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Myelitis associated with glial fibrillary acidic protein IgG: characterization and comparison with aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG myelitis

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Abstract

Background Awareness of the characteristics of glial fibrillary acidic protein autoantibody (GFAP-IgG) associated myelitis facilitates early diagnosis and treatment. We explored features in GFAP-IgG myelitis and compared them with those in myelitis associated with aquaporin-4 IgG (AQP4-IgG) and myelin oligodendrocyte glycoprotein IgG (MOG-IgG).

Methods We retrospectively reviewed data from patients with GFAP-IgG myelitis at the First Affiliated Hospital of Zhengzhou University and Henan Children's Hospital from May 2018 to May 2023. AQP4-IgG and MOG-IgG myelitis patients served as controls.

Results Thirty-four patients with GFAP-IgG myelitis were included (15 women, 12 children; median age at onset, 28.5 years). Over half experienced prodromal symptoms and required intensive care support. The median Expanded Disability Status Scale (EDSS) score was 4 at admission and 0 at final follow-up (median, 20 months). Cerebrospinal fluid (CSF) analysis showed markedly elevated leukocyte counts in 23 patients, elevated total protein in 28 patients, and decreased glucose levels in 9 patients. Longitudinally sagittal T2 and gadolinium-enhancing spinal cord lesions were detected. Features favoring GFAP-IgG over the other types included presence of fever and neck stiffness, requirement of intensive care and mechanical ventilation, higher monocyte-to-lymphocyte ratio (MLR), presence of hyponatremia, markedly elevated CSF leukocyte counts, increased CSF total protein levels, and decreased CSF glucose levels. Imaging findings more common in GFAP-IgG than in AQP4-IgG myelitis were longer diseased segments, central canal enhancement, and gadolinium-enhancing brain lesions. Higher EDSS scores at discharge distinguished GFAP-IgG from MOG-IgG.

Conclusion Clinical, laboratory, imaging, and outcome variables facilitate differential diagnosis of myelitis subtypes.

Keywords GFAP, AQP4, MOG, Myelitis, Characterization, Comparison

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Background

Transverse myelitis (TM) is an inflammatory myelopathy characterized by acute or subacute motor, sensory, and autonomic dysfunction [1]. Single or recurrent episodes of TM may eventually lead to permanent disability. Although immune-mediated and infectious mechanisms are considered to trigger TM [2], the disease etiology remains unclear in a considerable proportion of cases, which are classified as idiopathic [3]. The recent discovery of specific autoantibody markers such as the glial fibrillary acidic protein (GFAP)-IgG, aquaporin-4 (AQP4)-IgG, and myelin oligodendrocyte glycoprotein (MOG)-IgG, and radiological features of immune-mediated myelopathy can contribute to the etiological diagnosis of many cases previously known as "idiopathic TM", with significant prognostic value and therapeutic implications [4]. Early diagnosis and prompt aggressive treatment are crucial for the successful recovery of patients who experience acute attacks of immune-mediated TM. Fang et al. found that detection of GFAP-IgG in the cerebrospinal fluid (CSF) is associated with an inflammatory disorder of the central nervous system (CNS), called autoimmune GFAP astrocytopathy (GFAP-A), which is characterized by optic neuritis, meningitis, encephalitis, myelitis, or a combination of the above [5]. Although the clinical, radiological, and prognostic features in patients with GFAP-A have been well characterized [5–7], a thorough understanding of myelitis associated with GFAP-IgG is limited, especially when compared with AQP4-IgG or MOG-IgG myelitis. Previous reports have indicated that patients with GFAP-IgG often present spinal cord involvement with longitudinal extensive TM, and isolated myelitis is uncommon [8, 9]. Accumulating evidence has suggested that detection of GFAP-IgG clearly defines a novel clinical syndrome, which differs from AQP4-IgG and MOG-IgG myelitis [6, 9]. Few comprehensive comparative analyses of the clinical, magnetic resonance imaging (MRI), and outcome characteristics in the three disease entities have been performed to date.

In the present study, we sought to reveal clinical features, laboratory findings, radiological characteristics, treatment approaches, and clinical outcomes in patients with GFAP-IgG myelitis and compare them to AQP4-IgG and MOG-IgG myelitis.

Methods

Participant recruitment

We retrospectively analyzed the medical records of 34 patients with CSF-positive GFAP-IgG and myelitis at the First Affiliated Hospital of Zhengzhou University and Henan Children's Hospital from May 2018 to May 2023. The data of 13 patients were obtained from our previously published study [7]. The inclusion criteria were as follows: (1) positive CSF GFAP-IgG; (2) spinal cord involvement; (3) negative detection of other anti-neuronal antibodies in CSF or serum; (4) available clinical data. Patients with myelitis seropositive for AQP4-IgG ($n=30$) and MOG-IgG ($n=30$) from the First Affiliated Hospital of Zhengzhou University were included for comparisons. The inclusion criteria were as follows: (1) seropositive for AQP4-IgG or MOG-IgG; (2) spinal cord involvement; (3) absence of other anti-neuronal antibodies in CSF or serum; (4) fulfillment of the current diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) according to the 2015 Wingerchuk criteria [10](Wingerchuk et al. 2015) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) based on the 2023 Banwell criteria [11], respectively; (5) availability of clinical data. For autoantibody detection, cell-based assays were performed as previously described [7].

