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CASE REPORT

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Successful treatment with efgartigimod as an add-on therapy for acute attack of anti-NMDA receptor encephalitis: a case report

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Abstract

Background Anti-NMDA receptor encephalitis is an autoimmune, antibody-mediated inflammatory disease of the brain characterized by the presence of IgG antibodies targeting the excitatory N-methyl-D-aspartate receptor (NMDAR). Previous research has established that the neonatal Fc receptor (FcRn) regulates the transport and circulation of immunoglobulins (IgG). Efgartigimod, an FcRn antagonist, has been shown to enhance patient outcomes by promoting IgG clearance, and it has exhibited substantial clinical efficacy and tolerability in the treatment of myasthenia gravis. Efgartigimod has demonstrated potential efficacy in the treatment of various IgG-mediated autoimmune diseases. Nonetheless, to date, no studies have investigated the use of efgartigimod in the treatment of anti-NMDAR encephalitis.

Case presentation We present a case of a 42-year-old male patient diagnosed with anti-NMDAR encephalitis, initially treated with intravenous methylprednisolone(IVMP) and human immunoglobulin (IVIG) without clinical improvement. Subsequent administration of efgartigimod resulted in rapid clinical improvement; however, the patient experienced a relapse upon discontinuation of efgartigimod. Reintroduction of efgartigimod led to rapid and significant clinical improvement, accompanied by a marked decrease in anti-NMDAR antibodies and serum IgG levels in both serum and cerebrospinal fluid. The patient remained relapse-free during a 2-month follow-up period.

Conclusion This case demonstrates that efgartigimod is a potentially rapid and effective therapy for the treatment of the acute phase of anti-NMDAR encephalitis.

Keywords Anti-NMDA-receptor antibody encephalitis, Efgartigimod, FcRn inhibitor, IgG

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Introduction

Anti-NMDA receptor (NMDAR) encephalitis is an autoimmune, antibody-mediated inflammatory disease of the brain characterized by an acute or subacute onset of seizures, psychiatric and behavioral abnormalities, movement disorders, and cognitive deficits [1]. Acute phase treatment typically involves first-line immunotherapy, which includes intravenous high-dose corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PE), either alone or in combination. Second-line immunotherapy options include rituximab or cyclophosphamide [2]. Despite these therapeutic interventions, a substantial proportion of patients exhibit inadequate responses to both first- and second-line immunotherapies.

The expeditious elimination of pathogenic antibodies constitutes a therapeutic approach for immune-mediated antibody disorders. Contemporary research has identified anti-NMDAR antibodies as the etiological agents in anti-NMDAR encephalitis, predominantly of the IgG1 subclass targeting excitatory NMDA receptors [3–5]. Recently, the inhibition of neonatal Fc receptor (FcRn)-IgG interactions has emerged as a novel strategy for the depletion of IgG. Clinical application of FcRn antagonists has demonstrated efficacy in mitigating the disease by obstructing FcRn-IgG interactions, thereby diminishing the levels of circulating pathogenic IgG [6]. The FcRn antagonist efgartigimod has been shown to reduce serum concentrations of serum concentrations of IgG1, IgG2 and IgG3, IgG4, with a notable reduction in IgG1 levels [7]. Current research indicates that efgartigimod demonstrates significant clinical efficacy and tolerability in the management of myasthenia gravis [8, 9]. Efgartigimod has been considered to have a potential in the treatment of multiple IgG-mediated autoimmune diseases [10]. Furthermore, efgartigimod has been reported to be effective in the treatment of diseases such as neuromyelitis optica spectrum disease (NMOSD), anti-LGI1-associated encephalitis and Guillain-Barré syndrome (GBS) [11–13].

To the best of our knowledge, there have been no reported cases of anti-NMDAR encephalitis treated with efgartigimod. In this report, we present a case of anti-NMDAR encephalitis successfully managed with efgartigimod, resulting in rapid disease control. Notably, the observed changes in serum and cerebrospinal fluid (CSF) anti-NMDAR antibody levels, as well as serum IgG concentrations, demonstrated a correlation with clinical recovery that has not been previously described in the literature.

