Intravenous Immunoglobulin Therapy for Autoantibody-Positive Cerebellar Ataxia

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Abstract

Objective It has been reported that autoimmune cerebellar ataxias, such as anti-glutamic acid decarboxylase (GAD)-antibody-positive cerebellar ataxia and gluten ataxia, are treatable. Here, we examined the therapeutic efficacy of intravenous immunoglobulin (IVIg) on autoantibody-positive cerebellar ataxia.

Patients and Methods IVIg therapy was administered in seven autoantibody-positive cerebellar ataxia patients. Therapeutic efficacy was examined in terms of its effects on clinical symptoms and changes in brain perfusion using single photon emission computed tomography (SPECT).

Results Treatment was effective in four cerebellar cortical atrophy patients (two anti-GAD antibody-positive and two anti-gliadin antibody-positive) and in one anti-thyroid antibody-positive spinocerebellar ataxia type 3 (SCA3) patient, but not in two multiple system atrophy (MSA) patients. All four IVIg effective patients who underwent SPECT showed apparent increases in cerebellar perfusion.

Conclusion If cerebellar ataxia with an autoimmune mechanism is suspected and radiological findings do not reveal MSA, it is worth considering immunotherapy including IVIg.

Key words: anti-GAD antibody, anti-gliadin antibody, anti-thyroid antibody, cerebellar ataxia, IVIg, SCA3, SPECT

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Introduction

In progressive cerebellar atrophy, including cortical cerebellar atrophy, multiple system atrophy, and Machado-Joseph disease, the progression of cerebellar symptoms has been difficult to suppress. However, it has recently been reported that autoimmune cerebellar ataxias, such as anti-glutamic acid decarboxylase (GAD)-antibody-positive cerebellar ataxia and gluten ataxia, are treatable (1-3).

Intravenous immunoglobulin (IVIg) has become an important treatment for various autoimmune neurological diseases, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multi-focal motor neuropathy and myasthenia gravis (4, 5). There are also reports describing the efficacy of IVIg in treating autoimmune cerebellar ataxia (6-9).

We treated seven patients with autoantibody-positive cerebellar ataxia using IVIg. The therapeutic efficacy of this agent was examined in terms of its effects on the clinical symptoms and changes in brain perfusion of the patients, as determined using single photon emission computed tomography (SPECT). Here, we discuss the efficacy of IVIg in improving both the clinical characteristics of the patients and their different types of atrophy diagnosed by magnetic resonance imaging (MRI).

Patients and Methods

This study, approved by the ethics committee of our hospital, included seven autoantibody-positive cerebellar ataxia patients who gave their consent to participate in the study.

One patient (patient 3) was diagnosed as having spinocerebellar ataxia type 3 (SCA3). The clinical profiles of

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Table 1. Clinical Characteristics of Autoantibody-positive Cerebellar Ataxia Patients

Patient	Age	Disease	Disease	Autoantibody	Efficacy of IVIg	ICARS	rCBF	Locus length
	Sex	type	duration			Before →After	(mL/100 g/min) Before →After	(cm/min) Before →After
1	51 F	CCA	10 y	GAD Ab: 3.0 U/mL TPO Ab: 1.1 U/mL	Highly effective	46 → 35	38.2 → 47.4	2351 → 292
2	72 F	CCA	4 y	GAD Ab: 3360 U/mL TPO Ab: 21.6 U/mL, Tg Ab: 1.0 U/mL	Effective	6* → 2*	44.2 → 49.5	154 → 95
3	72 F	SCA3	5 y	TPO Ab: 2.5 U/mL	Effective	15* → 10*	40.7 → 45.7	969 → 850
4	84 F	CCA	7 y	IgA anti-gliadin Ab: 42.7 EU SS-AAb > 500 U/mL, TPO Ab: 1.0 U/mL	Effective	31* → 22*	n.d.	n.d.
5	51 M	CCA	5 y	IgA anti-gliadin Ab: 32.6 EU SS-AAb: 15.1 U/mL	Highly effective	19* → 5*	48.3 → 54.1	284 → 125
6	55 F	MSA-P	3 y	Microsome test: 102,400× Thyroid test: 1,600×	Ineffective	46 → 46	39.3 → 55.4	166 → 191
7	62 F	MSA-C	3 y	Anti-nuclear antibody titer: 1:320	Ineffective	3* → 3*	35.3 → 36.5	130 → 166

