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CASE SERIES

A Case Series of Anti-Metabotropic Glutamate Receptor 2 Antibody-Related Diseases with Distinct Neurological Involvement

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Background: Anti-metabotropic glutamate receptor 2 (mGluR2)-related diseases are rare autoimmune disorders of the central nervous system that primarily affect the cerebellum and are occasionally associated with malignancies.

Methods: Data, including demographics, symptoms, blood and cerebrospinal fluid (CSF) tests, and brain magnetic resonance imaging (MRI), were retrospectively collected from two patients with informed consent at Xiangya Hospital from February 2024 to October 2024. Autoantibodies associated with autoimmune encephalitis were tested using cell-based assays. The literature describing anti-mGluR2 antibody-related diseases was searched for in PubMed and five cases were reviewed.

Results: Two cases of anti-mGluR2 antibody-related diseases were reported: one with acute cerebellitis and the other with refractory seizures. Brain MRI showed cerebellar involvement in the cerebellitis patient. Anti-mGluR2 antibodies were detected in the serum but not in the CSF of both cases, and both responded well to immunotherapy. A review of five patients (all female, aged 3–78 years) found four with cerebellar ataxia or cerebellitis and one with immune-related epilepsy. Common symptoms included dysarthria, gait instability, and gaze/nystagmus, while seizures were rare. MRI revealed cerebellar involvement in most cases. Anti-mGluR2 antibodies were present in the serum of all patients but only in the CSF of two. Three patients responded well to immunosuppressive treatment, and two had malignancies.

Conclusion: Anti-mGluR2 antibody-related diseases are autoimmune disorders primarily characterized by ataxic manifestations, though seizures may also occur. The effectiveness of immunosuppressive treatment is uncertain and screening for tumors is necessary.

Keywords: metabotropic glutamate receptor 2, antibody, cerebellitis, cerebellar ataxia, seizure

Introduction

Metabotropic glutamate receptor 2 (mGluR2) is a member of the mGluR family, which is mainly located in the presynaptic membrane in central nervous system regions, such as the prefrontal cortex, cerebellum and hippocampus.[1–4] It negatively regulates the release of glutamate by inhibiting multiple pathways including protein kinase A (PKA) signaling and voltage gated Ca2+ channels.[4] Disturbance in mGluR2 results in neurological diseases, such as Parkinson's disease, brain injury caused by hypoxia-ischemia, epilepsy and ataxia.[3–7] Recently, Ruiz-García et al described two cases of cerebellar ataxia characterized by accompanying malignancies and mGluR2 antibodies.[8] Tissue slices from the cerebellum and hippocampus of rats and transfected cells confirmed the existence of mGluR2 antibodies in the serum and cerebrospinal fluid (CSF) of two patients, presumably caused by the expression of mGluR2 in malignancies. Another study reported the first Chinese case of a middle-aged woman with anti-mGluR2 antibody-related cerebellar ataxia without malignancies.[9] The role of mGluR2 antibodies in cerebellar ataxia is still not well understood. It may involve in disturbance in cerebellar long-term depression considering close relationship between

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voltage-gated calcium channel and mGluR2.[4,10] No cases of anti-mGluR2 antibody-related epilepsy have been reported although protective role of mGluR2 was considered in animal model. It may counteract neurotoxicity of glutamate through activation of a K+ conductance and inhibition of a Na+ -permeable channel.[7,11] In this article, we describe two cases presenting with markedly distinct central nervous system manifestations (ataxia and seizures) and positive mGluR2 antibodies. We integrated all published cases to ensure a better understanding of anti-mGluR2 antibody-related diseases.

Methods

Patient Data and Informed Consent

This study was approved by and performed under the ethical scrutiny of Xiangya Hospital, which conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from the guardians of both patients. After the guardians signed an informed consent form, all data related to these two patients who were referred to Xiangya hospital from February 2024 to October 2024 were retrospectively collected, integrated, and presented in this study.

