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## Cerebellar Ataxia and Glutamic Acid Decarboxylase Antibodies: Immunologic Profile and Long-term Effect of Immunotherapy

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### Abstract

**IMPORTANCE**—Current clinical and immunologic knowledge on cerebellar ataxia (CA) with glutamic acid decarboxylase 65 antibodies (GAD65-Abs) is based on case reports and small series with short-term follow-up data.

**OBJECTIVE**—To report the symptoms, additional antibodies, prognostic factors, and long-term outcomes in a cohort of patients with CA and GAD65-Abs.

**DESIGN, SETTING, AND PARTICIPANTS**—Retrospective cohort study and laboratory investigations at a center for autoimmune neurologic disorders among 34 patients with CA and GAD65-Abs, including 25 with long-term follow-up data (median, 5.4 years; interquartile range, 3.1-10.3 years).

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**Author Contributions:** Dr Graus had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Drs Ariño and Gresa-Arribas contributed equally to this work.

**Study concept and design:** Ariño, Saiz, Graus. **Acquisition, analysis, or interpretation of data:** All authors.

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**MAIN OUTCOMES AND MEASURES**—Analysis of clinicoimmunologic features and predictors of response to immunotherapy. Immunochemistry on rat brain, cultured neurons, and human embryonic kidney cells expressing GAD65, GAD67,  $\alpha 1$ -subunit of the glycine receptor, and a repertoire of known cell surface autoantigens were used to identify additional antibodies. Twenty-eight patients with stiff person syndrome and GAD65-Abs served as controls.

**RESULTS**—The median age of patients was 58 years (range, 33-80 years); 28 of 34 patients (82%) were women. Nine patients (26%) reported episodes of brainstem and cerebellar dysfunction or persistent vertigo several months before developing CA. The clinical presentation was subacute during a period of weeks in 13 patients (38%). Nine patients (26%) had coexisting stiff person syndrome symptoms. Systemic organ-specific autoimmunities (type 1 diabetes mellitus and others) were present in 29 patients (85%). Twenty of 25 patients with long-term follow-up data received immunotherapy (intravenous immunoglobulin in 10 and corticosteroids and intravenous immunoglobulin or other immunosuppressors in 10), and 7 of them (35%) improved. Predictors of clinical response included subacute onset of CA (odds ratio [OR], 0.50; 95% CI, 0.25-0.99;  $P = .047$ ) and prompt immunotherapy (OR, 0.98; 95% CI, 0.96-0.99;  $P = .01$ ). Similar frequencies of serum GAD67-Abs were found in patients with CA (24 of 34 patients [71%]) and in patients with stiff person syndrome (20 of 28 patients [71%]). However, GAD67-Abs were found in all of the cerebrospinal fluid samples examined (22 samples from patients with CA and 17 samples from patients with stiff person syndrome). Glycine receptor antibodies but not other cell surface antibodies were identified in 4 patients with CA. The presence of glycine receptor antibodies did not correlate with any specific clinical feature.

**CONCLUSIONS AND RELEVANCE**—In patients with CA and GAD65-Abs, subacute onset of symptoms and prompt immunotherapy are associated with good outcome. Persistent vertigo or brainstem and cerebellar episodes can herald CA and should lead to GAD65-Ab testing, particularly in patients with systemic organ-specific autoimmunities.

Autoimmunity is increasingly recognized as a cause of cerebellar dysfunction. Cerebellar ataxia (CA), associated with antibodies against the 65-kDa isoform of glutamic acid decarboxylase (GAD65-Abs), is one of the best-characterized cerebellar syndromes in which autoimmune mechanisms probably have a relevant pathogenic role.<sup>1</sup> After stiff person syndrome (SPS), CA is the second most frequent neurologic disorder associated with GAD65-Abs.<sup>2</sup> Current knowledge of the clinical and immunologic profile of CA with GAD65-Abs is based on small series and single case reports, and the long-term outcomes after immunotherapy are unknown.<sup>1,3</sup>