F: female; M: male; CCA: cortical cerebellar atrophy; SCA3: spinocerebellar ataxia type 3; MSA-P: multiple system atrophy parkinsonian type; MSA-C: multiple system atrophy cerebellar type; GAD: glutamic acid decarboxylase; Ab: antibody; TPO: thyroid peroxidase; Tg: thyroglobulin; IVIg: intravenous immunoglobulin; ICARS: international cooperative ataxia rating scale; n.d.: not determined. *ICARS score for posture and gait disturbances.

the other patients were classified into two types. The clinical characteristics of patients 1, 2, 4 and 5 resembled those of cerebellar cortical atrophy (CCA), with a familial incidence observed in patient 1. The clinical profiles of patients 6 and 7 corresponded to those of multiple system atrophy (MSA): MSA parkinsonian type and MSA cerebellar type, respectively. All patients were tested for autoantibodies (e.g., anti-nuclear antibody, anti-thyroglobulin antibody, anti-thyroid peroxidase (anti-TPO) antibody, anti-GAD antibody, anti-gliadin antibody and anti-Hu/Yo antibody).

After confirming that no improvement was achieved with placebos, IVIg therapy was administered for 5 days at 400 mg/kg/day. To assess the therapeutic efficacy of IVIg, the clinical symptoms prior to and following treatment were evaluated using the International Cooperative Ataxia Rating Scale (ICARS). However, it was thought that the use of only ICARS for evaluation was insufficient for objectively assessing the therapeutic efficacy of IVIg. Therefore, stabilometry, video photography and SPECT were also employed. Only those patients who showed obvious improvement after IVIg treatment were evaluated using ICARS, video photography and stabilometry.

SPECT using technetium-99m ethyl cysteinate dimer (Tc-99m ECD) was performed prior to and following 3 weeks of IVIg therapy in all the patients except for patient 6. Quantitative analysis of SPECT results was carried out using the Patlak plot method (10). The quantification of rCBF was carried out using the three-dimensional stereotaxic regions of interest (ROI) template method (3DSRT). 3DSRT is a fully automated rCBF quantification program. The blood flow in each ROI was quantified as the value in milliliters

per 100 g/min and expressed grouped in 12 segments including the cerebellar hemisphere (11). Cerebellar perfusion data shown in this study is reported as the average perfusion of bilateral cerebellar hemispheres. Postural stability was examined using a stabilimeter (MG 100; ANIMA Co., Tokyo, Japan). We measured locus length, the sway of the body's center of gravity, for 60 sec.

Results

Clinical profiles and results are summarized in Table 1. We describe the 5 IVIg effective patients in detail as follows.

Patient 1 (CCA type; IVIg therapy markedly effective): The patient was a 51-year-old woman, negative for diabetes mellitus, who experienced the onset of cerebellar ataxia at age 41. Her younger brother was also found to suffer from cerebellar atrophy. However, genetic tests for SCA types 1, 2, 3, 6, 7, 8, and 12 and dentatorubral-pallidoluysian atrophy revealed no gene abnormalities. IVIg was administered four times at intervals of one-half to one year and after each treatment, marked improvement of clinical symptoms and on the locus length of the stabilimeter were observed (Fig. 1: at the second IVIg treatment, the locus length of the stabilimeter decreased from 2,351 to 292 cm/min; at the third IVIg treatment, the ICARS score of 46 improved to 35; at the fourth treatment, the ICARS score of 58 improved to 39). The efficacy of IVIg continued for 3 months at the first treatment, but the effective period of IVIg shortened gradually and was 1 month at the last treatment. Soon after the first IVIg treatment, the anti-GAD antibody level was 1.7 U/

Figure 1. IVIg was administered four times and after each treatment, marked improvement of clinical symptoms and in the locus length of the stabilimeter were observed (at the second IVIg treatment, the locus length of the stabilimeter decreased from 2351 to 292 cm/min; at the third IVIg treatment, the ICARS score of 46 improved to 35; at the fourth treatment, the ICARS score of 58 improved to 39).

