GFAP-A and Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy: case reports

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Case Report

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Abstract

Background: Autoimmune glial fibrillary acidic protein astrocytic lesion GFAP-A is a new central nervous system autoimmune disease first described in humans at the Mayo Clinic in 2016. The diagnosis mainly depends on the IgG antibody of GFAP in cerebrospinal fluid (CSF). Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is a kind of inflammatory demyelinating disease of the central nervous system in which MOG antibodies are found in serology or cerebrospinal fluid. Today, clinicians also have a certain understanding of demyelinating diseases, but the mechanism of these diseases is still not very clear, so clinical cases are still worthy of attention and summary.

Case presentation: We report a case of GFAP-A and a case of Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy. Our cases show that the severity of GFAP-A is no less severe than that of Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy, but this is only a case-based guess.

Conclusions: Reading the literature, we found great heterogeneity in patients with these inflammatory demyelinating central nervous system diseases, which also brings difficulties to clinical diagnosis. Therefore, we believe that when clinically suspected demyelinating diseases of the central nervous system, APQ4, MOG, GFAP, MBP, and other related antibodies should be detected at the same time to avoid missed diagnosis.

Background

GFAP-A is a new central nervous system autoimmune disease first described in humans at the Mayo Clinic in 2016 [1]. The lesions mainly involved the brain, spinal cord, and optic nerve. Its clinical manifestations include myelitis, headache, abnormal vision, fever, ataxia, mental illness, dyskinesia, dementia, epilepsy, gastrointestinal reactions, etc. The disease is largely defined by detecting and confirming the reaction of Glial fibrillary acidic protein (GFAP) immunoglobulin G (IgG) in CSF. GFAP-A is sensitive to steroids. Once diagnosed, many patients can benefit from high-dose hormone therapy, but the disease is also easy to relapse. Craniocerebral MRI often shows linear perivascular Gd enhancement in the ventricular white matter [2,3], but this manifestation of MRI can't be used as the gold standard for the diagnosis of GFAP-A.

MOG is a membrane protein expressed on oligodendrocytes' surface and the myelin sheath's outermost surface. MOGAD is an inflammatory demyelinating disease of the central nervous system [4] in which MOG antibodies are found in serology or CSF. The main manifestations are as follows: acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorders (NMOSD), monophasic or recurrent solitary optic neuritis, transverse myelitis, atypical multiple sclerosis, brainstem encephalitis. The imaging lesions can be reflected in the cerebral cortex, brain stem, spinal cord, etc. Treatment mainly includes Intravenous methylprednisolone (IVMP), Intravenous immunoglobulin (IVIG), plasma exchange (PE), and protein A immunoabsorption (PAIA).
We report one GFAP-A and one Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy and compare the two cases.

