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ORIGINAL ARTICLE

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Level of CSF CXCL10 is highly elevated and decreased after steroid therapy in patients with autoimmune glial fibrillary acidic protein astrocytopathy

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Abstract

Objectives: To examine the chemokine profile in the cerebrospinal fluid (CSF) of patients with glial fibrillary acidic protein astrocytopathy (GFAP-A), central nervous system immune-related adverse event (CNS-irAE), neurosarcoidosis (NS), neuromyelitis optica spectrum disorders (NMOSD), multiple sclerosis (MS), and human T-cell leukemia virus-1 (HTLV-1)-associated myelopathy (HAM).

Methods: The study included 38 patients presenting to St. Marianna University Hospital between May 2013 and November 2021 with GFAP-A, CNS-irAE, NMOSD, MS, NS, HAM and noninflammatory neurological diseases (NIND). We recorded the age, sex, duration of disease, brain/spinal lesions on magnetic resonance imaging (MRI), blood data, and measured chemokines (CXCL9, −10, −13, CCL3, −4, −17, −20, −22) in CSF. In patients with GFAP-A, clinical symptoms, and CSF CXCL10 levels were compared before and after steroid treatment.

Results: Patients with GFAP-A had higher CSF levels of CXCL10, CXCL13, and CCL22 (10736.1 [8786.7–149079.0] pg/ml ($p < .05$), 378.4 [239.9–412.2] pg/ml ($p < .01$) and 159.9 [130.5–413.9] pg/ml ($p < .01$), respectively). The CSF levels of CXCL10 improved from 10736.1 [8786.7–149079.0] pg/ml to 1879.0 [783.9–4360.0] pg/ml in patients with GFAP-A by steroid therapy.

Conclusion: CSF CXCL10 levels were particularly high in GFAP-A, and changes in levels after treatment correlated with clinical improvements, suggesting CXCL10 involvement in GFAP-A pathogenesis.

KEYWORDS
autoimmune encephalopathy, autoimmune glial fibrillary acidic protein astrocytopathy, C-X-C motif chemokine ligand 10, Luminex

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1 | INTRODUCTION

In the immune system, there are two types of immunity: innate and acquired immunity. Acquired immunity has several subtypes of cellular immunity, depending on the type of helper T (Th) cells and their mechanism of action. Cellular immunity is primarily mediated by Th cells and killer T cells, and Th cells differentiate into Th1 or Th2 cells, depending on the antigen type and the surrounding cytokine environment. Additionally, other important subsets that modulate pathologies, such as regulatory T cells (Treg), Th17 cells, and follicular helper T cells (Tfh), have also been identified in recent years. The balance among these subsets is important for understanding the pathogenesis of immune diseases.[1–4]

Neuroimmunological diseases, such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), neurosarcoidosis (NS), and human T-cell leukemia virus-1 (HTLV-1)-associated myelopathy (HAM), differ in the Th balance and subsequent cytokine cascades that predominate in each disease, and chemokines have been investigated to characterize these diseases. Chemokines are essential for the migration of cells such as leukocytes and lymphocytes to the lesions. Chemokines are classified into four types—CC, CXC, C, and CX3C—according to their cysteine sequences. Chemokines can also identify the type of cells they recruit; thus, it is possible to classify chemokines as Th1-dominant if, for example, CXCL9 and 10 are high, CCL20 as Th17-dominant, and CCL17 and 22 as Th2-dominant. Chemokines have been studied in neuroimmunological diseases, especially in MS, NMOSD, and HAM, and findings indicate that MS is Th1 and 17 predominant,[5–8] and HAM is Th1 predominant.[9–13]

Recently, new concepts of immune-related neurological diseases have emerged, such as autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A)[14–16] and central nervous system immune-related adverse events (CNS-irAE).[17–19] The main cytokine and chemokine cascade of these diseases remains unknown. Therefore, this study investigated chemokine profiles for these diseases to determine which cascade is predominant and elucidate the pathogenesis of these diseases. We also assessed whether the chemokines could serve as markers of therapeutic response.

