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## Clinical and Immunologic Investigations in Patients With Stiff-Person Spectrum Disorder

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### Abstract

**IMPORTANCE**—Symptoms of stiff-person syndrome (SPS), stiff-limb syndrome (SLS), or progressive encephalomyelitis with rigidity, myoclonus, or other symptoms (SPS-plus) can occur

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with several autoantibodies, but the relative frequency of each antibody, syndrome specificity, and prognostic implications are unclear.

**OBJECTIVE**—To report the clinical and immunologic findings of a large cohort of patients with stiff-person spectrum disorder (SPSD), including SPS, SLS, and SPS-plus.

**DESIGN, SETTING, AND PATIENTS**—This study retrospectively examined a case series (January 1, 1998, through December 31, 2014) of immunologic investigations performed in a neuroimmunology referral center. The study included 121 patients with clinical features of SSPD. Data analysis was performed from July 1, 2015, through November 1, 2015.

**MAIN OUTCOMES AND MEASURES**—Analysis of clinical-immunologic associations, including autoantibodies to 8 proteins expressed in inhibitory synapses.

**RESULTS**—The median age of the patients was 51 years (interquartile range, 40–61 years), and 75 (62.0%) were female. Fifty (41.3%) had SPS, 37 (30.6%) had SPS-plus, 24 (19.8%) had SLS, and 10 (8.3%) had SPS or SLS overlapping with ataxia, epilepsy, or encephalitis. Fifty-two patients (43.0%) had glutamic acid decarboxylase (GAD65) antibodies (2 with  $\gamma$ -aminobutyric acid-A [GABA-A] receptor antibodies), 24 (19.8%) had  $\alpha_1$ -subunit of the glycine receptor (GlyR) antibodies (2 with GAD65 antibodies), 5 (4.1%) had other antibodies, and 40 (33.1%) tested negative for antibodies. None had gephyrin or glycine transporter antibodies. Among the main immunologic groups (GAD65 antibodies, GlyR antibodies, and antibody negative), those with GAD65 antibodies were more likely to be female (45 [86.5%] of 52, 8 [36.4%] of 22, and 18 [45.0%] of 40, respectively;  $P < .001$ ), have systemic autoimmunity (34 [65.4%] of 52, 7 [31.8%] of 22, and 13 [32.5%] of 40, respectively;  $P = .004$ ), and have longer delays in being tested for antibodies (median, 3 vs 0.5 and 1 year;  $P < .001$ ). Patients with GAD65 antibodies were more likely to develop SPS (27 [51.9%] of 52) or overlapping syndromes (8 [15.4%] of 52) than patients with GlyR antibodies (5 [22.7%] and 0 [0%] of 22, respectively), who more often developed SPS-plus (12 [54.5%] of 22 vs 7 [13.5%] in those with GAD65 antibodies); antibody-negative patients had an intermediate syndrome distribution. In multivariable analysis, symptom severity ( $P = .001$ ) and immunologic group ( $P = .01$ ) were independently associated with outcome. Compared with patients with GlyR antibodies, those with GAD65 antibodies (odds ratio, 11.1, 95% CI, 2.3–53.7;  $P = .003$ ) had worse outcome. Patients without antibodies had similar outcome than patients with GlyR antibodies (odds ratio, 4.2, 95% CI, 0.9–20.0;  $P = .07$ ).

**CONCLUSIONS AND RELEVANCE**—In SSPD, symptom severity and presence and type of antibodies are predictors of outcome.

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Stiff-person syndrome (SPS) is a disorder characterized by fluctuating muscle rigidity and painful spasms that occur spontaneously or are triggered by diverse stimuli.<sup>1,2</sup> Partial or segmental forms of the disorder, such as stiff-limb syndrome (SLS) and the more severe disease called progressive encephalomyelitis with rigidity and myoclonus (PERM), are usually considered within the spectrum of SPS,<sup>3–6</sup> but there is an increasing recognition of atypical and overlapping syndromes. For all these disorders, which we collectively termed *stiff-person spectrum disorder* (SPSD), there is evidence of underlying immune mechanisms that target proteins mainly expressed by the inhibitory synapses. Six autoantigens have been identified, including glutamic acid decarboxylase (GAD65),<sup>7,8</sup> the  $\alpha_1$ -subunit of the glycine receptor (GlyR),<sup>9,10</sup> amphiphysin,<sup>11</sup> gephyrin,<sup>12</sup> dipeptidyl peptidase-like protein 6