Case presentation

A 42-year-old male patient presented 16 days prior with headaches of unknown etiology, accompanied by lethargy, but without chills, fever, seizures, or cognitive impairments. Two days subsequent to the initial presentation, he developed episodic restlessness, incoherent speech, and auditory and visual hallucinations, each episode lasting approximately 10 min and resolving spontaneously. Intermittent periods were characterized by lethargy and drowsiness. The patient's condition progressively deteriorated, ultimately manifesting as abnormal movements with his eyes closed (The patient exhibited incoherent speech and uncontrollable movements when the patient closed his eyes. These movements were related to the content of the patient's previous daily work. The movements would stop when he opened his eyes. When asked why he had such uncontrollable speech and movements, the patient replied that he was at work). Given the severity of his psychiatric symptoms, he was admitted to a psychiatric hospital, where he experienced manic episodes and received treatment for schizophrenia. Despite these interventions, his condition remained refractory. A cranial MRI revealed no significant abnormalities. (Fig. 1). Lumbar puncture results indicated an intracranial pressure of 150 mmH2O, with cerebrospinal fluid (CSF) analysis revealing a nucleated cell count of 10×10^{6}/L (reference value 0–5/L), glucose level of 2.97 mmol/L (reference value 2.5–4.4 mmol/L), chloride level

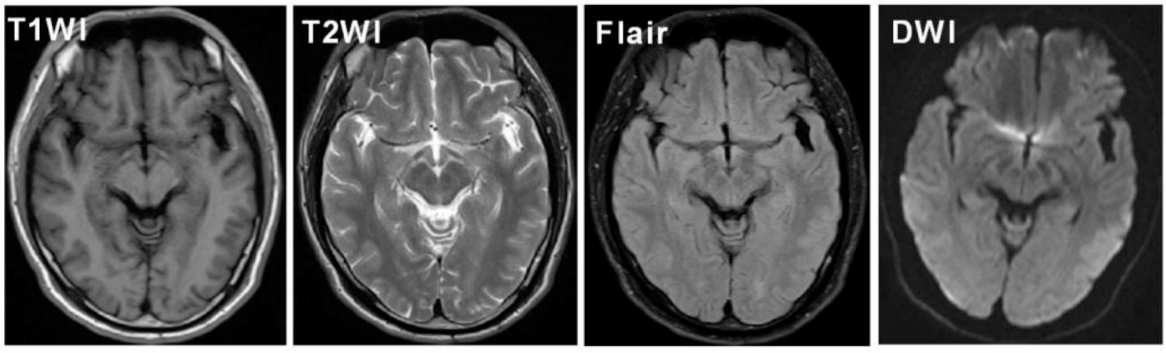

Fig. 1 The MRI findings of the patient, with T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), Fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) all indicating no abnormal signal changes

of 125.8 mmol/L (reference value 120–130 mmol/L), and protein level of 1.2 g/L (reference value 150–450 mg/L). Cytological examination, bacterial smear, and bacterial culture of the CSF were unremarkable. Both serum and CSF tests were positive for anti-NMDAR antibodies (1:100), while oligoclonal bands were negative in both serum and CSF. The diagnosis of Anti-NMDA-receptor antibody encephalitis was established, and the patient was administered a 1000 mg pulse therapy of methylprednisolone. Despite three days of treatment, the patient's psychiatric symptoms continued to deteriorate, necessitating his transfer to our hospital. The patient's medical history is notable for a lung effusion surgery performed three years prior, though the details of the procedure remain unspecified. Upon physical examination, the patient's vital signs were as follows: temperature 37.5℃, pulse 98 beats per minute, respiratory rate 20 breaths per minute, and blood pressure 135/75 mmHg. Cardiovascular, pulmonary, and abdominal examinations did not reveal any significant abnormalities. Neurologically, the patient was alert but exhibited decreased reactivity, orientation, memory, comprehension, and calculation abilities, and demonstrated a degree of uncooperativeness during the examination. The cranial nerve examination yielded normal results. Muscle tone in the limbs was within normal limits, and muscle strength was symmetrical at 4/5, accompanied by mild tremors in both upper extremities. The finger-to-nose test, Romberg test, and gait assessment indicated non-cooperation. Tendon reflexes in the limbs were graded as (++), and the bilateral Babinski sign was negative, with no signs of meningeal irritation. The Modified Rankin Scale (MRS) score was 4, and the Brief Psychiatric Rating Scale (BPRS) score was 55.