Data collection

Data of interest collected from electronic medical records included demographics, clinical symptoms, serological examinations, CSF parameters, neuroimaging findings, treatment strategies, and outcomes. Serological examinations included neutrophil, lymphocyte, and monocyte counts (normal range: $1.8–6.3\times10^9$/L, $1.1–3.2\times10^9$/L and $0.1–0.6\times10^9$/L, respectively), and sodium levels (normal range: 135–153 mmol/L). CSF parameters comprised leukocyte counts (normal range: $0–5\times10^6$/L), total protein and glucose levels (normal range: 150–450 mg/L and 2.5–4.5 mmol/L, respectively), and detection of viral antibodies (IgM) or DNA (Epstein–Barr virus [EBV], cytomegalovirus, coxsackie virus, measles virus, herpes simplex viruses I and II, human parvovirus B-19, influenza b virus, parainfluenza virus, adenovirus, rubella virus, herpes zoster virus, and echovirus). The Expanded Disability Status Scale (EDSS) was used to assess neurological function at admission, hospital discharge, and last follow-up. The final follow-up visit was October 2023.

Statistical analysis

The SPSS 25.0 software was used for statistical analysis. Continuous variables are presented as medians (range, 1st–3rd quartile) and categorical variables as numbers (percentages). Continuous variables were tested for normality of the distribution with Kolmogorov-Smirnov test. Differences of continuous variables between groups were compared using the Student's t-test (for normally distributed data) or Mann–Whitney U test (for non-parametric data). The chi-square or Fisher's test were used to compare categorical variables.

Results

Demographic and clinical characteristics of patients with GFAP-IgG

Demographics and clinical characteristics are summarized in Table 1. Of the 34 enrolled patients, 15 (44%) were women and 12 (35%) were children (<18 years of age), with a median (interquartile range [IQR]) age of 28.5 years (10.8–44.3 years). The median (IQR) length of hospital stay was 23.5 days (15.8–30.5 days). Eighteen (53%) patients had prodromal symptoms (fever, fatigue, rhinorrhea, sore throat, and cough) due to presumed (n=13) or confirmed infection (influenza B virus, n=3; EBV, n=1), and one (3%) patient had received influenza vaccination 2 weeks before symptom onset (results not shown). Among the patients who experienced abdominal pain/distention, serum GFAP-IgG was assessed in four of them, with three positive and one negative (data not shown). Approximately half (44%) of the patients were wheelchair-dependent at attack nadir. Notably, over half (56%) of the patients were admitted to an intensive care unit (ICU). Mechanical ventilation was required for more than a third (38%) of the patients.

Laboratory characteristics of patients with GFAP-IgG

Serological and CSF findings are presented in Table 1. The median (IQR) neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) were 4.27 (2.43–6.77) and 0.43 (0.24–0.71), respectively, and hyponatremia was observed in 45% of patients. Serum GFAP-IgG testing was conducted in 30 out of the 34 patients, with 13 of these patients exhibiting positive results (results not shown). CSF samples from 30 patients were examined for the presence of IgM or DNA to assess viral infection. One patient was positive for herpes simplex virus I IgM and four for EBV DNA (results not shown). CSF analysis showed elevated leukocyte counts in 31 (91%) patients, markedly elevated leukocyte counts in 23 (68%) patients, elevated total protein levels in 28 (82%) patients, and decreased glucose levels in nine (26%) patients; a markedly elevated leukocyte count accompanied by protein levels>1.0 g/L was noted in 11 patients with GFAP-IgG.

MRI characteristics of patients with GFAP-IgG

Table 1 summarizes the MRI findings for the patients with myelitis with positive GFAP-IgG in CSF. 28 (82%) patients presented with longitudinally sagittal T2 lesions (LETM) (Fig. 1A and B). The median (IQR) vertebral length of the sagittal T2-hyperintense lesions was 13 (5.8–18) segments. Gadolinium-enhancing spinal cord lesions were detected in 14 (82%) of the 17 patients and five (29%) of these patients showed central canal enhancement (Fig. 1C and D). Twenty-three (72%) of 32 patients had abnormal brain hyperintense T2 signal, and 14 (64%) of 22 patients had gadolinium-enhancing brain lesions. Only two (9%) patients exhibited the characteristic linear perivascular radial gadolinium patterns (Fig. 1E and F).

Treatment and clinical outcome

Among the 34 patients, 33 (97%) were treated with intravenous methylprednisolone (IVMP), and 18 (53%) underwent intravenous immunoglobulin (IVIG) therapy. 23 patients had clinical improvement with IVMP and/or IVIG treatment. Only one (3%) patient received plasmapheresis (PE) treatment due to poor prognosis following combined IVMP and IVIG therapy. Four (12%) were treated with immunosuppression: three on mycophenolate mofetil, and one received rituximab. Two (6%) patients died of respiratory and circulatory failure during hospital admission (Supplementary Table 1). The median (IQR) EDSS score was 4 (3–6.5) at admission and 3 (0–8) at discharge. Four (12%) patients were readmitted because of myelitis recurrence. The median (IQR) follow-up was 20 (15–23.75) months. At the time of final analysis, eight patients had poor outcomes (EDSS score>2), with the median EDSS score being 0 (0–2.8). Severe pulmonary infection and malignant glioma were the cause of death in three and one patient (Supplementary Table 1), respectively, during follow-up. Detailed information on deceased patients with GFAP-IgG myelitis is summarized in Supplementary Table 1.

