

Autoimmune glial fibrillary acidic protein astrocytopathy with lesions distributed predominantly in the entire spinal cord

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Abstract: Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy has been considered a novel central nervous system autoimmune disease characterized by relapse and responsiveness to corticosteroid with a specific GFAP-Immunoglobulin G (IgG) being noted in cerebrospinal fluid. We report the case of a 21-year-old girl presenting with dysuria and weariness, who subsequently developed blurry vision, slight dysphagia, slurred speech, and sensory abnormality. GFAP-IgG was detected in her cerebrospinal fluid. Magnetic resonance imaging using both T2-weighted and contrast-enhanced T1-weighted images revealed a rare finding of lesions distributed mainly in the entire spinal cord rather than typical brain lesions. After treating with corticosteroids, her clinical symptoms were alleviated, and the spinal cord lesion enhancement was reduced. Our observations extend the clinical spectrum of autoimmune GFAP astrocytopathy. We suggest that rare distributed lesions in the entire spinal cord in patients with autoimmune GFAP astrocytopathy cannot be ignored by neurologists. The identification of potential atypical lesions broadens the understanding of autoimmune GFAP astrocytopathy.

Keywords: antibody, astrocytopathy, autoimmune, glial fibrillary acidic protein, spinal cord

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Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a novel central nervous system (CNS) autoimmune disease typically characterized by meningeal, brain parenchymal, spinal cord, or optic nerve inflammation and injury.¹ Immunoglobulin G (IgG) antibodies to GFAP in cerebrospinal fluid (CSF) is considered a specific biomarker of this disease.^{1–3} Primary clinical manifestations of autoimmune GFAP astrocytopathy include headache, abnormal vision, fever, psychosis, myelitis, ataxia, dyskinesia, and autonomic dysfunction,^{1,2,4,5} which can be easily misdiagnosed as other neurological diseases.

Identifying typical CNS lesions using magnetic resonance imaging (MRI) is helpful to improve early accurate diagnosis. Specifically, brain linear enhancement oriented radially to the ventricles has been viewed as a potential characteristic in patients with autoimmune GFAP astrocytopathy,^{2,3} while

other abnormalities in the CNS regions include the subcortical white matter, hypothalamus, midbrain, pons, cerebellum, and cervical or thoracic spinal cord can also be found.^{2,5} However, cases with lesions predominantly distributed in the entire spinal cord ranging from cervical segment to lumbar segment have not been reported yet.

Here, we report a rare case of autoimmune GFAP astrocytopathy with lesions distributed mainly in the entire spinal cord and extending up to the medulla oblongata.

Case presentation

A previously healthy 21-year-old girl experienced 1 week of significant dysuria and weariness, with the subsequent development of blurry vision, slight dysphagia, slurred speech, and sensory disturbance. Her past medical history and family history were both unremarkable. Routine

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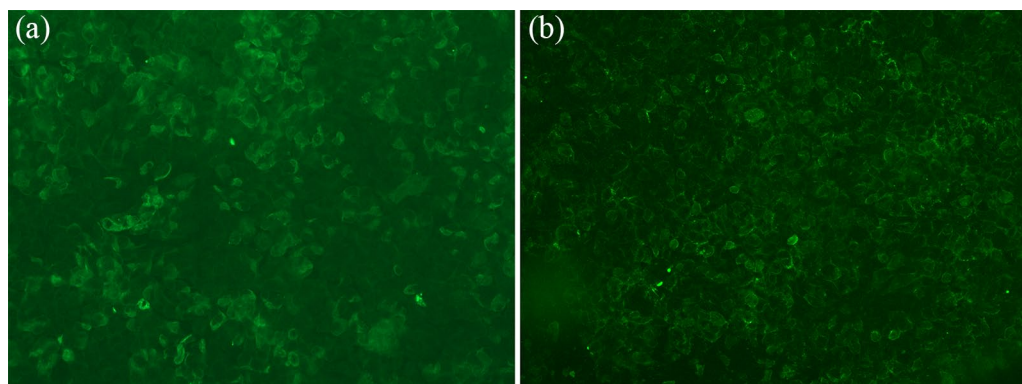


Figure 1. The immunoreactivity of the patient's glial fibrillary acidic protein-immunoglobulin G (GFAP-IgG) in cerebrospinal fluid (CSF) and aquaporin 4 (AQP4)-IgG in the serum. Using transfected cell-based immunofluorescence assays, GFAP-IgG was detected in the CSF (a) and AQP4-IgG was detected in the serum (b).

laboratory investigations revealed that complete blood count, liver and renal tests, tumor markers, rheumatoid factors, folic acid, and vitamin B12 were normal. Antithyroglobulin antibody (33.3 IU/ml; normal range: 0–4 IU/ml) and antithyroid peroxidase antibody (28.0 IU/ml; normal range: 0–9 IU/ml) were positive in the serum. Antinuclear and antineutrophil cytoplasmic antibodies, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis were negative. Electrocardiogram, chest X-ray, abdominal ultrasonography, and gynecological ultrasonography were normal.

