


# Possible coexistence of MOG-IgG-associated disease and anti-Caspr2 antibody-associated autoimmune encephalitis: a first case report

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**Abstract:** Myelin oligodendrocyte glycoprotein antibody-associated disease has been proposed as a separate inflammatory demyelinating disease of the central nervous system (CNS) since the discovery of pathogenic antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG). Antibodies targeting contactin-associated protein-like 2 (Caspr2), a component of voltage-gated potassium channel (VGKC) complex, have been documented to be associated with a novel autoimmune synaptic encephalitis with a low incidence. Herein, we reported an adult female with initial presentation of decreased vision in the right eye and subsequent episodes of neuropsychiatric disturbance including hypersomnia, agitation, apatheia, and memory impairment. Magnetic resonance imaging (MRI) revealed multiple lesions scattered in brain, brainstem, and cervical and thoracic spinal cord, showing hypointensity on T1-weighted images, hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) images. Heterogenous patchy or ring-like enhancement was observed in the majority of lesions. The detection of low-titer MOG-IgG exclusively in cerebrospinal fluid (CSF; titer, 1:1) and Caspr2-IgG in both serum and CSF (titers, 1:100 and 1:1) led to a possible diagnosis of coexisting MOG-IgG-associated disease (MOGAD) and anti-Caspr2 antibody-associated autoimmune encephalitis. The patient was treated with immunosuppressive agents including corticosteroids and immunoglobulin, and achieved a sustained remission. To the best of our knowledge, this is the first report on the possible coexistence of MOGAD and anti-Caspr2 antibody-associated autoimmune encephalitis, which advocates for the recommendation of a broad spectrum screening for antibodies against well-defined CNS antigens in suspected patients with autoimmune-mediated diseases of the CNS.

**Keywords:** autoimmune, contactin-associated protein-like 2, encephalitis, MOG-IgG-associated disease, myelin oligodendrocyte glycoprotein

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## Introduction

In the last decade, the development of antibody detection technique has remarkably expanded the knowledge on autoimmune-mediated diseases of the central nervous system (CNS). For instance, the discovery of pathogenic myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) has facilitated the identification of a novel disease entity, namely MOG-IgG-associated disease (MOGAD) with the characteristic manifestations of optic neuritis (ON), longitudinally extensive

transverse myelitis (LETM), acute disseminated encephalomyelitis (ADEM), brainstem encephalitis, or diencephalic syndrome suggestive of demyelination.<sup>1</sup> Similarly, antibody against contactin associated protein-like 2 (Caspr2) – a component of the voltage-gated potassium channel (VGKC) complex at the juxtaparanodal region of myelinated axons – refers to a recently recognized autoimmune encephalitis (AE) with a low incidence, and is also detected in several peripheral neurological syndromes including neuromyotonia and Morvan