Ancillary examinations revealed the following results: Hematological analysis showed a white blood cell count of 14.66 × 10^9/L, with a lymphocyte percentage of 2.5% and a neutrophil percentage of 96.9%. Immunoglobulin levels were as follows: Immunoglobulin G (IgG) at 26.76 g/L (reference range: 8–16 g/L), Immunoglobulin A (IgA) and Immunoglobulin M (IgM) were normal. The C-reactive protein level was recorded at 9.57 mg/L. Comprehensive laboratory evaluations, including blood electrolytes, cardiac enzyme profile, renal function tests, liver function tests, thyroid function tests, tumor markers, and a spectrum of anti-nuclear antibodies revealed no significant abnormalities. The electrocardiogram was within normal limits. Chest X-ray findings indicated mild infiltrates in both lungs and cardiomegaly. Abdominal ultrasound and echocardiography did not demonstrate any abnormalities. Electroencephalogram (EEG) Analysis: (1) Baseline Activity: The background rhythm exhibited irregularities characterized by low-amplitude fast waves, with an indistinguishable wake-sleep cycle. Neither pain nor light stimulation elicited significant enhancement or attenuation of the EEG signals. No abnormalities were detected during specialized provocation tests or through electrode assessments. Additionally, electromyography and cardiac monitoring revealed no irregularities. (2) Clinical Observations During Episodes: Several seizure events were documented, marked by a decrease in patient responsiveness. Manifestations included the patient lifting his head, sitting up, engaging in hand fumbling, shouting, and experiencing occasional tremors in the lower limbs. Concurrent EEG findings showed a gradually increasing background wave rhythm with abundant muscle artifact, and no sharp waves, spikes, or slow waves bursts were observed.

Patient was admitted to the intensive care unit (ICU) and continued with intravenous methylprednisolone (IVMP) pulse therapy, along with IVIG at a dosage of 0.4 g/kg/day for 5 consecutive days. The patient was administered a continuous infusion of dexmedetomidine and olanzapine to ameliorate psychiatric symptoms, supplemented with intermittent intramuscular haloperidol for the management of acute manic episodes. Despite the completion of IVIG therapy and a subsequent observation period of five days, there was no observed improvement in the frequency or severity of the episodic psychiatric symptoms. Furthermore, the patient began to exhibit intermittent generalized sweating, with a BPRS score of 84. Given the poor response to IVMP and IVIG, we considered alternative strategies to eliminate the pathogenic antibodies. A single 800 mg dose of the FcRn antagonist efgartigimod was administered. By the third day following this administration, there was a marked reduction in the patient's psychiatric symptoms and a notable decrease in the frequency of episodes. The sedation medications were discontinued, and by the fifth day, the psychiatric symptoms had completely resolved, allowing the patient to be transferred to a general ward for continued treatment. However, the patient occasionally experienced transient tremors in both lower limbs during sleep. On the seventh day, a second dose of efgartigimod at 800 mg was administered. By the eighth day, the patient had largely returned to baseline, exhibiting a Modified Rankin Scale score of 1 and a BPRS score of 37. Serum immunoglobulin levels were assessed, revealing IgG at 13.73 g/L, IgA at 2.23 g/L, and IgM at 0.46 g/L, with serum anti-NMDAR antibodies measured at a titer of 1:30. Upon discharge, the patient was prescribed prednisone and mycophenolate mofetil for maintenance therapy.

Fourteen days post-discharge (June11,2024), the patient presented with recurrent abnormal eye closure. Consequently, the dosage of mycophenolate mofetil and prednisone was increased. Despite these interventions, the patient's symptoms progressively deteriorated. The

