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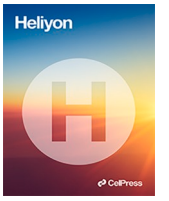

Case report

Glial fibrillary acidic protein astrocytopathy presented as meningitis: A case report

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ABSTRACT

Introduction: Glial fibrillary acidic protein (GFAP) astrocytopathy is a novel autoimmune neurological disorder and is diagnosed by GFAP-IgG in cerebrospinal fluid (CSF) measurement.
Case report: Herein, we described a 10-year-old boy with abnormal neurological symptoms and signs. GFAP-IgG was detected in CSF using cell-based assay (CBA), and his CSF showed an increase in lymphocytes, a slight decrease in glucose and an increase in protein level in the early stage. The cranial MRI showed multiple strips of T2-FLAIR hyperintense signal changes on the surface of medulla oblongata, pons, and gyrus in bilateral cerebral hemispheres. He was treated with immunoglobulin (IVIG) and high-dose methylprednisolone pulse treatment, and his clinical presentations gradually improved.
Conclusion: We highlight that patients with normal inflammatory markers in peripheral blood have obvious meningitis-like symptoms, and clinicians need to consider GFAP astrocytopathy. The early diagnosis and treatment of GFAP astrocytopathy are important for improving the prognosis.

1. Introduction

Glial fibrillary acidic protein (GFAP) is a major component of intermediate filament expressed in the cytoplasm of mature astrocytes, and plays a crucial role in formation of blood-brain barrier (BBB), the morphology and motility of astrocytes, and the regulation of synaptic functions [1]. GFAP astrocytopathy is a novel autoimmune neurological disorder which was first defined in 2016, and is diagnosed by measuring GFAP-IgG in cerebrospinal fluid (CSF) using cell-based assay (CBA) and/or tissue-based assay (TBA) [2,3]. GFAP astrocytopathy clinically resembles acute or sub-acute onset meningoencephalitis with or without spinal cord involvement, and meningoencephalitis is the predominant presentation in currently reported publications. The main clinical symptoms are fever, headache, psychosis, ataxia, vision abnormality, epilepsy, encephalopathy and myelitis and so on. Its characteristic inflammatory changes in CSF are lymphocytosis, slight decrease of glucose and increase of protein level, while the radiological sign of cerebral magnetic resonance imaging (MRI) is significant perivascular radial gadolinium enhancement. Immunotherapy is effective for this disorder, including corticosteroids, intravenous immunoglobulin, and immunosuppressants [4–6].

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Herein, we reported a ten-year-old boy with symptoms of fever, headache, vomiting, lethargy, blurred vision who was initially suspected of infectious meningitis. We detected GFAP-IgG in CSF by CBA, and finally diagnosed it as GFAP astrocytopathy. After intravenous injection of immunoglobulin and corticosteroid, the symptoms sustained improve.

2. Methods

We measured immune antibodies using CBA, and collected 5mL peripheral blood and 2mL CSF from the subject. The separated serum was used to incubate HEK293 T cells on a glass slide in a humidification chamber for 10min at room temperature. The slides were washed three times in phosphate-buffered saline (PBS) and incubated with anti-human IgG-fluorescein isothiocyanate (FITC) fluorescence secondary antibodies for 30 min at room temperature for 30min. After washing three times in PBS, the slides were observed under fluorescence microscopy.

3. Case report

The patient was a 10-year-old boy from China, who was the first and the only baby of his healthy, young and unrelated parents. No family history of similar problems was presented. The patient presented with headache, fever and vomiting at onset. He took medicine by himself for 3 days and was admitted to the local hospital without improvement. He performed a series of auxiliary examinations in the local hospital. There was no obvious abnormality in the etiology and MRI, but his CSF showed an increase in lymphocytes (WBC: range from 60 to 360 $\times$ 10^6/L; lymphocyte percentage: from 90% to 98%), a slight decrease in glucose (range from 2.04 to 2.62mmol/L, normal: 2.5–4.4mmol/L), and an increase in protein level (range from 0.94 to 1.57g/L, normal: <0.45g/L). They gave antibiotics (meropenem, 120mg/kg/d; vancomycin, 60mg/kg/d) and antiviral drugs (acyclovir, 30mg/kg/d) in consideration of intracranial infection, but the clinical therapeutic effect was unsatisfactory.