2 | METHOD

2.1 | Research subjects

This was a retrospective, observational study. The study included 38 patients who visited or were admitted to the Division of Neurology, St. Marianna University Hospital from May 2013 to November 2021, with six neuroimmunological diseases and noninflammatory neurological diseases (NIND) as control. The neuroimmunological diseases included NMOSD ($n = 4$), MS ($n = 13$), HAM ($n = 6$), NS ($n = 3$), GFAP-A ($n = 3$), and CNS-irAE ($n = 3$). The NIND group ($n = 6$) consisted of cortical cerebellar atrophy ($n = 1$), epilepsy ($n = 2$), suspected normal-pressure hydrocephalus ($n = 1$), Wallenberg syndrome ($n = 1$), and spinocerebellar degeneration ($n = 1$). The two epilepsy cases had no immune-mediated background.

All patients were adults (>18 years of age) with a confirmed diagnosis and not using immunosuppressive drugs (oral corticosteroids, steroid pulse therapy, intravenous immunoglobulin, plasma exchange, and other immunosuppressive drugs) at the time of sampling, except one MS and one NS patient.

2.2 | Clinical information collection

The following clinical data were evaluated: age, sex, duration of illness, blood data (WBC, CRP), spinal fluid data (cell count, protein count), modified Rankin Scale (mRS) on admission, and the presence of brain/spinal cord lesions by magnetic resonance imaging (MRI). Clinical information was assessed by two neurologists; specimen collection was performed by one neurologist, and MRI lesion confirmation was evaluated by two neurologists.

For patients with GFAP-A, additional clinical information on Mini-Mental State Examination (MMSE),[20,21] Frontal Assessment Battery (FAB),[22] Glasgow Coma Scale (GCS),[23,24] and mRS scores[25] were evaluated at admission, discharge, and ambulatory care. MMSE was administered to assess cognitive function and FAB was administered to assess executive function. According to Aiello et al., FAB measures verbal (FAB-1) and motor (FAB-2) executive function, as well as inhibition (FAB-3).[22] The level of consciousness was assessed by GCS and ADL was assessed by mRS scores. Evaluation parameters, including GCS, FAB, MMSE, and mRS scores, were obtained retrospectively from the electronic medical record. GCS and mRS scores were assessed by two neurologists, and MMSE and FAB were assessed by a physical therapist and a speech therapist, respectively.

2.3 | CSF chemokine assay

Lumbar puncture was performed during the acute or refractory phase in all patients. In patients with GFAP-A, lumbar puncture was performed prior to initiating therapy and several times after steroid pulse therapy. Polypropylene tubes were used to collect and store CSF. Routine laboratory tests, including cell count, total protein, and IgG levels, were conducted using small quantities of CSF. CSF aliquots were stored in cryotubes at −80°C. The frozen sample stocks were used to perform the tests in this study. CXCL10 was measured with a 20-fold sample dilution using a cytometric bead array (BD Biosciences, San Jose, CA, USA). We measured CSF concentrations of seven chemokines, including CCL3, CCL4, CCL17, CCL20, CCL22, CXCL9, and CXCL13, using Luminex Assay Human Premixed Multi-Analyte Kits (R&D Systems, Minneapolis, MN, USA). Samples were assayed according to the manufacturers' instructions. Fluorescence signals were detected using Luminex 200 xPONENT System (Merck Millipore, Darmstadt, Germany), and the data were analyzed with xPONENT 3.1 (Merck Millipore).