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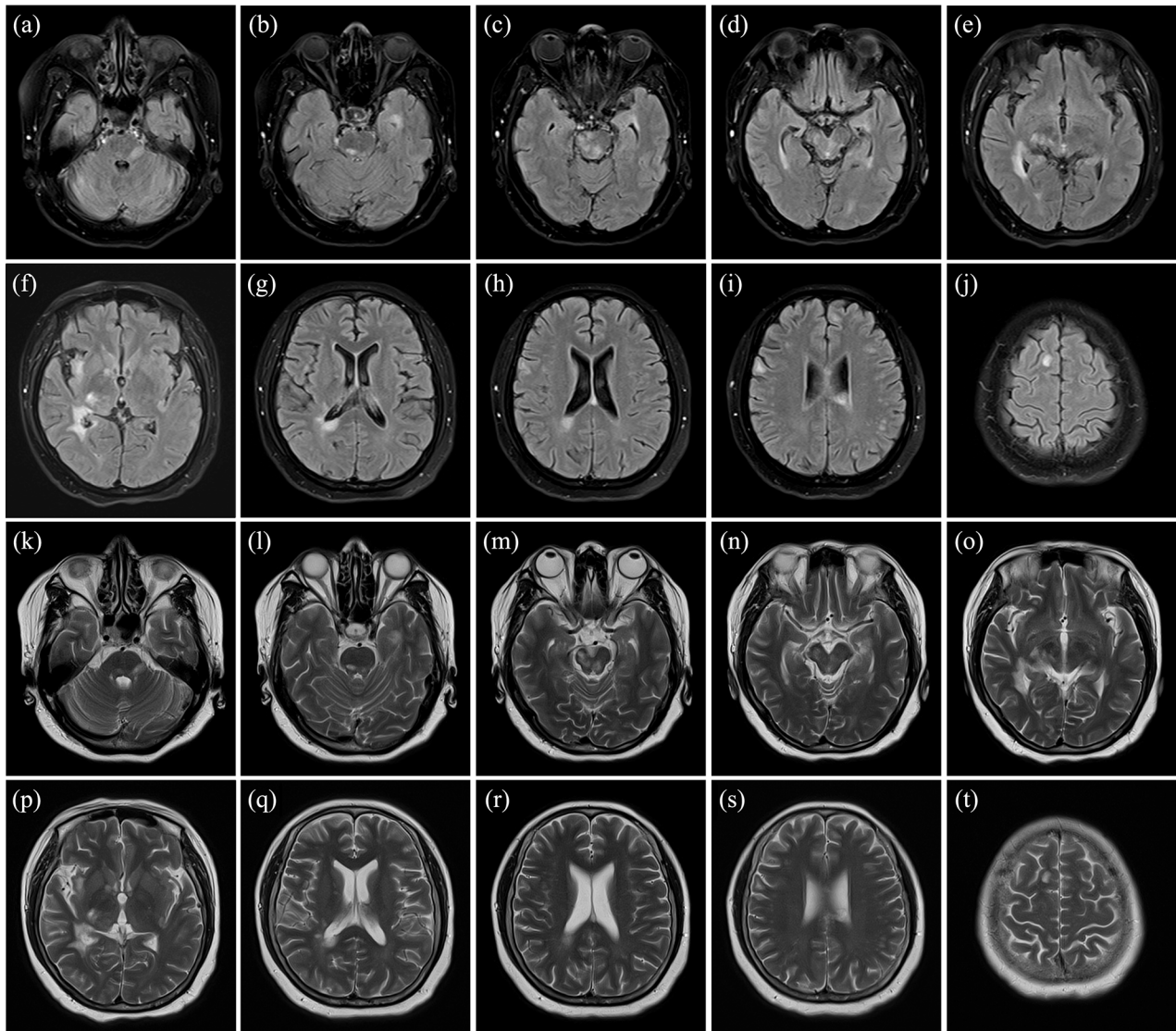
syndrome.<sup>2,3</sup> Meanwhile, overlapping or coexisting syndromes have been noticeable with double or multi-antibodies targeting distinct CNS antigens such as MOG, aquaporin-4 (AQP4), glial fibrillary acidic protein (GFAP), *N*-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated protein 1 (LGI1), and Caspr2.<sup>4-6</sup> However, double positivity for MOG-IgG and Caspr2-IgG in the same patient has not yet been reported. Herein, we present the first case of the possible coexistence of MOGAD and anti-Caspr2 antibody-associated autoimmune encephalitis in whom low-titer MOG-IgG was detected exclusively in cerebrospinal fluid (CSF) and Caspr2-IgG in both serum and CSF. This paper aims to strengthen the recommendation of screening for broad-spectrum antibodies for well-defined autoimmune diseases of the CNS when atypical clinical manifestations and/or radiological features are observed in patients with pre-existing autoimmune diseases.

### Case presentation

In late January 2020, a previously healthy 48-year-old female experienced acute decreased vision in her right eye. Ophthalmic examination revealed the right visual acuity was 0.3 (20/60) based on the Snellen chart. She did not receive any treatment, but the vision recovered spontaneously and increased to 0.6 (20/35) 2 weeks later. In late March, the patient was referred to local hospital with main complaints of dizziness, slurred speech, gait instability, and urinary incontinence. Shortly after admission, she experienced multiple episodes of neuropsychiatric disturbance including hypersomnia, agitation, apathia, and memory impairment. On neurologic examination, an Expanded Disability Status Scale (EDSS) score of 5.0 was obtained based on the abnormal findings including decreased visual acuity in the right eye with visual field defects, dysarthria, impaired muscle strength in the left limbs (BMRC grade 3), positive Romberg's test, numbness of distal fingers of the left hand, episodic urinary incontinence, and cognitive impairment. Meanwhile, a modified Rankin scale (mRS) score of 4.0 was obtained based on disability of attending to own partial needs, especially walk unassisted. Magnetic resonance imaging (MRI) revealed multifocal round or oval lesions scattered in bilateral frontal and parietal lobes, the left occipital lobe, the right insular subcortical and the left insular juxtacortical regions, as well as periventricular white matter, the body and splenium of the corpus callosum,