The association of GAD65-Abs with various syndromes such as SPS or CA has led to several hypotheses regarding the possible pathogenic role of these antibodies. The results of experimental investigations using monoclonal antibodies against different GAD65 epitopes suggest that the various neurologic syndromes could be related to the pattern of epitope recognition by human serum.<sup>4</sup> Alternatively, the occurrence of CA or SPS could result from additional mechanisms mediated by T cells<sup>5</sup> or antibodies against surface antigens such as those described in several autoimmune encephalitis.<sup>6</sup> In this regard,  $\gamma$ -aminobutyric acid B receptor and glycine receptor antibodies (GlyR-Abs) have been described in patients with concurrent GAD65-Abs and limbic encephalitis or SPS.<sup>7,8</sup>

In this study, we retrospectively examined a cohort of patients with CA associated with GAD65-Abs. We aimed to better characterize the clinical presentation, the immunologic profile, the presence of additional antibodies against cell surface antigens, and the long-term response to immunotherapy.

## Methods

### Patients

The study was approved by the ethics committee of the Hospital Clinic, Barcelona, Spain. Written informed consent was obtained from all patients for the storage and use of serum and cerebrospinal fluid (CSF) samples for research purposes. Patients with CA and GAD65-Abs who were seen at the Hospital Clinic or whose serum or CSF samples were examined at the Institut d'Investigacions Biomèdiques August Pi i Suny, Barcelona, Spain, between December 15, 1994, and April 4, 2013, were included in the study if they met the following criteria: (1) predominant or isolated cerebellar dysfunction at presentation and the absence of another cause that could explain their CA, (2) available clinical information, and (3) the presence of high serum titers of GAD65-Abs confirmed by radioimmunoassay and immunohistochemistry.<sup>3</sup> Evidence has shown that positive serum immunoreactivity using rat cerebellar sections is associated with high GAD65-Ab levels on radioimmunoassay (usually >2000 U/mL).<sup>2</sup> Overall, 49 potential study patients were identified, 15 of whom were excluded because of a lack of clinical information. Long-term follow-up data were obtained in 25 of 34 patients (74%) (median, 5.4 years; interquartile range, 3.1-10.3 years). Data were obtained from clinical records, and information was collected from referring neurologists using a structured questionnaire mainly focused on the clinical presentation, the presence of neurologic symptoms preceding the cerebellar syndrome, concomitant symptoms of rigidity and spasms, and the response to immunotherapy. The onset of CA was defined as subacute when the cerebellar symptoms reached their nadir or required neurologic assessment within the first 3 months of symptom presentation. Ten patients were examined and followed up by 1 or more of us. Neurologic disability was measured by the modified Rankin Scale (mRS).<sup>9</sup> Patients with a history of cancer who met the criteria for definite or possible paraneoplastic neurologic syndrome were excluded from the study.<sup>10</sup> Serum and CSF samples used in the study were deposited in the Neuroinmunología collection of biological samples registered in the biobank of the Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain.

### Autoantibody Assays

All laboratory techniques have been previously reported and are described in detail in the eMethods in the Supplement. These include immunohistochemistry on frozen rat brain, immunoblot of human GAD65 recombinant protein (Diamyd),<sup>3</sup> immunocytochemistry on cultures of rat hippocampal and cerebellar granular neurons,<sup>3,11,12</sup> and immunocytochemistry on human embryonic kidney 293 cells transfected with the  $\alpha$ -1 subunit of the GlyR (obtained by gift) and with GAD65 and GAD67 (OriGene).<sup>8</sup>

## Statistical Analysis

Nonparametric tests were used when the distribution of the analyzed variables differed from normal using the Kolmogorov-Smirnov test. Good outcome was defined as an mRS score of less than 3 at the last follow-up visit, and bad outcome was defined as an mRS score of 3 or higher. In treated patients, improvement was defined as a decrease of at least 1 point on the mRS at the last follow-up visit compared with the score at diagnosis. For the multivariate analysis, a generalized linear model<sup>13</sup> was used that included relevant or significant ( $P < .10$  on univariate analysis) factors. As a dependent variable to analyze response to treatment, we used the change in mRS scores from the onset to the last follow-up visit. Odds ratios (95% CIs) were used to measure the effect of predictors on the exponential function of the regression coefficient. Statistical software (SPSS Statistics version 19; IBM) was used for the analyses.

