

Prevalence, Clinical Profiles, and Prognosis of Stiff-Person Syndrome in a Japanese Nationwide Survey

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Abstract

Background and Objectives

To elucidate current epidemiologic, clinical, and immunologic profiles and treatments of stiff-person syndrome (SPS) in Japan.

Methods

A nationwide mail survey was conducted using an established method. Data processing sheets were sent to randomly selected departments of internal medicine, neurology, pediatrics, psychiatry, and neurosurgery in hospitals and clinics throughout Japan to identify patients with SPS who were seen between January 2015 and December 2017.

Results

Thirty cases were identified as glutamic acid decarboxylase 65 (GAD65)-positive SPS cases on the basis of detailed clinical data of 55 cases. Four patients had α_1 subunit of glycine receptor (GlyR) antibodies, and 1 patient had both GAD65 and GlyR antibodies. The total estimated number of patients with GAD65-positive SPS was 140, and the estimated prevalence was 0.11 per 100,000 population. The median age at onset was 51 years (range, 26–83 years), and 23 (76%) were female. Of these, 70% had classic SPS, and 30% had stiff-limb syndrome. The median time from symptom onset to diagnosis was significantly longer in the high-titer GAD65 antibody group than in the low-titer group (13 months vs 2.5 months, $p = 0.01$). The median modified Rankin Scale (mRS) at baseline was 4, and the median mRS at the last follow-up was 2. Among the 29 GAD65-positive patients with ≥ 1 year follow-up, 7 received only symptomatic treatment, 9 underwent immunotherapy without long-term immunotherapy, and 13 received long-term immunotherapy such as oral prednisolone. The coexistence of type 1 diabetes mellitus and the lack of long-term immunotherapy were independent risk factors for poor outcome (mRS ≥ 3) in the GAD65-positive patients (odds ratio, 15.0; 95% CI 2.6–131.6; $p = 0.001$; odds ratio, 19.8; 95% CI 3.2–191.5; $p = 0.001$, respectively).

Discussion

This study provides the current epidemiologic and clinical status of SPS in Japan. The symptom onset to the diagnosis of SPS was longer in patients with high-titer GAD65 antibodies than in those with low-titer GAD65 antibodies. The outcome of patients with SPS was generally favorable, but more aggressive immunotherapies are necessary for GAD65-positive patients with SPS.

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Japanese SPS Study coinvestigators are listed in the appendix at the end of the article.

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Glossary

CBA = cell-based assay; **EIA** = enzyme immunoassay; **GAD65** = glutamic acid decarboxylase 65; **GlyR** = glycine receptor; **IVIg** = IV immunoglobulin; **IVMP** = IV methylprednisolone; **mRS** = modified Rankin Scale; **PERM** = progressive encephalomyelitis with rigidity and myoclonus; **PNS** = paraneoplastic neurological syndrome; **RIA** = radioimmunoassay; **SLS** = stiff-limb syndrome; **SPS** = stiff-person syndrome.

Introduction

Stiff-person syndrome (SPS) is a rare autoimmune neurologic disorder characterized by progressive axial muscle stiffness, CNS hyperexcitability, and stimulus-sensitive painful muscle spasms.¹ Women are predominantly affected (62–70% of cases), with most patients presenting in their 40s to 50s.^{2–4} SPS is classified into classic SPS and SPS variants, including stiff-limb syndrome (SLS) and progressive encephalomyelitis with rigidity and myoclonus (PERM), on the basis of clinical presentation.^{1,5} Most patients with SPS have antibodies against glutamic acid decarboxylase 65 (GAD65), the rate-limiting enzyme in the production of the inhibitory neurotransmitter γ -aminobutyric acid (GABA).^{1,6,7} Amphiphysin antibodies are also detected in some patients with paraneoplastic SPS.⁵ Patients with PERM may present with symptoms similar to classic SPS but with additional features, including brainstem symptoms, hyperreflexia, myoclonus, and dysautonomia.^{8,9} PERM is associated with glycine receptor (GlyR) α 1 subunit antibodies and generally responsive to immunotherapy.^{4,10} Since the initial description of SPS in 1956, marked progress has been made in the clinical characterization of SPS.¹¹ However, no large-scale epidemiologic studies have been conducted except for 1 clinic-based study that reported an estimated prevalence of one to two cases per million population.¹² GAD65 antibodies are useful diagnostic markers, but their role in the pathogenesis of SPS is unclear.^{1,13} Moreover, their clinical relevance is questionable in patients with low GAD65 antibody titers.¹⁴ It has also been reported that the outcome is poor in patients with GAD65 antibodies.^{3,4} As some patients respond poorly to conventional immunotherapies, the exact nature of GAD65 antibody-associated SPS needs to be clarified. Against this backdrop, we conducted a nationwide epidemiologic survey of SPS in Japan and compared the clinical features among different immunologic groups (autoantibody-associated patients).