patient experienced hallucinations, incoherent speech, and other cognitive disturbances, in addition to tremors in both upper limbs. Subsequently, the patient was readmitted on June 22, with a BPRS score of 45. A repeat cranial MRI revealed no significant abnormalities. On June 25, the patient's serum IgG level was measured at 6.96 g/L, and the serum anti-NMDAR antibody titer was determined to be 1:30. Due to the absence of cerebrospinal fluid anti-NMDAR antibody testing, it remains inconclusive whether the recurrence of the condition was attributable to increased intrathecal antibody synthesis. Efgartigimod treatment commenced on June 25, with an initial intravenous dose of 800 mg, followed by a second 800 mg dose on June 30. Post-treatment, the patient's auditory and visual hallucinations, incoherent speech, and other psychiatric symptoms gradually resolved, with a reduction in abnormal closing of the eyes and only slight tremors in the upper limbs. By July 12, the patient exhibited a cessation of abnormal eye closure, resolution of upper limb tremors, and significant improvement in mental state, as evidenced by a BPRS score of 37. On July 16, laboratory assessments revealed a serum IgG level of 5.74 g/L, serum anti-NMDAR antibody titer of 1:10, and cerebrospinal fluid anti-NMDAR antibody titer of 1:1 (Fig. 2), with a Modified Rankin Scale (MRS) score of 1. Subsequent BPRS scores on August 12 and September 1 were consistently 27 (Fig. 3), accompanied by an MRS score of 0. Follow-up evaluations over the past two months indicated no recurrence of symptoms.

Discussion

Anti-NMDAR encephalitis is an inflammatory brain disease mediated by autoimmune antibodies. First identified in 2007, this condition was subsequently linked to a series of autoantibodies targeting neuronal cell surface or synaptic proteins [14]. Research indicates that autoimmune encephalitis (AE) constitutes approximately 10–20% of all encephalitis cases, with anti-NMDAR encephalitis representing 54–80% of AE cases [15]. Clinically, anti-NMDAR encephalitis predominantly affects young women and is characterized by a subacute or acute onset, typically reaching its peak within two to several weeks. The prodromal symptoms typically encompass fever and headache, with primary manifestations including abnormal behavior, seizures, memory decline, involuntary movements, and decreased consciousness [1, 16]. Cranial MRI findings may range from normal to nonspecific, occasionally revealing periventricular FLAIR and T2 hyperintensities, or scattered cortical or subcortical FLAIR hyperintensities [17]. Intracranial pressure can be either normal or elevated, while cerebrospinal fluid analysis may show a normal or slightly elevated white cell count and a mildly increased protein content, Oligoclonal bands in cerebrospinal fluid may test positive, and

