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Case Report

Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy Presenting with Area Postrema Syndrome-like Symptoms without Medulla Oblongata Lesions

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Short Title: Autoimmune glial fibrillary acidic protein astrocytopathy

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Abstract

Introduction: Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a recently described steroid-responsive meningoencephalomyelitis positive for cerebrospinal fluid (CSF) anti-GFAP antibody. Area postrema syndrome (APS) involves intractable hiccups, nausea, and vomiting, which is caused by medulla oblongata (MO) impairment. APS is a characteristic symptom of aquaporin-4 (AQP4) autoimmunity, and it helps to differentiate between AQP4 and GFAP autoimmunity. Conversely, although six cases of autoimmune GFAP astrocytopathy with APS and MO lesions have been reported, the association between GFAP autoimmunity and APS is unclear. We report the case of a patient with autoimmune GFAP astrocytopathy presenting with APS-like symptoms without MO lesions and discuss the mechanisms underlying the symptoms.

Methods: CSF anti-GFAP antibody was detected using cell-based assays and immunohistochemical assays.

Results: A 54-year-old Japanese man developed persistent hiccups, intermittent vomiting, fever, anorexia, and inattention. Brain magnetic resonance imaging (MRI) showed periventricular lesions with radial linear periventricular enhancement, suggesting autoimmune GFAP astrocytopathy. However, no obvious MO lesions were identified on thin-slice images. Spinal cord MRI revealed hazy lesions with patchy enhancement along the cervical and thoracic cord. CSF analysis demonstrated inflammation, with positive results for anti-GFAP antibodies. Anti-AQP4 antibodies in the serum and CSF were negative. Esophagogastroduodenoscopy revealed gastroparesis and gastroesophageal reflux disease, and vonoprazan, mosapride, and rikkunshito were effective only against persistent hiccups. Steroid therapy was initiated, allowing clinical and radiological improvements. Repeated MRIs demonstrated no obvious MO lesions.

Conclusion: This report suggests that autoimmune GFAP astrocytopathy presents with APS-like symptoms without obvious MO lesions. The possible causes of hiccups were gastroparesis and cervical cord lesions. Gastroesophageal reflux disease was not considered a major cause of the hiccups. Intermittent vomiting appeared to be associated with gastroparesis, cervical cord lesions, and viral-like symptoms. Testing for anti-GFAP antibodies should be considered in patients with APS-like symptoms in the context of typical clinical-MRI features of autoimmune GFAP astrocytopathy.

Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a recently described steroid-responsive meningoencephalomyelitis (or limited forms thereof) characterized by positivity for anti-GFAP antibodies in the cerebrospinal fluid (CSF) [1-3]. Magnetic resonance imaging (MRI) frequently shows a linear perivascular enhancement radially oriented around the ventricles, and longitudinally extensive lesions in the spinal cord (spanning >3 contiguous vertebral body segments) [2, 3]. To date, more than 300 cases have been reported [3].

The area postrema (AP) is an emetic reflex center located at the caudal end of the fourth ventricle at the junction of the medulla oblongata (MO) and spinal cord [4]. Impairment of the AP, nucleus tractus solitarius, and reticular formation, which are in the MO, can cause intractable hiccups, nausea, and/or vomiting, which define an area postrema syndrome (APS) [5, 6]. APS is one of the core clinical characteristics of anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD) [7]. A total of 8.9%-43% of cases experienced APS at some point during the disease course [8-10], 7.1%-15.9% at disease onset [9-12]. APS is also encountered in anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, although it is less frequent and less typical than that in anti-AQP4 antibody-positive NMOSD [10, 13, 14]. In a comparative study of patients with myelitis associated with anti-AQP4 vs GFAP antibodies, APS was more common in patients with anti-AQP4 antibodies [15]. However, APS has been reported in patients with autoimmune GFAP astrocytopathy and MO lesions, which may lead to diagnostic uncertainty [16-21].

Herein, we report the case of a patient with autoimmune GFAP astrocytopathy presenting with APS-like symptoms without any obvious MO lesions.

Materials and Methods

CSF anti-GFAP antibody testing was performed using a cell-based assay (CBA) and immunohistochemical assay according to the methods outlined in a previous study [22].

Results

A 54-year-old Japanese man with a history of hypertension was admitted with anorexia and inattention for 1 month and hiccups for 3 days. The patient had no prior infections or vaccinations. Neurological examination revealed disorientation, bilateral spasticity in the lower limbs, hyperreflexia in all limbs, and bilateral positive Chaddock's sign but negative meningeal signs.