Methods

Epidemiologic Survey

A nationwide mail survey of SPS was conducted in 2018 in Japan.

The survey targeted 5 departments (internal medicine, neurology, pediatrics, psychiatry, and neurosurgery). First, the study centers were randomly selected from a complete list of hospitals and clinics in Japan in the Nationwide Epidemiologic Survey Manual issued by the Research Committee on Epidemiology of Intractable Disease.¹⁵ Selection rates were

determined on the basis of 8 categories that were defined in accordance with the number of beds in a hospital: (I) university hospitals, 100%; (II) hospitals with \geq 500 beds, 100%; (III) hospitals with 400–499 beds, 80%; (IV) hospitals with 300–399 beds, 40%; (V) hospitals with 200–299 beds, 20%; (VI) hospitals with 100–199 beds, 10%; (VII) private clinics or hospitals with $<$ 100 beds, 5%; and (VIII) specific neuromuscular centers dealing with intractable diseases, 100%.

We sent our first survey, which included a questionnaire and the diagnostic criteria for SPS adopted from the work of Dalakas¹ (eTable 1, links.lww.com/NXI/A904), to each of the randomly selected study centers. The aim of the first survey was to obtain data on the number of patients with SPS who had visited the respective study centers from January 1, 2015, to December 31, 2017.

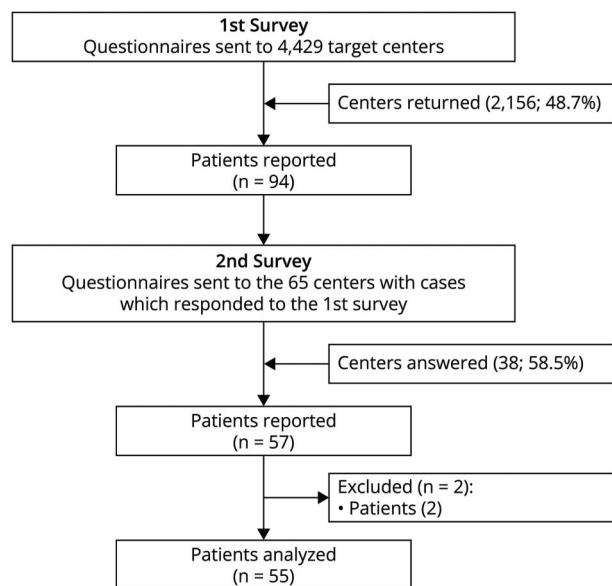
Second, the estimated number of patients was calculated for each category using the following formula: total estimated number of patients = reported number of patients / (selection rate \times response rate) = reported number of patients / (number of responding centers / total number of study centers). Finally, the total estimated number of patients for all categories was determined. Ninety-five percent confidence intervals (95% CIs) were calculated, assuming a multinomial hypergeometric distribution. This method has been validated in previous nationwide surveys of intractable diseases in Japan.^{16–18}

In the second survey sent to the study centers that reported the number of patients with SPS, a predefined format was used to collect the detailed clinical data of each patient (Figure 1).

Evaluation of Clinical Features, Treatment, and Outcome

We collected the detailed clinical data of patients with SPS through the second survey and classified the patients into 3 groups: (1) classic SPS: rigidity of the axial trunk, sometimes involving the proximal limbs, in association with muscle spasms resulting in abnormal axial posture¹⁹; (2) SLS: affecting one or more limbs with distal rigidity and abnormal posture of hands or feet^{20,21}; and (3) PERM: progressive encephalomyelitis accompanied with rigidity and myoclonus^{3,22} (eTable 1, links.lww.com/NXI/A904). The detailed history, time from symptom onset to diagnosis, examination findings, and serologic and electrophysiologic data at the time of initial evaluation of all patients were documented. Treatments were classified as follows: (1) symptomatic treatment (e.g., GABAergic drugs), (2)

Figure 1 Flowchart of the Nationwide Survey



SPS = stiff-person syndrome.

first-line immunotherapy (IV methylprednisolone (IVMP), IV immunoglobulin (IVIg), or plasma exchange alone or in combination), (3) second-line immunotherapy (rituximab, cyclophosphamide), and (4) long-term oral immunotherapy (prednisolone (PSL), azathioprine, tacrolimus).⁴ The time from diagnosis to immunotherapy and/or IVIg and the improvement of symptoms were also documented. The disability level was assessed using the modified Rankin Scale (mRS) at baseline and at the last follow-up.²³

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee of Tokushima University Hospital. Written informed consent was obtained from the patients or their proxies.

Antibody Assays

GAD65 antibodies were measured by radioimmunoassay (RIA), enzyme immunoassay (EIA), or ELISA using commercially available kits (SRL, Inc. or BML, Inc., Tokyo, Japan). GAD65 antibodies were considered positive when the antibody titers were >1.4 U/mL with RIA, ≥ 5 U/mL with EIA, and ≥ 5 U/mL with ELISA.