TABLE 1 Patient background for each neuroimmune disease

	GFAP-A	NS	HAM	CNS-irAE	NMOSD	MS	NIND
Number (N)	3	3	6	3	4	13	6
Age	58 [43–69]	66 [59–71]	66 [45–82]	79 [78–82]	52 [33–90]	33 [19–61]	69 [18–76]
Female	0(0%)	1(33.3%)	5(83.3%)	2(66.6%)	3(75%)	8(61.5%)	4(64%)
Disease duration [Y]	0.05 [0.03–1.17]	2.0 [0.28–11.0]	13.0 [0.8–17]	0.05 [0.02–1.13]	0.14 [0.01–0.36]	0.41 [0.02–35.0]	2.43 [0.0–24.0]
CSF cell/mm^3]	36 [10–154]	8 [2–22]	8 [3–17]	8 [3–9]	4 [3–68]	8 [3–9]	1 [<1–1]
CSF protein [mg/dl]	132 [91–256]	75.0 [35–95]	41.0 [23–56.7]	54 [40–733.5]	42.3 [41–149.2]	34.0 [16–61]	30.0 [13–43.8]
Serum WBC [10^3/mm^3]	8.5 [4.6–10.6]	4.7 [3.4–9.9]	5.1 [3.0–5.9]	4.9 [1.9–6.8]	5.2 [3.3–8.3]	5.9 [4.3–11.0]	7.15 [5.5–12.8]
Serum CRP [mg/dl]	1.13 [0.10–2.15]	0.12 [<0.03–0.12]	0.26 [<0.03–0.31]	7.89 [6.52–8.6]	0.15 [<0.03–0.23]	0.08 [<0.03–0.13]	0.15 [<0.03–0.15]
mRS at admission	5 [4–5]	1 [1–2]	2 [2–4]	5 [5–5]	1 [1–4]	1 [0–1]	0 [0–2]

Abbreviations: GFAP-A; autoimmune glial fibrillary acidic protein astrocytopathy, NS; neurosarcoidosis, HAM; HTLV-1-associated myelopathy, CNS-irAE; immune-related adverse events, NMOSD; neuromyelitis optica spectrum disorders, MS; multiple sclerosis; NIND; noninflammatory neurological diseases.

2.4 | Statistical analysis

Clinical data such as GCS, MMSE, and FAB were expressed as mean (±standard deviation) with descriptive statistics; chemokine measurements were compared multiple times by Kruskal–Wallis test and Dunn's post hoc test. Data analysis was performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA.). All p-values were two-sided, and statistical significance was set at <.05.

3 | RESULTS

3.1 | Autoimmune neurological disease and clinical features

The clinical information of 38 patients with six neuroimmunological diseases ($n = 32$) and NIND ($n = 6$) are summarized in Table 1. The duration of illness was very short (0.05 [0.03–1.17] years) in patients with GFAP-A and CNS-irAE and long (13.0 [0.8–17.0] years) in patients with HAM. Blood inflammatory marker concentrations and CSF cell/protein counts did not differ significantly. The mRS scores of patients with GFAP-A and CNS-irAE were high (worse than 5), and that of patients with MS, NMOSD, and NS were low (mRS: 1).

3.2 | CSF chemokine profile of each disease

We compared the levels of CSF chemokines of six neuroimmunological diseases with that of NIND (Figure 1). Patients with GFAP-A had significantly higher CSF levels of CXCL10, CXCL13, and CCL22 (10736.1 [8786.7–149079.0] pg/ml ($p < .05$), 378.4 [239.9–412.2] pg/ml ($p < .01$) and 159.939 [130.5–413.9] pg/ml ($p < .01$), respectively). The CSF levels of CXCL9 was higher in patients with CNS-irAE (1102.746 [793.1–2461.9]), CCL17 was higher in NS patients (556.4 [104.4–707.3] pg/ml), and CXCL10 was higher in HAM patients (6162.2 [4294.5–12628.2] pg/ml). No chemokines showed statistically significant differences in patients with NMOSD and MS. The levels of CXCL10 in the CSF of NIND was 187.6 [92.3–266.0] pg/ml. Levels of all other chemokines were below the limit of quantification. The limit of quantification for CXCL9, CXCL13, CCL3, CCL4, CCL17, CCL20, and CCL22 was 709.1, 16.21, 92.8, 115.4, 104.4, 5.93, and 45.8 pg/mL respectively.

