Letter to the Editor

Anti-metabotropic-glutamate-receptor 2-related encephalitis with cerebellar ataxia: a case description

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Introduction

Metabotropic glutamate receptors (mGluR) are a family of G-protein-coupled receptors activated by the neurotransmitter glutamate. They are divided into eight different subtypes according to different physiological and pathological characteristics (1). Anti-metabotropic-glutamate receptor 2 (mGluR2) is a subtype within the mGluR family and located in the preterminal portions of axons. mGluR2 is distributed mainly in the Purkinje cell layer and the granular layer in the cerebellum (2). The main physiological function of mGluR2 is to regulate glutamatergic and gamma-aminobutyric acid (GABA) synaptic transmission. However, the pathogenic mechanism of anti-mGluR2 antibodies to cerebellar ataxia is not clear. The possible pathogenesis is that anti-mGluR2 antibodies may attack the neurons in brainstem and cerebellum, producing inflammatory reaction (2,3).

In this case study, we report a female patient with progressive immune-mediated cerebellar ataxia with negative tumor screening. Sixteen months after clinical onset, anti-mGluR2 antibodies were found in the serum. She received high-dose glucocorticoids intravenously (1 g/day for 3 days, and then 0.5g/day for another 3 days) followed by oral administration of prednisolone (60 mg/day). After 1 month of treatment, her score of SARA (Scale for the assessment and rating of ataxia) changed from 17 to 14. She was relieved slightly from ataxia.

Case presentation

A 56-year-old Chinese woman was admitted to Binyang Hospital for a 13-month history of progressive ataxia found by her family. The initial symptom was gait instability in March 2020. After 1 month, she could not have dinner with chopsticks accurately and engage in the manual work that she used to do, such as carrying heavy objects. She developed dysarthria 2 months later. At her local hospital, the diagnosis of ataxia related to hypothyroidism was given and a replacement therapy with levothyroxine was started. This treatment had no effect on her ataxia. Her ataxia worsened gradually. In June 2021, a magnetic resonance imaging (MRI) of the brain was done. It showed a cerebellar ataxia and a Hot Cross Buns (HCB) sign in T2-weighted (T2W) images in the pons as shown in *Figure 1*. The initial diagnosis of cerebellar subtype of multiple system atrophy (MSA) was considered. Family history of ataxia was negative. Neurological examinations showed a cerebellar syndrome with 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. Her orientation, cognitive

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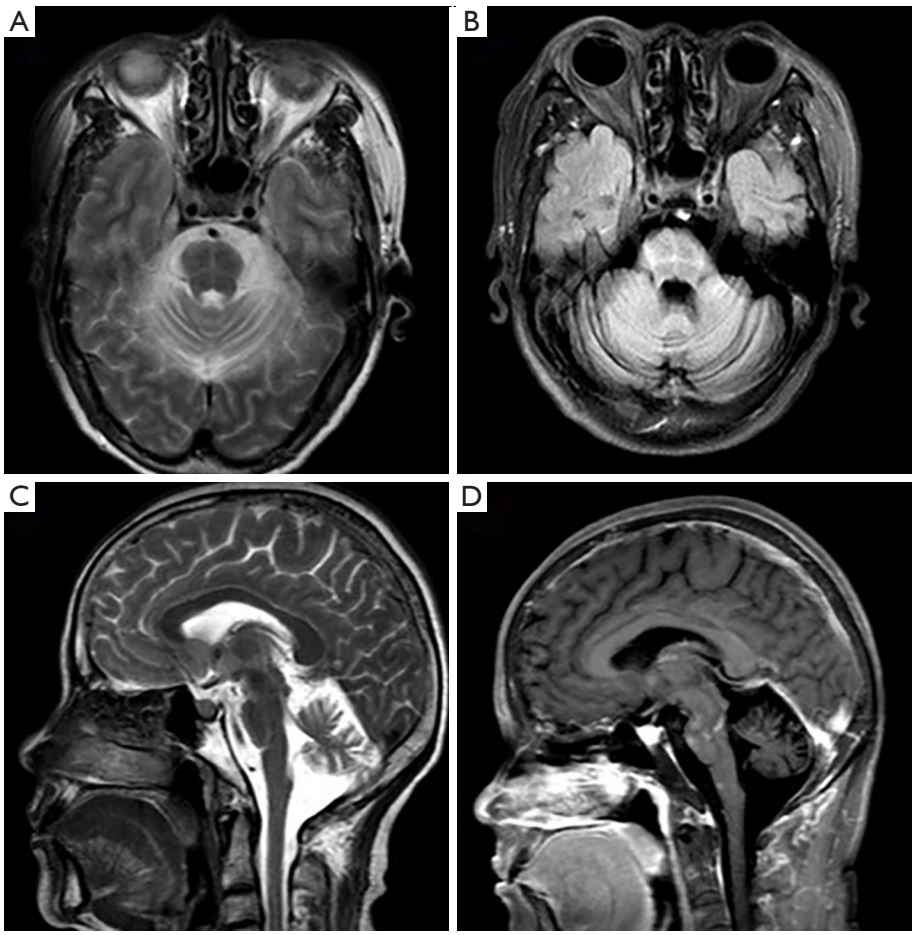