Amphiphysin antibodies were measured using commercial immunoblotting assay (EUROIMMUN AG, Lübeck, Germany).

Dipeptidyl-peptidase-like protein 6 (DPPX) antibodies were measured with an IIFT Autoimmune Encephalitis Mosaic 6 test kit (EUROIMMUN AG, Lübeck, Germany) or an in-house cell-based assay (CBA) through the courtesy of Dr. Josep Dalmau (Barcelona, Spain).²⁴

Both GlyR and GABA_B receptor (GABA_BR) antibodies were measured with an established in-house CBA (eMaterial, links. lww.com/NXI/A910) through the courtesy of Dr. Keiko Tanaka (Niigata University, Japan).

Some GlyR antibody tests were performed at Oxford University, Oxford, and the Laboratory of Experimental Neuroimmunology, IDIBAPS-Hospital Clinic, Barcelona, using previously reported CBA techniques.^{8,25} Autoantibodies against other SPS-associated antigens, including GABA_BR, were also examined in IDIBAPS-Hospital Clinic.^{4,24,26}

Statistical Analysis

Continuous and categorical variables were reported as median (range) and number (percentage), respectively. Comparisons across 2 or more groups were performed using the Kruskal-Wallis test (continuous variables) and the χ^2 or Fisher exact test (categorical variables). Pairwise comparisons were performed using the Wilcoxon rank-sum test (continuous variables) and Fisher exact test (categorical variables). Factors that influenced the outcome of SPS were assessed using univariable binary logistic regression.

Odds ratios (profile likelihood 95% CIs) were used to measure the effect of predictors. SPSS version 19 and SAS version 9.4 were used for the analysis.

Data Availability

Any data not published in the article will be shared anonymously on request by any qualified investigator.

Results

First Survey

In the first survey, we randomly selected 4,429 (28.0%) study centers from a total of 15,848 hospitals and clinics with internal medicine, neurology, pediatrics, psychiatry, and neurosurgery departments across Japan, listed in the Nationwide Epidemiologic Survey Manual issued by the Research Committee on Epidemiology of Intractable Disease. Of these, 2,156 (48.7%) responded, reporting 94 patients with SPS in total (Figure 1).