Lumbar puncture revealed a high white blood cell count ($24/\text{mm}^3$) with 70% monocytes and an elevated protein level of 0.59 g/l (normal range: 0.15–0.45 g/l). Human cytomegalovirus IgG and rubella virus IgG antibodies were positive. CSF levels of IgA, IgG, and IgM were 6.42 mg/l, 62.2 mg/l (normal range: 0–34 mg/l), and 1.53 mg/l, respectively, and the IgG index was 1.21. Viral, fungal, and bacterial polymerase chain reaction (PCR), cultures, and cytology were negative and no malignant cells were found in the CSF.

Cervical spinal cord MRI showed diffuse cord edema. A clinical diagnosis of neuromyelitis optica spectrum disorders was originally considered and thus this patient received intravenous immunoglobulin 0.4 g/kg per day for five consecutive days with minimal improvement. Using transfected cell-based immunofluorescence assays, we detected GFAP-IgG in the CSF (Figure 1a) and aquaporin 4 (AQP4)-IgG in

serum (Figure 1b). GFAP and AQP4 antibodies in the CSF and serum were assessed by an immunofluorescence assay using rat hippocampus tissue, and by a cell-based assay using HEK293 cells transfected with GFAP and AQP4, as reported previously.^{4,5} Both tests were repeated the following day using the new experimental materials and the same equipment to confirm the positive findings when positive results were first detected. Tests of other autoantibodies in CSF and serum, including MOG-IgG, MBP-IgG, AQP1-IgG, NMDAR-IgG, AMPA1-IgG, AMPA2-IgG, LGI1-IgG, CASPR2-IgG, and GABABR-IgG, were negative. As GFAP-IgG was reported to be a specific biomarker of autoimmune GFAP astrocytopathy and CSF is more reliable than serum for GFAP-IgG testing,^{1–6} other similar diseases were additionally and carefully ruled out and the diagnosis of autoimmune GFAP astrocytopathy was confirmed.

Thorough brain and spinal cord MRI examinations were performed. Interestingly, spinal cord MRIs showed longitudinally extensive spinal cord lesions involving the cervical, thoracic, and lumbar spinal cord in T2-weighted images, with spinal cord central canal, patchy, punctate, and pia enhancement lesions extending up to the medulla oblongata in T1-weighted images (Figure 2). Surprisingly, MRI scans of the cerebral hemisphere, midbrain, pons, and cerebellar were normal. The most common characteristic of autoimmune GFAP astrocytopathy (linear, radial perivascular patterns of enhancement throughout the cerebral white matter) was not found in this patient (Figure 2a).