Figure 1 Brain MRI findings. Brain MRI obtained on June 2021 showed a hot cross bun sign in the pons in T2-weighted (A) and FLAIR (B) images, along with cerebellar and brain stem atrophy in sagittal section of T2-weighted (C) and contrast-enhanced (D) images. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

function, strength, deep-tendon reflexes, deep sensory and plantar reflexes were all normal. She did not describe any autonomic symptoms and suffer from any other symptom of unexplained autonomic dysfunctions such as voiding difficulties with post-void urinary residual volume ≥100 mL, urinary urge incontinence, neurogenic orthostatic hypotension (≥20/10 mmHg blood pressure drop) within 3 minutes of standing, or head-up tilt test (4).

Laboratory results showed that serum thyrotropin (34.80 mIU/L; reference: 0.34–5.65 mIU/L) and anti-thyroperoxidase antibody levels (267.70 IU/mL reference: 0–30 IU/L) were elevated. Blood biochemical tests, including tumor markers (carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 19-9, cancer antigen 125, cancer antigen 153, cancer antigen 50, serum ferritin, neuron-specific enolase) were unremarkable. Lumbar puncture on September 6, 2021 showed that biochemical tests and the cytology of the cerebrospinal fluid (CSF) were normal. The patient did not suffer from early and severe autonomic dysfunction. She had a subacute onset which was not fully in accordance with the diagnostic criteria of MSA, so extensive investigation for autoantibodies was carried out on her serum and CSF. Anti-mGluR2 antibodies in the serum were positive with the titer of 1:30 detected by indirect immunofluorescence on cell-based assays (KingMed, Guangzhou, China), while negative in the CSF as shown in *Figure 2* on September 6, 2021. Other antibodies include anti-mGluR1/mGluR5/mGluR8/Kelch-like Protein 11 (KLHL11)/glutamic acid decarboxylase-65 (GAD65)/Homer3/RhoA GTPase-activating protein 26 (ARHGAP26)/ATP1A3/carbamylated protein (CARP VII)/neurochondrin (NCDN)/glutamate receptor δ2 (GluRδ2)/