(DPPX),<sup>13,14</sup> and the  $\gamma$ -aminobutyric acid-A (GABA-A) receptor (GABA<sub>A</sub>R).<sup>15</sup> Some of these immune responses have been suggested to be associated with distinct variants of SPSD,<sup>16</sup> but the degree of syndrome specificity and implications for treatment and prognosis are unclear. Because some autoantigens were recently discovered and SPS is a rare disease, most studies have focused on a limited number of autoantibodies (GAD65 or GlyR) and well-defined syndromes (SPS or PERM) without examining the entire spectrum of clinical-immunologic associations and the implications of being antibody negative. To address these issues, we investigated the clinical features of 121 patients with SPSD, determined the presence of autoantibodies to 8 potential targets of the inhibitory synapse, and compared the syndromes among the most frequent immunophenotypes. In addition, we provide the treatment, outcome, and prognostic factors of 75 patients for whom long-term follow-up information was available.

## Methods

### Study Design and Participants

We retrospectively reviewed the clinical information of patients with SPSD seen by us (57 cases) or whose serum or cerebrospinal fluid (CSF) samples were referred to our laboratory for antibody testing from January 1, 1998, through December 31, 2014. Data analysis was performed from July 1, 2015, through November 1, 2015. Stiff-person spectrum disorder was clinically defined by the presence of symptoms of axial stiffness and muscle spasms not restricted to the classic presentation of SPS but also including forms with partial or distal limb distribution or symptoms of encephalomyelitis. Clinical information was obtained by us or the referring physicians with a structured questionnaire.

One hundred forty-six patients were initially identified as having possible SPSD. Of these, 20 were excluded after other disorders were identified (eMaterial in Supplement) and another 5 because of suboptimal information. Overall, 121 patients had the final diagnosis of SPSD, comprising 4 groups: (1) classic SPS: rigidity in axial trunk, sometimes involving proximal limbs, in association with muscle spasms, resulting in abnormal axial posture<sup>1</sup>; (2) SLS: affecting 1 or more limbs with distal rigidity and abnormal posturing of hands or feet<sup>5</sup>; (3) SPS-plus, including patients with all or partial elements of PERM: brainstem dysfunction, myoclonus, upper or lower motor neuron symptoms, sensory deficits, sphincter or autonomic dysfunction, seizures, and cognitive changes<sup>6</sup>; and (4) overlapping syndromes, including patients with SPS or SLS in association with cerebellar ataxia, epilepsy, or limbic encephalitis.<sup>17–20</sup>

### Key Points

#### Question

Do autoantibodies have prognostic implications in stiff-person spectrum disorder (SPSD)?

#### Findings

In this retrospective case series that included 121 patients, those with glutamic acid decarboxylase antibodies had worse outcome than patients with glycine receptor

antibodies or patients who tested negative for antibodies. In contrast, the type of syndrome did not predict outcome.

### Meaning

In SPSS, the presence and type of autoantibodies are predictors of outcome.

Treatments were classified as (1) symptomatic (eg, GABAergic drugs), (2) first-line immunotherapies (intravenous corticosteroids, intravenous immunoglobulin, or plasma exchange alone or combined), (3) second-line immunotherapies (rituximab, cyclophosphamide), and (4) long-term oral immunotherapy (prednisone, azathioprine, mycophenolate mofetil, cyclosporine).

The delay to diagnosis was calculated as the difference between the patient's age at the time of autoantibody testing and the age at symptom onset. Neurologic disability was measured using the modified Rankin Scale (mRS).<sup>21</sup> The degree of improvement was calculated as the difference between the maximum mRS score during the disease and the score at the last follow-up. Improvement of at least 1 point with an mRS score of 0 to 2 at the last follow-up was considered a good outcome; a score of 3 or higher or no change in the mRS score was considered a bad outcome. Written informed consent for studies was obtained from patients or their families. The study was approved by the institutional review boards of the Hospital of the University of Pennsylvania and Hospital Clinic, University of Barcelona.