Cell-Based Assay

Plasmids that encode certain nervous antigens, such as mGluR2, are transfected into pre-prepared HEK293 cells with the assistance of appropriate transfection reagent. So that these cells can express corresponding antigens, as previously reported.[8] The plasmids also carry gene segment that encodes green fluorescent protein to demonstrate green fluorescence. If there are targeted antibodies present in the patient's serum or CSF, the antibodies combine with the antigens, which further interact with fluorescein-labeled secondary antibodies. The results were observed using a fluorescence microscope.[12] Dual fluorescence detection was employed, with red fluorescence labeling antibodies in the sample and green fluorescence labeling cells expressing the target antigen. True positive signals were identified only when the red fluorescence specifically colocalized with the green fluorescence at the corresponding cellular regions. Titration was started at 1:10 and 1:1 in the serum and CSF, respectively. Detection was performed at the Jiangsu Simcere Diagnostic Laboratory.

Literature Review

We performed a literature review using the PubMed database. The key words used for searching included: "mGluR2", "seizures", "cerebellitis", "encephalitis" and "cerebellar ataxia". Two published studies comprising three patients were recruited and reviewed.

Results

Case 1

A previously healthy 7-year-old girl presented with acute onset of dizziness, headache, and vomiting, followed by altered consciousness, and was subsequently referred to Xiangya Hospital. Physical examination revealed confusion, weakness of the limbs (especially the upper limbs), rigidity of the neck, and gaze to the right side in both eyes. Serum C-reactive protein, erythrocyte sedimentation rate, and procalcitonin levels were within normal ranges. Blood tests targeting lymphocytes showed elevated B cells (1064/uL; reference range: 304–777/uL). Blood tumor markers, including cancer antigen 125, 153, and neuron-specific enolase, were negative. Brain magnetic resonance imaging (MRI) revealed abnormal signals and swelling of the cerebellum, resulting in supratentorial interstitial edema, enlargement of the ventricles, and cerebellar tonsillar herniation (Figure 1A–C). Electroencephalogram (EEG) revealed sharp waves and spikes in the bilateral rolandic regions. The intracranial pressure (ICP) was 175 mmH2O. Leukocyte, glucose, and protein levels in the cerebrospinal fluid (CSF) were within normal ranges. Interleukin-6 was predominantly increased in the CSF (388 pg/mL; reference range: <5.9pg/mL). Further autoimmune encephalitis antibody screening in the serum and CSF based on a cell-based assay (CBA) showed the presence of mGluR2 antibody in the serum (1:10), but not in the CSF, 10 days after onset (Figure 2A). Oligoclonal bands revealed breakdown of the blood–brain barrier (BBB) (Figure 2B). The patient was diagnosed with anti-mGluR2 antibody-related cerebellitis. Contrast-enhanced computed tomography (CT) displayed no signs of malignancy in chest, abdomen, and pelvis. Immunotherapy was then initiated,