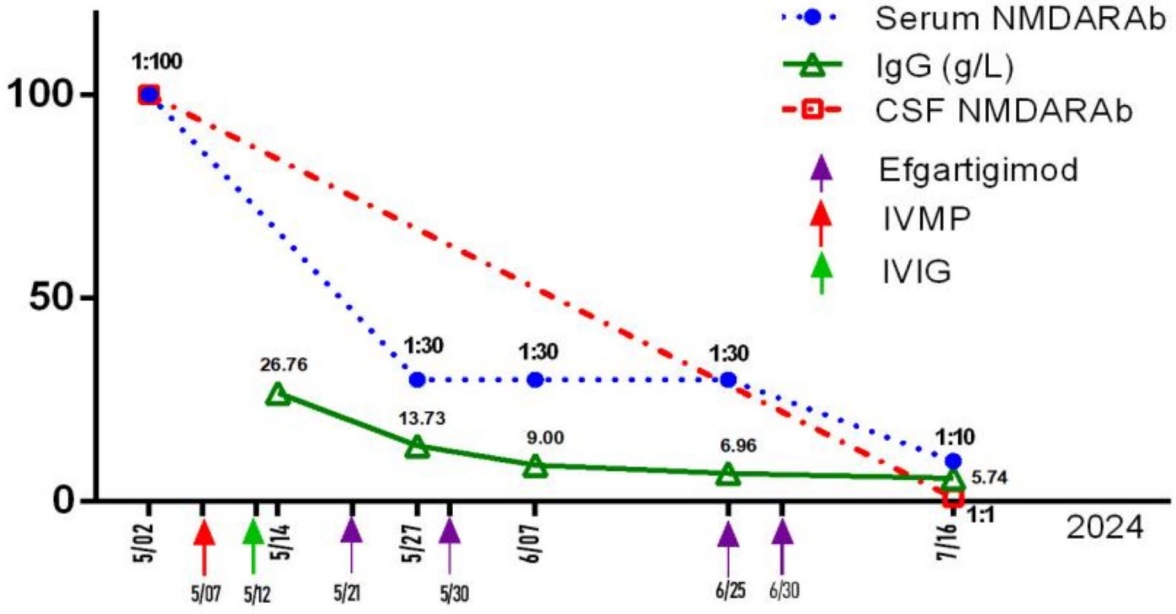

Fig. 2 Changes in serum NMDAR antibodies (NMDARAb) and Immunoglobulin G (IgG) levels. The continuous test results for serum NMDARAb demonstrate a decrease in titer and subsequent stabilization following the administration of efgartigimod. The titer further decreases after re-administration of efgartigimod. Additionally, the serum IgG and the CSF NMDARAb indicate a sustained decrease in titer post-efgartigimod treatment

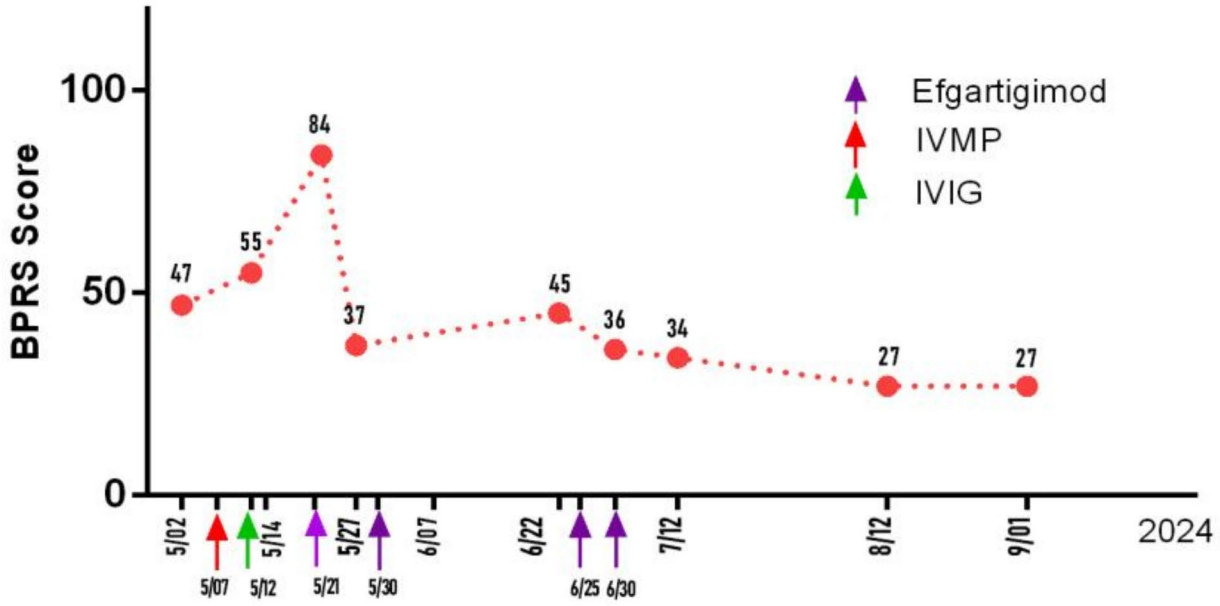

Fig. 3 The correlation between patient BPRS scores and therapeutic interventions. The data indicate that the BPRS score continued to rise following administration of IVMP and IVIG. However, a significant reduction in the BPRS score was observed after treatment with efgartigimod. Approximately two weeks post-efgartigimod treatment, the patient's condition recurred, as evidenced by an increase in the BPRS score. Subsequent administration of efgartigimod once again resulted in a decrease in the BPRS score