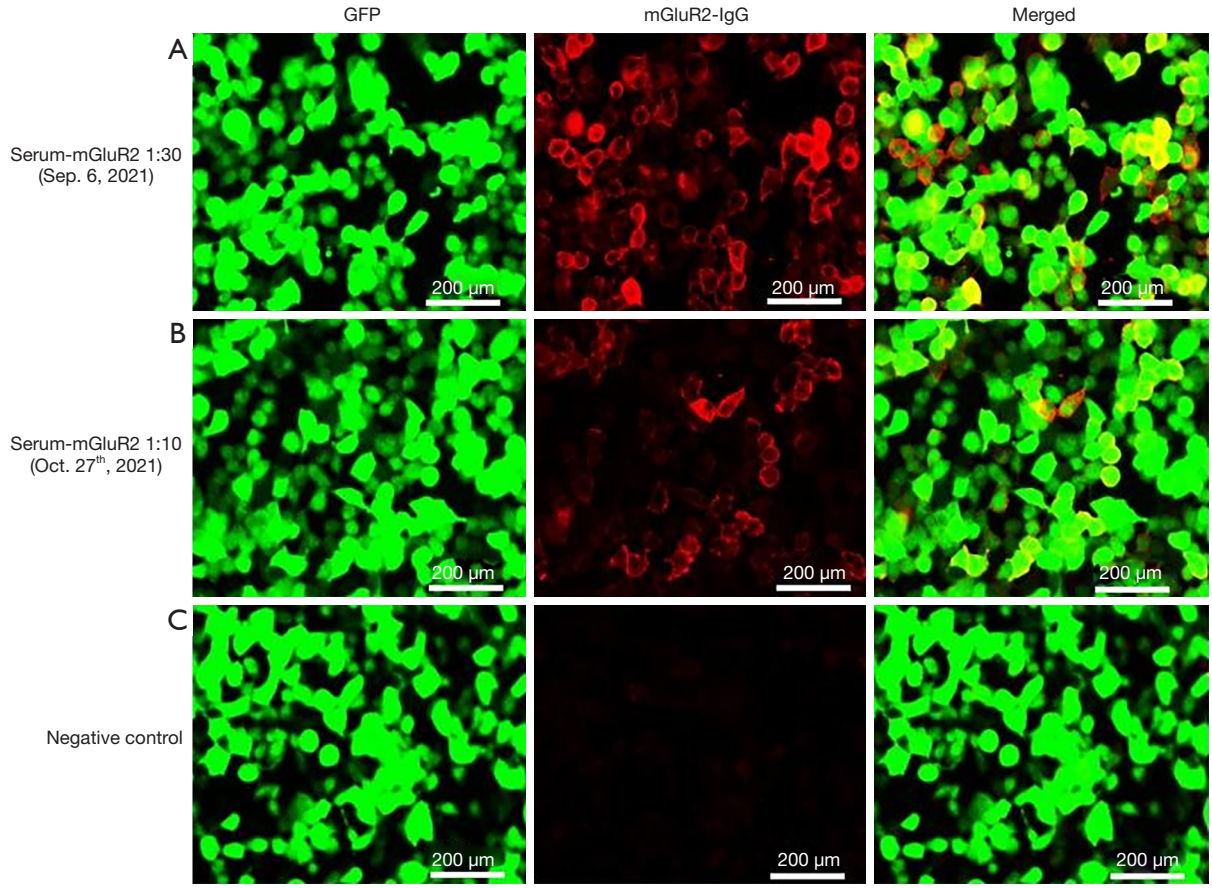

Figure 2 Positive anti-mGluR2 antibodies in serum (200×). (A) The titer of 1:30 on September 6, 2021 (before steroid treatment); (B) the titer of 1:10 on October 27th, 2021 (post steroid treatment); (C) the negative control. The results above were detected by indirect immunofluorescence on cell-based assays. GFP, green fluorescent protein; anti-mGluR2, anti-metabotropic-glutamate receptor 2.

contactin-associated protein-like 2 (CASPR2)/Yo. Purkinje cell cytoplasmic antibody type 2 (PCA-2) was negative. Paraneoplastic antibody assays [anti-Titin/Recoverin/protein kinase C gamma (PKCγ)/GAD65/Zic4/delta notch-like epidermal growth factor-related receptor (DNER)/SOX1/Ma2/Ma1/Amphiphysin/circovirustype 2 (CV2)/Ri/Purkinje cell cytoplasmic autoantibody type 1 (Yo)/neuronal nuclear (Hu)] antibody on September 6, 2021 in the serum were negative. Autoimmune encephalitis antibody assays [anti-GAD65/N-methyl-D-aspartate receptor (NMDAR)/anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)1/AMPAR2/$GABA_B$ receptor (GABABR)/leucine rich glioma inactivated 1 (LGI1)/CASPR2/Hu/Ma2/Yo/Ri/CV2/Amphiphysin/DNER/Aquaporin 4 (AQP4)/Myelin Oligodendrocyte Glycoprotein (MOG)/glial fibrillary acidic protein (GFAP)] checked on September 18th, 2021 were negative both in the serum and the CSF. Malignant cells weren't detected in the CSF cytology examination. Ultrasound evaluation showed diffuse change of the thyroid gland and a mixed echogenicity in the right thyroid lobe (TI-RADS 3). Heterogeneous endometrial echogenicity was found by transvaginal ultrasonography and negative human papillomavirus (HPV) testing in leucorrhea. Tumor screening by ultrasonography of thyroid, breast, abdomen, urinary system did not find any evidence of tumor. The chest computer tomography (CT) and electroencephalogram (EEG) were also normal.

