OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Reviews

# Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports

**Harini Sarva[1*], Andres Deik[2], Aman Ullah[1] & William L. Severt[3]**

[1] Department of Neurology, Maimonides Medical Center, Brooklyn, NY, USA, [2] Parkinson Disease and Movement Disorders Center, Department of Neurology, University of Pennsylvania, PA, USA, [3] Department of Neurology, Division of Movement Disorders, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel Medical Center, New York, NY, USA

## Abstract

**Background:** "Classic" stiff person syndrome (SPS) features stiffness, anti-glutamic acid decarboxylase (anti-GAD) antibodies, and other findings. Anti-GAD antibodies are also detected in some neurological syndromes (such as ataxia) in which stiffness is inconsistently present. Patients with otherwise "classic" SPS may either lack anti-GAD antibodies or be seropositive for others. Hence, SPS cases appear to fall within a clinical spectrum that includes conditions such as progressive encephalomyelitis with rigidity and myoclonus (PERM), which exhibits brainstem and autonomic features. We have compiled herein SPS-spectrum cases reported since 2010, and have segregated them on the basis of likely disease mechanism (autoimmune, paraneoplastic, or cryptogenic) for analysis.

**Methods:** The phrases "stiff person syndrome", "PERM", "anti-GAD antibody syndrome", and "glycine receptor antibody neurological disorders" were searched for in PubMed in January 2015. The results were narrowed to 72 citations after excluding non-English and duplicate reports. Clinical descriptions, laboratory data, management, and outcomes were categorized, tabulated, and analyzed.

**Results:** Sixty-nine autoimmune, 19 paraneoplastic, and 13 cryptogenic SPS-spectrum cases were identified. SPS was the predominant diagnosis among the groups. Roughly two-thirds of autoimmune and paraneoplastic cases were female. Anti-GAD antibodies were most frequently identified, followed by anti-amphiphysin among paraneoplastic cases and by anti-glycine receptor antibodies among autoimmune cases. Benzodiazepines were the most commonly used medications. Prognosis seemed best for cryptogenic cases; malignancy worsened that of paraneoplastic cases.

**Discussion:** Grouping SPS-spectrum cases by pathophysiology provided insights into work-up, treatment, and prognosis. Ample phenotypic and serologic variations are present within the categories. Ruling out malignancy and autoimmunity is appropriate for suspected SPS-spectrum cases.

**Keywords:** Stiff person syndrome, stiff limb syndrome, stiff trunk syndrome, progressive encephalomyelitis with rigidity and myoclonus, anti-glutamic acid decarboxylase antibodies, anti-glycine receptor antibodies

**Citation:** Sarva H, Deik A, Ullah A, et al. Clinical spectrum of stiff person syndrome: a review of recent reports. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D85M65GD

*To whom correspondence should be addressed. E-mail: sarvaharini@gmail.com

**Editor:** Elan D. Louis, Yale University, USA

**Received:** July 25, 2015 **Accepted:** December 22, 2015 **Published:** March 4, 2016



**Funding:** None.

**Financial Disclosures:** Dr. Severt is a speaker for Teva Pharmaceuticals and Allergan.

**Conflict of Interest:** The authors report no conflict of interest.

**Ethics Statement:** This study was reviewed by the authors institutional ethics committee and was considered exempted from further review.

## Introduction

"Stiff man" syndrome was first described in 1956 by Moersch and Woltman.[1,2] Along with observations from 13 other cases, they described a 49-year-old man with progressive stiffness in his neck, shoulders, and upper back, episodic painful muscle spasms, and difficulty walking. Multiple similar case descriptions have since followed. The term "stiff man" was recently replaced by the gender-neutral "stiff person syndrome" (SPS), which gained significant traction after Blum and Jankovic[3] reported that approximately 20 of the 84 reported cases between 1967 and 1991 were female. It was Asher,[4] however, in 1958, who first proposed this terminology.