cerebrospinal fluid anti-NMDAR antibodies may be positive [18, 19]. In this instance, the patient initially exhibited headache as a prodromal symptom, subsequently developing clinical features consistent with encephalitis syndrome, including delayed responses, hallucinations, manic behavior, and abnormal eye closure. Cranial MRI did not reveal significant abnormalities; however, cerebrospinal fluid analysis demonstrated a mildly elevated white cell count and increased protein concentration. Both serum and cerebrospinal fluid tested positive for anti-NMDAR antibodies at a titer of 1:100, thereby confirming the diagnosis of anti-NMDAR encephalitis. The International Autoimmune Encephalitis Alliance's recommendations for the diagnosis and treatment of AE include first-line and second-line immunotherapy during the acute phase. Despite advancements in treatment, a subset of patients continues to experience suboptimal outcomes, underscoring the necessity for the development of novel therapeutic approaches to address the full spectrum of autoimmune encephalitis (AE) cases. Early intervention in autoimmune encephalitis is associated with improved prognoses, emphasizing the critical importance of implementing rapid and efficacious treatment strategies during the initial stages of the disease. Empirical research has established that anti-NMDAR antibodies, predominantly of the IgG1 subclass, are pathogenic in anti-NMDAR encephalitis. Furthermore, studies have indicated a potential correlation between the titer of anti-NMDAR antibodies and the clinical severity observed in patients [20, 21]. IVIG and PE therapy have demonstrated efficacy in the treatment of autoantibody-mediated diseases, underscoring the potential of antibody blockade and clearance strategies. The neonatal Fc receptor (FcRn), which is ubiquitously expressed in adults, is instrumental in regulating immunoglobulin G (IgG) levels by facilitating IgG recycling, thereby extending its half-life and maintaining its plasma concentration [22]. Efgartigimod, an antagonist of FcRn, disrupts the interaction between FcRn and IgG, resulting in the degradation of IgG within lysosomes. This inhibition of IgG recycling leads to the clearance of pathogenic antibodies, thereby ameliorating clinical symptoms. Efgartigimod has demonstrated substantial efficacy in the treatment of myasthenia gravis without reducing IgA or IgM levels [8, 23]. Clinical studies have indicated a decrease in serum concentrations of IgG1, IgG2, IgG3, and IgG4, with a pronounced reduction in IgG1. Currently, efgartigimod is approved for the treatment of myasthenia gravis, and ongoing clinical trials are investigating its potential in various inflammatory diseases characterized by pathogenic autoantibodies, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy,

and inflammatory myopathy [23]. Previous studies have demonstrated the efficacy of efgartigimod in treating neuromyelitis optica spectrum disorder (NMOSD), Guillain-Barré syndrome (GBS), and anti-IgGI1 antibody encephalitis. In this particular case, efgartigimod therapy was initiated following the ineffectiveness of methylprednisolone and IVIG therapy. The patient exhibited significant clinical improvement after the administration of the second dose of efgartigimod (800 mg). However, it is important to note that the patient had also received methylprednisolone and IVIG therapy during the initial hospitalization, thereby complicating the attribution of the observed therapeutic effects solely to efgartigimod. However, following a recurrence of the condition, subsequent administration of efgartigimod rapidly stabilized the patient's clinical status. This therapeutic response was associated with changes in serum and cerebrospinal fluid anti-NMDAR antibodies, as well as serum IgG concentrations, which correlated with clinical improvement. Efgartigimod exhibited significant and rapid efficacy in managing the patient's condition. At present, efgartigimod has been discontinued, and the patient is maintained on corticosteroids and mycophenolate mofetil for ongoing therapy. A 2-month follow-up has shown no recurrence of the condition.