## Results

### Clinical Characteristics at Diagnosis

The median age of patients was 58 years (range, 33-80 years); 28 of 34 patients (82%) were women. Twenty-nine patients (85%) had concomitant systemic organ-specific autoimmune disorders. Type 1 diabetes mellitus was present at diagnosis in 13 patients (38%), and the incidence increased to 17 of 25 patients (68%) during the follow-up period. Twenty-one patients (62%) had other organ-specific autoimmune disorders, mainly thyroiditis and pernicious anemia (Table 1). Thirteen patients (38%) had subacute presentation of CA lasting for weeks, while the other 21 patients (62%) had a chronic course progressing during months or years. Overall, the demographic features and autoimmune clinical associations of 34 patients with CA were similar to those of 28 patients with SPS and GAD65-Abs.

Gait ataxia was the most common clinical presentation (31 patients), followed by limb ataxia (25 patients) that was asymmetric in 20, dysarthria (24 patients), and nystagmus (20 patients). Muscle rigidity and spasms were identified in 9 patients (26%), and 4 of them manifested electromyographic features of SPS (Table 2). Muscle rigidity and spasms occurred at the time of their CA in 5 patients and 2 to 5 years later in 3 patients. In 1 patient, leg spasms triggered by emotional stimuli or anxiety were present 2 years before the onset of her CA. Four patients also had epilepsy. In 3 of them, their epilepsy antedated the diagnosis of CA by 15, 13, and 2 years. Two of these patients met the criteria for refractory temporal lobe epilepsy. The fourth patient developed 2 generalized seizures 18 months after the onset of CA.

Neurologic symptoms antedating the diagnosis of CA were reported in 9 patients (26%), with 2 different profiles. Six patients reported fluctuating vertigo 7 to 26 months before developing CA. All manifested exacerbations that lasted days to weeks. During this period, the neurologic examinations showed no signs of CA. The remaining 3 patients had at least 1 episode of transient neurologic deficit, suggesting brainstem or cerebellar involvement, 2 to 24 months before the diagnosis of CA. The first patient had an episode of isolated vertical diplopia that lasted 10 days. The second patient had 2 episodes of dysarthria and gait ataxia that lasted a few days. The third patient developed dysarthria and right arm ataxia that lasted

for 2 months and resolved spontaneously. The presence of prodromal symptoms was 3 times more common in men ( $P = .07$ ).

### Long-term Outcomes

Long-term follow-up data were available for 25 patients. Figure 1 shows the type and duration of treatment during the course of the disease. Five patients received no immunotherapy, and 2 patients were untreated for more than 2 years. None of them improved, and the condition in 3 patients slowly deteriorated. Twenty patients received immunotherapy, which in 10 patients included intravenous immunoglobulin (IVIg), while 9 patients received intravenous methylprednisolone alone (4 patients) or in combination with IVIg (4 patients) or rituximab (1 patient). One patient was treated with oral prednisone (1 mg/kg/d). Among treated patients, 17 received various types of maintenance therapy: 6 were treated with IVIg during a median of 56.2 months (interquartile range, 24.4-121.5 months), and 11 received 1 or more regimen of oral corticosteroids, azathioprine, or mycophenolate mofetil.

The eFigure in the Supplement shows the degree of disability at diagnosis, at the end of the first treatment (up to 6 months), and at the last follow-up visit. At the last follow-up visit, 11 patients had an mRS score of less than 3 (good outcome), and 14 patients had an mRS score of 3 or higher (bad outcome). Patients with good outcome had a better mRS score at diagnosis than patients with bad outcome (median, 2 vs 3;  $P = .01$ ) and responded to immunotherapy more frequently (6 patients [55%] vs 1 patient [7%],  $P = .01$ ) (Table 3).