On day 10, he was transferred to our facility for further treatment. At that time, his main symptoms were fever, headache and vomiting. Neurological examinations were notable for neck stiffness, hyperreflexia of knee tendon, positive finger-nose test, positive Babinski and Kernig sign. Then the patient underwent a thorough examination in our hospital, including routine laboratory tests (including routine blood, *C*-reactive protein, coagulation tests, and liver and renal function tests), etiological detection and imaging inspections. A serum viral assay of Epstein-Barr virus (EBV) revealed the presence of EBV-capsid antigen (CA)-IgG, EBV-CA-IgM and EBV-nuclear antigen (NA)-IgG, and other pathogens (HSV 1 and 2, MP, CP, TB, PPD, G test, GM test, bacterial culture) were negative in serum. The cranial MRI showed multiple strips of T2-FLAIR hyperintense leisons (Fig. 1A) and enhancement (Fig. 1B) on the surface of medulla oblongata, pons, and gyrus in bilateral cerebral hemispheres. According to his clinical manifestations and examinations, bacterial and tuberculous meningitis couldn't be ruled out, so antibiotics (meropenem, 120mg/kg/d; vancomycin, 60mg/kg/d) and symptomatic therapies were given empirically.

On day 13, his temperature was normal, but he still had headache, vomiting, and new symptoms of ataxia. He developed drowsiness and confusion and gradually worsened on day 14. Combined with his whole medical history, immune diseases of the central nervous system (CNS) cannot be excluded. Therefore, we performed electroencephalogram (EEG), lumbar puncture,

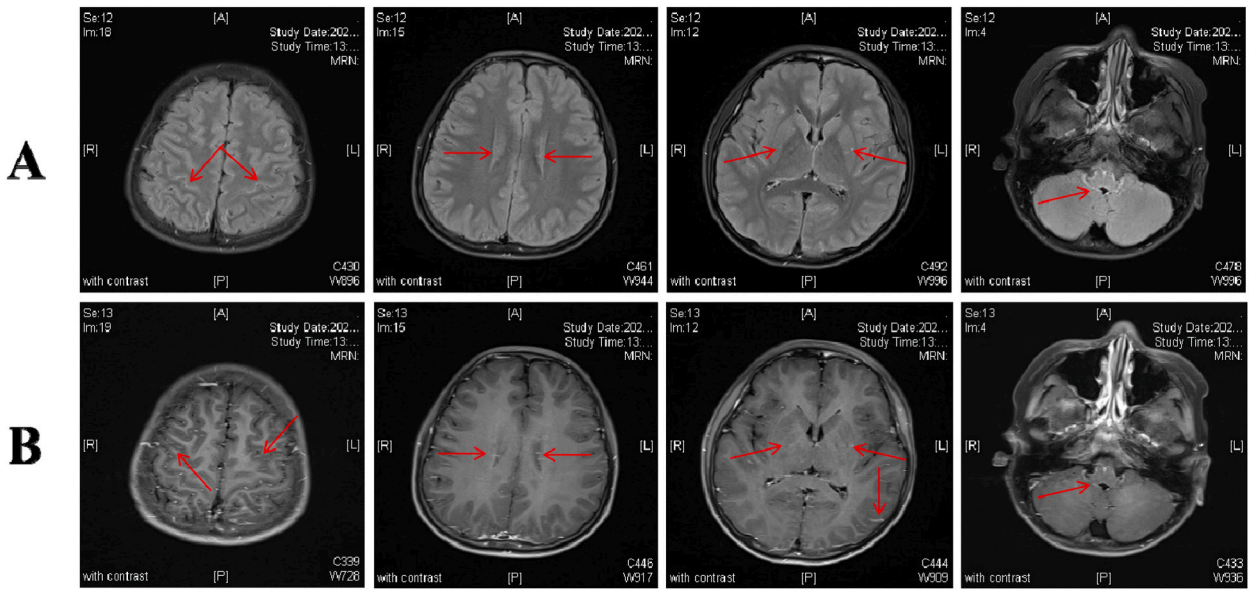

Fig. 1. Representative image of cranial MRI. (A) MRI images of the brain on the 11th day of onset.
The cranial MRI showed multiple strips of T2-FLAIR hyperintense leisons on the surfaces of medulla oblongata, pons, and gyrus in bilateral cerebral hemispheres. (B) Linear enhancement was shown on enhanced cranial MRI.