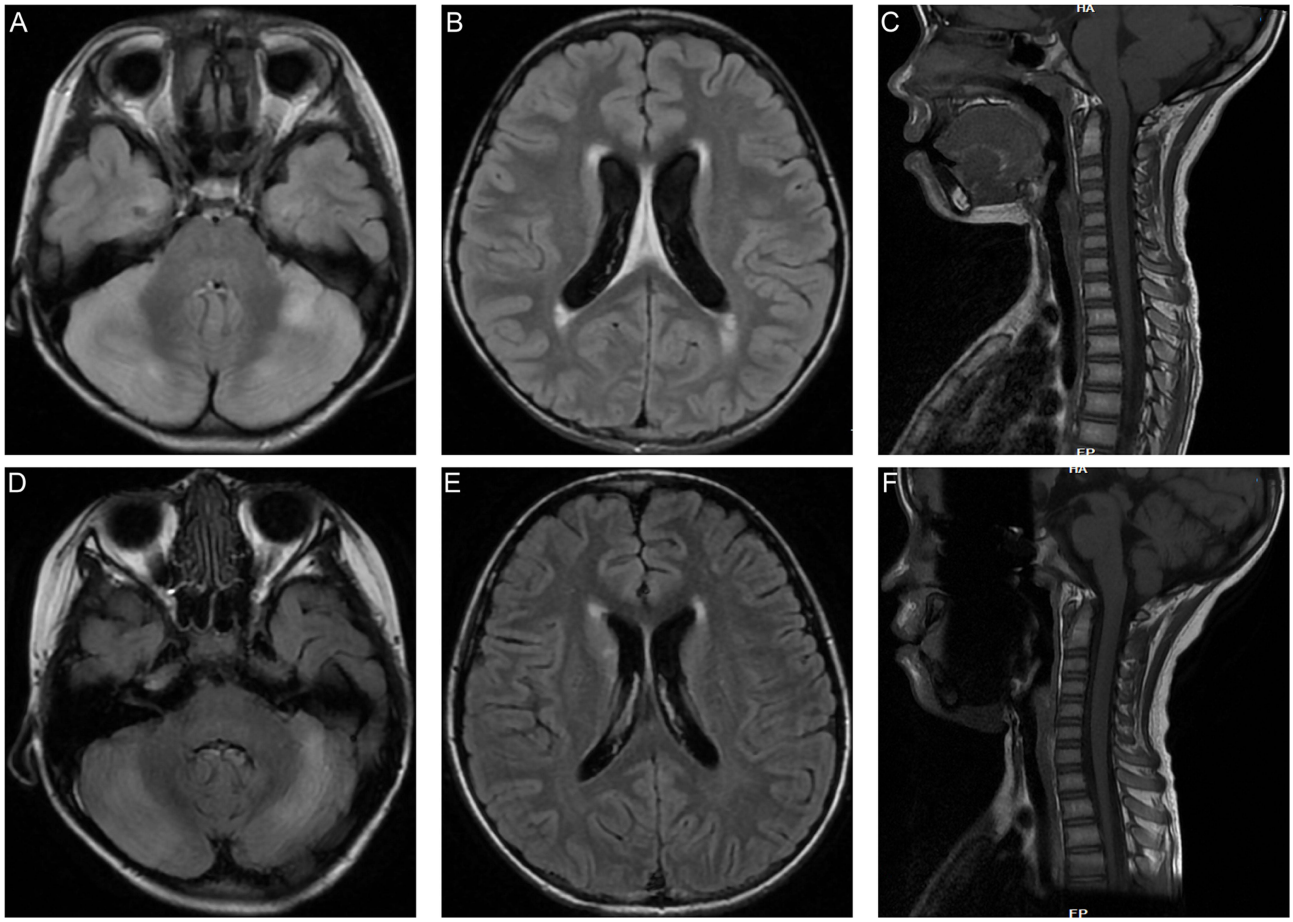

Figure 1 Brain images of case 1. (**A**–**C**) Initial brain images of the patient. (**A**) Hyperintensity and swelling of Cerebellum in T2-weighted fluid attenuated inversion recovery (T2FLAIR). (**B**) Hyperintensity around lateral ventricles and enlargement of lateral ventricles in T2FLAIR. (**C**) Cerebellar tonsillar herniation in T1 sequence. (**D**–**F**) Brain images after treatment. (**D**) Remaining existence of Hyperintensity in Cerebellum. (**E**) Reduced hyperintensity around lateral ventricles. (**F**) Resolved cerebellar tonsillar herniation and predominant cerebellar atrophy.

including intravenous immunoglobulin (IVIG; total 2 g/kg) and intravenous methylprednisolone (IVMP; 3d, 15 mg/kg) with tapering prednisone and tocilizumab (4 mg/kg, twice; 8 mg/kg, once). Hypertonic saline and mannitol were applied to lower ICP. After the initial immunosuppressive treatment, the patient responded to simple orders and gradually regained muscle strength, with no significant improvement in gaze, headache, or neck rigidity. Due to the persistence of headache and increased partial pressure of carbon dioxide in arterial blood gas analysis, as well as extreme swelling of the cerebellum according to MRI, refractory high ICP was considered. Surgery was then performed, and an Ommaya reservoir was placed to reduce the ICP. There were no complaints of headaches, and the rigidity of the neck disappeared. Progressive immunosuppressive treatment was initiated based on the severity of the condition. Plasma exchange (three times) followed by ofatumumab (subcutaneous injection, 20 mg, four times) was applied, with the latter targeting high B cell levels. The patient's consciousness and muscle strength fully recovered. Dysarthria and dysmetria on the finger–nose test appeared later and gradually disappeared. The CSF IL-6 in CSF were within the normal range. Peripheral B cells were predominantly decreased (2/uL; reference range: 304–777/uL). The latest brain MRI demonstrated resolved cerebellar tonsillar herniation and predominant cerebellar atrophy (Figure 1D–F).