3.3 | GFAP-A symptoms and treatment course

Figure 2 shows the time-course change of clinical symptoms and the levels of CSF CXCL10 before and after steroid treatment in three patients with GFAP-A. After steroid treatment, all the clinical symptoms (GCS, FAB, MMSE, and mRS scores) improved in all three patients. Furthermore, the CSF levels of CXCL10 decreased from 10736.1 [8786.7–149079.0] pg/ml to 1879.0 [783.9–4360.0] pg/ml (on days 36, 79, and 40 from the first day of steroid pulse therapy), but not to the levels of NIND (187.6 [92.3–266.0] pg/ml). To note,

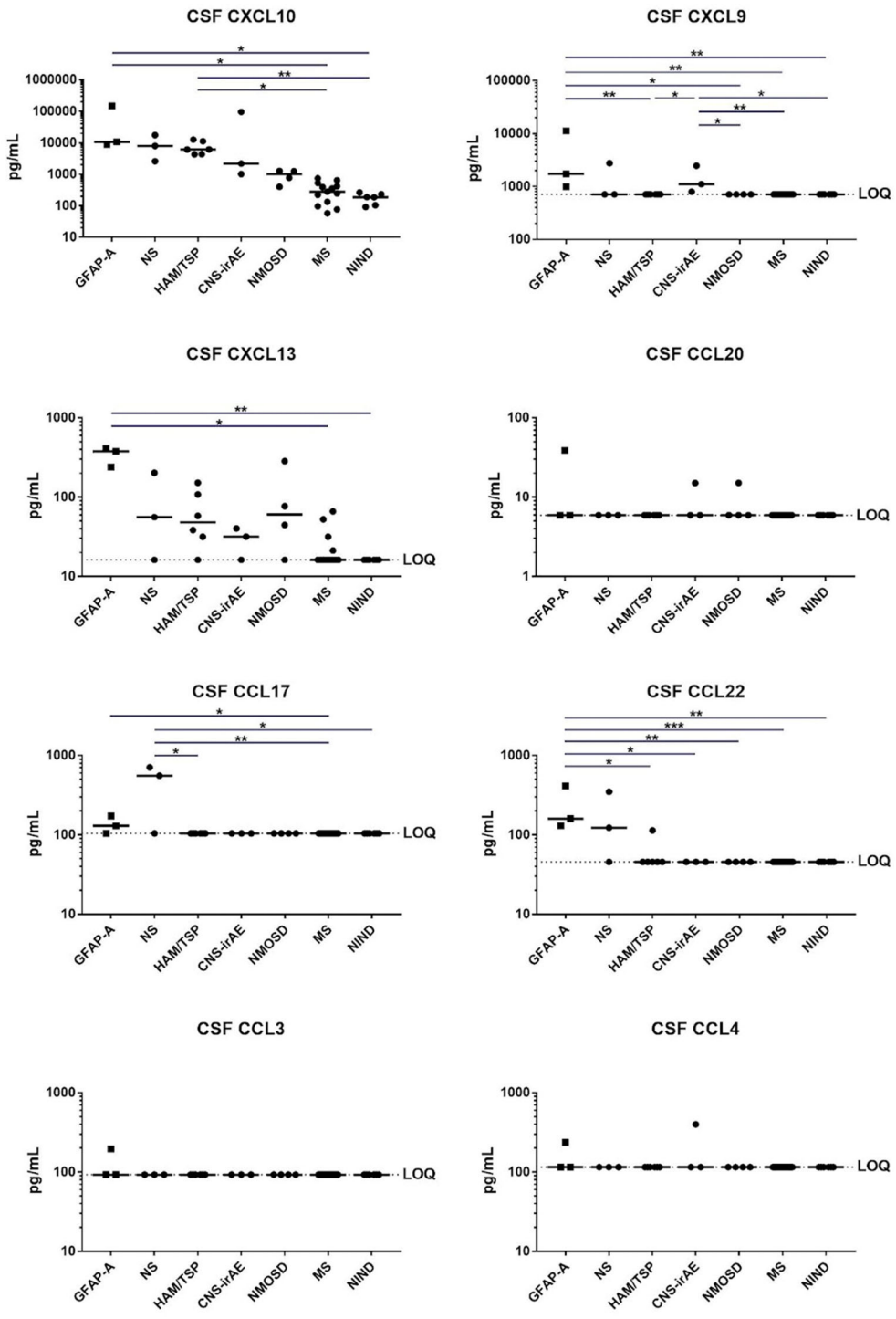


FIGURE 1 CSF chemokine levels in the patient with neuroimmunological disorders. Each of the eight CSF chemokines (CXCL10, CXCL9, CXCL13, CCL20, CCL17, CCL22, CCL3, and CCL4) was compared among seven patient groups [GFAP astrocytopathy (GFAP-A), $n = 3$; neurosarcoidosis (NS), $n = 3$; HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM), $n = 6$; immune-related adverse events with CNS symptoms (CNS-irAE), $n = 3$; neuromyelitis optica spectrum disorders (NMOSD), $n = 4$; multiple sclerosis (MS), $n = 13$; noninflammatory neurological diseases (NIND), $n = 