immunological and pathogenic examination of CSF. EEG showed diffuse slow background across all leads (Fig. 2A). The trend of cell counts and protein content in CSF were shown in Fig. 2B, and the next generation metagenome sequencing of viral and bacterial genomes was negative in CSF. It was very likely that immune neurological disorders would be considered. Then he was treated with one course of intravenous immunoglobulin (IVIG) therapy (20g each time for 3 consecutive days) on day 16. Over the course of several days, his symptoms were relieved, but he still had mild headache and ataxia.

He appeared blurred vision on day 18, and we conducted an ophthalmological examination. Fundoscopy revealed optic disc edema, which returned to normal after 1 week of treatment (Fig. 2C). We detected GFAP-IgG in patient's CSF (titer is 1:10) (Fig. 2D) and he was diagnosed as GFAP astrocytopathy on the 19th day. He received high-dose methylprednisolone pulse therapy (500mg for 4 consecutive days, 3 cycles) and then followed by an initial 45mg/d prednisone orally during the intermittent period. His symptoms and signs were getting better gradually, and cranial MRI was normal after 3 weeks of treatment. Considering that GFAP is often accompanied by other autoimmune antibodies, we tested antibodies of CSF (including AQP4, MOG, MBP) or serum (including GFAP, NMDAR, paraneoplastic antibodies), and the results were negative. Up to the present follow-up of 8 months, low-dose prednisone acetate is still being maintained.

4. Discussion

Autoimmune GFAP astrocytopathy is a novel autoimmune neurological disorder first described in 2016 that is mainly presented as meningoencephalitis with or without myelitis. Currently, there is no definite diagnostic criteria for autoimmune GFAP astrocytopathy, and its diagnosis mainly depends on the detection of GFAP-IgG in CSF by CBA and/or TBA. According to the published literature [7–9], the diagnosis of GFAP astrocytopathy is mainly based on the following factors: (1) initial clinical symptoms resemble those of meningitis; (2) exclude other diseases, especially infectious diseases; (3) expression of GFAP-IgG in CSF which is specific for the diagnosis; (4) corticosteroids therapy is effective.

In the present study, the case started with symptoms of fever, headache and vomiting; physical examination showed stiff neck, positive Babinski sign and Kernig sign, which were all manifestations of meningitis. In addition, his CSF showed increased lymphocytes, slightly decreased glucose, and elevated protein level; cranial MRI showed significant enhancement, especially in the base of the skull and the meninges and so on. These clinical symptoms and related auxiliary tests supported the diagnosis of meningitis, especially tuberculous meningitis, and this explained why he was originally diagnosed with infectious meningitis. Previous studies have shown that 15% of patients with fever and headache as the main symptoms have viral meningitis, while patients with fever, headache and