### Antibody Assays

Paired serum and CSF samples were available from 65 patients, only serum from 50, and only CSF from 6. Antibody studies were performed using previously reported techniques, which are described in the eMaterial in the Supplement. Serum or CSF samples of 245 patients were used as controls, including samples from 30 healthy individuals, 20 patients with neurodegenerative diseases, and 195 patients with immune-mediated central nervous system disorders (eMaterial in Supplement).

### Statistical Analysis

Demographic information and symptoms were analyzed using the Fisher exact test, Fisher-Freeman-Halton test (an extension for rxc contingency tables), or Mann-Whitney test, as appropriate. Because of a skewed distribution, log transformation was used for duration of follow-up. The maximum mRS score was dichotomized as low (range, 0–3) or high (range, 4–6). Factors that influenced outcome were assessed by univariable binary logistic regression. Factors associated with a bad outcome ( $P < .10$ ) were included in a multivariable binary logistic regression model and approached by backward stepwise procedure; only the variables that remained significant were considered as independent predictors. Odds ratios (95% CIs) were used to measure the effect of predictors. SPSS statistical software, version 19 (SPSS Inc), was used for the analyses.

## Results

### General Clinical Features

Seventy-five (62.0%) of 121 patients were women. The median age at symptom onset was 51 years (interquartile range [IQR], 40–61 years), and the median delay to diagnosis was 2 years (IQR, 0–4 years). Fifty patients (41.3%) had SPS, 37 (30.6%) had SPS-plus, 24 (19.8%) had SLS, and 10 (8.3%) had SPS or SLS overlapping with cerebellar ataxia (6 cases), epilepsy (3 cases), or limbic encephalitis (1 case). Clinical features, diagnostic tests, and outcome according to immunologic groups are listed in Table 1 and according to the type of syndrome in eTable 1 in the Supplement.

Neurophysiologic studies were performed in 84 patients, revealing continuous motor unit activity in 52 (61.9%), with a similar proportion of positive cases across all syndromes (eTable 1 in the Supplement). Only 7 patients (5.8%) had abnormal magnetic resonance imaging findings, including high T2 signal in temporal lobes in 2 patients with overlapping syndromes (1 limbic encephalitis and 1 epilepsy) and focal or diffuse high T2 signal in 5 patients with SPS-plus (2 brain, 2 brainstem, and 1 spinal cord abnormalities). Three patients (2.5%) had cancer (2 breast, 1 colon), 1 each presenting with SLS, SPS-plus, and overlapping syndromes.

Patients with SPS-plus had higher mRS scores (more disabled) than those with SPS and SLS (median, 4; IQR, 3–5; median, 4; IQR, 2.5–4 [ $P = .001$ ]; and median, 3; IQR, 2–4 [ $P = .002$ ], respectively) (eTable 1 in the Supplement). In addition to first-line immunotherapy, patients with SPS-plus were more likely to receive long-term oral immunotherapy than those with other syndromes, and patients with overlapping neurologic syndromes were more likely to receive second-line immunotherapy (eTable 1 in the Supplement). Symptomatic GABAergic drugs were more frequently used in typical SPS (42 [84.0%] vs 16 [66.6%] in SLS, 21 [56.7%] in SPS-plus, and 5 [50.0%] in overlapping syndromes,  $P = .006$ ).

### Antibody Findings

Eighty-one patients (66.9%) had autoantibodies against inhibitory synaptic proteins, including 52 (43.0%) with GAD65 (2 with concurrent GABA<sub>A</sub>R antibodies), 24 (19.8%) with GlyR (2 with concurrent GAD65 antibodies), 5 (4.1%) with other antibodies (2 GABA<sub>A</sub>R, 2 amphiphysin, 1DPPX), and 40 (33.1%) who were antibody negative. Paired serum and CSF samples were studied in 26 (50.0%) of 52 patients with GAD65 antibodies and 14 (58.3%) of 24 patients with GlyR antibodies; in 3 (11.5%) of 26 patients, GAD65 antibodies were detected only in CSF, and in 6 (42.8%) of 14 patients, GlyR antibodies were detected only in serum. None of the patients had antibodies against gephyrin, glycine transporter (GlyT) 1 or GlyT2. Three patients (2.4%) of 121, without antibodies against any of the 8 target antigens, had serum antibodies against unknown neuronal cell surface antigens determined in live neuronal cultures.