6$]. Horizontal bars indicate the median values. Statistical analysis was conducted using the Mann–Whitney *U*-test. The *p*-value was determined using the Kruskal–Wallis test followed by Dunn's post hoc test with Prism 7 software. ***$p < .001$, **$p < .01$, *$p < .05$. LOQ = limit of quantification.

CSF CXCL10 levels decreased before the improvement of clinical symptoms in cases 1 and 2.

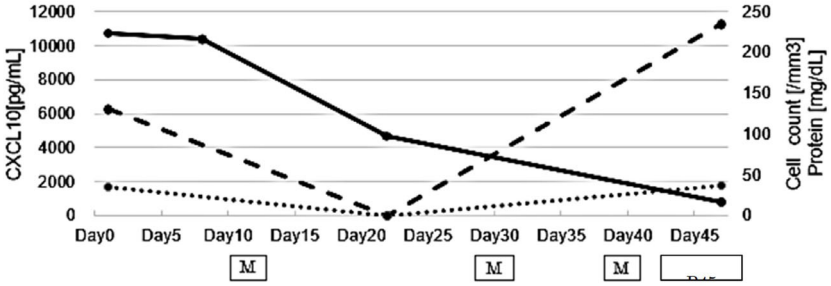
4 | DISCUSSION

We estimated the predominant cascade of GFAP-A and CNS-irAE by examining the chemokine profile of CSF. In this study, the chemokine profile demonstrated the following: CNS-irAE as Th1-predominant diseases as reported previously.[9–13,26] GFAP-A was the first to demonstrate a predominance of Th1 + Tfh/B cells, suggesting that cellular immunity is important in its pathogenesis. While previous reports reported high CSF CCL20 levels[27] and low CSF CXCL1, CXCL5, and CXCL7 levels,[28] the present study is the first to describe the chemokine profile (high levels of CXCL9, CXCL10, CXCL13, and CCL22) of GFAP-A.

Among the neuroimmunological diseases in this study, GFAP-A showed a characteristic chemokine profile. GFAP-A has been recently