According to her symptoms, laboratory results, MRI examination results, the diagnosis of cerebellar ataxia associated with anti-mGluR2 antibodies was established and she received high-dose glucocorticoids (1 g/day for 3 days, and then 0.5 g/day for another 3 days) intravenously, followed by oral prednisone 60 mg/day with slow tapering. On October 27th, 2021, after 1 month of steroid treatment,

her anti-mGluR2 antibody titer in serum dropped to 1:10. However, her ataxia did not improve significantly. She still had gait instability and dysarthria at follow-up on February 20, 2023.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Anti-mGluR2 antibodies are a novel biomarker of paraneoplastic cerebellar ataxia (5). The recent study indicated that the potential pathogenic effect of anti-mGluR2 antibodies is not mediated by downregulation or internalization of neuronal surface's mGluR2 as the other autoantibodies against ion channel coupled receptors. Anti-mGluR2 antibodies are a group of antibodies against neuronal surface antigens. Ruiz-García *et al.* found robust immunoreactivity of anti-mGluR2 antibodies on the cell surface of live rat hippocampal neurons as well as in the granular cell layer of cerebellar and hippocampus in rat brain sections (5). Brainstem atrophy in the current patient shows that anti-mGluR2 antibodies might also attack the neurons in brainstem. This is the first report of a patient from southern China with cerebellar ataxia associated with anti-mGluR2 antibodies. To date, only two cases with anti-mGluR2 antibodies associated paraneoplastic cerebellar ataxia are reported in literature as summarized in *Table 1*. Small cell tumor of unknown origin and alveolar rhabdomyosarcoma were found in the two patients, respectively (5). Up to now, extensive tumor screening was negative in our case. In most cases with paraneoplastic syndrome, the tumor may be found even a few years after the appearance of the neurologic syndrome, so further oncological screening such as gastrointestinal endoscopy and PET/CT is still needed for this patient.

At the beginning, the progressive ataxia in this patient was considered to be caused by hypothyroidism (6) or Hashimoto's encephalopathy (HE). However, her symptoms of ataxia did not improve significantly with levothyroxine replacement or high-dose glucocorticoids, such as previous reports suggest (7,8). Thus, ataxia relating with hypothyroidism or HE was ruled out. Secondly, her progressive ataxia with dysarthria and an HCB sign revealed by MRI suggests of MSA. However, she did not suffer from any other symptom of unexplained autonomic dysfunctions such as voiding difficulties with post-void urinary residual volume ≥100 mL, urinary urge incontinence, neurogenic orthostatic hypotension (≥20/10 mmHg blood pressure drop) within 3 minutes of standing, or head-up tilt test tilt test (4). According to the criteria for the diagnosis of MSA (4), the diagnosis of MSA in our patient was not certain from her current data. The HCB sign is thought to be due to the selective loss of myelinated transverse pontocerebellar fibers and neurons in the pontine raphe (9). Besides MSA, the HCB sign is also found in other diseases, such as natalizumab-associated progressive multifocal leukoencephalopathy (10) and encephalitis (11). Wei *et al.* found extensive brain stem hypoperfusion in the progression of the anti-AMPAR encephalitis (12). Schlapakow *et al.* also found a pontine HCB sign in a patient with immune-mediated cerebellar ataxia (13). They initially diagnosed the patient with MSA, but this diagnosis had to be corrected due to lacking autonomic dysfunction and the detection of anti-amphiphysin antibodies in the serum. To further study whether anti-mGluR2 antibodies is common in patients with cerebellar ataxia, eight patients with subacute or chronic course of cerebellar ataxia recruited from our hospital with or without an HCB sign in the pons were compared with our patient as shown in *Table 2*. Most of them had similar clinical manifestations, except patient 4, who had an inflammatory syndrome with mild pleocytosis and elevated protein in the CSF. Anti-mGluR2 antibodies were only found in our patient. This is the unique feature of this present report. Our patient and patient 5 slightly improved with steroid treatment. The reason why she did not fully recover may be caused by the serious damage of "cerebellar reserve". Hence, early immunotherapy may allow patients to recover well in the restorable stage (14).