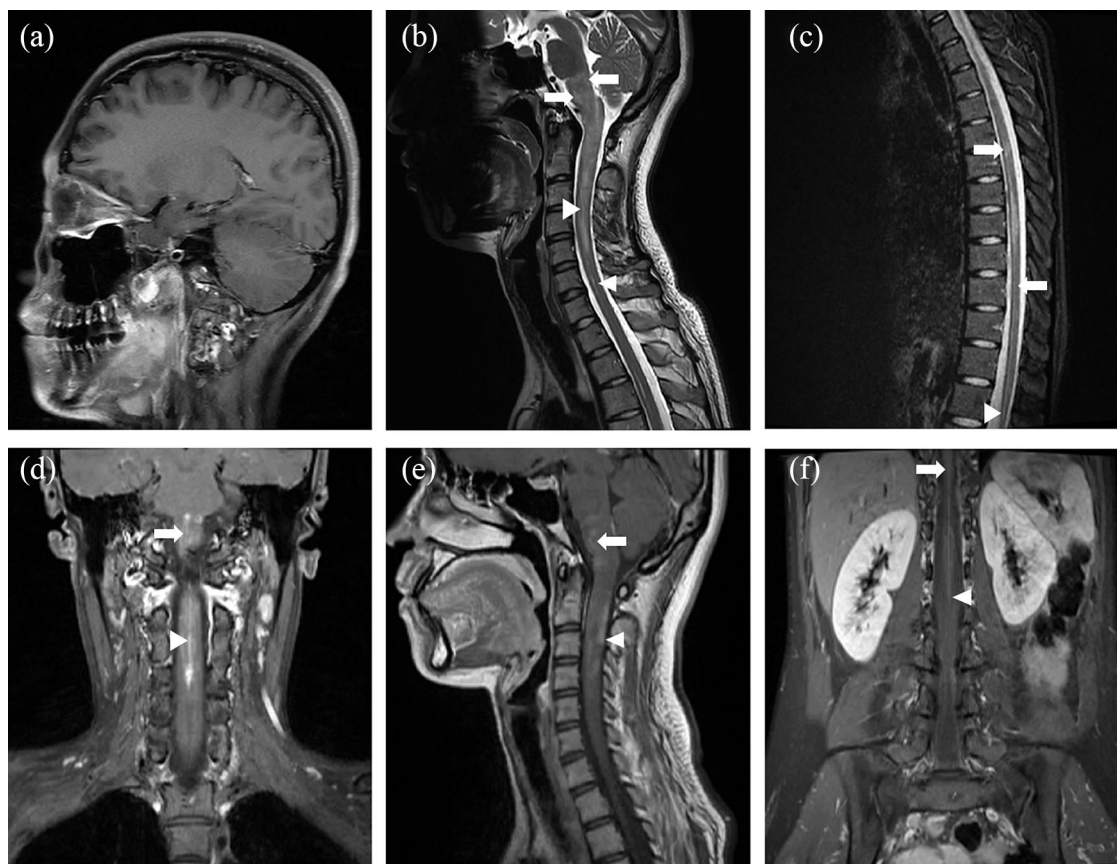


Figure 2. Brain and spinal cord magnetic resonance imaging (MRI) performed before systemic treatment. Contrast enhanced brain MRI was normal [a]. Spinal cord MRI sagittal and coronal sequences show longitudinally extensive T2-hyperintense lesions with poorly defined margins [medulla oblongata (b, arrow), cervical (b, arrowhead), thoracic (c, arrow), lumbar (c, arrowhead) spinal cord] accompanied by spinal cord central canal, patchy, punctate, and pia gadolinium enhancement on the medulla oblongata (d, e; arrow) and the cervical (d, e; arrowhead), thoracic (f, arrow) and lumbar (f, arrowhead) spinal cord.

Given her symptoms and MRI results, the diagnosis of autoimmune GFAP astrocytopathy was finally considered. The patient was treated with intravenous methylprednisolone (500 mg for 4 days) followed by a 50% reduction of the dose after 3–5 days, and subsequent oral methylprednisolone (60 mg/day), which was then tapered (reduced 4 mg/day every 2 weeks). Owing to the potential possibility of relapse, she received mycophenolate mofetil 500 mg twice daily. Four weeks after discharge, the patient's neurological symptoms had significantly improved.

During the follow-up period, the patient reported mild sensory abnormality and was independent in all activities of daily living 3 months after the diagnosis of GFAP astrocytopathy. Repeated MRI scans were performed, showing residual T2 hyperintensities and T1-gadolinium enhancement in the

spinal cord and medulla oblongata with no evidence of new lesions (Figure 3).

Discussion

Autoimmune GFAP astrocytopathy is a novel and rare autoimmune disease of the CNS. Clinical manifestations of autoimmune GFAP astrocytopathy include one or more of the following: meningitis, encephalitis, myelitis, and optic disc papillitis.² The presence of GFAP-IgG in the CSF is considered a specific biomarker.^{1,4} The characteristic pattern of MRI is brain linear perivascular radial gadolinium enhancement in the white matter perpendicular to the ventricle.^{1,3,4} In GFAP-IgG myelitis, primarily central gray matter involvement is typical.⁷ Corticosteroid-responsiveness is not specific to GFAP astrocytopathy (also typical of MOG antibody disease),⁸ but is a hallmark of this disorder.²