Case Presentation

CASE 1

A 69-year-old woman was admitted to the hospital on February 6, 2022. One month before admission, she had neck pain and headache, accompanied by dizziness, blackness, and tinnitus, and occasionally presented numbness and discomfort in both upper limbs. There are no symptoms such as fever, general fatigue, disturbance of consciousness, and so on. Her first diagnosis department is not a department of neurology, but a department of spinal surgery. Her MRI suggested vertebra instability, intervertebral disc herniation, and demyelination of white matter. As a result, the outpatient physician attributed her symptoms to the lesions of her cervical and lumbar vertebrae, so the patient chose to treat her at home. Three days before admission, the headache and neck pain were significantly aggravated, which lasted for 1–2 minutes each time. The symptoms occurred occasionally during the day and aggravated at night. The patient was admitted to the department of spinal surgery outpatient again and was admitted to the hospital with cervical spondylosis. After admission, she took an MRI (Fig. 1a-c) of the brain which suggested a little old cerebral infarction under the bilateral frontoparietal cortex with marginal gliosis and multiple old luminal infarctions, and demyelination of white matter. At the same time, the department of spinal surgery also treated her symptoms. On February 7, the patient’s headache and neck pain was not relieved, and she presented with blurred vision, nausea, and vomiting during the headache; on February 8, the patient developed visual ghosting when she had a headache, so she asked for an ophthalmic consultation. The patient’s eye examination showed that the lens was slightly cloudy; the fundus showed that the boundary of the solid disc was not clear, and a large number of bleeding could be seen around the optic disc; The retina is ruddy. The ophthalmologist diagnosed optic nerve edema and gave her hormones and mecobalamin treatment. On February 9, the patient's pain was relieved, but his vision was still declining, so he asked the department of neurology for consultation, then transferred to the department of neurology for further treatment. On February 11, the patient experienced spasms in both lower limbs when he had a headache and had a slight trance of consciousness after the headache attack. According to neck pain and headache accompanied by hearing and vision loss, the neurologist located the condition as NMOSD. To make a diagnosis, she underwent a lumbar puncture, and her CSF pressure reached 350cmH2O (reference range 80-180mmH2O) and the color was slightly red. The doctor sent her cerebrospinal fluid for routine, biochemical, exfoliative cytology, the acid-fast bacillus smear, bacterial culture, and specific antibody tests. Cerebrospinal fluid results showed that chlorine: 112.8mmol/L (reference range 120-130mmol/L), glucose: 4.94mmol/L (reference range 2.50-4.50mmol/L). At the same time, given the color of the CSF, she was applied for intracranial vascular CTA, and her intracranial vessels were not significantly abnormal. Because of the numbness of both lower limbs, we also gave her EMG / evoked potentials, the results showed that: 1, multiple single nerve damage; 2, bilateral median nerve evoked potential suggested abnormal brachial plexus-cervical spinal
cord segment; 3, bilateral tibial nerve somatosensory evoked potential was abnormal; 4, the right visual evoked potential was abnormal; 5, bilateral auditory brainstem response was normal. On February 15, her CSF-specific antibodies test results came back: GFAP positive (antibody titer 1:32) (Examination of autoimmune antibodies in the CSF via indirect immunofluorescence (cell-based assay)) (Fig. 2G1). According to the symptoms and results, the patient was diagnosed with GFAP-A. After the diagnosis, she was immediately given a high dose of hormone shock therapy. And her condition was quickly brought under control after a course of treatment was over.

**CASE2**

The patient, a 35-year-old woman, was admitted to the hospital on May 12, 2022. She had been ill for about two months before she was admitted. Her symptoms began to appear on March 16, 2022. On January 1, she was vaccinated with COVID-19 (Beijing Kexing), there were almost 2 months before she developed the symptoms. Since the onset of the disease, the patient has experienced the following changes: itching of the left ear skin (16 March 2022), itching of the face and scalp (7 April 2022), numbness of the left limb with loss of appetite, nausea, and vomiting (3 May 2022), left abdominal pain, left scalp pain and constipation (8 May 2022). Since her spontaneous illness, she has visited many hospitals, but the examination results are not significantly abnormal. After admission, a series of examinations were perfected. The positive results were as follows: the head MRI (Fig. 3–4) indicated that the spinal cord levels of C1-3 and T5-6 were striped with high signal intensity (14 May 2022). Before admission, she also underwent a head MRI examination in other hospitals, but no abnormality was found. After hospitalization, her serological examination showed that the anti-cyclic citrullinated peptide antibody (CCP) was positive; the biochemical routine of the cerebrospinal fluid showed that nucleated cells increased (11*10⁶), monocyte ratio increased (93%), and other indicators were normal; EMG / evoked potential: 1. left median nerve somatosensory evoked potential abnormal; 2. other nerves were not abnormal. The results of antibody detection in blood and CSF showed that the MOG antibody (antibody titer: 1:10) (Fig. 2M1) in serum and GFAP antibody (antibody titer: 1:32) (Fig. 2G2) in CSF were positive (Examination of MOG and GFAP antibodies in the CSF via indirect immunofluorescence (cell-based assay)), while serology and CSF of AQP4 and MBP antibodies were negative. So far, according to her clinical manifestations and the results of nuclear magnetic resonance and antibody tests, the doctor diagnosed her with MOGAD. After a definite diagnosis, the patient received hormone shock treatment, and her symptoms were not significantly relieved at the end of the course of treatment. Reexamine the head MRI (Fig. 5): the previous hyperintense of the C1-3 and T5-6 spinal cord levels was enhanced (30 May 2022). As a result, the patient was treated with immunoglobulin, and her symptoms still did not improve significantly after a week of immunoglobulin. at this time, the doctor advised her to try PE, but for economic reasons, the patient rejected to treat with PE. In the end, she left some symptoms and was discharged from the hospital.

