

[ CASE REPORT ]

## Acute Cerebellar Ataxia Associated with Anti-glutamic Acid Decarboxylase Antibodies Mimicking Miller Fisher Syndrome

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### Abstract:

We herein report the case of a 53-year-old man with cerebellar ataxia with anti-glutamic acid decarboxylase antibody (GAD-Ab) who mimicked Miller Fisher syndrome (MFS). He developed ophthalmoplegia, diplopia, and gait ataxia for one week. The serum and cerebrospinal fluid GAD-Ab titers were greatly increased, and the GAD-Ab index suggesting intrathecal antibody synthesis was elevated, while GQ1b-Ab was negative. After steroid pulse therapy and following prednisolone, his symptoms dramatically improved over the course of 11 months with the simultaneous decline of GAD-Ab titers. This case indicates that cerebellar ataxia with GAD-Ab can present with acute neurological findings mimicking MFS, and that steroid therapy has an excellent therapeutic effect.

**Key words:** anti-GAD, ataxia, acute onset, corticosteroid, Miller Fisher syndrome

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### Introduction

Glutamic acid decarboxylase (GAD) is an intracellular enzyme expressed by central neuronal and pancreatic islet cells which mediates the formation of  $\gamma$ -aminobutyric acid (GABA) from L-glutamic acid. GABA exerts paracrine functions in pancreatic islets and acts as an inhibitory neurotransmitter in the central nervous system. Previous reports have shown that neurological syndromes were associated with anti-GAD antibodies (GAD-Ab), such as stiff-person syndrome, limbic encephalitis, cerebellar ataxia, and autoimmune epilepsy (1-3). The clinical symptoms of cerebellar ataxia with GAD-Ab were similar to those of sporadic cerebellar ataxia. However, it is recognized that cerebellar ataxia with GAD-Ab could be improved by immune therapy (1, 2, 4-12).

Previous cases of cerebellar ataxia with GAD-Ab generally showed either subacute or chronic courses. However, cases of acute cerebellar ataxia with GAD-Ab are rare and the characteristics of its clinical symptoms are therefore unclear (1, 2, 4-11). Regarding the neurological findings of this disorder, most cases showed gait ataxia, and some cases

demonstrated nystagmus including downbeat nystagmus (1, 4). However, the incidence and characteristic of ophthalmoplegia have not yet been elucidated.

We herein present a patient with acute cerebellar ataxia with GAD-Ab who developed ophthalmoplegia, diplopia, and gait ataxia mimicking Miller Fisher syndrome (MFS) who completely recovered following early immune therapy.

### Case Report

A 53-year-old healthy man developed vertigo. Six days after onset, the patient developed diplopia and gait disturbance, and these symptoms became exacerbated over the next few days. At ten days after onset, he was admitted to our hospital. No antecedent infection was noted prior to the onset of these symptoms. The patient was alert and well oriented. His speech was fluent and his hearing was normal. The initial neurological examination revealed moderate bilateral external ophthalmoplegia in every direction, diplopia, and downbeat nystagmus in the left gaze. His deep tendon reflexes were normal, and plantar responses were flexor bilaterally. Although his muscle strength and sensory examinations were normal, he was unable to walk and had severe

cerebellar syndrome, including ataxia of the lower limbs and trunk. His gait score for the Scale for the Assessment and Rating of Ataxia (SARA) (13) was 7. A laboratory analysis showed normal WBC and serum vitamin B<sub>1</sub> levels. Hemoglobin A1c, islet cell antibodies, and insulinoma-associated antigen-2 antibodies were within the normal limits. Anti-gliadin IgA and IgG; anti-thyroid; anti-nuclear; anti-DNA; anti-SS-A; anti-acetylcholine receptor; and anti-GM1, -GQ1b, -GT1a, and -GD1b IgG and IgM antibodies were negative. Whole-body computed tomography (CT) and gastroenterological endoscopy showed no evidence of malignancy lesions. On the day of admission, a cerebrospinal fluid (CSF) examination showed normal WBC (2/mm<sup>3</sup>), normal protein concentration (35 mg/dL), IgG index of 0.55, and the absence of oligoclonal IgG bands. The results of brain magnetic resonance imaging with enhancement and single-photon emission CT (SPECT) were normal. Nerve conduction studies of the bilateral upper and lower limbs showed a normal motor and sensory function. The serum and CSF GAD-Ab titers determined by radioimmunoassay (RIA) were greatly increased at 36,000 IU/mL and 430 IU/mL, respectively. The index score of anti-GAD antibody [CSF anti-GAD antibody titer × serum albumin (mg/L)/serum anti-GAD antibody titer × CSF albumin (mg/L)] was 2.31 (normal: ≤1) (2). This finding suggested the intrathecal synthesis of GAD-Ab. Fifteen days after onset, the patient was started on immunomodulatory therapy with intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for 5 days. Although his external ophthalmoplegia and diplopia except for the left gaze improved at 21 days after onset, and those in the left gaze improved at 28 days after onset, his gait ataxia persisted and his SARA gait score remained at 7 after IVIG. Twenty-nine days after onset, he was started on intravenous methylprednisolone (IVMP) for 5 consecutive days, followed by oral prednisolone (40 mg/day). Shortly after IVMP initiation, the patient's gait ataxia demonstrated a significant improvement and he could walk without support (SARA gait scores after onset: 33 days=5; 38 days=3; and 52 days=1). At 38 days after onset, a CSF examination showed a normal WBC (1/mm<sup>3</sup>) and a normal protein concentration (32.3 mg/dL), while the serum and CSF GAD-Ab titer determined by RIA declined to 15,500 IU/mL and 210 IU/mL, respectively. The anti-GAD antibody index score also declined to 1.44. He recovered without any sequela, and oral prednisolone was stopped 11 months after onset. No symptomatic recurrence was observed during a follow-up evaluation 2 years after onset.