Among 20 patients who were treated, 10 showed clinical improvement (1 point on the mRS during the first 6 months of treatment), which in 7 patients (35%) persisted at the last follow-up visit. Four of them were treated with pulses of intravenous methylprednisolone, and 3 were treated with IVIg. Four patients also received maintenance immunotherapy (for 1.1-4.9 years) with oral immunosuppressors (3 patients) or IVIg (1 patient). Improvement after immunotherapy was more common in patients with subacute onset (5 of 7 subacute patients [71%] vs 2 of 13 chronic patients [15%],  $P = .02$ ). Age, sex, mRS score at diagnosis, the presence of type 1 diabetes mellitus or other autoimmune disorders, and evidence of cerebellar atrophy on magnetic resonance imaging at diagnosis were similar in responders and nonresponders. On multivariate analysis, favorable predictors of clinical response included subacute onset of CA (odds ratio, 0.50; 95% CI, 0.25-0.99;  $P = .047$ ) and prompt immunotherapy (odds ratio, 0.98; 95% CI, 0.96-0.99;  $P = .01$ ).

### Immunologic Studies

All serum and CSF samples from patients with CA and SPS included in the study showed reactivity to human embryonic kidney cells transfected with GAD65. Similarly, all but one CA serum samples were positive in immunoblots of GAD65 recombinant protein, suggesting that the antibodies from patients with CA and SPS recognize linear epitopes. The assessment of GAD65-Abs by immunohistochemistry revealed that in all cases the predominant IgG isotype was IgG1. Additional isotypes were detected in a small proportion of patients, including IgG3 in 2 of 34 patients with CA and 2 of 28 patients with SPS and IgG2 in 2 of 34 patients with CA and 6 of 28 patients with SPS.

The frequencies of serum GAD67-Abs were similar in patients with CA (24 of 34 patients [71%]) and in patients with SPS (20 of 28 patients [71%]). GAD67-Abs were found in all CSF samples available from 22 patients with CA and from 17 patients with SPS. GAD67-Abs were present in CSF samples but not in serum samples of 7 patients with CA and 4 patients with SPS having paired serum and CSF samples (Figure 2). Serum and CSF samples from patients with CA did not immunoreact with live hippocampal and granular cerebellar neurons, and none manifested antibodies against *N*-methyl-D-aspartate,  $\gamma$ -aminobutyric acid B, and  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate receptors or leucine-rich glioma-inactivated protein 1, dipeptidyl peptidase-like protein 6, and contactin-associated protein 2 antigens. In contrast, 4 patients with CA had GlyR-Abs in serum samples but not in the 2 CSF samples available. The presence of GlyR-Abs did not correlate with any specific clinical feature, no patient had associated symptoms of SPS, and only one patient responded to immunotherapy.

## Discussion

To our knowledge, this is the first study to describe the long-term outcomes in a series of patients with CA and GAD65-Abs. Our findings indicate that patients with subacute presentation of CA are more likely to respond to immunotherapy and achieve good functional status (mRS score, <3) and confirm that a shorter delay in the initiation of immunotherapy predicts clinical improvement.<sup>14</sup>

Previous autopsy studies<sup>15,16</sup> of patients with CA and GAD65-Abs revealed selective loss of Purkinje cells. However, the clinical improvement observed in some of our patients indicates that part of the cerebellar dysfunction at the time of diagnosis may be due to functional impairment that can be reversed by early onset of immunotherapy. Although the pathogenic role of GAD65-Abs is unclear, studies<sup>17,18</sup> have shown that they interfere with the  $\gamma$ -aminobutyric acid-ergic synaptic transmission in tissue culture systems and that these effects are reversible after removing the GAD65-Abs. In addition, intracerebellar injection of GAD65-Abs induces an increase in glutamate levels that may lead to glutamate excitotoxic effects.<sup>4</sup> These neurochemical and neurophysiological abnormalities could initially affect the function of Purkinje cells without causing irreversible damage but may cause their death in the long run.

