluR1 and GluR2 subunits are expressed in tumors of patients with anti-AMPAR-E, suggesting that the presence of neuronal antigens in tumors may trigger the production of anti-neuronal antibodies [1]. This indicates a potential relationship between disease relapse and tumor presence. Additionally, studies have shown that about 60% of patients with anti-AMPAR-E are accompanied by tumors, such as lung cancer and breast cancer [6], and some patients may have underlying tumors. For example, our patient underwent tumor-related tests during the early stages of the disease, which did not reveal any signs of tumors; however, lung cancer was discovered when encephalitis recurred. Therefore, it remains unclear whether the recurrence of encephalitis in the patient in this study is attributed to abnormal expression of AMPAR in the tumor or if the tumor itself triggers an autoimmune response, leading to the production of excessive amounts of pathogenic anti-AMPAR antibodies. Further research is needed to clarify these issues.

In conclusion, with the development of antibody detection technology, anti-AMPAR-E has been gradually recognized. We would like to emphasize the following points based on our experience with this case: (1) Early Treatment: Anti-AMPAR-E presents with complex and diverse clinical manifestations and has a high recurrence rate. Therefore, it should be treated with immunosuppressive therapy as early as possible. For patients with severe anti-AMPAR-E, timely initiation of second-line therapy or combination immunosuppressant therapy is crucial. (2) Tumor Screening: For patients with anti-AMPAR-E who do not have tumors in the early stages, even if short-term prognosis appears good, regular tumor-related screening is necessary to detect any underlying tumors earlier, thereby improving long-term prognosis. (3) Monitoring Parameters: It is important to perform repeated antibody titer measurements or dynamic EEG monitoring for patients with severe anti-AMPAR-E to achieve better therapeutic effects. (4) Management of Hyperammonemia: Regular monitoring of ammonia levels and adequate treatment of hyperammonemia are essential. Since our treatment experience is based solely on a single case, the evidence is insufficient. Therefore, more basic and clinical studies are needed to confirm these observations.

Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Anti-AMPAR-E	anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis
GCS	Glasgow coma scale
IVIG	Intravenous immunoglobulin
CSF	Cerebrospinal fluid
ICU	Intensive care unit
GluR	Glutamate receptor
MRI	Magnetic resonance imaging
CT	Computed tomography
EEG	Electroencephalogram
IVMP	Intravenous methylprednisolone pulse
VPA	Valproate
NMDAR	n-methyl-d-aspartate receptor

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Author contributions
C Y drafted the manuscript; L B, J D, Z C collected the patientInformation and the data; G X substantively revised the manuscript; X Y Analysis of data and substantively revised the manuscript. All authors read and approved the fnal manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
We declare that the study follows the tenants of the Declaration of Helsinki. For this case report, we obtained written consent from the patient to participate.

Consent for publication
Written informed consent was obtained from the patient' s parent for publication of this case report and any accompanying images.

Competing interests
The authors declare no competing interests.

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