□ CASE REPORT □

Stiff-person Syndrome Associated with Cerebellar Ataxia and High Glutamic Acid Decarboxylase Antibody Titer

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Abstract

Glutamic acid decarboxylase (GAD) is the main target of humoral autoimmunity in patients with insulin-dependent diabetes mellitus (IDDM) and stiff-person syndrome. We reviewed the case of a 46-year-old woman who had cerebellar ataxia before getting stiff-person syndrome and IDDM with high anti-GAD autoantibody titers. This was a rare case in which there were both the clinical symptoms of stiff-person syndrome and cerebellar ataxia. In western blot analysis her serum reacted with 65-kDa proteins from rat cerebellum, cerebral cortex, and spinal cord. Autoantibodies to GAD may cause functional impairment of γ-aminobutyric acid (GABA) neurons in the spinal cord as well as in the cerebellum.
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Key words: anti-GAD autoantibody, insulin-dependent diabetes mellitus, γ-aminobutyric acid neuron, cerebellum

Introduction

Glutamic acid decarboxylase (GAD) catalyzes the conversion of glutamic acid to γ-aminobutyric acid (GABA). Anti-GAD autoantibodies (anti-GAD-Abs) are present in stiff-person syndrome (SPS), polyendocrine autoimmune syndrome, and insulin-dependent diabetes mellitus (IDDM) (1). Several reports have described the association between progressive cerebellar ataxia and anti-GAD-Abs (2–7), but only two have dealt with patients with anti-GAD-Abs who had both SPS and cerebellar ataxia. Anti-GAD-Abs was postulated to lead to common functional impairment of GABA-nergic synaptic transmission in the spinal cords of patients with SPS and in the cerebellum of patients with cerebellar ataxia. We reported the case of a 46-year-old woman who developed SPS and IDDM ten years after the onset of cerebellar ataxia.

Case Report

A 46-year-old Japanese woman experienced clumsiness of the right hand in August 1988 and two months later developed dysarthria. Her condition gradually worsened over the next ten years. Cerebellar ataxia was diagnosed because of her right upper extremity ataxia and slurred speech. Magnetic resonance imaging (MRI) showed mild cerebellar atrophy (Fig. 1A). In 1998, she complained of severe trunk stiffness with board-like rigidity of the abdomen and painful muscle spasms, but there was no rigidity of the extremities. In 2000, she suffered polyuria and dry mouth. DM was diagnosed because of her high fast blood glucose and glycosylated hemoglobin A_{1c} (HbA_{1c}) levels. There was no family history of cerebellar ataxia or IDDM. A neurological examination showed mild dysmetria and dysdiadochokinesia of the right upper limb. Her speech was slurred. The saccadic eye movements were slowed. Muscle strength was almost normal, and her deep tendon reflexes were moderately hyperactive, but pathological reflexes were absent. A complete blood cell count and routine blood biochemical analysis results were in the normal range, except that blood sugar which was 372 mg/dl and HbA_{1c} 12.4% (normal: 4.3–5.8). Serological test showed an anti-GAD-Abs titer of 192,900 U/ml (normal: <5 U/ml). Islet-cell autoantibody and gastric parietal-cell antibody were detected. No other immunological abnormalities were found. Insulin secretion was not induced by an intravenous glucagon injection; the respective serum level of C-peptide immunoreactivity before and 6 minutes after glucagon (1 mg) injection being <0.1 and <0.1 ng/ml. The CSF had a anti-GAD-Abs titer of 396 U/*l*. Anti-Yo antibody and anti-Hu antibody were not detected. Gene analysis for familial spinocerebellar ataxia (SCA1, 2, 3, 6, 8) found no abnormalities. MRI showed asymmetric cerebellar atrophy of the right hemisphere, but no brainstem atrophy (Fig. 1B). An electromyographic examination detected continuous motor unit activity of the abdominal muscles at rest. Attempts to relax her did not change this motor unit activity. Surface electromyography also showed continuous contraction of the abdominal and paraspinal muscles (Fig. 2A). An intravenous injection of 2 mg diazepam markedly decreased the contraction (Fig. 2B). Her trunk rigid-