Case 2

A previously healthy 4-year-old girl was referred to Xiangya Hospital with refractory seizures resistant to valproic acid and clobazam a few days after influenza. Febrile seizures and afebrile seizures occurred alternately. She experienced tonic, myoclonic, and absence seizures, which were confirmed using EEG. Frequency of seizure was approximately 4–8

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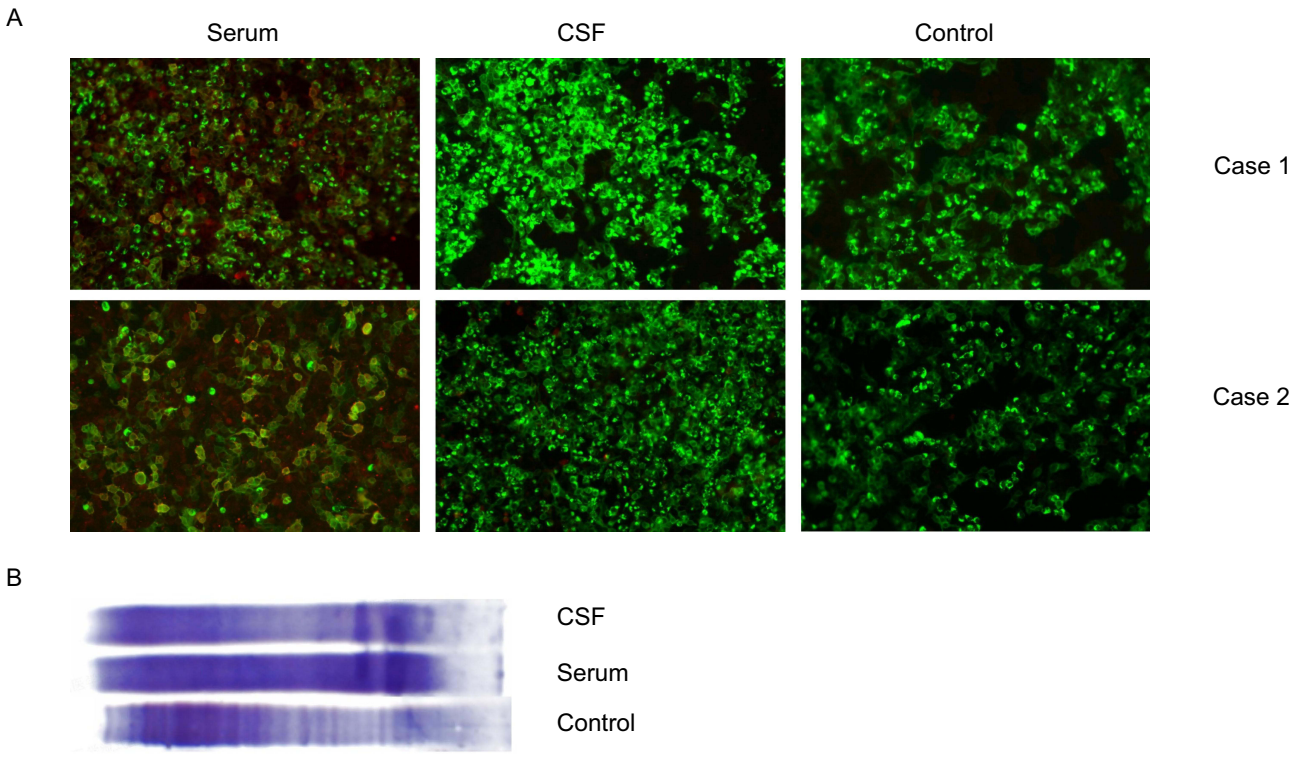

Figure 2 mGluR2 Antibodies test and Oligoclonal bands. (**A**) positive mGluR2 antibodies in the serum (1:10) and negative in the CSF both in case 1 and 2. (**B**) Oligoclonal bands seen in both CSF and serum in case 1.