Ophthalmological examination revealed bilateral optic disc edema and mild vitritis. After admission, he developed fever and intermittent vomiting. His hiccups were not remitted by metoclopramide or chlorpromazine. Brain MRI revealed multiple periventricular fluid-attenuated inversion recovery (FLAIR) lesions with radial linear periventricular enhancement. There were no obvious MO lesions identified on thin-slice brainstem images (slice thickness, 3.0 mm; slice gap, 0.3 mm). Spinal cord MRI revealed hazy, centrally-located T2 lesions with patchy enhancement along the cervical and thoracic spinal cord (Fig. 1). Blood tests showed weakly positive results for antinuclear antibody (1:40) but negative results for anti-thyroid antibodies, anti-AQP4 antibody (CBA), anti-MOG antibody (CBA), anti-glutamic acid decarboxylase antibody, and bacteria. CSF examination revealed increased intracranial pressure (270 mmH_2O), pleocytosis (74/μL, lymphocytes 72/μL), elevated protein levels (118 mg/dL), and positive oligoclonal bands but negative results for anti-AQP4 antibody (CBA), anti-*N*-methyl-D-aspartate receptor antibody, bacterial and fungal cultures, acid-fast staining, β-D-glucan, cryptococcal antigen, herpes simplex virus DNA, varicella zoster virus DNA, and cytology. Whole-body computed tomography and gallium scintigraphy findings were normal.

Esophagogastroduodenoscopy showed gastroesophageal reflux disease and retention of stomach contents after an overnight fast, suggesting gastroparesis. Thereafter, vonoprazan, mosapride, and rikkunshito were started, and the hiccups resolved. We diagnosed the patient with encephalomyelitis of unknown etiology and started intravenous methylprednisolone (IVMP, 1 g for 3 days), followed by oral prednisolone (PSL). After three rounds of IVMP and 4 weeks of oral PSL, his disorientation, fever, anorexia, and intermittent vomiting were remitted. On brain MRI, the periventricular FLAIR lesions shrank, and the enhancement disappeared. The spinal cord lesions were also resolved. Repeat CSF analysis confirmed the increased intracranial pressure with resolution of the inflammatory findings (white blood cell count, 19/μL; protein levels, 44 mg/dL; oligoclonal bands not retested). Anti-GFAP antibody was detected in the initial CSF with a delay, and the patient was diagnosed with autoimmune GFAP astrocytopathy. However, 3 weeks after steroid treatment was ceased, he developed fever, nausea, intermittent vomiting, anorexia, and postural tremor, and brain MRI showed recurrence of FLAIR lesions and enhancement. Considering the disorder relapse, we restarted IVMP and oral PSL 60 mg and noted clinical and radiological improvements. The PSL dose was tapered to 9 mg, and the patient remained relapse-free for 9 months. Repeated brain MRI did not reveal any obvious MO lesions.

Discussion

We described an unusual case of autoimmune GFAP astrocytopathy presenting with APS-like symptoms without MRI evidence of MO lesions. To date, there have been six cases of autoimmune GFAP astrocytopathy presenting with APS and MO lesions (Table 1) [16-21], one of which was positive for anti-AQP4 antibodies [17]. Long et al. [23] reported intractable hiccups and nausea in 1 of 19 cases of autoimmune GFAP astrocytopathy, but it was unclear whether MO lesions were present. Dumonceau et al. [24] described two cases of autoimmune GFAP astrocytopathy presenting with intractable hiccups without apparent AP lesions in a cohort study of 46 patients, but MO lesions were not evident. Therefore, this study is worthwhile to report in detail a case of autoimmune GFAP astrocytopathy presenting with APS-like symptoms without MO lesions.

There are several possible mechanisms underlying the persistent hiccups in our case. The first possible cause is gastroparesis. Gastroparesis can cause hiccups, and this explanation is supported by the fact that symptomatic treatment, including prokinetic agents, is effective [25]. Autoimmune GFAP astrocytopathy patients occasionally present with autonomic dysfunction, including orthostasis, gastrointestinal motility disorder, bladder dysfunction, erectile dysfunction, and ejaculatory dysfunction [2, 22]. Wang et al. [26] reported a patient with autoimmune GFAP astrocytopathy whose initial symptom was prolonged abdominal symptoms (periumbilical distention, anorexia, defecation dysfunction, and weight loss). The gastroparesis in our patient was perhaps an autonomic dysfunction associated with autoimmune GFAP astrocytopathy. The direct effect of GFAP autoimmunity on the hiccups and gastroparesis cannot be excluded because the enteric ganglia and nerves in the mouse stomach are immunoreactive to the serum and CSF from patients with autoimmune GFAP astrocytopathy, and GFAP is expressed in the enteric nervous system, even though anti-GFAP antibody is believed not to be pathogenic [1, 2, 27].