Fifteen (6.1%) of 245 controls had GlyR antibodies in serum: 4 had cerebellar ataxia, 2 had epilepsy, 4 had anti-N-methyl-D-aspartate receptor encephalitis, and 5 had multiple sclerosis. Five controls (2.0%) had GABA<sub>A</sub>R antibodies: 1 had cerebellar ataxia, 3 had epilepsy, and 1 had anti-N-methyl-D-aspartate receptor encephalitis. Paired CSF samples

were available from 12 of these 20 patients, and all tested negative for GlyR and GABA<sub>A</sub>R antibodies. The titers of GlyR antibodies in serum tended to be lower in the controls than in patients with SPSD (median titer, 1/80; range, 1/40 to 1/640; vs median titer, 1/160; range, 1/40 to 1/1280;  $P = .06$ ). The titers of GABA<sub>A</sub>R antibodies in serum of controls and patients with SPSD were similar (median titer, 1/40; range, 1/20 to 1/160; vs median titer, 1/40; range, 1/20 to 1/40;  $P = .09$ ). None of the controls with GlyR antibodies had symptoms of SPSD; 4 of 5 controls with serum GABA<sub>A</sub>R antibodies had prominent seizures.

### Clinical Comparisons of Immunologic Groups

These studies focused on the main immunologic groups (GAD65 antibodies, GlyR antibodies, and antibody negative), which comprised 114 (94.2%) of 121 patients; the 2 patients with coexisting GAD65 and GlyR antibodies were excluded. Patients with GAD65 antibodies or antibody-negative patients were more likely to develop SPS than those with GlyR antibodies, who more frequently developed SPS-plus ( $P = .002$ ; see list of symptoms in Table 1). Patients with GAD65 antibodies were investigated for antibodies later than those with GlyR antibodies or antibody-negative patients (median delay to diagnosis, 3 years; IQR, 1–6 years; 0.5 year; IQR, 0–2 years [ $P < .001$ ]; and 1 year; IQR, 0–5 years [ $P = .02$ ], respectively) and had lower maximum mRS scores (lower symptom severity) compared with those of the other 2 groups (median mRS score for GAD65, 3.5; IQR, 2–4; GlyR, 4; IQR, 3.5–5 [ $P = .01$ ]; and antibody negative, 4; IQR, 3–5 [ $P = .05$ ], respectively). Patients with GAD65 antibodies were more likely to be female (45 [86.5%] of 52, 8 [36.4%] of 22, and 18 [45.0%] of 40, respectively;  $P < .001$ ) and had more frequent systemic autoimmune or endocrine disorders (34 [65.4%] of 52, 7 [31.8%] of 22, and 13 [32.5%] of 40, respectively;  $P = .004$ ). On the other hand, patients with GlyR antibodies had more frequent CSF pleocytosis than those of the other 2 groups (7 [38.9%] of 18 vs 2 [10.0%] of 20 for the GAD65 group and 4 [14.8%] of 27 for the antibody-negative group,  $P < .001$ ). None of the antibody-negative patients had CSF oligoclonal bands (11 [47.8%] of 23, 5 [29.4%] of 17, and 0 of 19 in the GAD65 antibodies, GlyR antibodies, or antibody-negative groups, respectively;  $P < .001$ ). No significant differences were identified in terms of age at onset of symptoms, electrophysiologic findings, immunotherapies used, and relapses among the 3 immunological groups (Table 1).

Because SPSD without antibodies has been infrequently reported in the literature,<sup>16</sup> we further assessed the clinical features of the 3 immunologic groups to compare only those patients with SPSD and electromyographic findings of agonist-antagonist continuous motor unit activity. This subgroup analysis revealed that the antibody-negative patients still composed one-third of the cases, and the main distinctive clinical features among immunologic groups were similar to those indicated above (eTable 2 in the Supplement).