thalamus, periaqueductal gray matter, brainstem, the left cerebellar peduncles, and cervical and thoracic spinal cord, as manifested with hypointensity on T1-weighted images, and hyperintensity on both T2-weighted and fluid attenuated inversion recovery (FLAIR) images (Figures 1 and 2). Gadolinium (Gd)-enhanced MRI showed heterogenous patchy or ring-like enhancement in the majority of lesions (Supplemental Figure S1). Video-electroencephalography showed no remarkable findings except a slow wave background rhythm. No abnormalities were observed on electromyography. Serological tests for infections, autoimmune, and neoplastic parameters were all normal. Chest-abdominal-pelvic CT and gynecologic ultrasound scanning eliminated the possibility of associated malignancies. CSF analysis revealed a normal white blood cell count but with an increased lymphocyte ratio (90%) and a slightly elevated protein level of 456 mg/l (normal range: 80–430 mg/l). No oligoclonal IgG bands (OCBs) were detected in serum and CSF. Cell-based assays (CBA) revealed that serum MOG-IgG was negative while CSF MOG-IgG was positive with a low titer of 1:1 (Figure 3a). This finding was verified by indirect immunofluorescence assay using monkey cerebellum tissue. The patient was treated with intravenous methylprednisolone pulse therapy (500 mg/day for 5 days, 250 mg/day for 3 days, 120 mg/day for 3 days) plus intravenous immunoglobulin (IVIg; 0.4 g/kg for five consecutive days). The patient was subsequently maintained on oral prednisone at 60 mg daily for 20 days. Symptomatic treatments including donepezil for cognitive impairment, and olanzapine and alprazolam for psychiatric disturbance were given, but 2 days later were self-stopped by the patient due to the unsatisfactory therapeutic effects obtained in her view. Thereafter, the patient was transferred by her relatives to our department for further comprehensive assessment of her condition.

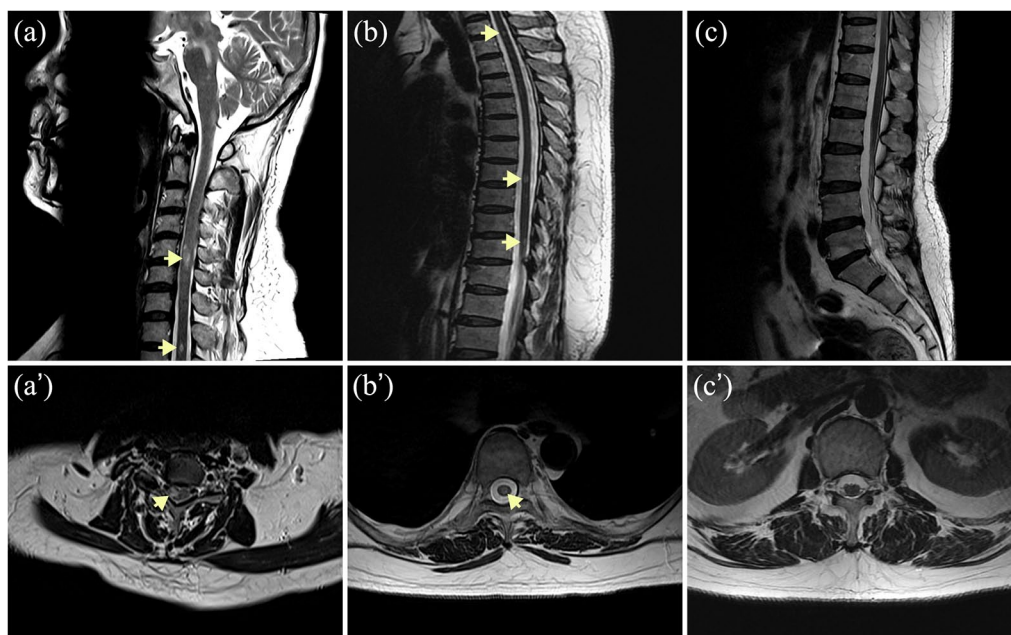
On admission, neurologic examination revealed numbness of distal fingers of the left hand, slightly unsteady gait, and positive Romberg's test. No motor deficits and pathologic reflexes were found. The Mini-Mental State Examination (MMSE) score was 27 and Montreal Cognitive Assessment (MoCA) score was 26, which revealed mild cognitive impairment especially in short-term memory and executive function. Neuro-ophthalmologic examination showed her visual acuity remained at 0.6 (20/35) in the right eye and 0.8 (20/25) in the left eye. Visual