The second possible cause of hiccups is cervical cord lesion. The cervical cord (C3-C5) is a part of "hiccups center," and its involvement triggers hiccups [5]. In patients with demyelinating diseases, APS can develop in spinal cord lesions without MO lesions [8, 28, 29]. Increased intracranial pressure may cause hiccups [25]. However, this explanation is unlikely in our patient because it persisted after the hiccups resolved. Gastroesophageal reflux disease, which was observed in our patient, is a major cause of hiccups [5], whereas reflux can be an effect of hiccups [30]. Considering that his hiccups coincided with a rash of encephalomyelopathy, the reflux may have involved the hiccups to a limited extent in our patient, even though symptomatic treatment including vonoprazan remitted his hiccups. Impairment of the supratentorial areas, including the temporal lobe, insula, and basal ganglia, can cause hiccups [31-34], but no lesions were found in these areas in our case.

The intermittent vomiting and nausea in our case also seemed to be associated with gastroparesis and cervical cord lesions, as mentioned above [8, 28, 29]. Additionally, autoimmune GFAP astrocytopathy often presents with viral-like symptoms (fever, fatigue, malaise, weight loss, and nausea or vomiting) [15], consistent with symptoms such as vomiting and nausea in our patient. Increased intracranial pressure probably does not cause these symptoms because of its persistence.

This report suggests that autoimmune GFAP astrocytopathy presents with APS-like symptoms without obvious MO lesions on imaging. The primary limitation is that thin-slice MRI was only performed on admission, which may fail to detect fine MO lesions that appeared during the course of the disease. Testing for anti-GFAP antibodies should be considered in patients with APS-like symptoms in the context of typical clinical-MRI features of autoimmune GFAP astrocytopathy. Further case reports are needed to elucidate the full clinical spectrum of autoimmune GFAP astrocytopathy.

Statements

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Statement of Ethics

Study approval statement: The study protocol was reviewed and approved by the Institutional Review Board of the Gifu University Graduate School of Medicine, Gifu, Japan (protocol number 27-43).

Consent to participate statement: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kosuke Iwami, Taichi Nomura, Sho Seo, Shingo Nojima, and Kazufumi Tsuzaka collected and interpreted the clinical data. Akio Kimura and Takayoshi Shimohata performed anti-GFAP antibody testing. Ichiro Yabe supervised the study. Kosuke Iwami wrote the manuscript and prepared the figures. All authors have critically revised and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this report. Further enquiries can be directed to the corresponding author.

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Figure Legends

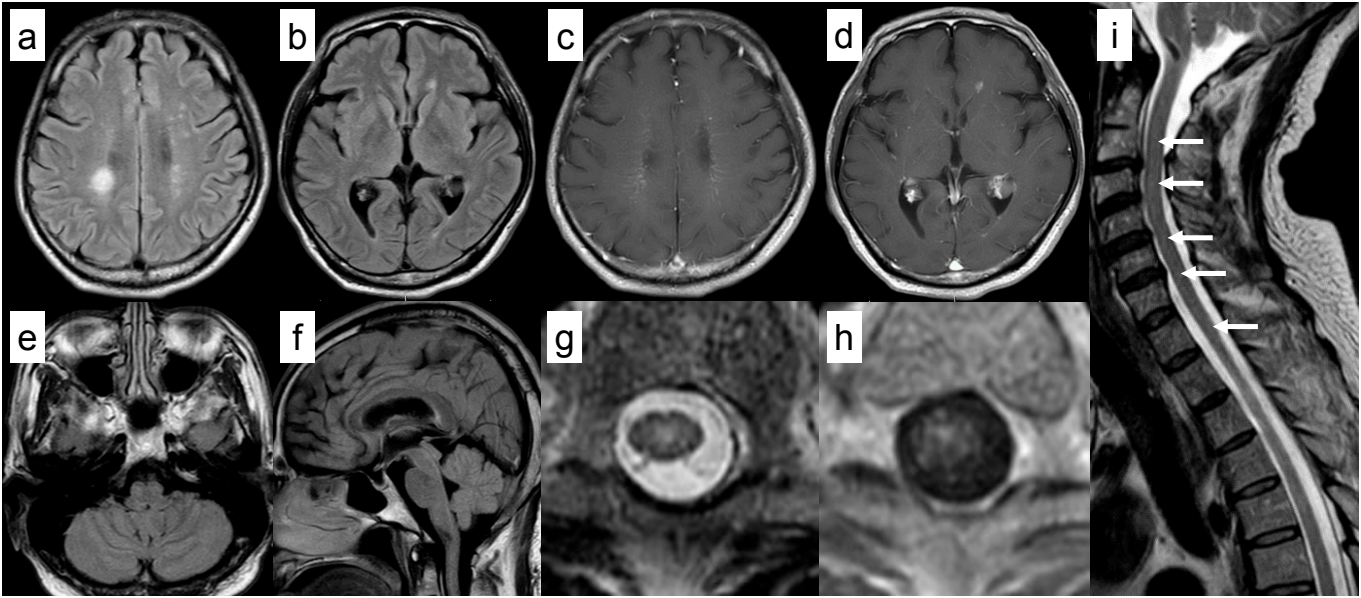
Fig. 1. Brain and spinal cord magnetic resonance imaging (MRI) findings on admission. a, b: periventricular fluid-attenuated inversion recovery (FLAIR) lesions; c: post gadolinium T1 sequence showing radial linear periventricular enhancement; d: enhancement suggestive of some FLAIR lesions; e, f: thin-slice images revealing no obvious medulla oblongata lesions; g, h: spinal cord MRI showing T2 lesions centrally located in Th3 (g) with enhancement (h); i: hazy T2 lesions along the cervical and thoracic spinal cord (white arrows).