**Discussion And Conclusions**
The diagnosis of case 1 was mainly based on the GFAP-A diagnostic criteria [1], which could be well confirmed by the following conditions: (1) acute onset, the main clinical manifestations were encephalitis, myelitis, and optic neuropathy; (2) other diseases were excluded by auxiliary examination; (3) positive expression of GFAP antibody in CSF (Fig. 1A); (4) demyelination of white matter in cranial MRI; (5) effective for high-dose steroid therapy. Case 1 we reported is also different from the previously reported GFAP-A cases. The first is the cerebrospinal fluid test results, we reported the first patient, her cerebrospinal fluid analysis results showed that the level of chlorine decreased, glucose levels increased, and the other indicators are in the normal range. However, most of the previous reports suggested that the level of glucose in cerebrospinal fluid decreased and the level of chlorine increased, while our results were the opposite. As an autoimmune-related disease, glucose in CSF of GFAP-A has been reported to increase and decrease, but how it affects the changes of glucose in CSF remains to be further studied. We found that in previously reported cases, there are always differences in cerebrospinal fluid examination indicators, and some even the opposite changes. We believe that these indicators of cerebrospinal fluid reflect the current situation of patients, and will constantly change with the progress and prognosis of the disease, so the difference in these indicators may be due to the patient's condition and the early, middle, and late stages of the disease, so it is risky to just rely on routine and biochemical indicators of cerebrospinal fluid to diagnose GFAP-A. However, we do not deny the importance of CSF detection, we believe that it has the value of auxiliary diagnosis and differential diagnosis, and reexamination is also necessary, the recovery of indicators can indicate the effectiveness of treatment. To our shock, her cerebrospinal fluid pressure reached 350cmH$_2$O. In this patient, we ruled out bleeding, tumor, etc, so we think her high intracranial pressure may be one of the manifestations of GFAP-A.

The diagnosis of Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy in case 2 is clear, which can be well confirmed by the following conditions: (1) acute onset, the main clinical manifestation is encephalomyelitis; (2) other diseases are excluded by auxiliary examination; (3) positive expression of GFAP antibody in CSF and MOG antibody in serum (Fig. 1b); (4) MRI has longitudinal extensive lesions of the spinal cord. the patient's serum MOG-IgG and CSF GFAP-IgG were positive in the second case. The patient's symptoms mainly indicated unilateral sensory disturbance, This may be because the myelopathy is left-sided. According to MRI, the lesions were the cervical spinal cord (C1-3) and thoracic spinal cord (T5-6). And the MRI findings of this patient were consistent with the long segment changes of NMOSD, however, the antibody detection did not detect AQP4 antibody but detected MOG antibody. Tracing back to the patient's medical history, the patient was vaccinated with a novel coronavirus vaccine more than 2 months (about 72 days) before the onset of the disease. In previous reports, it is not uncommon for MOGAD to occur due to COVID-19 vaccination [5], most of the symptoms occur about 7–32 days after vaccination [5]. In our case, there was an interval of 72 days between the onset of the disease and vaccination, so it is uncertain whether the vaccine can be used as a pathogenic factor for the patient. Interestingly, in the examination results of this patient, we found that she was positive for anti-CCP antibody, but the patient did not have corresponding clinical manifestations, so the diagnosis of RA was not valid. In previous reports, there is a correlation between NMOSD and systemic autoimmune diseases; but no correlation between MOGAD and systemic
autoimmune diseases [6]. In our second case, anti-MOG and anti-CCP antibodies coexisted. Although there were no joint-related symptoms, individuals with positive anti-CCP antibodies were more likely to develop RA [7] than those with negative anti-RA antibodies. More accurate evidence is needed to prove the relationship between MOGAD and anti-CCP antibodies.