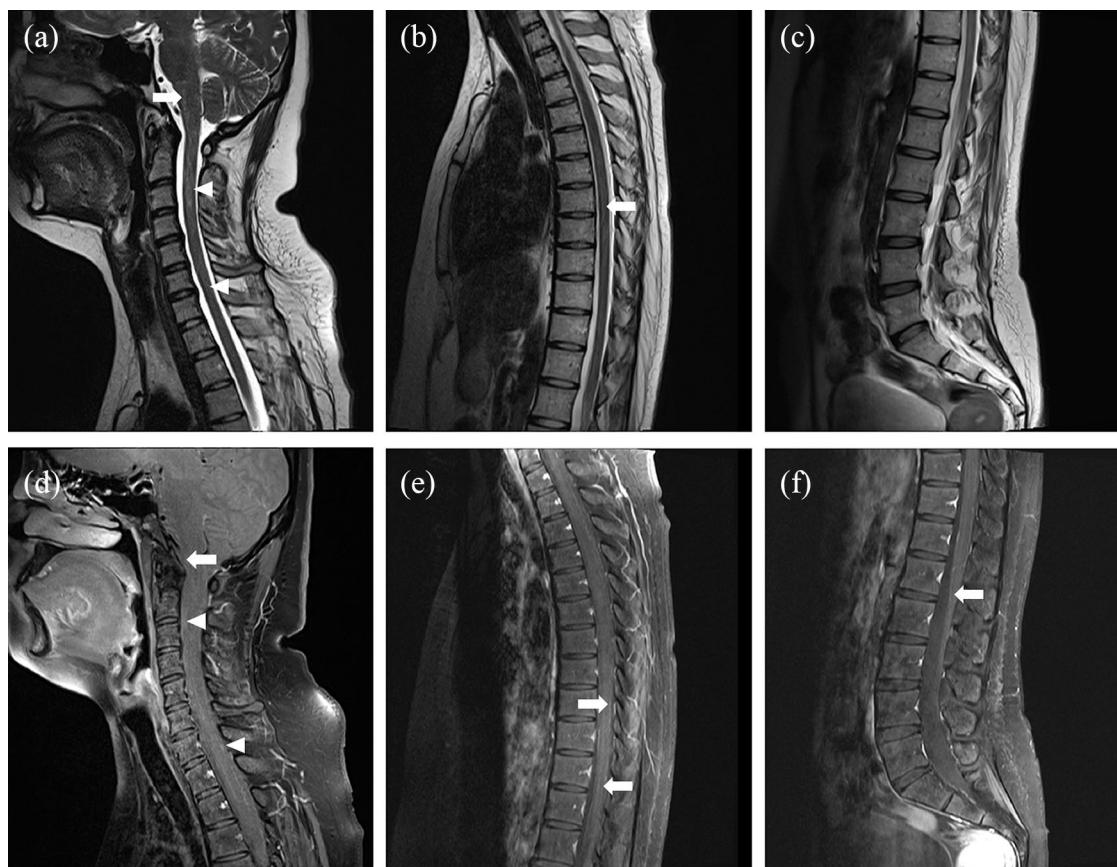


Figure 3. Spinal cord magnetic resonance imaging (MRI) performed 3 months after onset. Spinal cord MRI sagittal sequence show residual T2 hyperintensities [medulla oblongata (a, arrow), cervical (a, arrowhead), thoracic (b, arrow), lumbar (c) spinal cord] and T1-gadolinium enhancement [medulla oblongata (d, arrow), cervical (d, arrows), thoracic (e, arrows), lumbar (f, arrow) spinal cord], without evidence of new lesions.

In our patient, the main neurological manifestations were blurred vision, marked sensory and motor changes, and autonomic dysfunction, with the detection of GFAP-IgG in the CSF and lesions of the spinal cord. The patient was sensitive to steroids. Other similar diseases were carefully ruled out. All of these features matched the diagnosis of autoimmune GFAP astrocytopathy.²

Longitudinally extensive transverse myelitis (LETM) is characterized by contiguous inflammatory lesions of the spinal cord involving three or more vertebral segments. LETM mainly occurs in CNS autoimmune disease, such as neuromyelitis optica spectrum disorder (NMOSD) and chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids syndrome,^{9,10} which is often accompanied by brain lesions.^{9,11}

Although LETM is common,⁵ cases with lesions predominantly distributed in entire spinal cord have not been reported in patients with autoimmune GFAP astrocytopathy. Previous studies have indicated that six patients had longitudinally extensive myelitic abnormalities among eight GFAP-IgG positive patients with spinal cord MRI images.⁴ In the latter study, linear-appearing central canal enhancement was noted in 21% of spinal cord MRIs, but more generalized enhancement patterns were punctate or patchy. Sechi⁷ reported that spinal cord lesions in GFAP-IgG myelitis were commonly longitudinally extensive and centrally located. In another study,⁵ spinal cord MRIs were performed for 16 Chinese patients. Of these, 68.75% revealed longitudinally extensive spinal cord lesions. However, meningoencephalitis and meningoencephalomyelitis were the predominant phenotypes in previous reports, with isolated myelitis being rare.^{4,5,7}