Comparison of GFAP-IgG myelitis with AQP4-IgG myelitis

We compared features in GFAP-IgG myelitis (n=34) with those in AQP4-IgG myelitis (n=30) (Table 1). The proportion of women with GFAP-IgG myelitis was considerably lower than that with AQP4-IgG (15/34 (44%) vs. 26/30 (87%), P<0.01). The clinical features favoring GFAP-IgG over AQP4-IgG myelitis were presence of prodromal symptoms, fever, headache and neck stiffness. Blurred vision, limb numbness and limb pain were more frequent in AQP4-IgG than in GFAP-IgG myelitis. The percentage of cane/walker-dependent at attack nadir was higher in GFAP-IgG than in AQP4-IgG myelitis. ICU admission and mechanical ventilation were more frequently required in GFAP-IgG than in AQP4-IgG myelitis. However, the EDSS score at admission and discharge did not significantly differ between these two cohorts. Notably, the NLR and MLR in patients with GFAP-IgG were significantly higher than that in patients with AQP4-IgG myelitis, as was the percentage of patients with hyponatremia, markedly elevated CSF leukocyte counts, elevated CSF total protein levels, and decreased CSF glucose levels. On MRI of the spine, radiological features more common in GFAP-IgG than in AQP4-IgG myelitis were longer diseased segments (13 [5.8–18] vs. 6 [3–12.5], P=0.01) and central canal enhancement (5/17

Table 1 Comparison of key characteristics of GFAP-IgG, MOG-IgG and AQP4-IgG myelitis

	Myelitis, Number of patients (%)/Median (first quartile–third quartile)			P1 Value[a]	P2 Value[b]
	GFAP-IgG ($n=34$)	AQP4-IgG($n=30$)	MOG-IgG ($n=30$)		
Demographics					
Age at onset, y	28.5 (10.8–44.3)	36.5 (20.8–55.3)	8.5 (4.8–23.8)	0.09	<0.01
Women	15/34 (44%)	26/30 (87%)	13/30 (43%)	<0.01	0.95
Children (< 18 y)	12/34 (35%)	5/30 (17%)	21/30 (70%)	0.09	<0.01
Length of hospital stay, d	23.5 (15.8–30.5)	17.5 (12–23)	15.5 (12–21.3)	0.18	0.02
Clinical characteristics					
Prodromal symptoms	18/34 (53%)	5/30 (17%)	14/30 (47%)	<0.01	0.62
Fever	29/34 (85%)	3/30 (10%)	14/30 (47%)	<0.01	<0.01
Impaired consciousness	12/34 (35%)	5/30 (17%)	8/30 (27%)	0.09	0.46
Headache	19/34 (56%)	3/30 (10%)	12/30 (40%)	<0.01	0.21
Dizziness	11/34 (32%)	6/30 (20%)	4/30 (13%)	0.26	0.07
Blurred vision	4/34 (12%)	12/30 (40%)	7/30 (23%)	<0.01	0.22
Neck stiffness	14/34 (41%)	2/30 (7%)	4/30 (13%)	<0.01	0.01
Nausea and vomiting	20/34 (59%)	11/30 (37%)	7/30 (23%)	0.08	<0.01
Appetite loss	7/34 (21%)	3/30 (10%)	1/30 (3%)	0.41	0.09
Abdominal Pain/distention	5/34 (15%)	2/30 (7%)	6/30 (20%)	0.53	0.58
Limb numbness	6/34 (18%)	19/30 (63%)	6/30 (20%)	<0.01	0.81
Limb pain	4/34 (12%)	11/30 (37%)	2/30 (7%)	0.02	0.79
Limb weakness	27/34 (79%)	20/30 (67%)	16/30 (53%)	0.25	0.03
Ambulated independently at attack nadir	7/34 (21%)	10/30 (33%)	14/30 (47%)	0.25	0.03
Cane/walker dependent at attack nadir	12/34 (35%)	4/30 (13%)	6/30 (20%)	0.04	0.17
Wheelchair-dependent at attack nadir	15/34 (44%)	16/30 (53%)	10/30 (33%)	0.46	0.38
Urinary incontinence or retention	14/34 (41%)	14/30 (47%)	11/30 (37%)	0.66	0.71
ICU admission	19/34 (56%)	3/30 (10%)	5/30 (17%)	<0.01	<0.01
Mechanical ventilation	13/34 (38%)	1/30 (3%)	0/30 (0%)	<0.01	<0.01
EDSS score at admission	4 (3–6)	4 (3–6)	4 (4–5)	0.3	0.13
EDSS score at discharge	3 (0–8)	2 (2–6.3)	0 (0–2.3)	0.86	<0.01
Serological findings					
NLR	4.27 (2.43–6.77)	2.5 (1.59–3.61)	2.29 (1.55–5.41)	<0.01	0.07
MLR	0.43 (0.24–0.71)	0.23 (0.18–0.32)	0.22 (0.15–0.31)	<0.01	<0.01
Hyponatremia (<135 mmol/L)	15/33 (45%)	4/30 (13%)	2/30 (7%)	<0.01	<0.01
CSF findings					
Elevated leukocyte counts, > 5 cells/μL	31/34 (91%)	16/29 (55%)	23/29 (79%)	<0.01	0.33
Markedly elevated leukocyte counts, > 50 cells/μL	23/34 (68%)	4/29 (14%)	10/29 (34%)	<0.01	<0.01
Elevated total protein, > 450 mg/L	28/34 (82%)	9/29 (31%)	5/29 (17%)	<0.01	<0.01
Decreased glucose levels, <2.2 mmol/L	9/34 (26%)	1/29 (3%)	0/29 (0%)	0.03	<0.01
MRI spine					
Cervical cord lesions	27/34 (79%)	23/30 (77%)	26/30 (87%)	0.79	0.44
Thoracic cord lesions	29/34 (85%)	20/30 (67%)	21/30 (70%)	0.08	0.14
Lumbar cord lesions	9/34 (26%)	3/30 (10%)	5/30 (17%)	0.09	0.34
Longitudinally extensive sagittal T2 lesions (> 3 vertebral segments)	28/34 (82%)	24/30 (80%)	26/30 (87%)	0.81	0.90
≥2 cord lesions	15/34 (44%)	10/30 (33%)	9/30 (30%)	0.38	0.24
Conus	2/34 (6%)	0/30 (0%)	1/29 (3%)	0.53	1
Diseased segments	13 (5.8–18)	6 (3–12.5)	11 (5–19)	0.01	0.74
Gadolinium enhancement	14/17 (82%)	14/19 (74%)	6/13 (46%)	0.70	0.06
Spinal cord swelling	4/34 (12%)	6/30 (20%)	3/30 (10%)	0.58	1
Central canal enhancement	5/17 (29%)	0/19 (0%)	0/13 (0%)	0.02	0.05
Ring enhancement	0/17 (0%)	2/19 (11%)	0/13 (0%)	0.49	-
H sign	1/34 (3%)	1/30 (3%)	5/30 (17%)	1	0.15
MRI head					
Brain T2 lesions	23/32 (72%)	13/27 (48%)	22/26 (85%)	0.06	0.25