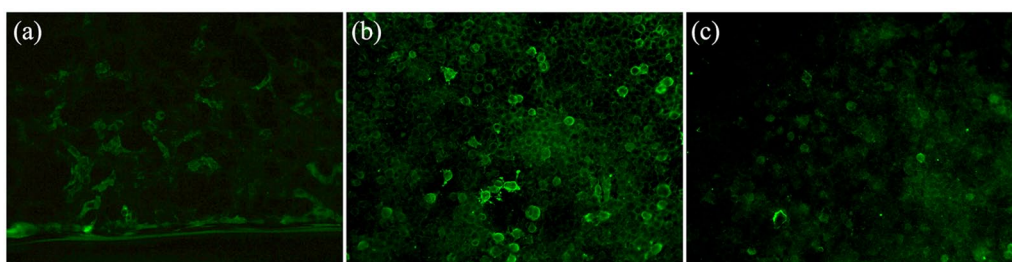
**Figure 1.** Brain MRI performed during acute attack. Axial FLAIR (a–j) and T2-weighted (k–t) images show multifocal round or oval hyperintense lesions in the left cerebellar peduncles (a, k), the temporal horn of the left lateral ventricle (b, c, l, m), brainstem (b–e, l–o), the left occipital lobe (d, n), the right thalamus (e, f, o, p), the right insular subcortical and the left insular juxtacortical regions (f, p), bilateral frontal and parietal lobes (i, j, s, t), periventricular white matter (f–h, p–r), and the body and splenium of the corpus callosum (g, h, q, r).  
MRI, magnetic resonance imaging.

field defects were observed in the infero-nasal quadrant and periphery of the right eye, and in the periphery temporal of the left eye. A visual evoked potential study disclosed no remarkable abnormalities in the left optic nerve but significantly decreased amplitude of P100 in the right. Optical coherence tomography (OCT) revealed the thinning of retinal nerve fiber layer (RNFL) in the temporal and superior preponderance of the right eye, with values of 35 $\mu$ m and 65 $\mu$ m, respectively. Collectively,

immunosuppressive therapy led to an obvious improvement with the EDSS and mRS scores reducing to 3.5 and 2.0, respectively. In parallel, CSF MOG-IgG turned negative. Tests for other autoantibodies in serum and CSF, including NMDAR-IgG, AMPAR1-IgG, AMPAR2-IgG, LGI1-IgG, GABA<sub>B</sub>R-IgG, and AQP4-IgG were all negative. Unexpectedly, but interestingly, Caspr2-IgG was positive both in serum and CSF with titers of 1:100 and 1:1, respectively (Figure 3b and c).



**Figure 2.** Spinal cord MRI performed during acute attack. T2-weighted sagittal cervical (a) and thoracic (b) spinal cord images show short-segment hyperintense lesions with well-defined borders (arrows). Axial cervical spinal cord image shows one lesion involving the anterior white matter and the lateral column [a', arrow], and thoracic spinal cord image shows one lesion involving the central gray matter [b', arrow]. No lesions are seen in lumbar spinal cord images [c, c']. MRI, magnetic resonance imaging.



**Figure 3.** Detection of MOG-IgG and Caspr2-IgG by transfected CBA. Representative photographs ( $\times 400$ ) show positive MOG-IgG in CSF [a; titer, 1:1] as well as positive Caspr2-IgG in both serum [b; titer, 1:100] and CSF [c; titer, 1:1]. Caspr2-IgG, antibodies against contactin-associated protein-like 2; CBA, cell-based assay; MOG-IgG, antibodies against myelin oligodendrocyte glycoprotein.