The retrospective design of this study and the multi-center locations of the patients make it difficult to recommend a particular type of immunotherapy. The effect of various immunotherapies has been described in single case reports (summarized in the eTable in the Supplement).<sup>19-29</sup> As in the present series, the most common treatments used were cycles of IVIg or methylprednisolone. Most of the described patients had a chronic presentation of symptoms, and treatment was started after a median delay of 12 months (range, 2-120 months). Improvement was reported in 13 of 16 patients (81%) compared with 7 of 20 patients (35%) in this series. However, the figures are not comparable because the degree of improvement reported in many of these case reports would not fulfill the required decrease of at least 1 point on the mRS as used herein (eTable in the Supplement).<sup>18-28</sup>



As in SPS,<sup>30,31</sup> we observed that patients with CA who responded to immunotherapy did so early, during the first 6 months. A lack of improvement in this short period should be an indication for switching to a second-line immunotherapy or stopping treatment.<sup>32</sup> Our study does not clarify whether maintenance immunotherapy is useful: 3 of 7 patients who improved with the initial treatment remained stable without subsequent immunotherapy.

We have identified a previously unrecognized feature to date of patients with CA and GAD65-Abs. Three patients (9%) reported episodes of diplopia or combinations of dysarthria and ataxia of unclear etiology months before the development of full-blown CA. In addition, 6 patients (18%) reported isolated vertigo in the absence of other symptoms of cerebellar dysfunction. We consider that vertigo in these patients was heralding the development of more widespread involvement of the cerebellum. This feature has been observed in other cerebellar syndromes. In patients with spinocerebellar ataxia, episodic vertigo antedated the development of gait ataxia by several years in 4% of patients.<sup>33</sup> Investigations of selective ischemic infarcts of the cerebellum indicate that patients who were seen with isolated vertigo more frequently had the infarct in the caudal vermis.<sup>34</sup> Taken together, these data suggest that in some patients GAD65 autoimmunity may result in subtle, focal, or transient symptoms, likely representing involvement of selective brainstem or cerebellar regions. In some patients, particularly those with diseases that are associated with GAD autoimmunity (eg, type 1 diabetes mellitus), the development of persistent vertigo of unknown etiology or episodes of diplopia, dysarthria, or ataxia, should lead to GAD65-Ab testing. In that clinical scenario, the detection of high-titer GAD65-Abs (usually >2000 U/mL) should raise concern about impending CA.

In our patients with CA, the immunologic response against GAD did not differ from that observed in patients with SPS. We found no significant increase in intrathecal production of GAD65-Abs in patients having CA compared with those having SPS, as previously suggested.<sup>35</sup> A relevant observation was that all patients in whom CSF samples could be analyzed manifested GAD67-Abs, despite that some of them did not have these antibodies in serum samples. The presence of GAD67-Abs only in CSF, along with previous demonstration of intrathecal synthesis of GAD65-Abs<sup>35</sup> and a different epitope repertoire noted between paired serum and CSF samples,<sup>36</sup> strongly supports the presence of GAD-specific B cells in the central nervous system and emphasizes the importance of examining the CSF in autoimmune disorders of the central nervous system.

Except for 4 patients with CA who had concomitant GlyR-Abs in serum samples, we did not find (as suggested in SPS<sup>37</sup>) other antibodies against neuronal surface antigens. Glycine receptor antibodies were initially described in patients having progressive encephalomyelitis with rigidity and myoclonus.<sup>38</sup> More recently, GlyR-Abs were reported in 12% to 15% of patients with SPS (with or without GAD65-Abs) and in 3% of patients with epilepsy.<sup>8,39,40</sup> In our patients, the significance of GlyR-Abs is unknown because the clinical course and outcome did not differ in patients without this antibody. In 2 of these 4 patients, CSF samples were available and were negative for GlyR-Abs in both of them. Although earlier described patients having progressive encephalomyelitis with rigidity and myoclonus showed GlyR-Abs in serum and CSF samples,<sup>41,42</sup> in patients with SPS or epilepsy GlyR-Abs were usually studied based on serum samples only.<sup>8,39,40</sup> Therefore, it is unclear

whether the presence or absence of GlyR-Abs in CSF is associated with different clinical phenotypes as recently reported in other autoimmune encephalitis.<sup>43</sup> Future studies should determine the degree of syndrome specificity of GlyR-Abs, comparing paired serum and CSF samples in larger groups of patients and control subjects.