To the best of our knowledge, there have been no reported case of using efgartigimod in the treatment of anti-NMDAR encephalitis. In the present case of anti-NMDAR encephalitis, the patient's condition was swiftly managed following treatment with the FcRn antagonist, efgartigimod. Notably, the alterations in serum and cerebrospinal fluid anti-NMDAR antibody titers, along with serum IgG levels, demonstrated a correlation with clinical recovery. Autoimmune encephalitis is an antibody-mediated central nervous system disease, and there exists a blood-brain barrier between the central nervous system and the circulatory system. Therefore, in addition to clearing the pathogenic antibodies from the periphery, it is also necessary to effectively remove the antibodies already present in the central nervous system. It is generally believed that large molecule drugs cannot pass through the blood-brain barrier, and the clearance of antibodies already present in the central nervous system is usually limited. In the treatment of this case, it was observed that after efgartigimod therapy, the serum anti-NMDAR antibody titer decreased from 1:100 to 1:10, and the CSF anti-NMDAR antibody titer decreased from 1:100 to 1:1. Pathogenic antibodies in both serum and CSF were significantly reduced, and total serum IgG levels were also significantly reduced. There is currently no evidence that efgartigimod can cross the blood-brain barrier in patients with encephalitis, but based on the observed clinical effects and laboratory results in this patient, efgartigimod was able to effectively clear the anti-NMDAR antibodies from both the serum and the central nervous system. There are currently no studies on whether and how efgartigimod may clear IgG from the central nervous system. Possible mechanisms have been proposed: (1) Efgartigimod clears circulating anti-NMDAR antibodies, creating a concentration gradient between the central nervous system and the circulation, allowing IgG to enter the circulation along the concentration gradient; (2) Autoimmune encephalitis is associated with disruption of the blood-brain barrier, allowing efgartigimod to enter the central nervous system and exert its effects; (3) FcRn is highly expressed in brain microvascular endothelial cells and choroid plexus epithelium, and efgartigimod may inhibit intracellular FcRn function, leading to lysosomal degradation of IgG entering endothelial and choroid plexus epithelial cells, thereby accelerating clearance of IgG from the central nervous system. Efgartigimod exerts a disease-modifying effect by clearing antibodies, but it does not inhibit the production of antibodies. So currently we still use corticosteroids and mycophenolate mofetil for maintenance treatment. Previous studies have suggested that the B-cell depleting agent Rituximab (anti-CD20 monoclonal antibody) can effectively treat and prevent the recurrence of NMDAR encephalitis [2]. A low dose of Rituximab can achieve the goal of depleting B cells and thus reducing antibody production. Inebilizumab (anti-CD19 monoclonal antibody) has a broader coverage of the B-cell lineage and a more potent B-cell depleting effect [24, 25]. A Phase IIb, double-blind, randomized controlled trial (NCT04372615) evaluating the efficacy and safety of Inebilizumab in the treatment of anti-NMDAR encephalitis is currently under study (https://clinicaltrials.gov/study/NCT04372615). This trial will prospectively study an optimized B-cell depletion therapy to promote better long-term outcomes in NMDAR encephalitis and to identify better biologic biomarkers to predict outcome.

This study has limitations, as it is a single-center case report without comparisons or repetitions. The patient also received concomitant treatment with corticosteroids and IVIG, so the effects cannot be solely attributed to efgartigimod. The follow-up period of only 2 months also does not represent the long-term prognosis. Currently, the FcRn antagonist efgartigimod is regarded as having significant potential in the treatment of various IgG-mediated autoimmune diseases. To our knowledge, this case report is the first attempt to use efgartigimod to treat anti-NMDAR encephalitis, and it has shown promising therapeutic effects. However, there are limitations due to it being a single case observation and the combined use of other medications. Future research, especially multicenter randomized controlled trials, is needed to further explore the efficacy and mechanisms of

action of efgartigimod in the treatment of anti-NMDAR encephalitis.

Abbreviations

NMDA	Nmethyl-D-aspartate
NMDAR	Nmethyl-D-aspartate receptor
MRI	Magnetic resonance imaging
CT	Computed tomography
FcRn	Neonatal Fc receptor
IVMP	Intravenous methylprednisolone
IVIG	Intravenous human immunoglobulin
CSF	Cerebrospinal fuid
NMOSD	neuromyelitis optica spectrum disease
GBS	Guillain-Barré syndrome
MRS	Modified Rankin Scale
BPRS	Brief Psychiatric Rating Scale
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgM	Immunoglobulin M

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

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Author contributions
Huasheng Huang and Huihui Qin: data acquisition. Huasheng Huang: preparation of the manuscript. Huihui Qin and Guangshun Han: participated in the clinical care of this patient. Yizhi Wei: figure creation. Jie Li: supervision of the study and edited the final manuscript. All authors have reviewed the data analysis process, writing of the manuscript, and approved the final article.

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Data availability
The main data collected during this study are included in this article. The data sets used in the current study are available from the corresponding author upon reasonable request. The figure used in the study is original and made by the authors.

Declarations

Ethics approval and consent to participate
This study was was in accordance with the ethical standards of Liuzhou People's Hospital affiliated to Guangxi Medical University and with the Helsinki declaration. The patient provided written informed consent according to the Declaration of Helsinki.

Consent for publication
Patient gave written informed consent for their personal or clinical details to be published in this study.

Competing interests
The authors declare no competing interests.

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