Patient 1

Figure 2. Cerebellar perfusion was markedly improved not only in the second IVIg treatment but also in the fourth IVIg treatment. At the second IVIg, cerebellar perfusion improved from 38.0 to 47.2 mL/100 g/min. At the fourth IVIg, cerebellar perfusion improved from 40.7 to 45.6 mL/100 g/min. rCBF: regional cerebral blood flow

mL (normal <1.5 U/mL) and the anti-TPO antibody level was negative. After the anti-GAD antibody level became negative, it became positive (3.0 U/mL) again as well as the anti-TPO antibody level (1.1 U/mL; normal <0.3 U/mL)

with the exacerbation of ataxia. Cerebrospinal fluid (CSF) GAD-antibody titer was 1.2 U/mL. The index for intrathecal synthesis of GAD-antibody was calculated using the following formula:

Figure 3. Autopsy showed moderate loss of cerebellar Purkinje cells.

CSF GAD-antibody titer / Serum GAD-antibody titer
CSF albumin / Serum albumin

The index was 253.2 which was consistent with positive intrathecal synthesis (12). On SPECT, cerebral perfusion markedly improved after each IVIg treatment (Figs. 2, 4, Table 1).

Patient 2 (CCA type; IVIg therapy effective): The patient was a 72-year-old woman who experienced the onset of cerebellar ataxia at age 68, and who suffered from type 1 diabetes mellitus. She was able to stand with her feet together but exhibited a mild sway; however, she was unable to stand on one foot. The heel-to-knee test revealed dysmetria. Her anti-GAD antibody level was 3,360 U/mL; her anti-TPO antibody level was 21.6 U/mL; and her anti-thyroglobulin antibody level was 1.0 U/mL (normal <0.3 U/mL). CSF examination showed 1 cell/ μ L, and the protein concentration was 43 mg/dL (normal 10 - 40 mg/dL). Brain MRI showed no obvious abnormalities but SPECT demonstrated decreased cerebellar perfusion. The patient was given a diagnosis of CCA. IVIg therapy ameliorated the dysmetria of the lower extremities and standing sway, and the locus length of the stabilimeter was decreased from 154 to 95 cm/min. Her ICARS score for posture and gait disturbances improved from 6 to 2. IVIg treatment also ameliorated cerebellar perfusion, as demonstrated by SPECT (Fig. 4, Table 1). After the IVIg treatment, the anti-GAD antibody level decreased to 2,040 U/mL. IVIg therapy was performed only once. Subsequently no exacerbation has been observed for 2 years.

Patient 3 (SCA3; IVIg therapy effective): The patient was a 72-year-old woman who experienced the onset of cerebellar ataxia at age 67. Her older sister also had walking ataxia. She was unable to walk unaided because of staggering. Her Romberg test was positive and her deep tendon reflex of the extremities decreased. Regarding the sensory system, numbness was observed at the terminals beyond the wrists and ankles, and her vibratory and positional senses had been compromised. The anti-TPO antibody level was 2.5 U/mL. CSF examination showed normal cell count, and

Figure 4. Apparent increases in cerebellar perfusion were observed in five of six patients, with only a slight increase in patient 5 (MSA-C). rCBF: regional cerebral blood flow.

the protein concentration was 40 mg/dL. A nerve conduction test indicated deterioration of the sensory nerve action potential in the sensory nerve tested. IVIg treatment ameliorated the numbness and staggering when walking, enabling the patient to walk unaided. The ICARS score for posture and gait disturbances improved from 15 to 10. Four months later, her numbness recurred with an accompanying exacerbated stagger when walking. IVIg therapy was given for the second time and was effective in relieving the conditions, although not to the same degree as the first treatment. Nevertheless, her cerebellar perfusion was ameliorated as shown by SPECT (Fig. 4, Table 1). After the IVIg treatments, the anti-TPO antibody level became negative.