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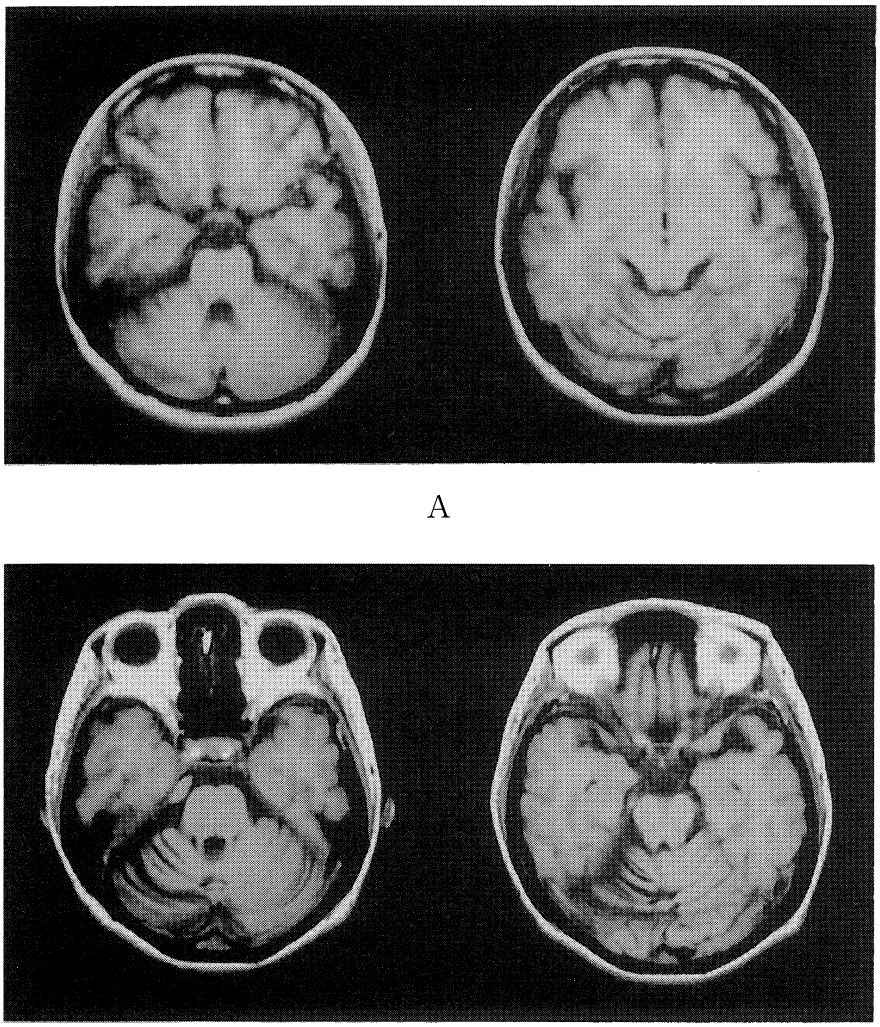

Figure 1. Magnetic resonance imaging (TR/TE=500/30). A: MRI in 1991, one year after the onset of cerebella ataxia. B: MRI in 1999 after onset of stiff-person syndrome. Cerebellar atrophy had developed.

ity was treated with oral diazepam, resulting in a dramatic reduction in rigidity and painful spasms. The diazepam treatment was slightly effective in reducing the right upper extremity ataxia.

Rat tissue samples were homogenized in lysis buffer and sonicated. The lysates, corresponding to 100 μg protein, were suspended in the same volume of Laemmli sample buffer. Proteins were separated electrophoretically in a 15% polyacrylamide gel and then blotted on a polyvinylidene difluoride (PVDF) membrane sheet. Those bound to the membrane were incubated with the patient's serum (diluted 1:500) and anti-human IgG labeled with horseradish peroxidase (DAKO, Glostrup, Denmark) (diluted 1:1,000). Antibody was detected with a horseradish peroxidase conjugate substrate kit (Bio-Rad Laboratories, Hercules, California, USA). On western blot analysis, the patient's serum recognized 65 kDa bands from rat cerebral cortex, cerebellum, and spinal cord (Fig. 3). No bands were detected in the control serum.

Discussion

SPS is a rare disorder characterized by muscle rigidity and episodic axial muscle spasms. Continuous contraction of opposing muscles is caused by involuntary motor unit firing at rest; a clinical and electrophysiological hallmark of SPS. The cause of this disorder is considered to be impairment of the GABA-nergic neuron in the spinal cord (8). It is related to the autoimmune pathogenesis because of the presence of anti-GAD-Abs together with various autoimmune diseases (8). GAD is expressed in two isoforms in neurons, GAD-65 and GAD-

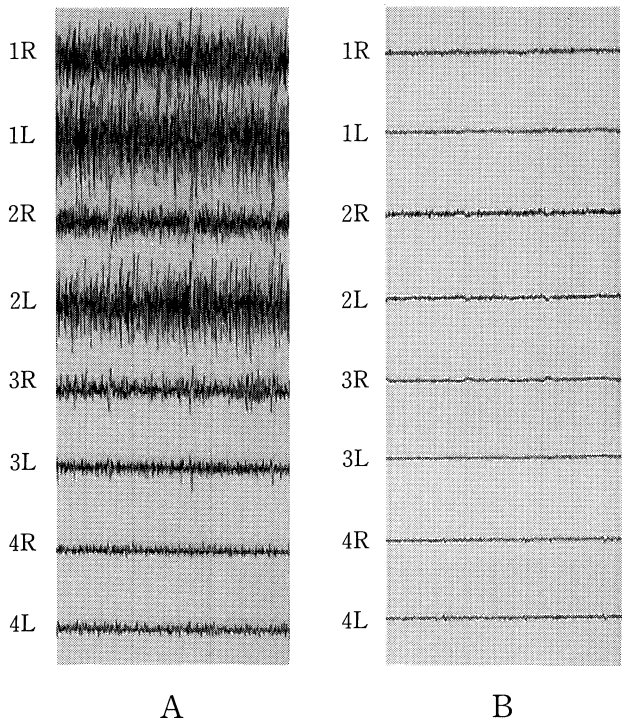

Figure 2. Surface electromyography. A: before the intravenous injection of diazepam. B: 2 minutes after the intravenous injection of diazepam (2 mg). Contraction of abdominal and paraspinal muscles has dramatically decreased. 1R, right straight abdominal muscle; 1L, left straight abdominal muscle; 2R, right paraspinal muscle; 2L, left paraspinal muscle; 3R, right brachial biceps muscle; 3L, left brachial biceps muscle; 4R, right deltoid muscle; 4L, left deltoid muscle.

