Self-remitting Elevation of Adenosine Deaminase Levels in the Cerebrospinal Fluid with Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Case Report and Review of the Literature

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Abstract:
A 29-year-old man presented with a high-grade fever, headache, and urinary retention, in addition to meningeal irritation and myoclonus in his upper extremities. A cerebrospinal fluid (CSF) examination showed pleocytosis and high adenosine deaminase (ADA) levels with no evidence of bacterial infection, including Mycobacterium tuberculosis. T2-weighted brain magnetic resonance imaging showed transient hyper-intensity lesions at the splenium of the corpus callosum (SCC), bilateral putamen, and pons during the course of the disease. The CSF was positive for anti-glial fibrillary acidic protein (GFAP) antibodies. He was diagnosed with autoimmune GFAP astrocytopathy. The present case shows that the combination of an elevated ADA level in the CSF and reversible T2-weighted hyper-intensity on the SCC supports the diagnosis of autoimmune GFAP encephalopathy.

Key words: autoimmune GFAP astrocytopathy, glial fibrillary acidic protein (GFAP), adenosine deaminase (ADA), urinary retention, myoclonus, reversible splenial lesion

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Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a recently emerging autoimmune disease of the central nervous system (CNS) (1, 2). The disease is diagnosed by the detection of IgG autoantibodies against GFAP-α, the predominant intermediate filament protein expressed on adult astrocytes, in the cerebrospinal fluid (CSF). Recent studies have shown that clinical manifestations of autoimmune GFAP astrocytopathy include steroid-responsive meningoencephalitis/encephalomyelitis, which often presents as a fever, headache, abnormal vision, ataxia, meningeal sign, consciousness disturbance, autonomic nervous system dysfunction, involuntary movements, hyponatremia, and other symptoms (1-4). However, it is difficult to diagnose the disease in the early stages because these features are common to many forms of autoimmune and infectious CNS diseases.

We herein report a case of autoimmune GFAP astrocytopathy that showed self-remitting elevation of ADA levels in the CSF with peculiar findings on brain magnetic resonance imaging (MRI). Our case suggests that elevation of CSF ADA without Mycobacterium tuberculosis infection supports the possibility of autoimmune GFAP astrocytopathy. In addition, in order to help physicians diagnose this rare CNS disease, features of other autoimmune-related CNS diseases with elevation of CSF ADA levels that have been reported to date are summarized.

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A 29-year-old man who had no previous illness was admitted to our hospital complaining of a high-grade fever and headache for 1 week. His body temperature was elevated (39.5 °C). His consciousness was clear, and a general physical examination showed no abnormalities. A neurological examination showed neck stiffness and Kernig’s sign. A blood examination showed a white blood cell count in the normal range (7,300/μL), slightly elevated C-reactive protein (CRP) (0.29 mg/dL), and mild hyponatremia (127 mEq/L). Lumbar puncture revealed a CSF pressure of 240 mmH₂O. The cell count was 46/μL (neutrophils 13, lymphocytes 33). The CSF protein concentration was elevated (108 mg/dL), and the glucose level was slightly decreased (44 g/dL; blood glucose 92 mg/dL).

A few days after admission, acute urinary retention and constipation developed. He required urinary catheterization and laxative medication. Myoclonus appeared in his upper extremities. His consciousness remained unchanged, and he had no symptoms suggesting myelopathy, such as hyper-reflexia. One week later, we found an elevated CSF ADA level (23.0 IU/L; normal range, 0-1.9 IU/L). The result of polymerase chain reaction (PCR) for tuberculosis was negative, and \( M. \) \textit{tuberculosis} bacilli were not cultured from the CSF. Myelin basic protein was normal (95.6 pg/mL; normal range, <102 pg/mL), and oligoclonal bands were negative. The interferon-\( \gamma \) release assay, which aids in the diagnosis of systemic tuberculosis infection, was negative. No tumor markers were significantly elevated in the blood test, and cytology of the CSF showed no evidence of malignant cells. Tests for anti-aquaporin-4 (AQP4) antibody, anti-myelin-oligodendrocyte glycoprotein (MOG) antibody, anti-N-methyl-D-aspartate receptor (NMDAR) antibody, and other autoantibodies suggesting collagen diseases or vasculitis were all negative. We checked for CSF IgG against GFAP by immunohistochemistry and a cell-based assay, as previously reported (2, 4). Strong immunoreactivity with the CSF sample was observed against astrocytes in the cerebellum, pial, subpial, and periventricular regions of the rat brain. We confirmed the presence of CSF IgG against GFAP using a cell-based assay with HEK293 cells expressing GFAP-\( \alpha \).

Brain MRI with T2-weighted fluid-attenuated inversion recovery (FLAIR) revealed hyper-intensity lesions in the splenium of the corpus callosum (SCC) on admission, which was 10 days after the onset (Fig. 1A). Follow-up MRI showed gradual remission of the SCC lesions (Fig. 1A) and

![Figure 1](image_url)
the transient appearance of hyper-intensity in the bilateral putamen 15 days after the onset (Fig. 1B) and in the pons 25 days after the onset (Fig. 1C). There were no gadolinium-enhanced lesions in the course of the disease. Spinal MRI and computed tomography (CT) of the chest, abdomen, and pelvis with contrast showed no abnormalities.

The patient received adjuvant therapy with glycerol and nonsteroidal anti-inflammatory drugs (NSAIDs). His general symptoms gradually improved, and the elevated CSF ADA levels decreased spontaneously (Fig. 2). Although a low-grade fever, minor myoclonus, and urinary retention lasted for one month, additional treatment with methylprednisolone pulse therapy ameliorated these symptoms. Three months later, all symptoms had disappeared completely.