The suspicion for an immunologic cause was raised by the observations of frequent comorbid diabetes (up to 35% in some series[5]) and other concomitant autoimmune diseases (vitiligo, celiac sprue, rheumatologic diseases, and thyrogastric disorders)[2,5,6] in patients with SPS. Glutamic acid decarboxylase (GAD) antibodies

(which in this manuscript will be referred to as anti-GAD antibodies, a non-specific term that includes both anti-GAD antibody isoforms, as described below) were first documented in association with SPS in 1988.[7,8] Anti-GAD antibodies inhibited GAD activity and the synthesis of gamma-aminobutyric acid (GABA) in vitro.[2]

GAD is a pyridoxal 5′-phosphate-dependent enzyme and the rate-limiting step in the synthesis of GABA. GAD is not only found in the brain and pancreatic B-cells, but also in lower amounts in the liver, kidneys, adrenal glands, ovaries, and testes.[9] There are two GAD isoforms, 65 and 67, which differ in their molecular weight, location, and enzyme activity. Within the central nervous system, GAD65 localizes to the synaptic vesicles and its activity increases in response to surging demands for GABA.[2] GAD67 localizes to the cytoplasm and generates a steady basal GABA level.[2] Anti-GAD antibodies are specific for either isoform: antibodies against GAD65 were reported in about 80% of SPS cases (at times, the terms anti-GAD and anti-GAD65 antibodies are used interchangeably in the literature), whereas anti-GAD67 antibodies were reported in about 60%, with co-existence presumed likely.[2,6,10]

An immune pathogenesis is accepted as the cause of SPS, but it remains unclear whether anti-GAD antibodies are directly pathogenic in vivo, unlike in diabetes.[2] There are different possible explanations for this. Whereas serum anti-GAD antibody titers in SPS are high enough to produce endocrine damage, diabetics have lower serum titers that are likely insufficient to cross the blood–brain barrier and lead to central nervous system (CNS) damage.[2] Extremely high titers of anti-GAD antibodies in SPS can trigger multi-antigen autoimmunity and the development of other concomitant autoimmune diseases, such as thyroid disease, but not necessarily vice versa.[9] Besides a difference in titers, in SPS both the linear and the conformational epitopes are recognized by anti-GAD65 antibodies, while in diabetes only the conformational epitopes are recognized, triggering a specific pathogenic mechanism.[2] Other arguments against a pathogenic role for these antibodies include the lack of correlation between disease severity and intrathecal synthesis and lack of evidence of T-cell-mediated damage of central GABAergic neurons.[5,10] In addition, antibody titers in SPS do not appear to vary with clinical response to treatment. Monitoring antibody titers during the course of treatment is, hence, unnecessary.[5,11]

Identification of the anti-GAD antibodies allowed the revision of the diagnostic criteria for SPS, which were first proposed in 1967 by Gordon et al.[12] In 2009 Dalakas[5] proposed two fundamental clinical symptoms, truncal and proximal limb stiffness, stemming from co-contraction of agonist and antagonist muscles and leading to hyperlordosis, and superimposed episodic spasms. According to Dalakas, the presence of all of the following are required for a diagnosis of SPS: 1) stiffness of the axial muscles, particularly in the abdomen and thoracolumbar paraspinals, leading to hyperlordosis; 2) superimposed painful spasms triggered by tactile or auditory stimuli; 3) electromyographic evidence of continuous motor unit activity in agonist and antagonist muscles; 4) absence of other neurological findings that may suggest an alternative diagnosis; and 5) positive serology confirmed by immunocytochemistry, Western blot, or radio-immunoassay.

Although these criteria best define the "classic" SPS phenotype, it is now clear that some patients have positive anti-GAD antibodies and stiffness that is confined to a limb (typically a leg, in what has been called stiff-limb syndrome, SLS).[13] Eventual spread of stiffness to the trunk was described.[13] SLS is likely due to local interneuronitis, in which there is selective destruction of spinal interneurons in the gray matter.[13] Interestingly, long-tract damage was not noted in these cases. The associated reflexive spasms likely result from an excessive response to descending reticulospinal activity at the segmental level, as shown electrophysiologically by hypersynchronous segmented discharges.[13] The exact cause of the interneuronitis is unknown but may be due to similar mechanisms that occur in the presence of intrinsic spinal cord tumors or vascular insufficiency.[13] These patients may develop urinary and transient brainstem symptoms (about 50%), have seropositivity to anti-GAD antibodies in about 15% of cases, and have a limited response to GABAergic treatments.[13,14] In fact, patients with stiff limb syndrome were reported likely to be wheelchair bound after a mean of 3.5 years.[13] Some authors also advocate for the existence of a distinct stiff-trunk syndrome,[14] and a jerking-man syndrome with generalized myoclonus.[13,15] The development of highly sensitive antibody detection assays also allowed the identification of anti-GAD antibodies in neurologic conditions where rigidity may be absent. Phenotypes include cerebellar ataxia, epilepsy, and cognitive impairment.[2] All of the above suggest the existence of a spectrum of SPS expanding well beyond the "classic" phenotype.