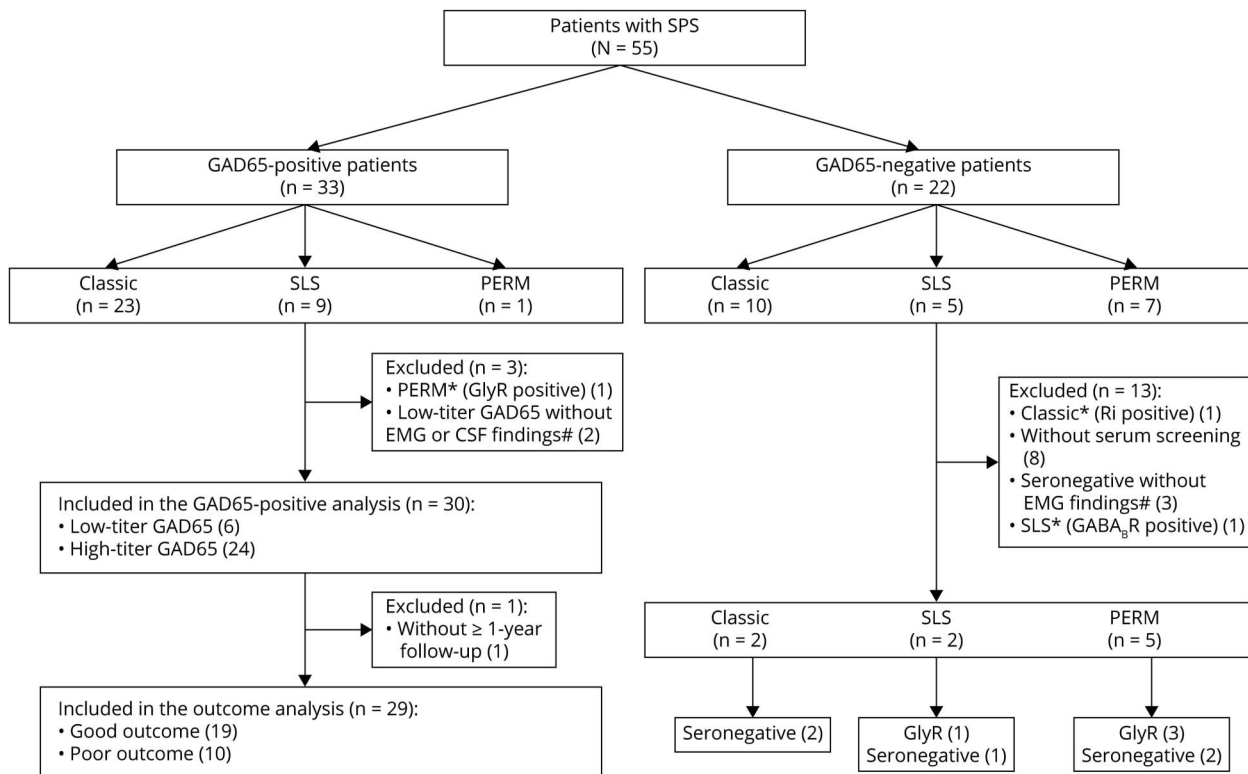
Second Survey

In the second survey, we sent questionnaires to 65 study centers to collect detailed clinical data of patients with SPS. The clinical data of 57 patients were initially collected from 38 study centers (58%) that responded to the second survey. Of these, one patient for whom SPS could not be differentiated from other neurologic disorders and another patient with insufficient information were excluded. The study population thus consisted of 55 patients with the final diagnosis of SPS (Figure 1).

Antibody Findings

Thirty-three of the 55 patients tested positive for GAD65 antibodies in serum, and 16 of 24 patients tested positive for GAD65 antibodies in CSF. The antibody titers and the test

Figure 2 Flowchart of the Clinical Study



GAD65 = glutamic acid decarboxylase 65; GlyR = glycine receptor $\alpha 1$ subunit. # Lack of antagonist inhibition on EMG is defined by continuous co-contraction of agonist and antagonist muscles (inhibitory to relax) as confirmed by EMG.

methods for each case are presented in eFigure 1 (links.lww.com/NXI/A909) and eTable 2 (links.lww.com/NXI/A905).

Amphiphysin antibodies were examined in serum samples from 31 patients, whereas DPPX antibodies were examined in both serum and CSF samples from 7 patients or only serum samples from 18 patients. None of the patients was positive for amphiphysin or DPPX antibodies, and 1 patient had Ri antibodies (eTable 2, links.lww.com/NXI/A905).

GlyR and GABA_BR antibodies were examined in both serum and CSF samples from 8 patients or only serum samples from 18 patients. GlyR antibodies were identified in 5 patients (both serum and CSF [n = 4], serum only [n = 1]). One of the 5 patients positive for GlyR antibodies was also positive for GAD65 antibodies (eTable 2, links.lww.com/NXI/A905). We confirmed that the serum sample of 1 patient was positive for GABA_BR antibodies by IIFT Autoimmune Encephalitis Mosaic 6 and in-house CBA using GABA_BR stably expressing HEK293 cells (data not shown). This patient had no other SPS-related autoantibodies.

GAD65-Positive Patients

The 33 GAD65-positive patients were classified into 3 groups on the basis of clinical phenotype: classic SPS (23 patients, 70%), SLS (9 patients, 27%), and PERM (1 patient, 3%)

(Figure 2). One patient with PERM who was positive for both GAD65 and GlyR antibodies was classified under another category. In this study, a high titer of GAD65 antibodies was defined as 1,800 U/mL with RIA, >10,000 U/mL with EIA, and >2,000 U/mL with ELISA on the basis of real data and a previous report.¹³ The 32 GAD65-positive patients were divided into 2 groups on the basis of antibody titer (8 patients with low-titer GAD65 antibodies and 24 patients with high-titer GAD65 antibodies) (eFigure 1, links.lww.com/NXI/A909, eMaterial, links.lww.com/NXI/A910). The range of low-titer GAD65 antibodies by measurement method is as follows: RIA: 2.6–1,023 U/mL; EIA: no applicable patient; and ELISA: 21.2–929 U/mL. Furthermore, low-titer GAD65-positive patients with SPS were defined on the basis of electrophysiology or CSF tests in addition to diagnostic criteria. On the basis of this low-titer criterion, 2 patients with a low titer of GAD65 antibodies were excluded. Therefore, of the 33 GAD65-positive patients with SPS, 30 were included in the GAD65-positive analysis. Twenty-three patients (76%) were female, the median age at onset of symptoms was 51 years (range, 26–83 years), and the median time of symptom onset to diagnosis was 12 months (range, 1–96 months). Finally, the 30 patients were classified into 2 groups on the basis of clinical phenotype: classic SPS (21 patients, 70%) and SLS (9 patients, 30%). Thirteen patients (43%) had type 1 diabetes mellitus (DM), and 11 (37%) had other autoimmune diseases, such as thyroid disease. Four (13%)