We compared these two patients carefully. Both patients were female and the titer CSF GFAP-IgG was 1:32. However, there are many differences between the two patients. We will compare them from the following aspects (as shown in Table 1).

In terms of inducement, the first case has no obvious inducement, and case 2 was vaccinated with COVID-19 before the onset of the disease, although there is no evidence of a necessary link between vaccination and the onset of the patient in our case. By reviewing the previous literature, we listed vaccination as a possible predisposing factor for the patient in case 2.

There were also noteworthy differences in clinical manifestations, case 1 showed meningoencephalitis, myelitis, and optic neuritis, such as headache, neck pain, dizziness, visual impairment, hearing impairment, numbness of both upper limbs, spasm of both lower limbs, mild abnormality of consciousness, course of the disease progressed rapidly. The patient in case 2 also showed a progressive course of the disease: left ear itching, facial and scalp pruritus, left limb numbness, loss of appetite, nausea, and vomiting, left abdominal distension, and constipation. The clinical manifestations of case 1 were consistent with those of most previously reported demyelinating lesions, while the patients of case 2 mainly showed unilateral sensory disorders, this may be due to the patient's unilateral myelopathy. Both patients had gastrointestinal symptoms of nausea and vomiting, whether this was caused by damage to the last area. We checked the MRI of the two patients in time. We did not find any lesion-related signal in the area postrema of the patient. However, although patient 1 had no obvious lesion signal on MRI, the EMG / evoked potential of the patient indicated that the brachial plexus-cervical spinal cord was abnormal. The high cervical spinal cord of patient 2 has pathological changes in MRI, so we think that there are two possible mechanisms of gastrointestinal symptoms: the first is caused by high cervical spinal cord lesions, and the second may be the characteristic manifestation of CSF GFAP-IgG.

Table 1 Comparison of Case one and Case two
<table>
<thead>
<tr>
<th>CASE1</th>
<th>CASE2</th>
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</thead>
<tbody>
<tr>
<td><strong>Possible trigger</strong></td>
<td>unclear</td>
</tr>
<tr>
<td><strong>clinical picture</strong></td>
<td>1. Pain in the neck and head, dizziness, dim outside and tinnitus, and occasional numbness in both upper limbs (2022-1-6); 2. Blurred vision, hearing loss, nausea, and vomiting 2022-2-7; 3. Double vision 2022-2-8; 4. Vision loss and spasms in both legs 2022-2-11;</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Demyelinating changes in white matter</td>
</tr>
<tr>
<td><strong>Cerebrospinal fluid</strong></td>
<td>1. color: Light red</td>
</tr>
<tr>
<td></td>
<td>2. cl⁻: 112.8mmol/L (range: 120-130mmol/L)</td>
</tr>
<tr>
<td></td>
<td>3. glucose: 4.94mmol/L (2.50-4.50mmol/L)</td>
</tr>
<tr>
<td></td>
<td>4. pressure: 350cmH₂O</td>
</tr>
<tr>
<td><strong>electromyography</strong></td>
<td>1. Multiple single nerve lesions; 2. Bilateral median nerve evoked potentials suggest abnormal brachial plexus-cervical medullary segments; 3. Bilateral tibial nerve somatosensory evoked potential abnormalities; 4. Abnormal right visual evoked potential; 5. Bilateral auditory brainstem response was normal.</td>
</tr>
<tr>
<td><strong>Antibody titer</strong></td>
<td>1. serum: Not checked</td>
</tr>
<tr>
<td></td>
<td>2. CSF: GFAP IgG 1:32</td>
</tr>
<tr>
<td><strong>Treatment plan and effect</strong></td>
<td>high-dose corticosteroids are effective</td>
</tr>
<tr>
<td><strong>prognosis</strong></td>
<td>Complete remission of symptoms</td>
</tr>
</tbody>
</table>