Among the group of 10 patients with SPS or SLS, and overlapping syndromes, 8 had GAD65 antibodies (5 cerebellar ataxia and 3 epilepsy), 1 had limbic encephalitis and amphiphysin antibodies, and 1 had cerebellar ataxia and was antibody negative. Five patients without GAD65 and GlyR antibodies had autoantibodies against other known antigens (2 amphiphysin, 2 GABA<sub>A</sub>R, and 1 DPPX; eMaterial in Supplement).

## Clinical Outcome

Clinical outcome was available for 75 patients (62.0%), with a median follow-up of 18 months (IQR, 11–60 months). Patients with GlyR antibodies had a greater degree of improvement than those with GAD65 antibodies or without antibodies (median change in mRS score for patients with GlyR antibodies, 3; IQR, 0.75–4; for patient with GAD65 antibodies, 1; IQR, 0–1 [ $P = .002$ ]; and antibody-negative patients, 1; IQR, 0–2 [ $P = .04$ ]) (Table 1). The eFigure in the Supplement shows patients' outcome according to the clinical syndrome and immunologic group. At the last follow-up, 40 patients (53.3%) had a bad outcome, and 35 (46.7%) had a good outcome. Nine patients (12.0%) died, 5 as a result of systemic complications (pneumonia, pulmonary embolism, sepsis, intestinal perforation, status epilepticus) and 4 of cardiorespiratory arrest; 6 patients had GAD65 antibodies, 2 were antibody negative, and 1 had GlyR antibodies. In univariable analysis, the factors significantly associated with a bad outcome were symptom severity and presence of GAD65 antibodies (Table 2). In multi-variable analysis, symptom severity and immunologic group were independently associated with outcome (Table 2). Compared with patients with GlyR antibodies, those with GAD65 antibodies (odds ratio, 11.1, 95% CI, 2.3–53.7;  $P = .003$ ) had worse outcome. Patients without antibodies had similar outcome than patients with GlyR antibodies (odds ratio, 4.2, 95% CI, 0.9–20.0;  $P = .07$ ).

## Discussion

This study reveals that in a cohort of 121 patients with SPSD only 50 (41.3%) had typical SPS, and the overall prognosis depended more on the underlying immune mechanism and severity of symptoms than on the type of syndrome. Among 8 potential autoantigens, GAD65 and GlyR were by far the most frequently identified, leading to 3 immunologic groups: GAD65 antibodies (43.0%), GlyR antibodies (19.8%), and antibody negative (33.1%).

The clinical features associated with GAD65 antibodies were similar in many respects to those previously reported.<sup>20,22–24</sup> When compared with patients with GlyR antibodies or without antibodies, those with GAD65 antibodies were more likely to be female and have systemic autoimmune or endocrine disorders. The main neurologic differences among the 3 immunophenotypes depended on the relative frequency of symptoms included within the spectrum of PERM (hyperekplexia, myoclonus, brainstem, pyramidal, sensory, or autonomic dysfunction), which were mainly associated with GlyR antibodies, whereas the development of classic SPS or SLS with or without overlapping syndromes (eg, cerebellar ataxia, epilepsy) more frequently occurred with GAD65 antibodies. Patients without antibodies had a distribution of symptoms between those associated with GlyR and GAD65 antibodies. Although these differences were statistically significant, there was no clear syndrome-immunologic specificity, indicating that any form of SPSD can potentially occur with any of the 3 main immunologic groups considered here.

A frequent concern that arises in clinical practice is how frequently other antibodies that are less accessible in clinical laboratories (eg, DPPX, GABA<sub>A</sub>R, gephyrin) are missed because they are not tested for. The current data indicate that in our setting (a reference center for autoimmune and paraneoplastic disorders of the central nervous system) the frequency of