Table 1 (continued)

	Myelitis, Number of patients (%)/Median (first quartile–third quartile)			P1 Value[a]	P2 Value[b]
	GFAP-IgG ($n=34$)	AQP4-IgG($n=30$)	MOG-IgG ($n=30$)		
Gadolinium enhancement	14/22 (64%)	2/14 (14%)	6/10 (60%)	<0.01	1
Linear perivascular radial gadolinium patterns	2/22 (9%)	0/14 (0%)	0/10 (0%)	0.51	1
Treatment					
IVMP	33/34 (97%)	30/30 (100%)	29/30 (97%)	1	1
IVIG	18/34 (53%)	12/30 (40%)	15/30 (50%)	0.30	0.81
PE	1/34 (3%)	0/30 (0%)	0/30 (0%)	1	1
Immunosuppressant	4/34 (12%)[c]	15/30 (50%)[d]	5/30 (17%)[e]	<0.01	0.84
Outcome					
EDSS score at last follow-up	0 (0–2.8)	0 (0–4.3)	0 (0–2)	0.94	0.13
Gait aid at last follow-up	1/28 (4%)	6/30 (20%)	1/29 (3%)	0.13	1
Urinary incontinence or retention at last follow-up	1/28 (4%)	2/30 (7%)	2/29 (7%)	1	1
Follow-up duration, mo	20 (15–23.75)	14.5 (8–34.3)	19.5 (11.3–28.5)	0.78	0.87

[a] Statistical comparison between GFAP-IgG myelitis and AQP4-IgG myelitis cases. [b] Statistical comparison between GFAP-IgG myelitis and MOG-IgG myelitis cases. [c] Mycophenolate mofetil (3), Rituximab (1). [d] Mycophenolate mofetil (12), Azathioprine (3)[e] Mycophenolate mofetil (4), Azathioprine (1)

(29%) vs. 0/19 (0%), $P=0.02$). It is worth noting that spinal cord lesions with ring enhancement (Fig. 1G and H) is seen only in NMOSD, and linear perivascular radial gadolinium patterns are seen exclusively in GFAP-A, despite the absence of significant differences. Gadolinium-enhancing brain lesions were more frequent findings with GFAP-IgG than with AQP4-IgG myelitis (14/22 (64%) vs. 2/14 (14%), $P<0.01$). The ratio of patients treated with immunosuppressants was significantly lower in GFAP-IgG than in AQP4-IgG myelitis (4/34 (12%) vs. 15/30 (50%), $P<0.01$), with a similar pattern observed for participants in need of a gait aid at last follow-up (1/28 (4%) vs. 6/30 (20%), $P=0.13$), although this difference did not achieve statistical significance. No statistically significant differences were observed in EDSS score at last follow-up, the ratio of patients with urinary incontinence or retention at last follow-up, and follow-up duration between the GFAP-IgG and AQP4-IgG myelitis groups.