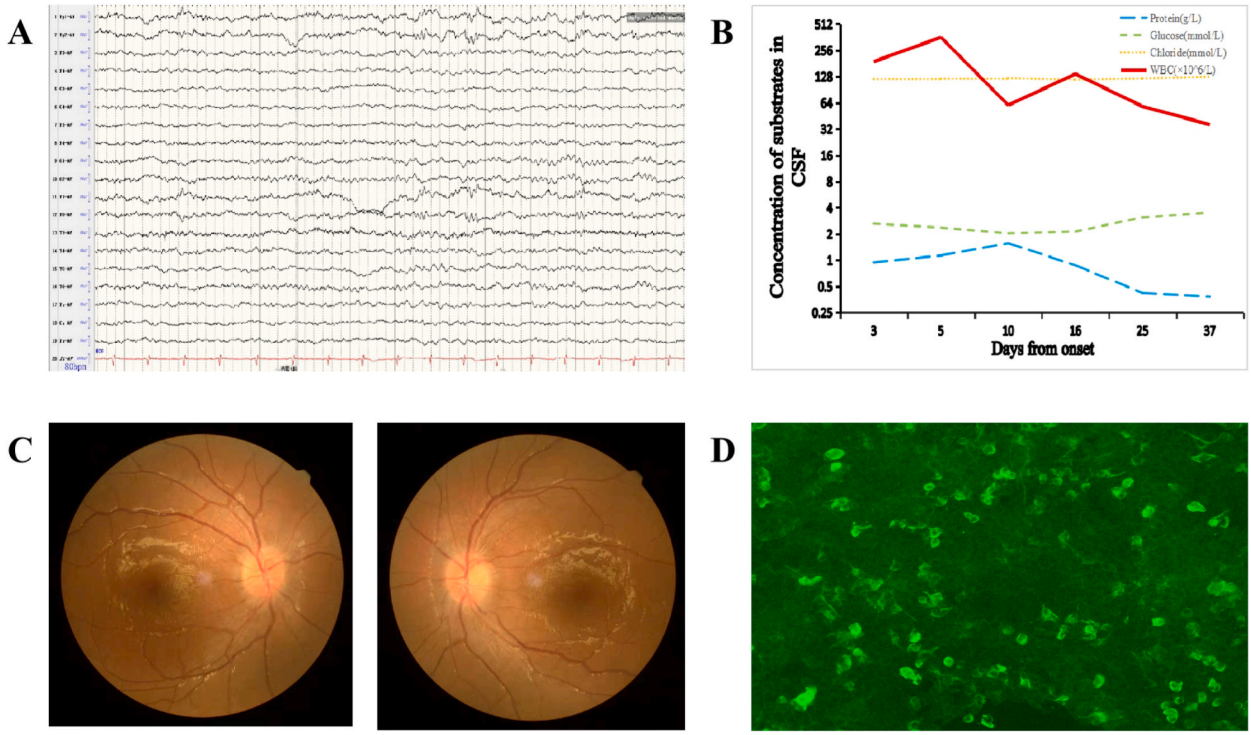

Fig. 2. Clinical laboratory and imaging evaluations of the patient. (A) Imaging of EEG. It showed diffuse slow background. (B) Changes in the concentration of each substrate in CSF at different times. When antibiotics were used only, although the number of cells decreased, the protein showed a progressive increase trend. When intravenous immunoglobulin (IVIG) and high-dose methylprednisolone were given, the number of cells and protein decreased progressively. (C) Fundoscopy pictures of patient. It revealed optic disc edema when he developed blurred vision. (D) Representative images of GFAP -IgG in CSF using CBA. We detected GFAP -IgG in CSF with a titer of 1:10.

neck stiffness are more likely to have bacterial meningitis [7,10]. Despite his symptoms, we finally excluded TBM on the basis of the following aspects: (1) the child had an acute onset and no history of fever, night sweats, or repeated cough. (2) all etiological detection about TB were negative, including T-SPOT of serum, PPD test, acid-fast staining and next-generation metagenomic sequencing analysis of CSF. (3) patient had no history of exposure to tuberculosis.

We summarized the results of laboratory and auxiliary examinations in this patient. Regarding etiological testing, we found EB virus infection, but the association between virus infection and GFAP astrocytopathy was not yet clear. At present, some studies had reported that GFAP astrocytopathy may co-exist with HSV or EB virus infection [11,12]. They speculated that viral infection might trigger the inflammation-mediated autoimmune response of the host, leading to the onset of GFAP astrocytopathy. Wu et al. found that about 80% (25/31) of patients had diffuse slow waves [13]. Our patient's EEG showed diffuse slow background, which was in accordance with their research. Most importantly, we only detected GFAP-IgG in CSF. Previous studies showed that GFAP astrocytopathy patients often co-existed with other autoimmune antibodies. The most common is NMDAR, AQP4 abd MOG, which indicated the presence of autoimmune encephalitis and demyelinating disease [1]. Yang et al. demonstrated that 11 of 35 patients (31.4%) had one or more antibodies in the blood or CSF in Chinese children, whereas 40% in Mayo Clinic [3,13]. Flanagan et al. reported that 35 of 102 patients (34%) had neoplasia, and 66% of the tumors were detected within 2 years of symptom onset, including ovarian teratoma, adenocarcinoma, and glioma [3,14]. However, no co-existing antibodies and tumors were found in our case.