antibodies other than GAD65 and GlyR is low. Indeed, only 5 patients (4.1%) had antibodies to amphiphysin, DPPX, or GABA<sub>A</sub>R, and none had antibodies to gephyrin, GlyT1, or GlyT2. These transporters were included because their mutations result in symptoms similar to those reported in mutations or autoimmunity to GlyR (hyperekplexia).<sup>25</sup> Compared with previous studies,<sup>24,26</sup> our findings reveal a larger group of seronegative patients (40 [33.1%] of 121 patients vs 16 [23.5%] of 68 patients<sup>24</sup> and 18 [18.2%] of 99 patients<sup>26</sup>). This finding is likely explained by the fact that 20 patients (16.5%) were referred to our center for assessment of novel or atypical antibodies after clinical or commercial antibody tests (mostly composed of GAD65, amphiphysin, or GlyR) tested negative. This referral pattern emphasizes even more the low frequency of DPPX and GABA<sub>A</sub>R antibodies among patients who test negative for the more common autoantibodies. The low frequency of amphiphysin antibodies has been reported in previous series.<sup>27,28</sup> Nevertheless, amphiphysin antibodies are important to consider in the paraneoplastic context, mainly breast and lung cancer.<sup>27</sup>

Detection of GABA<sub>A</sub>R antibodies in CSF or at high titers in serum ( > 1/160) is associated with encephalitis with severe seizures or status epilepticus but without SPSD.<sup>15</sup> Therefore, detection of these antibodies only in serum and at low titers should be interpreted with caution. Similar caution should be considered for low serum titers of GlyR antibodies, which as reported here and in previous studies<sup>29–31</sup> occurred in 6% to 10% of controls without SPSD (eg, multiple sclerosis, cerebellar degeneration, or epilepsy). When CSF was available, none of these patients had GlyR antibodies in CSF, a finding that needs confirmation with a larger number of patients. In contrast, for GAD65 antibodies, we used 2 previously validated techniques (immunohistochemistry with rat brain and cell-based assay) that only reveal these antibodies if they are present at moderate to high titers, similar to those associated with neurologic disorders; titers equivalent to radioimmunoassay values of 2000 U/mL or less (seen in many patients with diabetes mellitus) are not detected with the techniques used here.<sup>20,31</sup>

A novel finding of our study is that the underlying mechanism (eg, presence and type of antibodies) but not the type of syndrome (eg, SPS, SLS, SPS-plus, or overlapping syndrome) was an independent predictor of outcome. For example, although at disease diagnosis patients with GlyR antibodies had more severe neurologic deficits than patients with GAD65 antibodies (and similar to antibody-negative patients), the outcome of patients with GlyR was better than that of patients with GAD65 antibodies. This finding could be explained by an early diagnosis in patients with GlyR antibodies (as shown in our study), which is likely owing to a more rapid and severe symptom onset (eg, SPS-plus or PERM) and the presence of CSF inflammatory changes when compared with patients of the other groups. Moreover, patients with GlyR antibodies were treated more aggressively (eg, first-line immunotherapy combined with second-line or long-term oral immunotherapy) than those of the other 2 groups, who more often received first-line immunotherapy and symptomatic treatment. On the other hand, disorders associated with antibodies to cell surface antigens, such as GlyR, are usually more responsive to immunotherapy than those associated with intracellular antigens, such as GAD65 or paraneoplastic antigens.

Our study has limitations related to its retrospective nature and possible selection of cases toward complex syndromes (with elements of PERM or overlapping syndromes). These



limitations may explain the lower frequency of GAD65 antibody-positive cases compared with that of other series (52 [43.0%] of 121 patients vs 50 [73.5%] of 68 patients<sup>24</sup> and 79 [79.8%] of 99 patients<sup>26</sup>). Despite this, to our knowledge, the current series provides the most comprehensive autoantibody screening reported to date in SPSD. One could argue that using cultures of hippocampal neurons we missed antibodies directed to novel antigens restricted to the brainstem or spinal cord, a possibility to consider in future studies.