Comparison of GFAP-IgG myelitis with MOG-IgG myelitis

Table 1 presents the comparison of the features between GFAP-IgG myelitis ($n=34$) and MOG-IgG myelitis ($n=30$). Characteristics that differentiated individuals with GFAP-IgG myelitis from those with MOG-IgG myelitis included an older age at onset and a lower proportion of pediatric patients (28.5 [10.8–44.3] vs. 8.5 [4.8–23.8], $P<0.01$; 12/34 (35%) vs. 21/30 (70%), $P<0.01$). The percentage of women with GFAP-IgG myelitis was similar to that with MOG-IgG myelitis (15/34 (44%) vs. 13/30 (43%), $P=0.95$). The length of hospital stay was significantly longer in patients with GFAP-IgG than in patients with MOG-IgG myelitis (23.5 [15.8–30.5] vs. 15.5 [12–21.3], $P=0.02$). The presence of fever, neck stiffness, nausea and vomiting and limb weakness were distinguishing features favoring GFAP-IgG over MOG-IgG myelitis. The proportion of patients who ambulated independently at attack nadir was significantly lower in GFAP-IgG than in MOG-IgG myelitis (7/34 (21%) vs. 14/30 (47%), $P=0.03$). Compared with MOG-IgG myelitis, GFAP-IgG myelitis showed a higher frequency of ICU admission and mechanical ventilation, although the EDSS score at admission was not significantly different between the two cohorts. Patients with GFAP-IgG myelitis demonstrated a markedly higher MLR than those with MOG-IgG myelitis (0.43 [0.24–0.71] vs. 0.22 [0.15–0.31], $P<0.01$). Moreover, patients with GFAP-IgG showed a greater incidence of hyponatremia, markedly elevated CSF leukocyte counts, elevated CSF total protein levels, and decreased glucose levels compared with those with MOG-IgG myelitis. On MRI of the spine, detection of "H sign" (Fig. 1I) was more common in MOG-IgG than in GFAP-IgG myelitis (5/30 (17%) vs. 1/34 (3%), $P=0.15$), although it did not reach significance. Gadolinium-enhancing brain lesions were equally common in GFAP-IgG and MOG-IgG myelitis (14/22 (64%) vs. 6/10 (60%), $P=1$). There were no statistical differences in the frequency of brain T2 lesions and linear perivascular radial gadolinium patterns between two groups. Remarkably, a higher EDSS score at discharge was reported for patients with GFAP-IgG than in those with MOG-IgG myelitis, although no significant distinction was evident at last follow-up. Additionally, no significant differences were observed in the proportion of patients with urinary incontinence or retention and the follow-up duration between the GFAP-IgG and MOG-IgG myelitis groups.

Discussion

We identified unique characteristics associated with GFAP-IgG myelitis that are distinct from those in AQP4-IgG and MOG-IgG myelitis. Our clinical, serological, CSF, and MRI findings may provide insights into the pathophysiologic mechanisms involved in GFAP-IgG