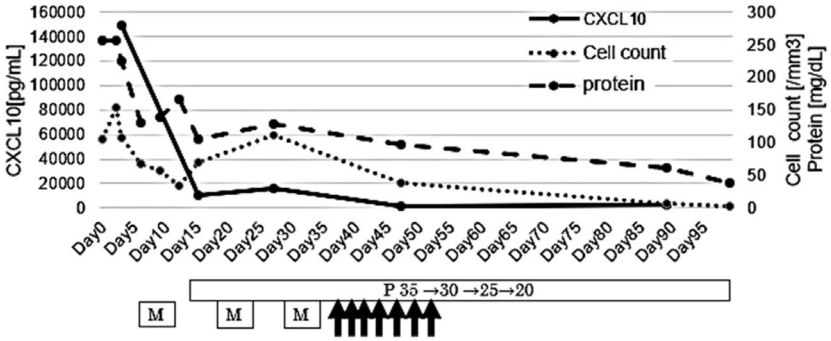
FIGURE 2 The clinical course of the GFAP-A cases. The clinical course of the GFAP-A case is shown. In three cases, improvements in CXCL10, consciousness disorder, and cognitive impairment were observed, in that order, after steroid therapy. As for steroids, the patients were also administered orally as maintenance therapy after the steroid pulse. Steroid doses were tapered according to the symptoms. The following should be noted. In case 1, a reincrease in cell count and protein was observed on day 47, but the clinical symptoms clearly showed a tendency to improve, and because the patient was positive for occult blood, it was considered to be influenced by occult blood.

Case 1



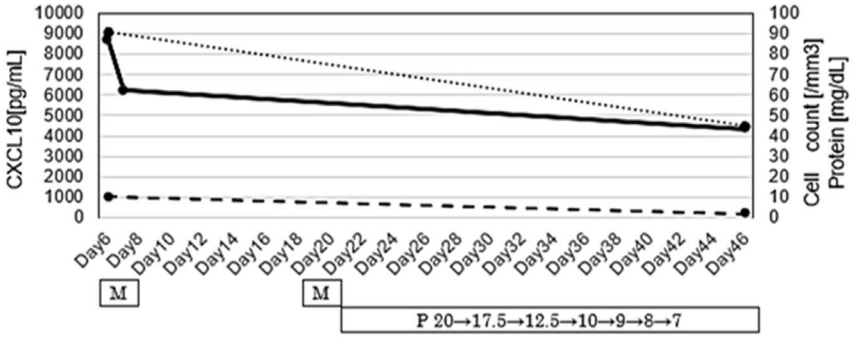
GCS	E4V3M5	E4V4M5	E4V4M6
FAB	Unmeasurable	Unmeasurable	6
MMSE	0	12	20
mRS	5	No data	3

Case 2



GCS	E4V4→2M6→4	E4V4M6	E4V5M6	E4V5M6
FAB	Unmeasurable		16	18
MMSE	Unmeasurable		no date	>20*
mRS	4		no date	3 2

Case 3



GCS	E4V2M5	E4V4M5	E4V5M6
FAB	Unmeasurable	no date	no date
MMSE	4	14	23
mRS	5	3	2

proposed to cause autoimmune meningoencephalitis and encephalomyelitis.[14–16] GFAP is one of the intermediate filaments abundantly expressed in astrocytes. This autoantibody (anti-GFAP antibody) is positive for GFAP-A. GFAP-A is difficult to diagnose, even with pathologic findings. Given the lack of guidelines for GFAP-A diagnosis, the measurement of CSF anti-GFAP antibodies is essential, but they could represent only an immunologic epiphenomenon rather than the nature of the disease, and the pathogenesis is not fully understood.[14–16,27,29–33] The chemokine profile of GFAP-A provides insight into the pathogenesis of the disease. In this study, CSF levels of CXCL9 and CXCL10 were elevated, indicating a Th1-predominant cascade. Kimura et al. reported elevated CCL20 in CSF,[27] but in this study there was no significant increase in CCL20 compared to controls, possibly because the sample size was small. CCL3 and CCL4 levels did not differ significantly from the control group. Furthermore, CCL17 was not elevated, but CCL22 was elevated, suggesting a small involvement of Th2/Treg cells. These results revealed that the pathogenesis of GFAP-A is predominantly Th1 + Tfh/B-cell and that Th2/Treg is involved in the pathogenesis. This cascade is consistent with the hypothesis that the antibody is not pathogenic because GFAP is present in astrocytic glial cells and that GFAP-specific CD8 + T lymphocytes are activated to produce an inflammatory state.[14–16,27,29–31] Although the significance of anti-GFAP antibodies on the Th1-dominant chemokine production observed in GFAP-A is still unknown, a T-cell-mediated inflammatory pathology may be involved.[14–16,27,29–35] The chemokine profiles in this study suggest that CXCR3 ligand interactions may be important in the pathophysiology of GFAP-A. Recent findings show that some neurological diseases are related to CXCR3 ligand interactions, which are pivotal in their pathogenesis.[9,12] Further evidence that CXCR3+ cells predominantly infiltrate the spinal fluid or CNS lesions in GFAP-A patients, with a trend toward elevated levels of Th1-dominant chemokines, may indicate that GFAP-A is a Th1-type cell-mediated inflammatory disease. As the present study did not examine the presence or absence of CXCR3 expression, further investigation is required. Therefore, future studies on the significance of these interactions in the pathogenesis of GFAP-A are important to clarify the suitability of CXCL10 as a biomarker or therapeutic target.