## Conclusions

Several practical implications can be derived from this and previous studies.<sup>32–34</sup> First, SPSD is a complex group of disorders, with multiple autoantigens but 3 predominant immunophenotypes (GAD65 antibodies, GlyR antibodies, and antibody negative). Second, this immunologic characterization and the severity of symptoms are predictors of outcome. Third, although PERM predominantly occurs with GlyR antibodies, it can potentially be associated with other autoantibodies. This implication is important because, contrary to the concept that PERM carries a poor prognosis,<sup>35</sup> our findings indicate that this depends on the underlying immune response (worse in patients with GAD65 antibodies than antibody-negative patients and patients with GlyR antibodies). Fourth, DPPX and GABAaR are infrequent in SPSD; our data do not support upfront testing for these antibodies unless the clinical context (eg, gastrointestinal symptoms, hyperekplexia, encephalopathy for DPPX,<sup>36</sup> or prominent seizures for GABAaR) suggest their investigation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical Features of the Main Immunologic Groups<sup>a</sup>

Clinical Feature	GAD65 Antibodies (n = 52 [43.0%])	GlyR Antibodies (n = 22 [18.2%]) <sup>b</sup>	Antibody Negative (n = 40 [33.1%])	P Value
Female sex	45 (86.5)	8 (36.4)	18 (45.0)	<.001
Age at onset, median (IQR), y	52.5 (39.0–62.0)	46.0 (39.0–60.0)	50.0 (39.0–59.0)	.74
Delay to diagnosis, median (IQR), y	3.0 (1.0–6.0)	0.5 (0–2.0)	1.0 (0–5.0)	<.001 <sup>c</sup>
Syndrome				
SPS	27 (51.9)	5 (22.7)	17 (42.5)	.002
SLS	10 (19.2)	5 (22.7)	7 (17.5)	
SPS-plus	7 (13.5)	12 (54.5)	15 (37.5)	
Overlapping syndromes	8 (15.4)	0	1 (2.5)	
Hyperekplexia	14 (26.9)	11 (50.0)	11 (27.5)	.009
Myoclonus	6 (11.5)	9 (40.9)	9 (22.5)	.07
Brainstem	3 (5.8)	10 (45.5)	7 (17.5)	.002
Pyramidal	7 (13.5)	11 (50.0)	11 (27.5)	.004
Sphincter	1 (1.9)	7 (31.8)	5 (12.5)	.008
Sensory	0	5 (22.7)	3 (7.5)	.01
Autonomic	5 (9.6)	7 (31.8)	6 (15.0)	.06
Insomnia	2 (3.8)	6 (27.3)	7 (17.5)	.045
Systemic autoimmune disorders <sup>d</sup>	34 (65.4)	7 (31.8)	13 (32.5)	.004
CMUA on EMG	26/36 (72.2)	6/14 (42.9)	16/30 (53.3)	.25
CSF pleocytosis	2/20 (10.0)	7/18 (38.9)	4/27 (14.8)	<.001
CSF OCBs	11/23 (47.8)	5/17 (29.4)	0/19 (0)	<.001
Maximum mRS score, median (IQR)	3.5 (2–4)	4 (3.5–5)	4 (3–5)	.02 <sup>c</sup>
Symptomatic treatment	46 (88.5)	10 (45.5)	24 (60.0)	<.001
Type of immunotherapy				
Nontreated	9/45 (20.0)	2/18 (11.1)	6/28 (21.4)	.17
First line only	22/45 (48.9)	4/18 (22.2)	11/28 (29.3)	
First line and long-term oral	4/45 (8.9)	7/18 (38.9)	4/28 (14.3)	
First and second line	7/45 (15.5)	5/18 (27.8)	6/28 (21.4)	
Other <sup>e</sup>	3/45 (6.7)	0	1/28 (3.6)	
Cases with follow-up	41 (78.8)	14 (63.6)	24 (60.0)	.13
Follow-up period, median (IQR), mo	34.0 (12.0–66.0)	11.0 (8.0–40.0)	12.0 (9.0–54.0)	.049 <sup>c</sup>
Relapsing course	13/41 (31.7)	6/14 (42.9)	6/24 (25.0)	.77
Final mRS score, median (IQR)	3 (1–3)	1 (1–3)	2.5 (1–4)	.14
Improvement				
Treated	24/32 (75.0)	11/14 (78.6)	11/19 (57.9)	.14
Nontreated	3/9 (33.3)	0	4/5 (80.0)	

Clinical Feature	GAD65 Antibodies (n = 52 [43.0%])	GlyR Antibodies (n = 22 [18.2%]) <sup>b</sup>	Antibody Negative (n = 40 [33.1%])	P Value
Change in mRS score, median (IQR)	1 (0–1)	3 (0.75–4)	1 (0–2)	.009 <sup>c</sup>

Abbreviations: CMUA, continuous motor unit activity; CSF, cerebrospinal fluid; EMG, electromyography; GAD65, glutamic acid decarboxylase; GlyR,  $\alpha 1$ -subunit of the glycine receptor; IQR, interquartile range; mRS, modified Rankin scale; OCBs, oligoclonal bands; SLS, stiff-limb syndrome; SPS, stiff-person syndrome; SPS-plus, progressive encephalomyelitis with rigidity, myoclonus, or other symptoms.