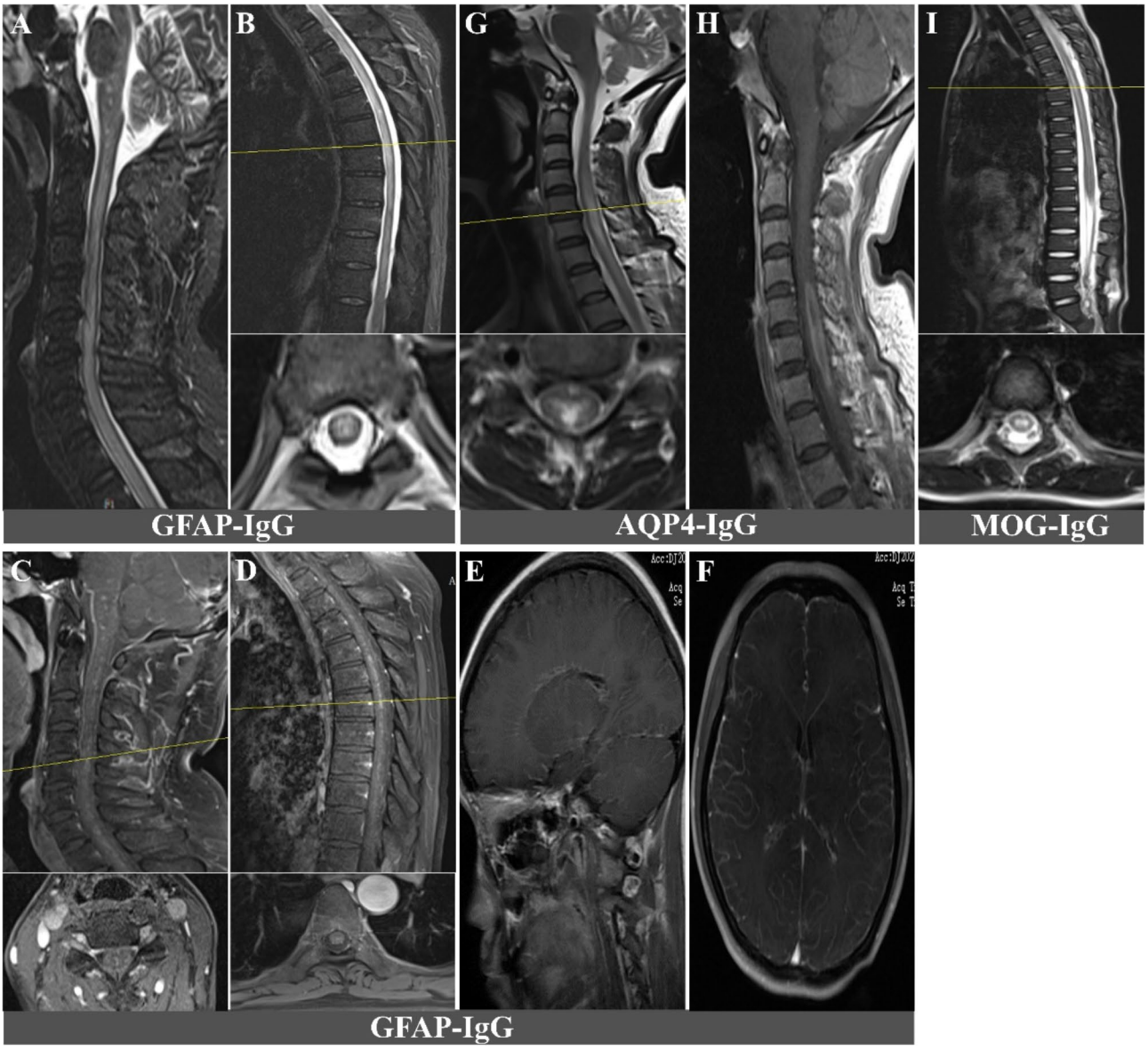

Fig. 1 MRI findings in GFAP-IgG, AQP4-IgG and MOG-IgG myelitis. Sagittal and axial sections showed longitudinally extensive T2 lesions (**A** and **B**), punctate enhancing lesions mainly located at central canal with or without linear pia and leptomeningeal enhancement (**C** and **D**) and linear perivascular radial gadolinium patterns (**E** and **F**) in patients with GFAP-IgG myelitis. Lesions in AQP4-IgG myelitis were generally more well-defined, accompanied by axial T2-hyperintensity lesions (**G**) with ring enhancement (**H**). Longitudinally extensive T2 lesions (**I**) and typical "H sign" (H, bottom panels) were detected in MOG-IgG myelitis patient (the yellow lines indicated the sagittal level at which the axial images below are located)

myelitis and facilitate clinicians select patients for CSF GFAP-IgG testing.

Predominance of women with positive GFAP-IgG was observed in a previous study in a Chinese population, with a women-to-man ratio of 2.17 and a median age of onset of 54 years (range, 23–73 years) [12]. However, we found a women-to-man ratio close to 1:1, with a lower age of onset. It should be noted that our study may not fully represent the entire patient population, given its specific focus on GFAP-IgG myelitis. Approximately 40–66% of the patients featured flu-like symptoms before the onset of neurologic symptoms [6], as consistently evidenced in our cohort. Viral infections may serve as triggers, although the exact direction of this relationship is not yet clear [6, 13]. The spectrum of clinical manifestations, including fever, blurred vision, and neck stiffness, among the 34 patients with GFAP-IgG myelitis was consistent with that reported in prior studies [7]. Whether blurred vision is secondary to optic neuritis remains unclear due to the constraints of our retrospective study. A recent publication highlights that involvement of visual system in GFAP-A is common and heterogeneous,

ranging from asymptomatic bilateral optic disc edema to severe bilateral vision loss, even though optic neuritis is rare [14]. Over 60% of GFAP-A patients with optic disc edema reported no visual symptoms, suggesting that this pathologic feature may be underdiagnosed [14]. This underscores the importance of conducting relevant evaluations, such as fundoscopic examination, even in the absence of visual symptoms. Notably, 15% of the patients experienced abdominal pain or distention. Li et al. emphasized that GFAP is uniquely expressed in enteric glia cells (EGCs), an important component of the enteric nervous system, and that serum GFAP-IgG partly colocalizes with immunoreactivity in the rat small intestine [15]. Therefore, symptoms of abdominal pain or distention may be related to EGC disruption. Our finding provides preliminary support for this hypothesis. In our study, a subset of patients with abdominal pain or distention showed a high prevalence of serum GFAP-IgG positivity. This observation suggests a potential association between serum GFAP-IgG and abdominal symptoms. However, it should be noted that abdominal symptoms could potentially also be caused by sensory disturbance or abnormal perception of the abdomen due to spinal cord injury, and we cannot completely rule out the role of spinal cord injury in causing these symptoms. Further research is needed to determine the exact mechanisms underlying the occurrence of abdominal pain or distention in patients with GFAP-IgG myelitis. Moreover, we found that urinary incontinence or retention and limb weakness were common symptoms in GFAP-IgG myelitis, with 79% of the patients requiring gait aid at attack nadir due to obvious motor deficits.