Table 1 Clinical Characteristics of Patients With Low-Titer and High-Titer GAD65 Antibodies

| Clinical characteristic | Low-titer GAD65 Antibodies (n = 6) | High-titer GAD65 Antibodies (n = 24) | p Value |
|--|------------------------------------|--------------------------------------|---------|
| Female (%) | 3 (50) | 20 (83) | 0.12 |
| Age at onset, y, median (range) | 43.5 (26 to 83) | 52.5 (23 to 71) | 0.42 |
| Time from symptom onset to diagnosis, mo, median (range) | 2.5 (2 to 48) | 13 (1 to 96) | 0.01 |
| Clinical phenotype (%) | | | 1.00 |
| Classic SPS | 4 (67) | 17 (71) | |
| SLS | 2 (33) | 7 (29) | |
| PERM | 0 (0) | 0 (0) | |
| Type 1 DM (%) | 3 (50) | 10 (42) | 0.53 |
| Other autoimmune diseases (%) | 1 (17) | 10 (42) | 0.26 |
| Malignancy (%) | 2 (33) | 2 (8) | 0.17 |
| Lack of antagonist inhibition on EMG ^a | 5/5 (100) | 8/10 (80) | 0.43 |
| CSF pleocytosis | 0/6 (0) | 2/16 (13) | 0.52 |
| Elevated CSF protein | 2/5 (29) | 3/15 (20) | 0.37 |
| mRS at baseline, median (range) | 3.5 (2 to 4) | 4 (1 to 5) | 0.15 |
| Follow-up period, m, median (range) | 47 (2 to 120) | 44 (15 to 192) | 0.98 |
| mRS at the last follow-up, median (range) | 2.5 (0 to 6) | 2 (0 to 4) | 0.56 |
| Change in mRS, median (range) | 0.5 (−2 to 2) | 2 (0 to 5) | 0.09 |

Abbreviations: DM = diabetes mellitus; GAD65 = glutamic acid decarboxylase 65; mRS = modified Rankin Scale; PERM = progressive encephalomyelitis with rigidity and myoclonus; SLS = stiff-limb syndrome.

^a Lack of antagonist inhibition on EMG is defined by the continuous co-contraction of agonist and antagonist muscles (with inability to relax) as confirmed by EMG.

had malignancies, including 2 with cancer (breast and lung) and 2 with thymoma. One patient was diagnosed before the onset of SPS symptoms; 1, during the course of evaluation of neurologic symptoms and 2, after the onset of SPS symptoms. These patients were scored for paraneoplastic neurological syndrome (PNS) according to the PNS care score, as follows: probable, 1 case, and non-PNS, 3 cases.²⁷ EMG studies were performed in 15 patients (50%), and CSF was examined in 22 patients (73%). Thirteen (87%) of the 15 patients lacked antagonist inhibition on EMG. The median follow-up was 47 months (range, 1–216 months). The median mRS at baseline was 4 (1–5), and the median mRS at the last follow-up was 2 (0–6) (eTable 3, [links.lww.com/NXI/A906](https://www.com/NXI/A906)).

Epidemiologic Study of Patients With GAD65-Positive SPS

From the first survey, the total estimated number of patients with SPS was 257 (95% CI 161–354), with an estimated period prevalence of 0.2 (0.13–0.28) per 100,000 population using the background population from 2015 to 2017 reported by the Ministry of Internal Affairs and Communications of Japan. Thirty cases (55%) were identified as GAD65-positive SPS cases on the basis of detailed clinical data of 55 cases obtained in the second survey. Taken together, the total

estimated number of patients with GAD65-positive SPS was 140, with a period prevalence of 0.11 per 100,000 population from 2015 to 2017.

Comparison Between Low-Titer and High-Titer GAD65 Antibody Groups

Six patients were assigned to the low-titer GAD65 antibody group, and 24 patients were assigned to the high-titer GAD65 antibody group. The high-titer GAD65 antibody group had significantly longer time from symptom onset to diagnosis than the low-titer GAD65 antibody group (13 vs 2.5 months, $p = 0.01$). We observed no significant differences in sex distribution, age at onset, clinical manifestations, comorbidity, EMG and CSF findings, and clinical improvement on the basis of mRS between the low-titer and high-titer GAD65 antibody groups (Table 1).

Clinical Characteristics, Treatment, and Longitudinal Outcomes of GAD65-Positive Patients

To evaluate clinical response to treatment, we excluded 1 patient without ≥ 1 year follow-up (Figure 2). Good outcome was defined by mRS of 0–2, and poor outcome was defined by mRS ≥ 3 after ≥ 1 year follow-up.^{3,4} We summarize the clinical

Table 2 Univariable Regression Analysis Assessing Predictors of Poor Outcome (mRS ≥ 3) at the Last Clinical Follow-up in 29 Patients With GAD65 Antibodies