## Discussion

The present patient developed acute gait ataxia, ophthalmoplegia, and diplopia. Although his deep tendon reflexes were normal, we initially considered MFS because 18% of patients with MFS have normal deep tendon reflexes at the initial neurological examination (14). However, the serum and CSF GAD-Ab titers determined by RIA were markedly

increased, and the intrathecal synthesis of GAD-Ab was demonstrated. Therefore, the patient was diagnosed with acute cerebellar ataxia associated with GAD-Ab and was started on immune therapy.

The present case illustrates two important clinical issues. First, cerebellar ataxia with GAD-Ab can present with acute neurological findings mimicking MFS. Although previous studies indicate that one third of cerebellar ataxia-associated GAD-Ab cases have subacute courses that progress for weeks and two thirds have chronic courses that progress for months or years (4-6), acute cerebellar ataxia associated with GAD-Ab, such as the present case, are rare. Moreover, the present case presented with MFS-like episodes characterized by acute gait ataxia, ophthalmoplegia, and diplopia. As a mechanism of these neurological manifestations, previous reports demonstrated that GAD-Ab acted on the terminals of GABAergic interneurons to depress GABA release from Purkinje cells, causing gait ataxia (7, 12, 15, 16). It has been reported that while the frequency of gait ataxia in patients with cerebellar ataxia with GAD-Ab was 95%, the frequency of dysarthria in those was 66% (4). In addition, this disease did not necessarily show a reduced perfusion in the cerebellar region by SPECT, such as was seen in the present case (17). These findings suggested the possibility that cases of cerebellar ataxia with GAD-Ab manifested more advanced dysfunction in cerebellar vermis than cerebellar hemisphere. On the other hand, the presence of GAD in the nerve terminal of neuromuscular junctions was reported (18). Although it was expected that this finding involved ophthalmoplegia and diplopia, the mechanism of these factors in cases of cerebellar ataxia with GAD-Ab remains unclear. Because Pittock et al. proposed that 21% of the patients with neurological syndromes associated with GAD-Ab included ophthalmoplegia (1), it should be kept in mind that cerebellar ataxia with GAD-Ab can manifest in such a manner that MFS is mimicked, coinciding with ophthalmoplegia. In the present case, the distinguishing features between cerebellar ataxia with GAD-Ab and MFS were normal deep tendon reflexes, nystagmus, the absence of albuminocytological dissociation, antecedent infection, and IgG antibodies to GQ1b as well as vertigo antedating the onset of cerebellar ataxia. Particularly, regarding vertigo, it has been reported that 26% of the patients with cerebellar ataxia with GAD-Ab develop neurologic symptoms (including vertigo) before developing cerebellar ataxia. Male cases are most likely to demonstrate this manifestation, such as observed in the present case (6). In terms of the initial symptoms of MFS, vertigo is atypical (14, 19). In the present case, vertigo antedating cerebellar ataxia was an important finding in making a differential diagnosis.

Second, steroid therapy has an excellent therapeutic effect for this condition. Although it is possible that the effect of IVIG had developed recently, the patient's gait ataxia improved immediately and significantly after steroid therapy. Although previous reports have demonstrated a pathogenic role of GAD-Ab in cerebellar ataxia-associated GAD-

Ab (7, 12, 15, 16), cellular immunity could also play a major pathological role (20). The development of a predominant Th1 response to GAD was observed, and peripheral T cells increased Interferon (IFN)- $\gamma$  production following exposure to GAD, which have cytotoxicity (20). Purkinje cells are particularly fragile to this cytotoxicity (16). Further, it was previously reported that patients with subacute and chronic cerebellar ataxia with GAD-Ab improved significantly following corticosteroid therapy (8, 9). These findings suggested that both cell-mediated and antibody-mediated mechanisms could play a central pathological role in cerebellar ataxia with GAD-Ab (3). In addition, corticosteroid therapy that acts on the wide-ranging immune system more than IVIG could also be effective. Corticosteroid therapy is not generally used as a treatment for MFS, Guillain-Barré syndrome, or Bickerstaff brainstem encephalitis (21). Therefore, it is important to distinguish cerebellar ataxia with GAD-Ab from these disorders in order to provide the most appropriate therapy.

An accurate diagnosis is of great prognostic significance in cerebellar ataxia with GAD-Ab. MFS generally has a benign course, resulting in a complete recovery with supportive care (19). However, cerebellar ataxia with GAD-Ab may progress if treatment is delayed, thereby causing irreversible damage of Purkinje cells (4, 10, 12, 16). In previous studies, most cases remained partially responsive and a full recovery was very rare (4). Postmortem examinations have demonstrated Purkinje cell depletion accompanied by disease progression (10). The importance of an early diagnosis and immune treatment has been proposed (4, 11). In cases of acute cerebellar ataxia with GAD-Ab (as in the present case), Purkinje cells may cause a reversible dysfunction and may not degenerate differently from subacute or chronic forms (12). Immune therapy at an early stage could therefore achieve a complete recovery.

In conclusion, it is important to consider acute cerebellar ataxia with GAD-Ab in the differential diagnosis of MFS. In cases with MFS-like episodes, we should measure the GAD-Ab titer and consider immediate immune therapy, including corticosteroids.

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

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