A substantial proportion of patients with GFAP-IgG myelitis presented with hyponatremia; the underlying mechanism involves inappropriate antidiuretic hormone secretion, as has been emphasized in several studies [16–18]. Notably, Zhang et al. reported three rare cases with overlapping positivity for EBV DNA and GFAP-IgG in CSF; the authors conjectured that viral infection induces astrocyte disruption, resulting in autoantigen exposure and autoimmunity overexpression [19]. Previous studies have revealed that herpes simplex virus I can trigger anti-N-methyl-D-aspartate receptor (NMDAR) autoimmune encephalitis (AE), potentially through mechanisms such as molecular mimicry, protein misfolding, and dysregulation of immune regulators [20, 21]. Evidence of herpes simplex virus infection in patients with GFAP-IgG has also been presented in the literature [22, 23]. Currently, it is unclear whether this is a biphasic disorder—infectious or autoimmune—or whether the infection induces subsequent immune-mediated myelitis, similar to the mechanism observed in anti-NMDAR AE [15, 20, 21]. The specific mechanisms involved warrant further research. Inflammatory changes, including elevated CSF leukocyte counts and total protein levels are now considered a major feature in CSF GFAP-IgG positivity [18], and GFAP-IgG myelitis may be prone to misdiagnosis as CNS infection. According to Liang et al., a mild increase in the CSF leukocyte count combined with a mismatched significant increase in CSF protein content may be among the factors distinguishing GFAP-A from tuberculous meningitis [18]. In contrast, we found that the CSF leukocyte count and protein levels increased significantly in 11 (32%) patients, disproving the above hypothesis. Therefore, testing for the presence of GFAP-IgG in CSF is pivotal for determining TM etiology.

In our study, LETM was common in patients with GFAP-IgG myelitis. The cervical and thoracic spinal cord are susceptible to damage, with two of the 34 (6%) cases involving the conus and approximately 44% of the patients presenting with multiple lesions, consistent with previous research [22]. Among the 17 patients who underwent gadolinium-enhanced examination of spinal cord in this study, 14 showed lesion enhancement. Of these, five patients exhibited enhancement in the central canal with or without linear pia and leptomeningeal enhancement, which was typical of GFAP-IgG myelitis [24]. In the present study, linear perivascular radial gadolinium patterns were present in only two. Perivascular inflammation in autoimmune GFAP-A might account for the typical imaging feature [25]. Remarkably, the occurrence is strikingly low. Given this, it might be crucial to highlight to clinicians that GFAP-IgG myelitis can occur in absence of the characteristic cerebral lesions.

High-dose corticosteroids, IVIG, and plasma exchange are the primary curative modalities in GFAP-IgG myelitis during the acute phase. Long-term treatment includes administration of oral steroids and immunosuppressants. Approximately 70% of patients respond well to steroid therapy, although some are prone to relapse [6, 12]. In this study, most patients recovered well after treatment, and long-term wheelchair dependence was rare. Among the patients who were subsequently readmitted, myelitis episodes were predominant. Currently, a series of observational studies at home and abroad suggest that, although the prognosis varies, outlook is generally good [9, 22, 26–28]. Despite this, the mortality in our cohort was substantial and has seldom been reported to be so high. It is important to mention that patient #1 had a history of Guillain-Barré syndrome (GBS) six months prior to the onset of GFAP-IgG myelitis. Although the EDSS score at admission was not high, the condition of patient rapidly deteriorated. Despite treatment with IVMP and IVIG, the patient ultimately succumbed to respiratory and circulatory failure. It remains elusive whether the activation of the immune system following GBS is related to the onset and rapid progression of GFAP-IgG myelitis. The case highlights that GFAP-IgG myelitis patients

with a prior history of GBS may require more aggressive and individualized treatment strategies. Future research is necessary to explore the immunopathogenesis between these two diseases. Patient #2 was diagnosed with gliomas before the onset of GFAP-IgG myelitis and later died from gliomas. Whether GFAP-IgG is a product of immune response triggered by GFAP expressed in gliomas still needs further investigation. Patient #3 demonstrated improvement in neurological function during hospitalization, as evidenced by a decrease in EDSS score from 4 at admission to 2 at discharge, following treatment with IVMP and IVIG. To prevent relapse, rituximab was subsequently administered. Unfortunately, the patient succumbed to severe pulmonary infection (Fungal pneumonia) three months after discharge. Rituximab, a B-cell depleting agent, has been employed to reduce the risk of relapse in patients with GFAP-A [9, 26]. However, its use in NMOSD has been associated with an increased incidence of infections [29]. This case highlights the importance of infection risk assessment when administering immunosuppressants and emphasizes the need for enhanced precaution action during and after treatment. In addition to the patients previously discussed, three other fatal cases were reported. Despite different EDSS scores at admission, all three patients showed no response to IVMP with or without IVIG. GFAP-IgG myelitis patients usually showed improvement after corticosteroid administration, with low overall mortality [24]; however, these cases indicate a deviation from expected outcomes. The marked deterioration in EDSS scores suggests that initial treatment regimens may not have been sufficient in reversing the progression of disease in these patients.