**Discussion**

We herein report a case of autoimmune GFAP astrocytopathy with self-remitting elevation of CSF ADA levels. In general, elevation of ADA in the CSF is an adjunctive biomarker for a clinical diagnosis of tuberculous meningitis (TBM) (5) and has been applied extensively in clinical practice for decades. According to a previous meta-analysis, CSF ADA levels >8 U/L suggest a diagnosis of TBM, with a sensitivity less than 59% and a specificity greater than 96% (6). Although our patient’s CSF ADA levels were higher than the cut-off value, antituberculous medication was withheld because of his good general condition and spontaneous recovery of his symptoms during elevation of CSF ADA.

In addition to its significant value for the diagnosis of TBM, elevated CSF ADA levels can suggest other diseases, such as nontuberculous infectious meningitis (7-13), lymphoproliferative disorders (14, 15), and autoimmune-related CNS disease (16-20). In particular, a recent retrospective study found that the elevation of ADA levels was a unique CSF finding in patients with autoimmune GFAP astrocytopathy (4). Along with other characteristic features that have been reported in patients with autoimmune GFAP astrocytopathy (1-4), such as a fever, headache, autonomic nervous system dysfunction, involuntary movement, and hyponatremia, the elevation of the CSF ADA levels led us to this diagnosis in our patient.

Our search of the PubMed database yielded 21 cases of CNS disease with elevated CSF ADA levels caused by autoimmune-related mechanisms. The clinical profiles of these cases are summarized in Table. There were 7 published articles, which reported 14 case series of GFAP astrocytopathy (4), 3 cases of immune-related adverse events (irAE) induced by immune checkpoint inhibitors (16, 18), and 1 case each of multiple sclerosis (17), Vogt-Koyanagi-Harada disease (19), sarcoid meningitis (21), and meningencephalitis of unknown etiology (21). The ADA levels ranged from 7 to 91.41 IU/L. All cases except one showed pleocytosis (median 90.5 cells/μL, range 13-981 cells/μL) and elevated protein levels (range 71-286 mg/dL) in the

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Figure 2. Clinical course and treatment. mPSL: methylprednisolone, CSF: cerebrospinal fluid, ADA: adenosine deaminase
CSF. All patients were treated with high-dose corticosteroid therapy, and nine patients also received antituberculous medication at the same time or antecedently. All patients responded well to steroid therapy except one patient who died from progression of lung cancer (16). These studies confirmed that CSF ADA was observed in patients with autoimmune-related CNS diseases. There is no doubt about the importance of performing diagnostic treatment for TBM in order to judge the response to antituberculous medication. It is advisable not to delay steroid therapy for patients with suspected steroid-responsive CNS disease. Furthermore, although there is little compelling evidence for the diagnostic value of elevated CSF ADA levels, they might be a supportive finding for physicians suspicious of a rare CNS disease, as in our case. Most cases of autoimmune GFAP astrocytopathy were diagnosed as meningoencephalitis/encephalomyelitis of unknown etiology or acute disseminated encephalomyelitis (ADEM) (4, 20). In addition, coexisting neural antibodies, such as anti-NMDAR antibody, anti-AQP4 antibody, and others, have been frequently observed in autoimmune GFAP astrocytopathy (1-4). These data indicate that it is important to assess anti-GFAP antibody in patients with an elevated CSF ADA, even in cases with other diagnoses.

The mechanism underlying the elevation of CSF ADA in our case and other reported cases remains unclear. ADA has been frequently observed in autoimmune GFAP astrocytopathy (1-4). These data indicate that it is important to assess anti-GFAP antibody in patients with an elevated CSF ADA, even in cases with other diagnoses.

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cades related to the cell-mediated immune response in the early stage of autoimmune GFAP astrocytopathy cause the elevation of CSF ADA.

In our case, MRI findings also supported the diagnosis of autoimmune GFAP astrocytopathy. T2-weighted hyper-intensity involving the basal ganglia and brainstem is common in autoimmune GFAP astrocytopathy (3, 4). Furthermore, a recent report described a pediatric patient with autoimmune GFAP astrocytopathy presenting with reversible lesions of the SCC (26). Reversible splenial lesions have been reported in patients with heterogeneous pathogenesis triggered by viral infection, hypoglycemia, antiepileptic drug treatment, seizure, trauma, and other causes; these lesions are more common in children and young adults than in older adults (27, 28). Taken together with the findings from one previous pediatric case, our present findings suggest that reversible splenial lesions should be considered as a radiological feature in pediatric and young adult patients with autoimmune GFAP astrocytopathy. However, it is noteworthy that there were rare cases presenting with reversible splenial lesions among patients with TBM (29), and after ruling out TBM, the combination of reversible splenial lesions and an elevated CSF ADA was deemed to strongly suggest a diagnosis of autoimmune GFAP astrocytopathy.

Of note, the abnormalities on MRI that emerged and disappeared in the course of the disease were not necessarily coincident with the patient’s symptoms. Although previous reports revealed neuropathological features of patients with autoimmune GFAP astrocytopathy that showed inflammation, including intramyelinic edema or inflammatory infiltrate around small vessels (3), further analyses are needed to elucidate the pathologic mechanisms underlying the various MRI features of autoimmune GFAP astrocytopathy.

Conclusion

We herein report a case of autoimmune GFAP astrocytopathy wherein the combination of self-remitting elevation of CSF ADA and reversible T2-weighted hyper-intensity on SCC supported the diagnosis.

The authors state that they have no Conflict of Interest (COI).

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