Prior low-titer CSF MOG-IgG together with serum and CSF Caspr2-IgG positivity resulted in a possible diagnosis of coexisting MOGAD and anti-Caspr2 antibody-associated autoimmune encephalitis. Considering the partial remission obtained with immunotherapy in the patient, as a continuation of the prior maintenance treatment with oral prednisone, intravenous methylprednisolone at 60mg daily was subsequently given for six consecutive days followed by oral prednisone starting at 40mg daily

with a slow tapering schedule of 5mg every month. The patient was discharged in a stable condition, and remained so during the follow-up period. At 1 month after discharge, repeat brain and spinal cord MRI revealed no obvious changes in lesion burden, and the EDSS and mRS scores remained unchanged. Meanwhile, no malignancies were found on repeat chest-abdominal-pelvic CT at this time (approximately 6 months from disease onset). Face-to-face follow-up visits have been attended on schedule.

## Discussion

Discovery of new antibodies against CNS antigens such as AQP4, MOG, GFAP, NMDAR, LGI1, and Caspr2 has contributed to the identification of novel disease entities and expanded disease spectrum of autoimmune disorders of the CNS.<sup>1,7–10</sup> More recently, detection of two or even more antibodies in the same patient has helped to understand the complexity involved in these diseases,<sup>4,6,11,12</sup> and provided new insight into the possible mechanisms underlying the pathogenesis of overlapping or coexisting syndromes. In this paper, we reported the first case on the possible coexistence of MOGAD and anti-Caspr2 antibody-associated autoimmune encephalitis based on the evidence of low-titer CSF MOG-IgG together with serum and CSF Caspr2-IgG positivity. MOG has been demonstrated to be expressed exclusively in the CNS and be located on the outermost surface of myelin sheath and cell membrane of oligodendrocytes, acting as a cell adhesion molecule and a regulator of microtubule stability.<sup>1</sup> The predominant subtype IgG1 antibodies to MOG initiate CNS demyelinating process *via* T cell-mediated cytotoxicity and B cell-mediated immune responses with complement activation.<sup>1,13</sup> As part of VGKC complex, Caspr2 is located in the juxtaparanodal region of myelinated fibers in both CNS and peripheral nervous system (PNS), and participates in synapse synthesis and construction of central neural network.<sup>2,3,14,15</sup> Non-complement-activating IgG4 antibodies dominate in anti-Caspr2 antibody-associated autoimmune encephalitis.<sup>10,12</sup> Although mechanisms responsible for coexisting double or more autoantibodies are still undetermined, the phenomenon may be partially explained by the concept of epitope spreading, that is, persistent recognition and activation to self-antigens lead to chronic immune responses accompanying with the development of antibodies against diverse dominant epitopes within the same antigen (intramolecular) or to different antigens (intermolecular).<sup>5,16</sup> Previous studies have shown epitope spreading in pediatric multiple sclerosis (MS) patients and in animal models such as experimental autoimmune encephalomyelitis (EAE) and myasthenia gravis (EAMG).<sup>17–19</sup> Unfortunately in our case, it remains unclear whether MOG-IgG and Caspr2-IgG has emerged simultaneously or successively due to the missed testing of Caspr2-IgG at the patient's local hospital. Even so, the fact that the patient initially presented acute optic neuritis associated with MOG-IgG followed by neuropsychiatric disturbance highly suggestive of autoimmune

encephalitis appears to support the involvement of intermolecular epitope spreading from MOG to Caspr2 in the pathogenesis of the possible coexisting syndrome. Further investigation is needed to verify this hypothesis.

Detection of disease-specific antibodies is of crucial importance in the diagnosis of antibody-associated autoimmune disorders of the CNS. CBA has been preferentially recommended owing to its high sensitivity and specificity. Likewise in our case, positivity for Caspr2-IgG was determined by CBA with titers of 1:100 in serum and 1:1 in CSF, which was sufficient to make a diagnosis of anti-Caspr2 antibody-associated autoimmune encephalitis. By contrast, MOG-IgG was detected only in the first assay with a low titer of 1:1 in CSF. Despite previous evidence of almost exclusive extrathecal MOG-IgG synthesis, a small minority of patients have been observed with exclusive MOG-IgG (titer range, 1:2–1:128) in CSF,<sup>20–22</sup> where antibody-producing B cells could reside in the CNS reflecting intrathecal IgG synthesis rather than passive diffusion of serum antibodies into the CNS.<sup>20</sup> Apart from CBA, an indirect immunofluorescence assay using monkey cerebellum tissue also verified the presence of MOG-IgG. Although a low-titer CSF MOG-IgG has been speculated to be pathogenic and seems to present the characteristics of those with high-titer serum MOG-IgG,<sup>20</sup> the fact that CSF MOG-IgG titer of our case was lower than the presumed cut-off titer of 1:2 in previous studies is still not convincing enough to make a definite diagnosis, and eventually resulted in a possible diagnosis of MOGAD.