Patient 4 (CCA type; IVIg therapy effective): The patient was an 84-year-old woman who had onset of cerebellar ataxia at age 77 and had a history of Basedow's disease. Her antibody levels were as follows: anti-SS-A/Ro antibody, >500 U/mL (normal <10 U/mL); anti-SS-B/La antibody, 41.1 U/mL (normal <10 U/mL); anti-TPO antibody, 1.0 U/mL; IgA anti-gliadin antibody, 42.7 EU (normal <20 EU); and IgG anti-gliadin antibody, 21.9 EU (normal <20 EU). CSF examination showed normal cell count, and the protein concentration was 40 mg/dL. IVIg treatment was performed twice at an interval of one-half year, and her ICARS score for posture and gait disturbances improved from 31 to 22 at the first therapy and from 33 to 23 at the second therapy, indicating that IVIg therapy was moderately effective. After the IVIg treatment, the anti-TPO antibody level became negative, the anti-SS-A/Ro antibody level decreased to 391 U/mL, and the anti-SS-B/La antibody level decreased to 7.3 U/mL. The IgA anti-gliadin antibody level decreased to 3.7 EU. The patient died of aspiration pneumonia at age 85 and

autopsy was performed. Histopathology exam following autopsy showed lymphocytic infiltration in the parotid gland, indicating Sjögren syndrome. The cerebellum was slightly atrophic showing moderate loss of Purkinje cells (Fig. 3). SPECT was not conducted after treatment in this patient.

Patient 5 (CCA type; IVIg therapy markedly effective): The patient was a 51-year-old man with the onset of cerebellar ataxia occurring at age 46. Gaze-evoked nystagmus, dysarthria, and gait ataxia were observed. The patient showed a wide-based gait requiring assistance. Mild ataxia was observed in all limbs. His deep tendon reflex and proprioception were normal. He showed positivity for anti-SS-A/Ro antibody (15.1 U/mL) and IgA anti-gliadin antibody (32.6 EU), but negativity for anti-thyroid antibody. CSF examination revealed normal cell count, but the protein concentration was elevated (58 mg/dL). Following IVIg therapy, unassisted walking with a stable gait was possible, and his ICARS score for posture and gait disturbances improved from 19 to 5. The therapy also ameliorated cerebral and cerebellar perfusion as determined by SPECT (Fig. 4, Table 1). One month later, his ataxia worsened again. He then received the second IVIg treatment and started to take prednisolone and tacrolimus 3 mg/day. ICARS score for posture and gait disturbances improved from 20 to 5. Subsequent to treatment, no exacerbation has been observed for one year, and the anti-gliadin antibody level decreased to 23.6 EU while the anti-SSA/Ro antibody level decreased to 9.1 U/mL.

Changes in cerebellar perfusion in six patients determined by quantitative SPECT are shown in Fig. 4.

Discussion

In the present study, IVIg therapy was administered in seven autoantibody-positive cerebellar ataxia patients. Two patients assessed the treatment as highly effective, three rated it effective, and two considered it ineffective. The patients who considered the treatment to be highly effective were anti-GAD-antibody-positive, and anti-gliadin-antibody-positive (patients 1 and 5, respectively). The three patients who rated the treatment to be effective showed positivity for anti-thyroid antibody (patients 2, 3, and 4). Moreover, patient 2 was highly anti-GAD-antibody-positive, and patient 5 was anti-gliadin-, anti-SS-A/Ro- and anti-SS-B/La-antibody-positive. Of six patients who underwent SPECT, an apparent increase in cerebellar perfusion was observed in five. All of the four IVIg effective patients (patients 1, 2, 3, and 5) who underwent SPECT revealed evident increases in cerebellar perfusion.

In regards to autoimmune cerebellar ataxia, GAD-antibody-positive cerebellar ataxia (13, 14), gluten ataxia (15) and thyroid-antibody-positive cerebellar ataxia (16, 17) have been reported. In addition, other reports include that of a woman with systemic lupus erythematosus presenting with cerebellar ataxia with Purkinje cell antibodies (18), anti-ganglioside-antibody-positive cerebel-

lar ataxia (19), Sjögren syndrome (20) and neuro-Behçet disease (21). All five patients who responded to treatment in this study had some of the above-mentioned antibodies such as GAD antibody, gliadin antibody and thyroid antibody.