In MRI, the MRI of the second patient had a typical signal of MOGAD, and on her MRI, there were longitudinal extensive lesions of C1-3 and T5-6, while in the first patient, no characteristic signal of GFAP-A such as radial enhancement around blood vessels was found except for some myelin sheath changes in the white matter. In case 1, the CSF pressure reached 350cmH₂O (reference range 80-180mmH₂O), and the color was slightly red; the abnormal results were chlorine 112.8mmol/L (reference range 120-130mmol/L) and glucose 4.94mmol/L (reference range 2.50-4.50mmol/L). In case 2, except for the increase of nucleated cells (11*10⁶) and the increase of monocyte ratio (93%), the other indexes of cerebrospinal fluid were normal. This may be related to the different pathophysiological mechanisms of
GFAP-A and MOGAD. GFAP is an intermediate filament protein in astrocytes, the pathogenesis of GFAP-A is related to GFAP-specific cytotoxic CD8⁺T cells, microglia, and inflammatory factors involved in the inflammatory response. The pathogenesis of MOGAD is thought to be caused by the immune response caused by the entry of peripheral MOG antibodies into the central nervous system, including up-regulated expression of Th17, Treg, and Th1-related cytokines in cerebrospinal fluid [8]. The GFAP-IgG was considered to be non-pathogenic, while MOG-IgG is pathogenic, so in the first case we reported, we diagnosed GFAP-A according to the detection of antibodies in cerebrospinal fluid. However, in the second case, we had difficulty, because of whether there was dual pathogenesis in this patient, or whether the GFAP antibody just acted as a bystander didn't know, and finally, we diagnosed it as an Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy. However, what role GFAP-IgG and MOG-IgG play in the Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy needs to be further studied in the future.

Furthermore, regarding treatment and its effect had differences in the two cases, patients in case 1 were more sensitive to high-dose corticosteroids than those in case 2. From previous reports, most demyelinating diseases are sensitive to high-dose corticosteroids [2,4], however, the symptoms of the patient in case 2 relief were not obvious. We are also thinking about whether single antibody-positive patients are more sensitive to hormone therapy than multiple antibody-positive patients. After reviewing the relevant literature, we found that the previously reported patients with Overlapping syndrome of MOG-IgG-associated disease and autoimmune GFAP astrocytopathy were completely relieved by high-dose hormone treatment, which is contrary to our view. So whether the presence of multiple antibodies affects hormone sensitivity needs to be confirmed by more case studies.

**Abbreviations**

GFAP-A  
Autoimmune glial fibrillary acidic protein astrocytic lesion  
CSF  
cerebrospinal fluid  
MOGAD  
Myelin oligodendrocyte glycoprotein antibody-associated disease  
IgG  
immunoglobulin G  
NMOSD  
neuromyelitis optica spectrum disorders  
IVMP  
Intravenous methylprednisolone  
IVIG  
Intravenous immunoglobulin  
PE
Declarations

Ethical approval

The Institutional Review Board at Chongqing General Hospital approved this case report.

Consent for publication

Written informed consent for the publication of this case report was obtained from the patient.

Availability of data and materials

Not applicable

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

YX and LS collected information about the patient. YX wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable

References


**Figures**

**Figure 1**

These images are MRIs of Patient 1 after admission, showing some demyelinating lesions in white matter (as shown by the red arrow).
Figure 2

Demonstration of MOG-IgG and GFAP-IgG by transfected cell-based assay (CBA). Photographs showed positive GFAP-IgG in CSF (case1: G1, titer, 1:32; case2: G2, titer, 1:32) and positive MOG-IgG in serum (case2: M1, titer, 1:10).
Figure 3

MRI of patient 2 after admission: mainly indicated lesions (red arrow) of C1-3: sagittal section (1) - (3); transverse section 4 - 6.
Figure 4

MRI of patient 2 after admission: mainly indicated lesions (red arrow) of T5-6: sagittal section (7) - (8); transverse section 9 - 12.
Figure 5

MRI of patient 2 after treatment: mainly indicated lesions (red arrow) of C1-3(A)-(C), T5-6(D)-(F)