## Conclusions

Our findings reveal that patients with CA and GAD65-Abs may respond to immunotherapy and maintain good functional status for many years. The retrospective design of the study prevents our making definite recommendations, but in our experience the use of IVIg or corticosteroids should be considered in all patients with CA and GAD65-Abs, particularly those with subacute presentation. Early initiation of treatment likely offers a greater chance of improvement.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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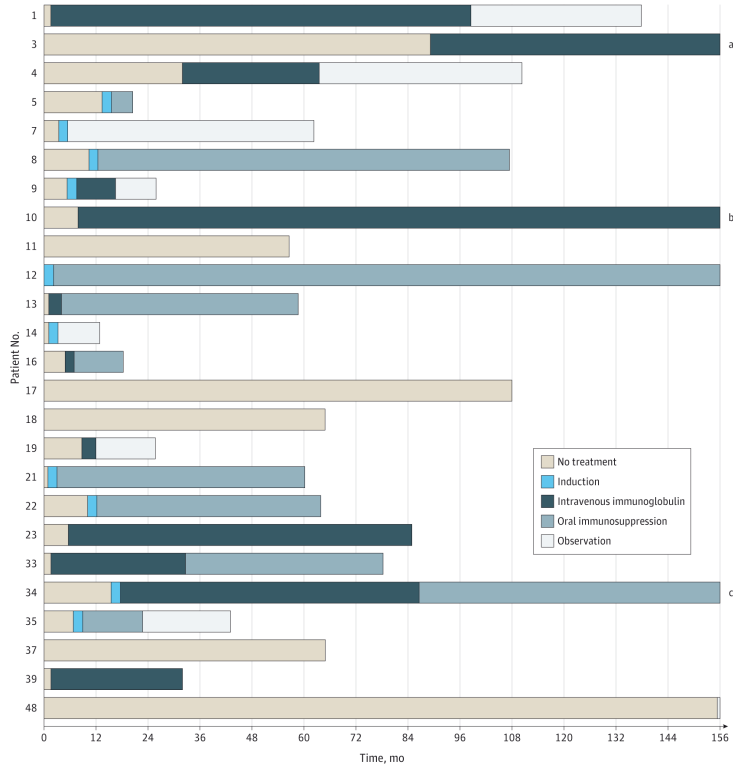
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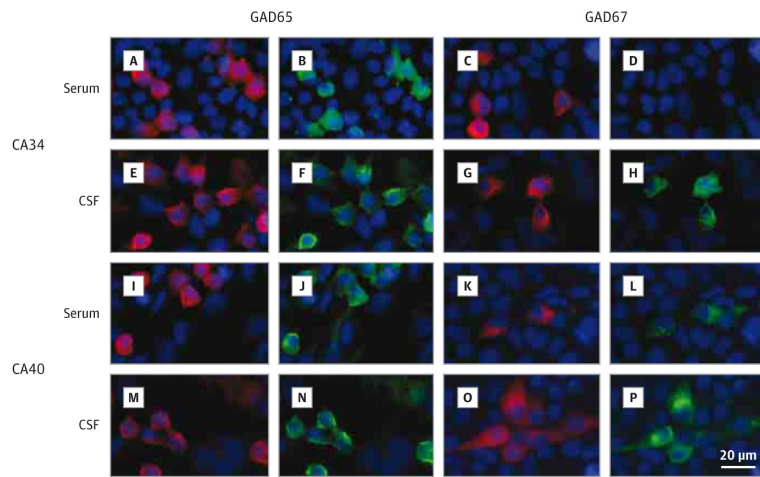


**Figure 1. Individual Therapy Regimens in 25 Patients With Long-term Follow-up Data** For visual purposes, periods of treatment or between-periods are approximate, and therapeutic schemes are simplified. See the Long-term Outcomes subsection of the Results section for a description of the types of induction therapy and oral immunosuppression.