MRI examination may also provide valuable clues for the diagnosis of autoimmune diseases of the CNS, since the distribution of lesions depend to a large extent on the region-specific expression of self-antigens. In our case, diffuse lesions involving brain and spinal cord particularly in subcortical white matter, juxtacortical regions and deep grey matter were noted mimicking ADEM-like pattern. The specific lesions combined with optic nerve involvement are highly suggestive of MOGAD, though the titer of MOG-IgG was low during the same period. Previous studies have shown that MOG-IgG titers were associated with severity of disease and prognosis,<sup>23–26</sup> but whether MRI lesion burden and activity in the CNS correlates with MOG-IgG titers during the course of the disease has not been addressed. Of note, the

first assay was performed 2 months after initial symptom onset in our case, but, unfortunately, it was not clarified whether the titer of MOG-IgG had increased from a lower level in parallel with the aggravation of symptoms or remained at a higher level at the earlier stage. Thus, dynamic monitoring of antibody titers and MRI lesion burden should be performed to clarify this point. Studies have revealed that the specific MRI manifestation associated with Caspr2-IgG include T2 hyperintensity in the medial temporal lobes, hippocampal atrophy, and mesial temporal or hippocampal sclerosis.<sup>3</sup> However, no similar abnormalities were found in our case. Moreover, ADEM-like pattern of lesions involving brain, brainstem, spinal cord, and optic nerves has not been reported in autoimmune encephalitis associated with Caspr2-IgG. Molecular imaging such as <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used recently to help identify anti-Caspr2 antibody-associated autoimmune encephalitis, and the most common abnormality was temporo-mesial hypometabolism.<sup>27,28</sup> Unfortunately, our patient could not afford the FDG-PET examination. In the future, more imaging techniques would be incorporated to present the detailed radiological features of autoimmune encephalitis associated with Caspr2-IgG.

Treatments of coexisting or overlapping syndromes may encounter several challenges, such as therapeutic options, duration of treatment, and timing of immunosuppressive agent initiation, given that diverse pathogeneses possibly underlie different antibody-mediated autoimmune diseases. In most cases, MOGAD has a favorable response to steroid treatment but could recur easily after rapid tapering of steroids.<sup>26,29-31</sup> Meanwhile, anti-Caspr2 antibody-associated autoimmune encephalitis is a IgG4-dominant disease, and intravenous immunoglobulin is adopted more commonly than steroids and other immunotherapies.<sup>10,14,32</sup> In our case, a combination of high-dose methylprednisolone and intravenous immunoglobulin was given, followed by oral prednisone with a slow tapering regime; the patient's clinical symptoms were significantly alleviated and a long-term remission was obtained. More fortunately, MOG-IgG declined to undetectable levels after immunotherapy, possibly predicting a benign disease course and a favorable clinical outcome. Nevertheless, contemporary high-titer Caspr2-IgG indicates a possible need for longer-term immunotherapy or other immunosuppressive

agents with higher efficacy. Since it has been proven that disease severity of MOGAD correlates with the fluctuation of MOG-IgG titers,<sup>23,24</sup> and symptom remission of autoimmune encephalitis is accompanied by a decline in Caspr2-IgG titers,<sup>33</sup> dynamic monitoring of clinical picture combined with antibody titers is required and is of great importance to guide treatment and prevent recurrence.

### Conclusion

To the best of our knowledge, this is the first report of the possible coexistence of MOGAD and anti-Caspr2 antibody-associated autoimmune encephalitis. Since the crucial role of disease-specific antibodies in diagnosing autoimmune diseases, as suggested by our case, screening for broad-spectrum autoantibodies against well-defined CNS antigens should be recommended in patients with suspected autoimmune diseases, especially when atypical clinical manifestations and/or radiological features are observed in patients with pre-existing autoimmune diseases. Given that coexisting antibodies possibly mediate adverse pathogeneses, therapeutic options should be assessed comprehensively and a long-term follow up is needed.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.


### Ethics statement and patient consent

Written informed consent was obtained from the patient for publication of this paper. The present study was approved by the Ethics Committees of Tangdu Hospital, Air Force Military Medical University.

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## Supplemental material

Supplemental material for this article is available online.

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