67, which share a sequence homology of 65% at the protein level. GAD is known to be the only protein specific for the GABA-nergic neuron that acts as an inhibitory neuron in the central nervous system. Up to 30% of patients with SPS have IDDM and up to 65% of SPS patients also have antibodies against GAD-65 and GAD-67 (1, 8). Anti-GAD-Abs are present in patients with SPS as well as in IDDM patients, but their titers in SPS are markedly higher than in IDDM. Anti-GAD-Abs in SPS inhibit the synthesis of GABA and recognize both the conformational and denatured forms of GAD (1, 7, 8). These findings support the speculation that there is a difference in the epitope of GAD in the two diseases.

Recent reports have described the association between anti-GAD-Abs and cerebellar ataxia (3, 5). The patients with cer-

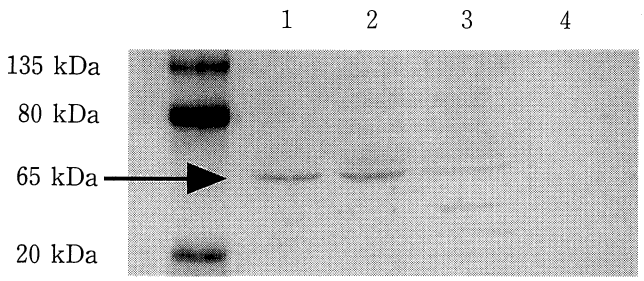

Figure 3. Western blot analysis of the patient's serum response to rat tissue homogenate. Lane 1, rat cerebrum: lane 2, cerebella: lane 3, spinal cord: lane 4, liver. The patient's serum recognized a 65 kDa protein in rat cerebrum, cerebellum, and spinal cord, which has a molecular weight similar to that of GAD-65.

Table 1. Clinical Features of Cerebellar Ataxia with Anti-GAD Antibodies

Author	Neurological symptoms	Clinical progress	Complication
1995 Honnorat (2)	gait disturbance slow eye movement peripheral neuropathy	slowly progressive (20 years)	(–)
1996 Giometto (3)	truncal ataxia slurred speech nystagmus	subacute (several months)	SPS
1997 Saiz (4)	Case 1 limb dysmetria, truncal ataxia dysarthria	subacute (2 months)	IDDM
	Case 2 limb dysmetria, truncal ataxia dysarthria, nystagmus	subacute (3 months)	IDDM
	Case 3 gait ataxia, dysarthria, nystagmus	slowly progressive (1 year)	IDDM
1997 Brashear (5)	ataxia	progressive	SPS
1999 Abele (6)	limb ataxia, gait ataxia, nystagmus	slowly progressive (13 years)	IDDM
1999 Ishida (7)	dysmetria, dysdiadochokinesia dysarthria	progressive (6 months)	IDDM
This report	dysmetria, dysdiadochokinesia dysarthria	slowly progressive (10 years)	IDDM+SPS

ebellar ataxia studied had very high anti-GAD-Abs titers. Their sera recognized a 65 kDa protein that corresponded to GAD-65 in western blot analysis of rat brain homogenates (3). The functional difference in the anti-GAD-Abs in cerebellar ataxia and SPS, however, was not clarified. Ishida et al reported a case of cerebellar ataxia with anti-GAD-Abs. Using a patch cramp technique with rat cerebella, he found that immunoglobulins in the CSF of the patient acted presynaptically causing a selective suppression of GABA-nergic transmission (7). Moreover, experimental evidence shows Purkinje cells rich in GAD may take up IgG from the CSF (9). The high anti-GAD-Abs levels were found in the serum as well as in the CSF of the patients. Anti-GAD-Abs may be internalized to neurons by Purkinje cells and interact with GAD, resulting in cerebellar dysfunction.

Honnorat et al described a patient without IDDM who had slowly progressive cerebellar ataxia, peripheral neuropathy, and slow saccadic eye movement (2). Saiz et al reported three patients with subacute cerebellar ataxia and IDDM (4). In the report of Abele et al, one patient who had had progressive cerebellar ataxia for 13 years showed clinical improvement after an intravenous injection of immunoglobulin (6). Only two reports showed the presence of a cerebellar disorder at the time of or after the development of SPS (Table 1) (3, 5). The present report is the first case of stiff-person syndrome occurring ten years after the onset of cerebellar ataxia. The presence of anti-GAD-Abs in our patient may be an indication of functional impairment of GABA-nergic neurons in the spinal cord as well as in the cerebellum.

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