With respect to anti-GAD-antibody-positive cerebellar ataxia, Honnorat et al reported 14 cases (22). Takenoshita et al showed that anti-GAD antibody presynaptically inhibited GABAergic transmission (23). Moreover, Manto et al reported an inhibitory effect on the potentiation of the corticomotor response normally associated with trains of repetitive nerve stimulation in rats through the intracerebellar administration of IgG obtained from patients with GAD antibody and neurological involvement (24). For the treatment of GAD-antibody-related nervous system diseases, a control study was conducted on patients with stiffperson syndrome (SPS) and the efficacy of IVIg was proven (25). For GAD-antibody-positive cerebellar ataxia, some cases with good response to immunotherapy have been reported. Abele reported a patient with progressive cerebellar ataxia and insulin-dependent diabetes mellitus who responded to IVIg therapy (6). In addition, Ances et al repeated IVIg therapy for a 55-year-old woman positive for anti-GAD antibody with accompanying SPS and cerebellar ataxia, and reported improvements on ataxia of the legs and arms and downbeat nystagmus (7). In GAD-positive CCA patients 1 and 2, clinical symptoms as well as cerebellar perfusion obviously improved with IVIg treatment. Thus, the efficacy of IVIg therapy was well-proven in our patients.

In the case of patient 1, the low titer of anti-GAD antibody was probably due to IVIg post-treatment. Anti-GAD antibody usually has an extremely high titer in GAD-antibody-positive cerebellar ataxia, such as in patient 2. However, low-titer cases have been occasionally reported. Selim and Drachman reported that two of six patients with anti-thyroid-antibody-positive cerebellar ataxia were anti-GAD antibody-weak-positive (2.6 U/mL and 2.5 U/mL; normal <2.5 U/mL) (16). In addition, Ikeda et al also reported low-titer anti-GAD-antibody-positive cerebellar ataxia (6.7 U/mL; normal <4.0 U/mL) (26). Saiz et al reported the importance of increased intrathecal synthesis of GAD-antibody to confirm that GAD autoimmunity is related to cerebellar ataxia (27). The anti-GAD antibody titer of patient 1 was very low. However, the ratio of intrathecal GAD antibody synthesis was extremely high, thus indicating that cerebellar ataxia is related to GAD autoimmunity. Although patient 1 was a chronic progressing case with a long duration of the disorder (i.e., 10 years), IVIg was highly effective. There is the possibility that Purkinje cells did not deteriorate irreversibly because neuronal damage was minimized due to the low titer of anti-GAD antibody.

Gluten ataxia patients are known to be positive for anti-gliadin antibody. Hadjivassiliou et al reported that anti-gliadin antibody cross-reacts with epitopes on Purkinje cells from human and rat cerebellum. They also reported post-mortem findings from two patients with gluten ataxia that have shown marked but patchy Purkinje cell loss (15). Like-

wise, in patient 4, autopsy showed moderate disappearance of cerebellar Purkinje cells. As a treatment for cerebellar ataxia patients positive for anti-gliadin antibody, IVIg therapy was performed on four patients with progressive cerebellar ataxia; marked improvements in two patients and mild improvements in one patient were reported (8). In addition, Sander et al reported an excellent response to IVIg therapy administered to an anti-GAD-antibody-positive gluten ataxia patient (3). In the present study, IVIg therapy was effective in anti-gliadin-antibody-positive patients 4 and 5, and SPECT showed improvements in cerebral blood flow in patient 5.

In Europe and the US, the prevalence rate of celiac disease is high, and there are many reports on gluten ataxia. Conversely, in Japan, celiac disease is extremely rare, and there are almost no reports of gluten ataxia. However, Ihara et al have recently reported that anti-gliadin antibody was found in five of 14 Japanese cerebellar ataxia patients (36%), and that only one person in 47 (2%) was positive in the general population (28). We also encountered two gliadin-antibody-positive cerebellar ataxia patients. Therefore, we speculate that it is not a rare disease in Japan.

For patients with anti-thyroid-antibody-positive cerebellar ataxia, Selim and Drachman reported six patients with the condition, and of these, the temporary effectiveness of IVIg therapy was observed in one patient (16). In addition, Nakagawa et al reported marked improvements in ataxic symptoms after steroid therapy in a Hashimoto's encephalopathy patient presenting with pure cerebellar ataxia (17). In the present study, four of five IVIg effective patients were anti-thyroid-antibody-positive, indicating the possibility that anti-thyroid antibody is related to cerebellar ataxia.