<sup>a</sup>Total follow-up: 283 months. Beyond 156 months, patient 3 was treated with oral immunosuppression for 63 months and then observation.

<sup>b</sup>Total follow-up: 209 months. Beyond 156 months, patient 10 continued treatment with intravenous immunoglobulins.

<sup>c</sup>Total follow-up: 197 months. Beyond 156 months, patient 34 continued treatment with oral immunosuppression.



**Figure 2.** Reactivity of Serum and Cerebrospinal Fluid (CSF) Samples to Fixed Human Embryonic Kidney Cells Expressing Glutamic Acid Decarboxylase 65 (GAD65) and GAD67

**Table 1**

Clinical and Immunologic Features of Patients Having CA or SPS With GAD65-Abs

Variable	CA (n = 34)	SPS (n = 28)	P Value
Age, median (range), y	58 (33-80)	56 (19-77)	.19
Female sex, No. (%)	28 (82)	26 (93)	.20
Type 1 diabetes mellitus at diagnosis, No. (%)	13 (38)	14 (50)	.25
Other organ-specific autoimmune disorder			
No. (%)	21 (62)	13 (46)	.17
Thyroiditis, No.	18	7	NA
Pernicious anemia, No.	7	3	NA
Vitiligo, No.	2	3	
Other, No. <sup>a</sup>	3	0	
Tumor, No. <sup>b</sup>	4	1	.36
Epilepsy, No. (%)	4 (12)	3 (11)	.61
GAD65-Ab radioimmunoassay, median (interquartile range), 1000 U/mL	20.8 (9.5-44.6)	15.0 (5.7-28.5)	.31
CSF oligoclonal bands, No./total No. (%)	16/22 (73)	5/17 (29)	.07
GAD65-Ab intrathecal synthesis, No./total No. (%) <sup>c</sup>	13/15 (87)	9/11 (82)	.57
X-fold of GAD65-Ab intrathecal production, median (range) <sup>d</sup>	8.9 (2.2-95.2)	5.3 (1.1-20.0)	.43
GAD67-Abs			
Serum, No. (%)	24 (71)	20 (71)	.45
CSF, No./total No. (%) <sup>e</sup>	22/22 (100)	17/17 (100)	NA

Abbreviations: CA, cerebellar ataxia; CSF, cerebrospinal fluid; GAD65-Abs, glutamic acid decarboxylase 65 antibodies; NA, not applicable; SPS, stiff person syndrome.

<sup>a</sup>Includes celiac disease, psoriasis, and myasthenia.

<sup>b</sup>Three tumors (thymoma, endometrial carcinoma, and breast cancer) diagnosed at least 7 years (range, 7-7.6 years) before the onset of their CA. The fourth patient manifested a myelodysplastic syndrome 6 years after the diagnosis of CA. The only tumor in patients with SPS was a case of breast cancer diagnosed 20 years after the onset of SPS.

<sup>c</sup>The index for intrathecal synthesis of GAD-Abs was calculated using the following formula: (CSF GAD-Ab Titer Divided by Serum GAD-Ab Titer) Divided by (CSF Albumin Level in Milligrams per Liter Divided by Serum Albumin Level in Milligrams per Liter).<sup>2</sup>

<sup>d</sup>Calculated in reference to the general IgG ratio instead of the albumin ratio in 13 patients with CA and 11 patients with SPS.<sup>2</sup>

<sup>e</sup>Seven patients having CA and 4 patients having SPS with CSF GAD67-Abs did not manifest these antibodies in serum.