CSF in the early stage of this case showed that lymphocytes increased, glucose decreased slightly, and protein level increased. The cranial MRI showed abnormal changes in the surface of medulla oblongata, pons and gyrus in both hemispheres. These clinical presentations of our case were consistent with the following studies. Some researches had found that most patients had inflammatory changes in CSF. Among them, McKeon et al. demonstrated that 90% had a lymphocyte-predominant elevation in white blood cells, 80% had elevated protein [1,3]. The most characteristic alterations of brain were linear perivascular radial gadolinium enhancement in the white matter perpendicular to the ventricle, which was observed in the Mayo Clinic [3]. Furthermore, more and more studies have had similar neuropathological findings, that is, inflammations (infiltration of lymphocytes, monocytes, and neutrophils), particularly around microvasculars. Long et al. conducted brain biopsies in patients and demonstrated that perivascular inflammation was encountered in the tissue ($CD3^+$ and $CD4^+$ T cells cuffing around brain vessels, accompanied by $CD8^+$ T cells $CD20^+$ B cells and CD138+ B cells) [15]. They also observed that $CD8^+$ T cells were frequently found adjacent to neurons and astrocytes [16]. Iorio et al. discovered inflammatory changes in local tissues with infiltration of macrophages and $CD8^+$ T cells in a patient's leptomeningeal biopsy specimen [17]. Additionally, GFAP specific cytotoxic $CD8^+$ T cells were involved in mediating GFAP in a transgenic mouse model of autoimmune GFAP meningoencephalitis, and avoided tolerance mechanisms before entering into the CNS [18]. Immune-mediated astrocyte dysfunction may be mainly due to the following two reasons: (1) The release of chemokines and subsequent recruitment of inflammatory cells, which further destroys brain tissue structure; (2) The presence of plasma membrane protein-directed IgG which has not been found, can trigger primary autoimmunity and destroy the function of astrocytes, while GFAP autoimmunity is a secondary phenomenon. But up to now, the specific mechanism is unknown. Taken together, the evidence suggested that T-lymphocyte-mediated immune responses play a crucial role in GFAP astrocytosis. We hypothesized that EB virus destroys the BBB and triggers an immune response in the host, which in turn attacks immune cells that release inflammatory cytokines or chemokines to further recruit inflammatory cells, which contributes to the development of GFAP astrocytosis. This may lead to an increase in the number of cells in CSF, the alteration of brain MRI, and the production of antibodies. The above hypothesis needs to be further clarified and confirmed experimentally.

There is no standard treatment for GFAP astrocytopathy as so far. During the acute phase, the therapy mainly includes high-dose corticosteroids, IVIG, and plasma exchange. Clinical and radiological signs would be rapidly improved upon treatment with corticosteroids. Approximately 20–50% of patients will relapse and require more prolonged treatment [1,6]. Our patient was treated with one course of IVIG and high-dose methylprednisolone pulse treatment, and then took prednisolone orally during the intermission. After treatment, he basically recovered to his baseline. Up to the present follow-up, he has not relapsed and the prednisone is currently being tapered. Our treatment may reduce the recurrence rate, but more evidence is needed. In addition, this study had some limitations. First, our sample number is too small, we only have one case. Second, we did not investigate the hypothesis we proposed. Further research is needed to fully understand the pathological mechanism of GFAP astrocytopathy.

5. Conclusion

In summary, autoimmune GFAP astrocytopathy is a novel and corticosteroid-responsive neurological disorder mainly presented as meningoencephalitis with or without myelitis. What we want to emphasize is that patients with normal inflammatory markers in peripheral blood have obvious meningitis-like symptoms, and clinicians need to consider GFAP astrocytopathy. The early diagnosis and treatment of GFAP astrocytopathy is of great significance to improve prognosis.

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of Shandong Provincial Hospital, the patient and his parents had signed written informed consent.

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Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Ya Guo: Writing – review & editing, Writing – original draft, Software. **Jiamin Guo:** Writing – review & editing, Formal analysis, Data curation. **Xueyu Wang:** Data curation. **Aihua Ma:** Formal analysis, Data curation. **Yuxing Gao:** Formal analysis, Data curation. **Jiacheng Chen:** Investigation, Data curation. **Cuili Nie:** Software. **Na Chen:** Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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