times per day. Before this episode, she had experienced two febrile seizures: the first at age one and the second at age two. No abnormalities were observed on physical examination. Hereditary epilepsy was first considered. Regular blood tests revealed mild anemia and normal electrolyte and blood sugar levels. Tests for metabolic diseases revealed negative results. No pathogenic or likely pathogenic variants were detected by whole-exon sequencing (WES), copy number variants (CNV) or mitochondrial DNA testing. Magnetic resonance imaging of the brain found no structural malformation. EEG revealed slow background rhythm, interictal generalized sharp wave complexes and spike wave complexes as well as myoclonic seizures and tonic seizures (Figure 3A–D). Levetiracetam and lamotrigine were added and clobazam was gradually tapered off while valproic acid remained unchanged. No significant improvement of seizure was observed and cognitive function started to deteriorate. Given that no distinct clues for hereditary, metabolic, and structural causes were revealed and seizures started after influenza, screening for immune-related causes was initiated. Blood test results for rheumatic diseases and malignancies were negative. Blood tests targeting lymphocytes showed slightly elevated B cell levels (791/uL; reference range: 304–777/uL). Leukocyte, sugar, and protein levels in the CSF were within normal ranges. The mGluR2 antibody was detected in the serum (1:10) but not in the CSF (Figure 2A). Immune-related epilepsy was considered in this case. Contrast-enhanced CT revealed no signs of malignancy in chest, abdomen, and pelvis. Sequential IVIG (2 g/kg, monthly) and IVMP (20 mg/kg/day, 3 days in a row, monthly) were initiated. After three months of immunotherapy, the frequency of seizures decreased dramatically (four seizures occurring in the penultimate month of immunotherapy and no seizures in the final month of immunotherapy) while EEG showed improved background rhythm and interictal discharges (Figure 4A and B).

Literature Review

With the inclusion of two cases in our study, a total of five cases of anti-mGluR2 antibody-related diseases were summarized (Table 1).[8,9] All patients (5/5) were female and the age of onset ranged from 3 to 78 years. Three were

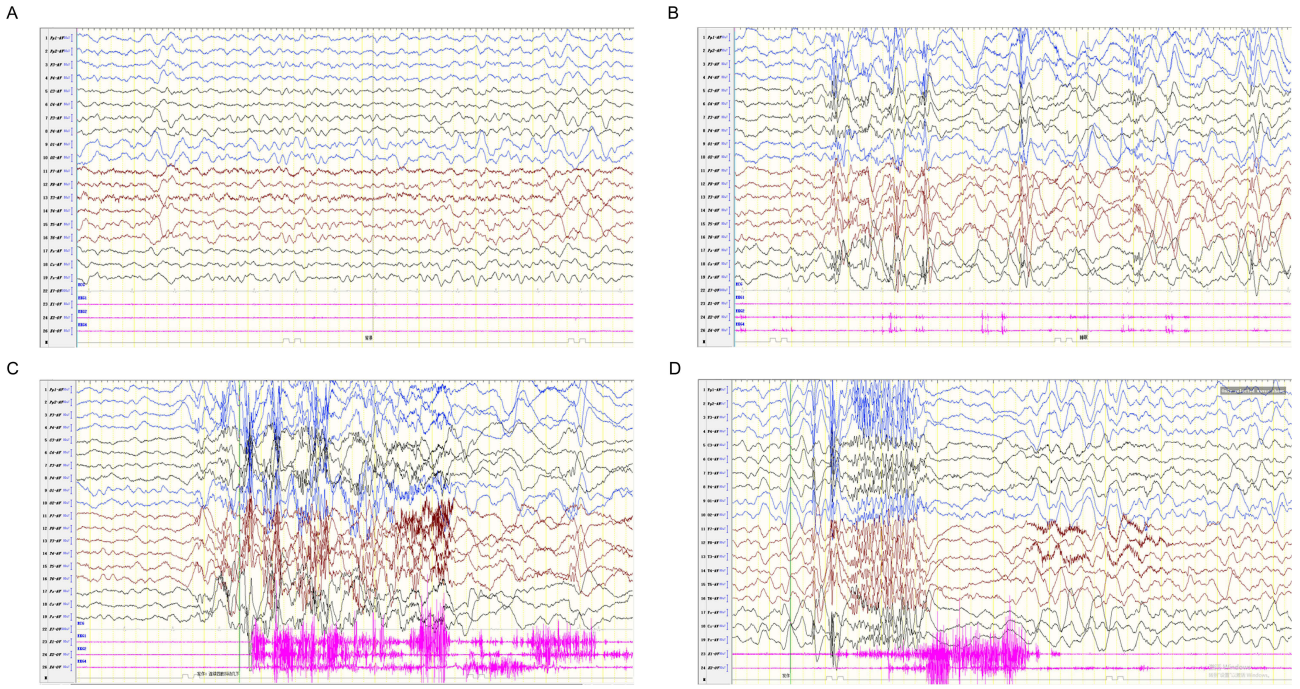

Figure 3 EEG before immunotherapy in the case 2. (**A**) Slow background rhythm. (**B**)Interictal discharges. (**C**) Myoclonic seizures. (**D**) Tonic seizures.