**Table 2**

Symptoms of SPS in 9 Patients With CA and GAD65-Abs Having Muscle Rigidity and Spasms

Sex/Age at Diagnosis, y	Distribution of Stiffness	Other SPS Symptoms	Neurophysiological Findings	Temporal Relationship With CA	Treatment	Clinical Course of SPS and CA
F/53	Legs	Frequent falls	Compatible with SPS <sup>a</sup>	Same time	IVIg	No change with SPS and CA
F/77	Legs, trunk	Leg spasms, lumbar pain	Compatible with SPS	2 y Later	Oral IS, rituximab	SPS improved and later relapsed, CA improved and then progressed
F/76	Right leg	Leg spasms	Compatible with SPS	Same time	IVIg, rituximab, chronic IS	Remission of SPS after first-line treatment and relapsing at last visit (5 y), slow partial improvement of CA
F/50	Legs first, then trunk	Leg spasms, lumbar hyperlordosis	Compatible with SPS	2 y Later	PE, oral IS, rituximab	SPS improved, CA stable
M/74	Leg, trunk	Leg spasms	Sensorimotor polyneuropathy	Same time	IVIg, oral IS	Improvement of both syndromes after 1 y
F/40	Right leg	Leg spasms	Signs of denervation	Same time	IVIg, oral IS	Both syndromes stable
F/59	Legs, trunk	Lumbar pain, hyperlordosis	Normal	Same time	IVIg, oral IS	No response after 4 mo, patient lost to follow-up data
F/52	Legs, first asymmetric	Leg spasms	Not done	5 y Later	IVIg, PE	Mild improvement of SPS spasms, CA stable
F/52	Legs	Leg spasms, agoraphobia	Normal under benzodiazepine treatment	2 y Before <sup>b</sup>	IVIg	Clear improvement of SPS after 1 cycle, no CA immediate effect, patient lost to follow-up data

Abbreviations: CA, cerebellar ataxia; F, female; GAD65-Abs, glutamic acid decarboxylase 65 antibodies; IS, immunosuppression; IVIg, intravenous immunoglobulin; M, male; PE, plasma exchange; SPS, stiff person syndrome.

<sup>a</sup>Continuous motor unit potentials firing at rest and during contraction of antagonist muscles in needle electromyographic recordings.

<sup>b</sup>The patient experienced leg spasms triggered by emotional stimuli and prominent anxiety. She was diagnosed as having conversion disorder until she developed CA.



**Table 3**

Clinical Features of 25 Patients With Long-term Follow-up Data by Good Outcome (mRS Score, <3) and Bad Outcome (mRS Score, ≥ 3)

Variable	Good Outcome (n = 11)	Bad Outcome (n = 14)	P Value
Age, median (range), y	69 (33-76)	54 (36-79)	.58
Female sex, No.	9	13	.41
Type 1 diabetes mellitus at diagnosis, No.	7	10	.50
Associated SPS or epilepsy, No.	5	5	.46
Subacute onset, No.	6	3	.09
mRS score at diagnosis, median (range)	2 (1-4)	3 (2-5)	.01
GAD65-Ab radioimmunoassay, median (interquartile range), 1000 U/mL	11.5 (6.6-20.8)	20.1 (9.3-31.5)	.28
Time to treatment, median (range), mo <sup>a</sup>	5.88 (0.99-64.95)	6.70 (0.13-165.40)	.49
Treated, No.	9	11	.62
Induction therapy <sup>b</sup>	3	5	.49
Maintenance therapy	7	10	.50
IVIg as chronic therapy <sup>c</sup>	3	4	.64
Improvement after therapy <sup>d</sup>	6	1	.01
Total duration of disease, median (range), y	5.02 (1.52-9.15)	8.01 (0.98-23.61)	.08

Abbreviations: GAD65-Ab, glutamic acid decarboxylase 65 antibody; IVIg, intravenous immunoglobulin; mRS, modified Rankin Scale; SPS, stiff person syndrome.

<sup>a</sup>From the onset of symptoms to immunotherapy.

<sup>b</sup>Includes high dose of corticosteroids, rituximab, or cyclophosphamide.

<sup>c</sup>The other patients received immunosuppressors (corticosteroids, azathioprine, or mycophenolate mofetil).

<sup>d</sup>Defined as sustained decrease in mRS score of at least 1 point in treated patients at the last follow-up visit compared with mRS score at diagnosis.