Over the past years a number of GAD-antibody-positive cerebellar ataxia patients have been reported, however a search conducted by the authors yielded no reports on its familial occurrences. In the present study, the younger brother of patient 1 also suffered from cerebellar atrophy and the incidence was of a familial nature. Patient 3 suffered from SCA3, a type of hereditary cerebellar atrophy, and she was positive for anti-TPO antibody. IVIg therapy was found to be effective in these two patients. There is a possibility that IVIg therapy in these two patients was effective against autoimmune encephalopathy complicated by hereditary cerebellar atrophy. In addition, in patient 4, it is also possible that IVIg therapy was effective against autoimmune polyneuropathy associated with chronic thyroiditis. Even among patients with familial cerebellar ataxia, there may be some with autoimmune neurological disorder complications who may react favorably to immunotherapy. It would therefore be necessary to analyze various autoantibodies (including anti-GAD, anti-gliadin, and anti-thyroid antibodies) to distinguish individual autoimmune conditions even in cases of familial cerebellar ataxia.

In the current study, all patients except patient 4 underwent SPECT before and 3 weeks after IVIg treatment. Apparent increases in cerebellar perfusion were observed in

five of six patients, and a slight increase was observed in an MSA patient where IVIg treatment was not effective. All four IVIg effective patients who underwent SPECT showed apparent increases in not only cerebellar perfusion but also cerebral perfusion. A favorable effect of IVIg therapy on cerebral perfusion in Rasmussen encephalitis (29, 30), thrombotic thrombocytopenic purpura (31) and Churg-Strauss syndrome (32) has been reported, suggesting that this agent has beneficial effects on brain perfusion by improving brain function via an immune mechanism. It is thought that autoantibodies such as anti-GAD and anti-gliadin antibodies cause functional impairment of cerebellar Purkinje cells in patients with autoimmune cerebellar ataxia. If immune abnormality is improved using IVIg therapy, the function of Purkinje cells might also be improved, as well as cerebellar perfusion as determined by SPECT. Therefore, the enhancement of cerebellar perfusion in the present study is thought to be an important finding and has become circumstantial evidence in the improvement of cerebellar function induced by IVIg therapy.

In patients 1, 2, 3, and 5, the improved clinical symptoms paralleled the increase in cerebellar perfusion. Patient 6 showed the most prominent increase in brain perfusion (Figs. 4, 5, Table 1); however, the patient's clinical symptoms failed to improve because of the fact that she had MSA characterized by marked involvement of the brain stem and cerebellar vermis. Likewise, IVIg therapy was not effective in patient 7 (MSA-C type). These results suggest that IVIg therapy may be effective for CCA but not MSA.

In the present study, in all IVIg effective patients, IVIg improved perfusion in not only the cerebellum but also the cerebrum. In anti-GAD antibody-positive, anti-gliadin antibody positive or anti-thyroid antibody positive patients, not only cerebellar damage but also various central nervous system disorders, such as epilepsy and dementia, have been reported (2, 33, 34). Furthermore, SPECT studies have reported abnormal cerebral perfusion in celiac disease (35) and Hashimoto's thyroiditis with normal thyroid function (36). In autoimmune cerebellar ataxia, diffuse central nervous system disorders without apparent clinical symptoms may occur; as IVIg improves immunological abnormalities, perfusion improves in not only the cerebellum but also the cerebrum.

Although our own therapeutic experience has been limited, the results of the present study suggest that an autoimmune mechanism might be partly involved in progressive cerebellar atrophy patients. In addition, it might be involved not only in patients with sporadic cerebellar ataxia but also in those with familial cerebellar ataxia. In this regard, all patients with cerebellar ataxia should undergo human leukocyte antigen (HLA) typing and be tested for various autoantibodies (including anti-GAD, anti-gliadin, and anti-thyroid antibodies). If cerebellar ataxia with an autoimmune mechanism is suspected and radiological findings do not reveal MSA, it would be worth considering immunotherapy including IVIg before irreversible Purkinje cell injury occurs.

Figure 5. Cerebellar perfusion improved from 39.3 to 55.4 mL/100 g/min after IVIg treatment. rCBF: regional cerebral blood flow.

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