Despite some shared features, GFAP-IgG myelitis presents distinct differences from AQP4-IgG and MOG-IgG myelitis in terms of clinical presentation, as well as serological and CSF findings. Different from previous studies [30], the proportion of pediatric patients with GFAP-IgG was lower than that in MOG-IgG myelitis. Thus, compared with MOG-IgG, GFAP-IgG myelitis appears to be associated with a notably higher age at onset. The proportion of women with GFAP-IgG was similar to that with MOG-IgG myelitis but significantly lower than that with AQP4-IgG myelitis. Several other features that distinguished GFAP-IgG myelitis from AQP4-IgG and MOG-IgG myelitis including higher frequencies of fever, neck stiffness, and hyponatremia during acute attack, which may be clues for GFAP-IgG detection. Although no difference in the EDSS score at admission was recorded between the three cohorts, more patients with GFAP-IgG myelitis required ICU admission and mechanical ventilation during hospitalization, implying a heavier symptom burden. The higher MLRs, CSF leukocyte counts, and total protein levels indicate a severe inflammatory response, especially in the CNS, which may partly explain the presence of more severe symptoms in the patients with GFAP-IgG myelitis.

Compared to the more circumscribed lesions in AQP4-IgG, spinal cord lesions in GFAP-IgG myelitis typically exhibit longitudinally extensive T2 hyperintensity with less defined edges, and post-contrast enhancement may involve the central canal and present as punctate or leptomeningeal, which are consistent with previous studies [6, 9, 24]. T2 hyperintensity restricted to the spinal cord gray matter ("H sign") has been identified as a radiological feature of MOG-IgG myelitis, which is useful for distinguishing between GFAP-IgG and MOG-IgG myelitis [30, 31]. In our study, the "H sign" was more common in MOG-IgG than in GFAP-IgG myelitis, although it did not reach significance. Additionally, gadolinium enhancement in spinal cord lesions was more prevalent in GFAP-IgG than in MOG-IgG myelitis. Yet, on head MRI, the occurrence of post-gadolinium enhancement in brain lesions among patients with GFAP-IgG was comparable to that detected in patients with MOG-IgG, but notably higher than that in patients with AQP4-IgG myelitis. It is important to note that while four patients with GFAP-IgG myelitis unfortunately died, these extreme outcomes did not significantly affect the median EDSS score at last follow-up. The median EDSS score of 0 at last follow-up reflects that a significant proportion of patients in the three cohorts experienced good recovery from myelitis, likely due to early diagnosis and effective treatment strategies.

However, the retrospective design and varying age and sex distributions in the three cohorts may have influenced the results and are among the main limitations of this study. Specifically, the subgroup with MOG-IgG myelitis appears to be unrepresentatively young, which has major implications for clinical and paraclinical presentation. Another limitation is the absence of concurrent serum glucose levels measurements alongside CSF glucose levels, which hinders the formal assessment of hypoglycorrhachia. Moreover, it is noteworthy that not all GFAP-IgG myelitis patients underwent comprehensive tumor screening during their hospitalization or follow-up, potentially leading to an underestimation of tumor occurrence rates. Multicenter prospective studies with larger sample sizes are warranted to validate our results.

Conclusion

Our study provided evidence of clinical features, radiological findings, and clinical outcomes of GFAP-IgG myelitis and compared key characteristics in myelitis with GFAP-IgG, AQP4-IgG, and MOG-IgG, which may help clinicians to raise awareness of this disease at an early stage.

Abbreviations

AE	Autoimmune encephalitis
AQP4-IgG	Aquaporin-4 autoantibody
CNS	Central nervous system
CSF	Cerebrospinal fluid
EBV	Epstein–barr virus
EDSS	Expanded disability status scale
EGC	Enteric glia cells
GFAP-A	Glial fibrillary acidic protein astrocytopathy
GFAP-IgG	Glial fibrillary acidic protein autoantibody
ICU	Intensive care unit
IQR	Interquartile range
IVMP	Intravenous methylprednisolone
IVIG	Intravenous immunoglobulin
LETM	Longitudinally sagittal t2 lesions
MLR	Monocyte-to-lymphocyte ratio
MRI	Magnetic resonance imaging
NLR	Neutrophil-to-lymphocyte ratio
NMDAR	N-methyl-d-aspartate receptor
TM	Transverse myelitis
MOG-IgG	Myelin oligodendrocyte glycoprotein autoantibody

Supplementary Information

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Supplementary Material 1

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Author contributions
YYX and WZ contributed to the conception, design, and original draft preparation. AH, WS, XZ, YX, YM, and YL were involved in data collection, management, and analysis. CW was responsible for data interpretation and revised the manuscript. NX reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2022-KY-0053). All participants or their parents or guardians supplied informed consent for the use of their data prior to inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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