In our case, this patient met the diagnosis of autoimmune GFAP astrocytopathy rather than NMOSD. Specifically, GFAP antibody was detected in CSF, which is considered a specific biomarker for autoimmune GFAP astrocytopathy.² In patients with GFAP antibody, the coexistence of AQP4-IgG is common.⁴ In a series of 30 Chinese patients, 10 GFAP-IgG patients had at least one other specific autoantibody.⁵ In our case, the AQP4-IgG was detected in the serum. Compared with AQP4-IgG lesions, GFAP-IgG myelitis involves relatively subtle lesions with poorly defined margins and less swelling.⁷ In GFAP-IgG myelitis, spinal cord central canal, especially patchy, punctate, or pia enhancement is typical,^{3,4} unlike the ring-like appearance of parenchymal enhancement that is typical of autoimmune NMOSD.¹² The patient responded well to steroid therapy and reported mild sensory abnormality during the follow-up period, while the risk of relapse of NMOSD is high throughout the disease regardless of the antibody level. The 3-month follow-up results showed significant lesion reduction of T2 hyperintensities and T1-gadolinium enhancement in the spinal cord and medulla oblongata, as well as a good recovery. This patient showed a favorable corticosteroid response, similar to a previously published patient with GFAP astrocytopathy.¹³ More importantly, other similar diseases were carefully ruled out. Although the patient had acute myelitis, which is a core clinical characteristic of NMOSD, the typical neuroimaging characteristics were not detected. In addition, the patient did not display optic neuritis.

This case showed lesions extending up to the medulla oblongata. To the best of the authors' knowledge, medulla oblongata involvement has been reported in patients with GFAP-IgG in the literature. Considering that this imaging finding has been reported in NMOSD,¹⁴ we speculate that medulla oblongata involvement might indicate a severe neurologic deficit in autoimmune GFAP astrocytopathy.

To the best of the authors' knowledge, only a few studies have focused on the clinical or imaging characteristics of patients with coexisting antibodies of GFAP-IgG and AQP4-IgG. In previous Mayo clinic studies,^{1,4} patients with GFAP-IgG commonly displayed coexistence of additional kinds of autoantibodies, including NMDA-R-IgG, AQP4-IgG, and MOG-IgG. The studies described that 41 patients had one or more

coexisting antibodies in CSF or serum (40%), of which AQP4-IgG was the second most common.^{1,4} Patients with coexisting AQP4-IgG seem largely indistinguishable from those positive for GFAP-IgG alone, though occasional NMOSD cases have been reported.² A recent study exploring the overlapping syndromes in autoimmune GFAP astrocytopathy showed that although two or more kinds of autoantibody may occur in patients with GFAP-IgG, no further clinical differences could be found between the patients with and without overlapping syndrome, except for the age at onset.¹⁵ Specifically, patients with overlapping syndrome had an earlier onset compared with those without overlapping syndrome.¹⁵ In addition, patients with GFAP-IgG coexisting with AQP4-IgG usually had it occur simultaneously at the initial attack.¹⁵ MRI features of patients with GFAP-IgG showed that the brain or spinal cord could be normal, except for common findings that included myelitis, brain lesions, and characteristic radial enhancing patterns in the white matter with the coexistence of AQP4-IgG.¹⁵

Interestingly, in our patient, GFAP-IgG and AQP4-IgG were detected simultaneously at the initial attack at the young age of 21 years. In contrast to the common imaging findings of patients with GFAP-IgG coexisting with AQP4-IgG, lesions of our patient were predominantly distributed in the entire spinal cord (cervical, thoracic, and lumbar segment). The findings extend our understanding of neurological phenotypes of GFAP astrocytopathy.

Conclusion

This case demonstrates the novel occurrence of autoimmune GFAP astrocytopathy in a female patient, with confirmation of the detection of GFAP-IgG in the CSF. The finding of lesions distributed predominantly in the entire spinal cord is a novel feature in this case of autoimmune GFAP astrocytopathy. This observation enhances the utility of early MRI diagnosis, even in the absence of typical clinical symptoms and the detection of GFAP-IgG.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics statement

The patient is aware of all the content, medical data, and images presented in this article and agreed for it to be published as a case report scientific research paper in any scientific research magazine. The present study was approved by the Ethics Committee of the Jining No 1 People's Hospital.

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