| Variable | Good outcome (n = 19) | Poor outcome (n = 10) | Univariable analysis | |
|--|--------------------------|--------------------------|----------------------|---------|
| | | | OR (95% CI) | p Value |
| Female (%) | 15/20 (79) | 8/10 (25) | 0.94 (0.11–5.98) | 0.94 |
| Age at onset, y, median (range) | 50 (23–71) | 52 (25–67) | 0.98 (0.92–1.04) | 0.53 |
| Time from symptom onset to diagnosis, mo, median (range) | 12 (1–84) | 12 (2–96) | 0.99 (0.96–1.02) | 0.48 |
| Clinical phenotype (%) | | | | |
| Classic SPS | 13/19 (68) | 7/10 (70) | — | |
| SLS | 6/19 (32) | 3/10 (30) | — | |
| PERM | 0 (0) | 1 (0) | — | |
| Type 1 DM (%) | 4/19 (21) | 8/10 (80) | 15.00 (2.60–131.58) | 0.002 |
| Other autoimmune diseases (%) | 9/19 (47) | 2/10 (20) | 0.28 (0.04–1.48) | 0.14 |
| Malignancy (%) | 1/19 (5) | 2/10 (13) | 4.50 (0.38–105.43) | 0.23 |
| mRS ≥ 4 at baseline | 11/19 (58) | 7/10 (63) | 0.59 (0.10–2.88) | 0.52 |
| Time from diagnosis to immunotherapy, mo, median (range) | 0 (0–7) | 1 (0–9) | 0.85 (0.51–1.24) | 0.38 |
| Time from diagnosis to IVIg, mo, median (range) | 1 (0–7) | 1 (0–3) | 1.01 (0.54–2.02) | 1.00 |
| Type of therapy | | | | |
| Without immunotherapy | 6/19 (32) | 1/10 (10) | 0.24 (0.01–1.76) | 0.17 |
| Without effective long-term immunotherapy | 2/19 (11) | 7/10 (70) | 19.83 (3.17–191.47) | 0.001 |
| With effective long-term immunotherapy | 11/19 (58) | 2/10 (20) | 0.18 (0.02–0.96) | 0.05 |

Abbreviations: DM = diabetes mellitus; GAD65 = glutamic acid decarboxylase 65; mRS = modified Rankin Scale; PERM = progressive encephalomyelitis with rigidity and myoclonus; SLS = stiff-limb syndrome. All p values were calculated by the likelihood ratio test.

characteristics, treatments, and longitudinal outcomes of 29 GAD65-positive patients with a median follow-up of 48 (15–180) months in eTable 4 (links.lww.com/NXI/A907).

Seven (39%) of 18 GAD65-positive patients having mRS ≥ 4 at baseline showed poor outcome. Among the 29 GAD65-positive patients, 7 were given only symptomatic treatment and 22 received immunotherapy and/or symptomatic treatment. On the basis of the immunotherapy regimen, we defined the effective long-term immunotherapy group as follows: first-line immunotherapy followed by maintenance therapy (oral prednisolone and/or tacrolimus; monthly IVIg; repeated IVIg within 4 months).

The types of therapy were finally classified as follows: (1) without immunotherapy, (2) immunotherapy without effective long-term immunotherapy, and (3) effective long-term immunotherapy. The time from diagnosis to immunotherapy and/or IVIg and the improvement of symptoms were also documented.

For the symptomatic treatment group, the median mRS was 4 (range, 1–5) at baseline and 1 (range, 1–3) at the last follow-up.

We further classified the 22 GAD65-positive patients who received immunotherapy into 2 groups as follows: 9 with immunotherapy but without effective long-term immunotherapy and 13 with effective long-term immunotherapy. The median mRS at baseline was the same at 4 (range, 2–5) for both immunotherapy groups, but the median mRS at the last follow-up was slightly lower for the effective long-term immunotherapy group (2; range, 0–4) than for the immunotherapy but without effective long-term immunotherapy group (3; range, 0–4) (eTable 4, links.lww.com/NXI/A907).

Clinical Outcomes of GAD65-Positive Patients

To identify the risk factors for the GAD65-positive patients, data of 19 (65.5%) patients with good outcome and 10 (34.5%) patients with poor outcome (mRS ≥ 3) were analyzed. In the univariable regression analysis, the risk factor that was significantly associated with poor outcome was the presence of type 1 DM (odds ratio 15.0; 95% CI 2.60–131.58; $p = 0.002$) and the lack of effective long-term immunotherapy (odds ratio 19.8; 95% CI 3.17–191.47; $p = 0.001$) (Table 2). One patient with type 1 DM had mild polyneuropathy, and another patient without type 1 DM had a history of cerebral infarction. However, neither had neurologic complications

aside from SPS to explain the neurologic disability. There was no significant difference in the time from symptom onset to diagnosis and the time from diagnosis to immunotherapy including IVIg between the 2 groups (Table 2).

GlyR-Positive, Seronegative, and Other Categories

The 22 GAD65-negative patients were grouped according to clinical phenotype as follows: classic SPS (10 patients, 45%), SLS (5 patients, 23%), and PERM (7 patients, 32%). One patient with classic SPS who was Ri-positive and 8 who did not undergo antibody screening were excluded. Of the 8 GAD65-negative patients, 3 who did not take an EMG test or did not show lack of antagonist inhibition on EMG were excluded. Of the 10 patients screened for antibodies and/or lack of antagonist inhibition on EMG, 4 had autoantibodies against GlyR and 1 had autoantibodies against GABA_BR. One GABA_BR-positive patient had SLS but not limbic encephalitis or status epilepticus. We excluded this GABA_BR-positive patient from the SPS category. The Ri-positive patient was classified into other categories (Figure 2, eTable 5, links.lww.com/NXI/A908).