CXCL10 levels >10 000 pg/mL in GFAP-A suggests that CSF CXCL10 may be a clinically useful biomarker of GFAP-A, as reported in HAM that correlates with disease activity, treatment response, and treatment prediction, as well as functional prognosis.[9–13] Although GFAP-A is rare, many patients have shown improvement in symptoms and decreased recurrence rates with steroid therapy, like other astrocytopathies, such as NMOSD.[15] In this study spinal fluid CXCL10 levels in patients with GFAP-A decreased before the improvement of GCS, MMSE, and FAB, and later ADL in all three patients (Figure 2). Treatment efficacy has been often determined by symptomatic improvement or resolution/improvement of lesions based on imaging, and there was no biomarker such as CXCL10. The results of the present study highlight the potential of CXCL10 as a measure of treatment efficacy in GFAP-A. To the best of our knowledge, this is the first study that reported on the reduction in CXCL10 levels after treatment. However, other chemokines such as CXCL9, CXCL13, and CCL22, which were increased in the CSF of GFAP-A patients, are also possible to decrease by steroid therapy. The longitudinal data of the changes of these chemokines including CXCL10 is necessary in a future study.

Although many patients with GFAP-A respond to steroid therapy, 20%–50% of cases recurred, with some cases showing poor prognosis or serious sequelae.[34,36] Current therapies for refractory and relapsed cases include mycophenolate mofetil, azathioprine, rituximab, and cyclophosphamide.[34] While the treatment response to the steroid is good in the early phase of the disease, early intervention and accurate evaluation of treatment efficacy are necessary, because patients who start treatment late may have sequelae and, in some cases, relapse or recurrence.[14–16] The remaining high level of CSF CXCL10 after steroid treatment compared with that of NIND may suggest that steroid therapy only is not adequate for these GFAP-A patients. It would be important to clarify whether additional immunosuppressive treatment would be necessary for these patients in a future study.

This study was limited by the minimal sample size as a result of the rarity of neuroimmunological diseases. Nevertheless, this study provides some important findings and challenges important for clinical care. Future studies in larger populations are needed.

Chemokine profiles can be analyzed in neuroimmunological diseases to elucidate the pathology and discover biomarkers. In this study, CSF CXCL10 levels were particularly high in GFAP-A among six neuroimmunological diseases, and changes in levels before and after treatment correlated with clinical outcomes. CXCL10 may be involved in the pathogenesis of GFAP-A.

AUTHOR CONTRIBUTIONS

TK, TS, KI, and YY contributed to the conception and design of the study; TK, TS, KI, and YY conducted the statistical analysis; TK, TS, KI, and YY analyzed and interpreted the results; TK, TS, KI, and YY drafted the article; and TK, TS, KI, and YY critically revised the article. All authors read and approved the final article.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DISCLOSURE OF ETHICAL STATEMENTS

Approval of the research protocol: The protocol for this research project was approved by the Institutional Review Board of St. Marianna University School of Medicine (#4983, #1646), and it conforms to the provisions of the Declaration of Helsinki.

Informed Consent: All informed consent was obtained from the subjects.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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