Table 1. Previously reported cases of autoimmune GFAP astrocytopathy with APS and our case

Publication (Year)	Age (years) /Sex	APS	MRI findings	CSF findings	Anti-AQP4 Antibody findings	Immunomodulatory treatment	Outcome
Ciron (2020) [16]	41/F	Intractable nausea and vomiting	Brain: Periventricular lesions with radial linear periventricular enhancement Spinal cord: Longitudinally extensive lesion extended to AP	Intracranial pressure: Not available WBC: 195/μL (predominantly lymphocytes) Protein: 183 mg/dL	Negative	Steroids and rituximab	Improved (intractable nausea and vomiting resolved without immunotherapy)
Lin (2020) [17]	72/M	Persistent hiccups	Brain: Hippocampus, midbrain, pons, MO, and meninges lesions with radial linear periventricular enhancement Spinal cord: Normal	Intracranial pressure: Not available WBC: 199/μL (predominantly lymphocytes) Protein: 126.73 mg/dL	Positive	IVMP, gamma globulin, oral methylprednisolone, mycophenolate mofetil	Improved
Zhang (2020) [18]	43/F	Intractable hiccups, nausea, and vomiting	Brain: Hypothalamus, left pedunculi cerebelli, and MO lesions Spinal cord: Cervical cord lesions	Intracranial pressure: 140 mmH_2O WBC: Normal Protein: Normal	Negative	Intravenous methyltrienolone and oral prednisone	Improved (intractable hiccups were slightly alleviated by omeprazole)
Adachi (2021) [19]	46/M	Hiccups and vomiting	Brain: Bilateral basal ganglia, corona radiata, pons, and right MO lesions Spinal cord: Normal	Intracranial pressure: 130 mmH_2O WBC: 111/μL (predominantly lymphocytes) Protein: 122 mg/dL	Negative	IVMP and oral prednisolone	Improved

Gao (2021) [20]	21/F	Intractable nausea and vomiting	Brain: Dorsal MO and right middle cerebellar peduncle lesions Spinal cord: Not available	Intracranial pressure: 135 mmH_2O WBC: 50/μL Protein: 42 mg/dL	Negative	IVMP and oral prednisone	Improved
Koh (2021) [21]	45/M	Nausea and persistent hiccups	Brain: Subtle leptomeningeal enhancement around the MO Spinal cord: Long segment leptomeningeal enhancement predominantly the cervical cord	Intracranial pressure: Not available WBC: 178/μL (predominantly lymphocytes) Protein: 169 mg/dL	Negative	IVMP, oral prednisolone, and intravenous immunoglobulin	Improved
Our case	54/M	Persistent hiccups, intermittent vomiting, and nausea	Brain: Periventricular lesions with radial linear periventricular enhancement Spinal cord: Hazy lesions with patchy enhancement along the cervical and thoracic cord	Intracranial pressure: 270 mmH_2O WBC: 74/μL (predominantly lymphocytes) Protein: 118 mg/dL	Negative	IVMP and oral prednisolone	Improved (persistent hiccups were remitted by vonoprazan, mosapride, and rikkunshito)

GFAP: Glial fibrillary acidic protein
APS: Area postrema syndrome
MRI: Magnetic resonance imaging
CSF: Cerebrospinal fluid
AQP4: Aquaporin-4
AP: Area postrema
WBC: White blood cell
MO: Medulla oblongata
IVMP: Intravenous methylprednisolone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