The 9 GAD65-negative patients were finally classified into 3 groups on the basis of clinical phenotype: classic SPS (2 patients, 22%), SLS (2 patients, 22%), and PERM (5 patients, 56%).

The patients with classic SPS were seronegative. One patient with SLS was seronegative, whereas the other patient with SLS had GlyR antibodies. Of the 5 patients with PERM, 3 were positive for GlyR antibodies and 2 were seronegative. Among the 9 GAD65-negative patients, 5 (56%) had malignancies (lung cancer, tongue cancer, lymphoma). Patients in the GlyR-positive group and the seronegative group showed severe symptoms at baseline, but those in the GlyR-positive group showed great improvement after treatment compared with those in the seronegative group. Half of the patients in the GlyR-positive group received first-line and second-line immunotherapies (eTable 3, links.lww.com/NXI/A906).

The clinical characteristics of the GlyR-positive group, the seronegative group, and the other categories are summarized in eTable 5 (links.lww.com/NXI/A908).

Discussion

We elucidated the current epidemiologic, clinical, and immunologic profiles of GAD65-positive SPS in Japan and the treatments given. The estimated prevalence of GAD65-positive SPS was 0.11 per 100,000 population. The prevalence, sex distribution, age at onset, and predominance of classic SPS were similar to those reported previously.^{2-4,12,28} The outcome of GAD65-positive SPS was generally favorable compared with those of previous studies.^{3,4,28}

Patients with GAD65 antibodies, regardless of titer, had a high frequency of type 1 DM, other autoimmune diseases, and CSF

oligoclonal bands (OCBs), although no significant differences were observed between the high-titer and low-titer GAD65 antibody groups. The time from symptom onset to diagnosis was significantly longer in the high-titer GAD65 antibody group than in the low-titer GAD65 antibody group. The fact that 2 patients in the low-titer GAD65 antibody group showed high-titer GAD65 antibodies while their progress was being monitored (data not shown) underscored the need to re-examine GAD65 titer after a period of time. Although the median mRS at baseline was slightly higher in the high-titer GAD65 antibody group than in the low-titer GAD65 antibody group, there was no significant difference in the median mRS at the last follow-up between the 2 groups. These findings are in line with previous studies indicating that anti-GAD65 antibody titers are not correlated with response to therapies, such as IVIg and rituximab.^{29,30}

Interestingly, a high titer of intrathecal GAD65 antibodies was detected in 1 patient with a low titer of serum GAD65 antibodies (eFigure 1, links.lww.com/NXI/A909, eMaterial, links.lww.com/NXI/A910). This finding of intrathecal production of GAD65 antibodies is considered the strongest evidence linking a neurologic syndrome to autoimmunity.^{31,32} This means that even when serum GAD65 antibody levels are low, it is important to test CSF for GAD65 antibodies, as recommended in previous studies.^{13,31}

We also found an independent association between type 1 DM and the lack of effective long-term immunotherapy, and these risk factors were related to poor outcome in patients with GAD65 antibodies. Baseline disease severity and the presence of GAD65 antibodies are poor prognostic factors in SPS.⁴ However, the frequency of poor outcome (mRS ≥ 3 at the last follow-up in GAD65-positive patients with high disease severity (mRS ≥ 4 at baseline)) of 39% was lower than that (80%) of a previous study.³

In our cohort, type 1 DM was detected only in the GAD65-positive group. Type 1 DM and SPS share a common immunogenetic background.² In this study, 11 (61%) patients with high disease severity underwent long-term immunotherapy. However, poor-outcome patients who had type 1 DM tended to avoid long-term immunotherapy, such as oral prednisolone, although they had severe symptoms at baseline (eTable 4, links.lww.com/NXI/A907).

The outcome of GAD65-positive patients with SPS is expected to worsen when the diagnosis is made at a very late stage or effective immunotherapy is not initiated early on.²⁸ We suppose that the outcome of GAD65-positive patients with SPS is favorable because the time from onset to diagnosis and the time from diagnosis to initiation of treatment are shorter than those previously reported.^{4,28}

Improvement brought about by IVIg infusion may last for 1–4 months, and repeated infusions are required if there are benefits after the first infusion.³³ A study of GAD65-positive

patients has demonstrated the long-term efficacy of IVIg maintenance therapy; however, monthly IVIg maintenance therapy is infrequently prescribed in Japan.³⁴ In this study, 1 good-outcome patient received monthly IVIg, and 3 good-outcome patients received an IVIg induction dose at approximately 4- to 7-month intervals, whereas 5 poor-outcome patients received an IVIg induction dose at approximately 4- to 12-month intervals (eTable 4, links.lww.com/NXI/A907). Taken together, the long-term benefits of IVIg may not be sufficiently gained in GAD65-positive patients with poor outcome.