initially diagnosed with cerebellar ataxia, one in our study was diagnosed with cerebellitis, and the other was considered immune-related epilepsy. Dysarthria (4/5), gait instability (3/5), and gaze/nystagmus (3/5) were observed in most cases, followed by changes in consciousness, nausea/vomiting, and dysmetria on the finger–nose test (2/5). Only one patient presented with refractory seizures. Brain MRI revealed cerebellar involvement in most patients (4/5), comprising abnormal signals and atrophy. Diffuse white matter involvement (1/5), brainstem involvement (1/5), and signs of high intracranial pressure (1/5) were also observed. No MRI abnormalities were observed in the patients who presented with seizures. IL-6 levels in the CSF were elevated in one patient and routine CSF tests were normal in four patients. Anti-mGluR2 antibodies were present in the serum of all patients, but were positive in the CSF of only two patients. Intravenous glucocorticoids were administered to all of the patients (5/5), followed by IVIG (4/5), rituximab (1/5), tocilizumab (1/5), plasma exchange (1/5), and ofatumumab (1/5). Three patients showed a good response to immunotherapy, while the remaining patients showed a poor response to immunosuppressive treatment. Two patients had malignancies including neuroendocrine cancer and rhabdomyosarcoma.

Discussion

Here, we describe two patients with anti-mGluR2 antibody-related diseases with markedly different clinical presentations. To the best of our knowledge, these two phenotypes have not been reported before, which has expanded the spectrum of anti-mGluR2 antibody-related diseases.

Unlike in previous studies, cerebellar ataxia was not predominant in our cases. Changes in consciousness may be a feature of cerebellitis, particularly in critical cases.[13,14] A previous study also reported changes in consciousness in one patient.[8] The status of confusion could not enable the cooperation of neurological examinations indicating cerebellar ataxia, such as gait, finger–nose, and heel-to-knee tests. Severe headache and stiffening/pain of the neck are also red flags in critical cases.[14] In this study, signs of cerebellar ataxia prevailed when consciousness was regained in case 1, which corresponded with cerebellar atrophy on MRI. This evidence explains the situation in case 1. The specific mechanism of cerebellar ataxia caused by anti-mGluR2 antibody is not very clear. Activation of Gβγ subunits of mGluR2 can inhibit voltage gated Ca2+ channels (VGCC) and VGCC plays a significant role in long-term depression (LTD). Impairment of LTD can be one of potential mechanisms in cerebellar ataxia.[4,10] In the other case, cerebellar-related symptoms were not