Interestingly, anti-GluR2 antibodies in both serum and CSF were positive in previous report by Ruiz-García *et al.* (5). However, anti-mGluR2 antibodies were positive only in the serum in this cerebellar ataxia case. The possible reason is anti-GluR2 antibodies were produced in the peripheral blood and entered into the CNS via a leaky/damaged blood brain barrier. In previous reports, McKeon and Wang reported 3 anti-mGluRs encephalitis patients with positive antibodies only in the serum (15,16). Here, we report a unique case of anti-mGluR2 antibody associated encephalitis with cerebellar ataxia, with an HCB sign in the pons and cerebellar atrophy. This report indicates that

Table 1 Comparison of three cases with cerebellar ataxia and positive anti-mGluR2 antibody

Case	Age (year)	Sex	Sign	Brain MRI	Disease course	Response to immunotherapy	Tumor	Reference
1	78	Female	Gait instability, dysarthria and progressive ataxia	A diffuse FLAIR hyperintensity in the white matter of the cerebellar hemispheres	3 years	Poor	Small cell tumor of unknown origin	(4)
2	3	Female	Irritability, dysarthria, horizontal right-beating nystagmus, limb and truncal ataxia and broad-based gait requiring bilateral support	Patchy gadolinium enhancement in the cerebellar folia	3 days	Good	Alveolar rhabdomyosarcoma	(4)
Current study	56	Female	Wide-based gait, bilateral horizontal nystagmus, right eyelid ptosis, mild dysarthria and dysmetria on finger-nose and heel-to-knee tests, positive Romberg sign	Cerebellar atrophy and a hot cross bun sign in the pons	16 months	Poor	No malignancies identified	–

anti-mGluR2, anti-metabotropic-glutamate receptor 2; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

Table 2 The anti-mGluR2 antibody in cases with cerebellar ataxiaa

Patient	Sex	Age at onset (year)	Current age (year)	Onset/ course	Cerebellar signs	Parkinsonism	Urinary symptoms	Tumor	CSF findings	Anti-mGluR2 antibody	HCB	Time to HCB (month)	Treatment with steroids	Follow-up (month), outcome
1 (current patient)	F	56	57	Subacute	Yes	No	None	No	Normal cytology and biochemical analysis	Serum (1:30 before treatment, 1:10 after treatment); CSF (–)	Yes	13	Yes	12, poor
2	M	70	73	Chronic	Yes	No	None	No	None	Serum (–)	Yes	11	No	36, poor
3	M	51	53	Chronic	Yes	No	Urinary incontinence	No	Normal cytology and biochemical analysis	Serum (–); CSF (–)	Yes	9	No	15, poor
4	M	66	69	Chronic	Yes	No	None	No	Cells 65×10^6/L; protein 687.40 mg/L	Serum (–); CSF (–)	Yes	14	No	36, poor
5	F	40	41	Chronic	Yes	Yes	None	No	Normal cytology and biochemical analysis	Serum (–); CSF (–)	No cerebellar atrophy	–	Yes	2, poor
6	F	54	56	Chronic	Yes	Yes	None	No	None	Serum (–)	Yes	6	No	2, poor
7	F	60	63	Chronic	Yes	No	None	No	Normal cytology and biochemical analysis	Serum (–); CSF (–)	Yes	24	No	3, poor
8	F	59	63	Chronic	Yes	No	None	No	None	Serum (–)	Yes	36	No	2, poor
9	F	58	60	Subacute	Yes	No	None	Gastric stromal tumor	Normal cytology and biochemical analysis	Serum (–); CSF (–)	No cerebellar atrophy	–	No	1, poor

CSF, cerebrospinal fluid; HCB, hot cross buns; F, female; M, male; L, litre; anti-mGluR2, anti-metabotropic-glutamate receptor 2.

anti-mGluR2 antibodies causes should be considered in subacute or chronic course of cerebellar ataxia. Starting an immunotherapy in an early stage of the disease may benefit with a better prognosis.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1185/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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