<sup>a</sup>Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup>Excludes 2 patients with concurrent GAD65 and GlyR antibodies.

<sup>c</sup>Mann-Whitney test: delay to diagnosis for patients with GAD65 antibodies vs GlyR antibodies,  $P < .001$ ; GAD65 antibodies vs antibody negative,  $P = .02$ ; and GlyR antibodies vs antibody negative,  $P = .052$ ; maximum mRS score for patients with GAD65 antibodies vs GlyR antibodies,  $P = .01$ ; GAD65 antibodies vs antibody negative,  $P = .05$ ; and GlyR antibodies vs antibody negative,  $P = .44$ ; follow-up period for patients with GAD65 antibodies vs GlyR antibodies,  $P = .04$ ; GAD65 antibodies vs antibody negative,  $P = .053$ ; and GlyR antibodies vs antibody negative,  $P = .70$ ; and change in mRS score for GAD65 antibodies vs GlyR antibodies,  $P = .002$ ; GAD65 antibodies vs antibody negative,  $P = .41$ ; and GlyR antibodies vs antibody negative,  $P = .04$ .

<sup>d</sup>Fifty-four patients (44.6%), including 18 with type 1 diabetes mellitus, 13 with thyroiditis, 2 with celiac disease, 2 with psoriasis, 2 with vitiligo, 2 with Raynaud syndrome, and 15 with thyroid, antinuclear antibody, double-stranded DNA, or gastric parietal cell antibodies.

<sup>e</sup>Includes 3 patients who received long-term oral immunotherapy (not preceded by first-line therapy) and 1 patient who received chemotherapy for colon cancer.

**Table 2**

Variables Related to a Bad Outcome (mRS Scores of 3–6 or No Improvement)

Variable	Odds Ratio (95% CI)	P Value
<b>Univariable Analysis</b>		
Sex	1.56 (0.59–4.1)	.37
Age at onset	1.02 (0.99–1.05)	.18
Clinical syndrome		.85
SPS (n = 32)	...	...
SLS (n = 14)	0.58 (0.16–2.1)	.40
SPS-plus (n = 25)	0.72 (0.25–2.1)	.54
Overlapping syndromes (n = 4)	...(0–∞)	.99
Delay to diagnosis <sup>a</sup>	1.20 (0.96–1.48)	.11
Maximum mRS group (4–6 vs 0–3)	3.9 (1.50–10.4)	.005
Follow-up period (log <sub>e</sub> )	0.89 (0.57–1.41)	.63
Immunotherapy		
Nontreated	...	...
Treated	1.18 (0.37–3.8)	.78
Immunologic group		
GlyR antibodies (n = 14)	...	...
Antibody negative (n = 22)	2.5 (0.60–10.4)	.21
GAD65 antibodies (n = 39)	4.5 (1.20–16.9)	.03
<b>Multivariable Analysis</b>		
Maximum mRS group	7.5 (2.3–24.5)	.001
Immunologic group		.01
GlyR antibodies	...	...
Antibody negative	4.2 (0.90–20.0)	.07
GAD65 antibodies	11.1 (2.3–53.7)	.003

Abbreviations: ellipses, data not applicable; GAD65, glutamic acid decarboxylase; GlyR,  $\alpha$ 1-subunit of the glycine receptor; log<sub>e</sub>, natural logarithm; mRS, modified Rankin scale; SLS, stiff-limb syndrome; SPS, stiff-person syndrome; SPS-plus, progressive encephalomyelitis with rigidity, myoclonus, or other symptom.

<sup>a</sup>For patients tested for autoantibodies after 5 years of symptom onset (n = 15), the delay to diagnosis was considered 6 years.