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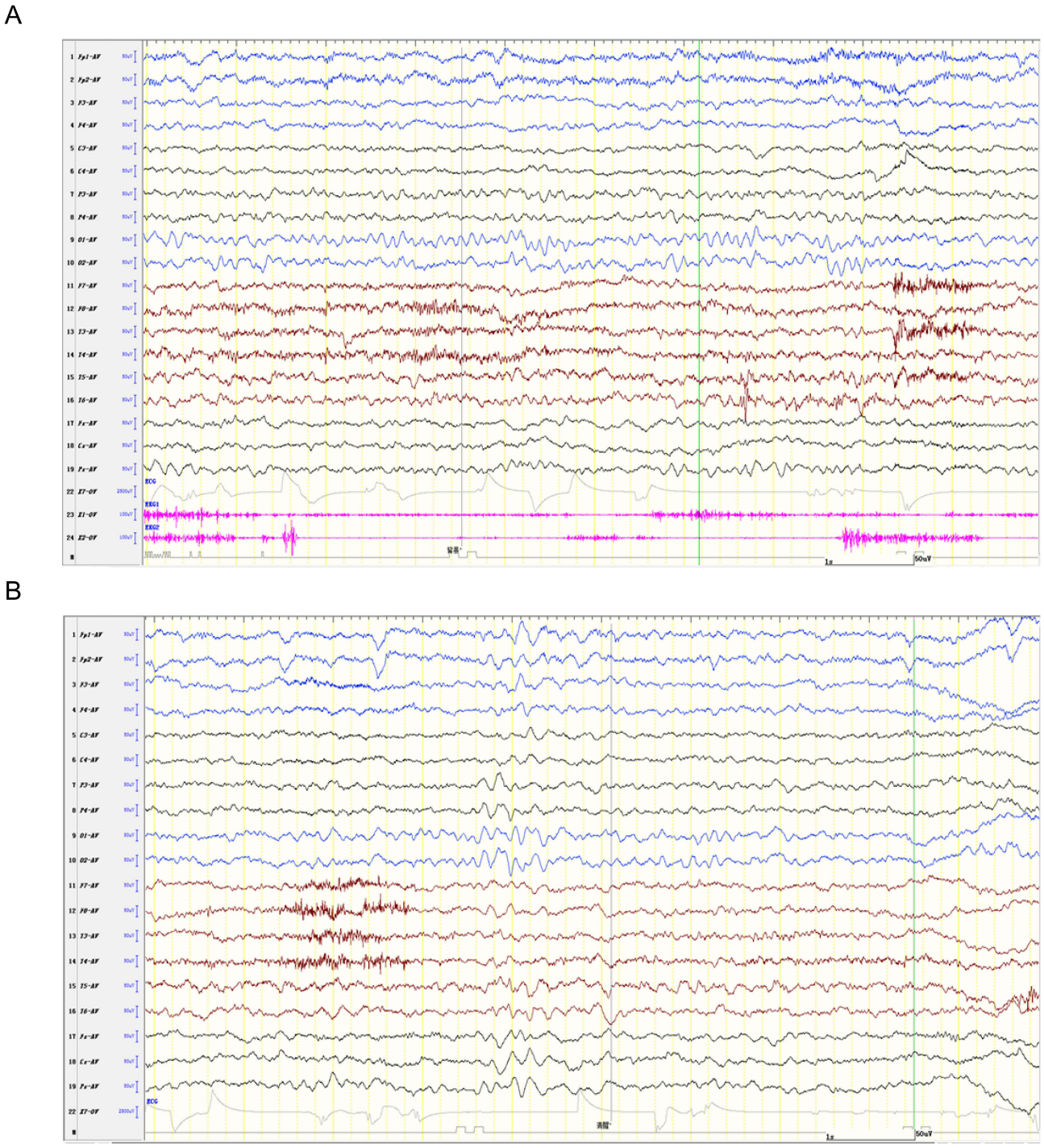

Figure 4 EEG after immunotherapy in the case 2. (**A**) Normal background rhythm. (**B**) Improved interictal discharges.

observed. However, the patient also presented with refractory seizures. Since mGluR2 is widely distributed in cortical areas and plays an inhibitory role in the brain, disturbance of mGluR2 by antibodies theoretically results in abnormal excitatory neuronal activities.[1,6,7] Activation of mGluR2 may counteract neurotoxicity of glutamate through activation of a K+ conductance and inhibition of a Na+ -permeable channel.[7,11]

Brain MRI is another indicator of anti-mGluR2 antibody-related cerebellitis and cerebellar ataxia. Cerebellar involvement without specific patterns was observed in most patients. In case 1 in our study, swelling of the cerebellum was highlighted and life-threatening, which led to cerebellar tonsillar herniation and required timely surgery. A previous

Table 1 Summary of Clinical Features of Patients With Anti-mGluR2 Antibody Related Diseases