Autopsies performed on patients with GAD65-positive SPS have demonstrated the infiltration of cytotoxic T cells or focal perivascular lymphocyte cuffing in the spinal cord and neuronal loss.^{35,36} Because GAD65 is an intracellular protein and GAD65 antibodies may not be the direct causative factor, patients with GAD65 antibodies are believed to be in an immunologically activated condition. Our observations suggest the need to consider early aggressive immunotherapy including IVIg maintenance therapy for GAD65-positive patients with high disease severity to prevent immune reactions and neuronal reactions.

Patients with GlyR antibodies were more frequently found in the PERM group than in the classic SPS group, consistent with a previous report.⁴ The age at onset in the GlyR-positive group was also similar to that reported previously, namely most patients with PERM presented with symptoms in their fifth or sixth decade.^{5,9} We found anti-GlyR antibodies in 8% (one patient) of GAD65-positive patients who were screened for GlyR antibodies, confirming the previous finding that GlyR antibodies were also found in 10–15% of GAD65-positive patients.^{37,38} Our data are in agreement with the results of the previous study describing that seronegative and GlyR-positive patients showed higher disease severity than GAD65-positive patients, although the outcomes of the GlyR-positive patients were better than those of the GAD65-positive patients.⁴ This finding could be explained as follows: more rapid and severe symptom onset in PERM than in SPS, GlyR-positive patients received more aggressive treatment than GAD65-positive patients, and the nature of GlyR, that is, it is a cell surface antigen.⁴ Indeed, in this study, half of patients in the GlyR-positive group underwent a combination of first-line and second-line immunotherapies.

Patients in the seronegative group showed poorer outcome than those in the GAD65-positive or GlyR-positive group. The poor outcome might be explained by the absence of immunotherapy or insufficient immunotherapy as previously reported.⁴ Moreover, half of the seronegative patients were associated with malignancies. There may be another etiology in seronegative SPS because the GAD65-seronegative patients had a higher frequency of malignancies than the GAD65-seropositive patients.³ In addition, there was a coincidental finding that could not be related to PNS.

Autoantibodies against 6 antigens, including GAD65, GlyR, amphiphysin, gephyrin, DPPX, and GABA_AR, but not GABA_BR,

have been reported in patients with SPS.^{6-8,26,39,40} Most patients with GABA_BR antibodies develop early seizures or status epilepticus as a component of limbic encephalitis and rapidly progressive cognitive decline.⁴¹⁻⁴⁴ Our patient with GABA_BR antibodies did not show well-known clinical features, such as seizures and cognitive impairment; instead, this patient showed painful spasms of the legs that might lead to misdiagnosis. The detection of GABA_BR antibodies in SPS requires careful interpretation.

This study has the following limitations:

1. We used a random sampling method; the reason being that enormous effort was required to conduct a survey of not only neurologists but also internists in Japan. The estimated response rate of the first survey was 48.7%, and this estimate was based on a method in which nonresponse study centers were taken into consideration.¹⁵
2. From the 94 patients reported in the first survey, the final number of patients from whom detailed clinical data could be obtained decreased to 55. We could not derive conclusive information from this small data size. In addition, because we could not statistically confirm whether the presence of GAD65 antibodies had an effect on poor outcome, we focused our prognostic analysis on only GAD65-positive patients.
3. Because the anti-GlyR antibody test was recently established in Japan, this study might have been skewed toward GAD65-positive patients.
4. We did not perform CBA to detect GAD65 antibodies nor did we find any correlation between GAD65 pattern on immunohistochemistry and GAD65 antibody levels, as previously reported.⁴⁵
5. Many clinical variables potentially associated with poor outcome were examined in patients with GAD65 antibodies (number of patients = 10). Multiple testing may have led to the increase in alpha error. However, because of the hypothesis-generating nature of this study, no correlation of alpha error was conducted. Therefore, the *p* values between 0.05 and 0.004 (Table 2) should be considered carefully.
6. Because outcome measures other than median mRS were lacking, we decided to focus on detailed clinical information including treatment content.
7. The maintenance therapy varied. Corticosteroids were most commonly used, although one anecdotal report showed limited benefits. Case reports showed that tacrolimus was effective when used after steroid therapy.⁴⁶ Because there were cases in which prognosis was good with oral steroids and/or tacrolimus after IVMP or an IVIg induction dose, steroid and tacrolimus were included in the effective treatment category. Immunotherapeutic options other than IVIg require further evidenced-based consideration.

In conclusion, our study demonstrated that the estimated prevalence of GAD65-positive SPS is 0.1 per 100,000

population, and the outcome of GAD65-positive patients is generally favorable. To establish a clinical correlation with GAD65 antibodies, further investigation including newly identified autoantibodies in a larger sample size is necessary.

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Disclosure

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Appendix 1 (continued)

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Continued

Appendix 2 (continued)

| Name | Location | Role | Contribution |
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Appendix 2 (continued)

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