Reference PMID	31826987[8]	31826987[8]	37456291[9]	This Paper (Case 1)	This Paper (Case 2)
Gender	Female	Female	Female	Female	Female
Age of onset	78y	3y	56y	7y	4y
CNS symptoms	Gait instability and dysarthria	Fever, nausea, and vomiting, followed by somnolence and gait instability	Gait instability, abnormal hands movement	Dizziness, headache (mainly occipital region), vomiting and change of consciousness	Refractory seizures
Neurological examination	/	Disclosed irritability, dysarthria, horizontal right-beating nystagmus, limb and truncal ataxia, and broad-based gait requiring bilateral support	Wide base gait, bilateral gaze horizontal nystagmus, mild right eyelid ptosis and dysarthria, dysmetria on finger-nose and heel-to-knee tests, and a positive Romberg sign	Confusion, weakness of limbs (especially upper limbs), rigidity of neck and gaze to the right side with both eyes, dysmetria on finger-nose test, dysarthria	No abnormalities
Brain MRI	Focal hyperintense cerebellar lesions in T2-weighted images that later evolved to diffuse involvement of the cerebellar white matter	Patchy gadolinium enhancement in the cerebellar folia	Hot cross bun sign in the pons, along with cerebellar and brain stem atrophy.	Abnormal signals and swelling of cerebellum and resulting supratentorial intestinal edema and enlargement of ventricles	No abnormalities
CSF tests	NA	Normal	Normal	Increased IL-6	Normal
mGluR2 antibody	Positive in the serum and CSF	Positive in the serum and CSF	Positive in the serum Negative in the CSF	Positive in the serum Negative in the CSF	Positive in the serum Negative in the CSF
Immunotherapy	IVIG, IVMP, rituximab	IVIG, IVMP	IVMP	IVIG, IVMP, PE, tocilizumab, ofatumumab	IVIG, IVMP
Responsiveness to immunotherapy	Poor response	Good response	Poor response	Good response	Good response
Identified malignancies	Small-cell neuroendocrine cancer of unknown origin	Alveolar rhabdomyosarcoma of the right axillary region	No	No	No

Abbreviations: CNS: Central nervous system; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; NA: not available; IVIG: intravenous immunoglobin; IVMP: intravenous methylprednisolone; PE: plasma exchange.

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study reported a similar case of cerebellitis caused by different antibodies, hypothetically due to the cytotoxicity of excessive glutamate.[15,16] Although inconclusive, cerebellar atrophy may predict unsatisfactory outcomes for immune-related diseases.[17–19] Although no abnormalities in brain images were found in the other cases in our study, long-term follow-up is still required for further investigation.

Although a primary study that first reported anti-mGluR2 antibody-related cerebellar ataxia showed the presence of both serous and CSF antibodies, another study found only serous antibodies.[8,9] Similar to other mGluR autoimmunity and anti-myelin oligodendrocyte glycoprotein antibody-associated diseases, breakdown of the blood–brain barrier may play a significant role in the pathological process.[20,21]

Immunosuppressive treatment can be an auxiliary diagnostic tool combined with other necessary tests, as proven in case 2. Considering the obviously elevated IL-6 levels in the CSF and B cells in the peripheral blood and the terrible situation of the first patient, tocilizumab and ofatumumab were sequentially administered. These have previously been used in febrile infection-related epilepsy syndrome and multiple sclerosis, leading to favorable outcomes.[22,23] In case 2, sequential IVIG and IVMP treatment was effective. In some autoimmune encephalitis, prolonged immunotherapy including IVIG and IVMP was applied depending on severity of diseases.[24] However, owing to the lack of sufficient data, the effectiveness of immunosuppressive treatment for anti-mGluR2 antibody-related diseases is difficult to estimate. Early treatment may result in better outcomes.[19,25] Therefore, early and progressive immunosuppressive therapy is required. Meanwhile, some antibodies predict favorable outcomes that require regular screening for tumors.[19] In a previous study, cancer was found four months after the onset of cerebellar ataxia.[8] Tumor treatment is recommended for longer survival or improvement in neurological symptoms.[19,26]

Limitations

We reported only two cases of anti-mGluR2 antibody-related diseases and did not investigate the potential mechanisms underlying the condition. Additionally, the limited number of studies available hinders further exploration of the disease spectrum and the development of standardized immunotherapy protocols. More research is needed in the future.

Conclusion

Ataxic manifestations such as gait instability and dysarthria commonly occur in anti-mGluR2 antibody-related diseases. Seizures are another manifestation that occurs at a lower frequency. Brain MRI and antibody testing are important auxiliary diagnostic tests. The effectiveness of immunotherapy remains uncertain, and tumor screening is required.

Informed Consent for Participation and Publication

Written informed consent was obtained from the legal guardians of all participants who agreed on participation and publication.

Ethical Standards

This study was approved by the Ethics Committee of Xiangya Hospital of Central South University and conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. Ethics Committee of Xiangya Hospital of Central South University approved the publication of these two cases with details. Written informed consent was obtained from the legal guardians of all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Have drafted or written, or substantially revised or critically reviewed the article; Have agreed on the journal to which the article will be submitted; Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; Agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declare no conflicts of interest in this work.

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