Patients within this SPS spectrum have antibodies against other proteins of the GABAergic synapse, including amphiphysin and gephyrin, which may be identified in isolation.[10,16] Amphiphysin is a cytosolic pre-synaptic vesicle protein. Anti-amphiphysin antibodies are often associated with malignancy, and phenotypically these cases may differ from anti-GAD65 positive SPS with more prominent neck and arm stiffness.[17] In addition, these antibodies were also detected in neurologic conditions such as encephalopathy, myelopathy, and neuronopathy.[17] Gephyrin interacts with the GABA receptor-associated protein (GABARAP) in the assembly of the GABA-A receptor.[10,16] Interestingly, about 70% of patients with anti-GAD65 seropositivity may also have antibodies against GABARAP.[10,16]

Antiglycine receptors (anti-GlyR antibodies) are present in some SPS-spectrum cases, and are the hallmark of progressive encephalomyelitis with rigidity and myoclonus (PERM). In this condition there is prominent brainstem, autonomic, and spinal cord involvement. Concurrent anti-GAD antibodies can also be found.[18] In a study of 45 prospective and 56 retrospective cases of PERM, approximately 33 of the former and 10 of the latter were positive for anti-GAD antibodies.[18] Histology from available specimens demonstrated inflammatory and microglial changes and cell loss in the pons, medulla, cerebellum, spinal cord, and autonomic ganglia.[13] Patients with PERM had increased T2 fluid-attenuated inversion recovery signal of spinal cord and brainstem on magnetic resonance imaging

(MRI).[18] Despite its severity, the response to immunomodulatory therapies, including methylprednisolone, can be robust.[13,18]

Glycine receptors belong to a family of ligand-gated ion channels composed of two alpha- and three beta-subunits. Activation of these receptors leads to chloride influx, membrane hyperpolarization, and reduction in neuronal excitation. There are three types of glycine receptors: alpha 1, 2, and 3. The first type localizes to the brainstem, thalamus, hypothalamus, superior colliculus, and spinal cord. The distribution of the others remains incompletely defined.[18]

Other antibodies were found in patients within the spectrum of SPS. In a study examining the antibody profile of 13 patients with SPS, eight were found to have non-organ-specific antibodies, including antibodies to nuclear, smooth muscle, and mitochondrial antigens, six had thyrogastric antibodies, five had islet-cell antibodies, and four had anti-GAD antibodies.[9]

Given the considerable phenotypical variability found in patients with anti-GAD antibodies, the presence of different auto-antibodies associated with similar phenotypes, and seronegative patients fulfilling almost all of Dalakas' criteria for "classic" SPS, classifying patients within the SPS spectrum-based on their phenomenology can be, in our opinion, impractical and ambiguous. Instead, we argue that a classification based on likely etiology offers the most useful guidance in terms of prognosis and treatment response. Under this framework, cases within the SPS spectrum can be segregated into one of three mutually exclusive groups:[9,19,20] 1) autoimmune cases, defined by autoantibody positivity (in serum and/or cerebrospinal fluid [CSF]) in the absence of an underlying malignancy; 2) paraneoplastic cases, encompassing all cases emerging in the context of cancer; and 3) cryptogenic cases, that is, all seronegative cases in which an immunologic cause cannot be identified. All cases with malignancy were labeled as paraneoplastic, as the original reports described a mostly positive clinical response to anti-cancer treatments. If the cancer therapy did not produce a response in the SPS-spectrum disorders, the malignancy would more likely be a comorbidity rather than a likely cause. This breakdown is purely an operational classification based on the published papers' reported diagnosis. It was difficult for us to determine if each case met Dalakas' criteria in their entirety, as phenotypic descriptions were incomplete in a number of the reports, despite the reported diagnoses. To better understand the characteristics, disease behavior, and treatment response of SPS-spectrum cases within each of these groups, we here review cases and case series of SPS and related disorders published between 2010 and early 2015.

## Methods

In January 2015, we searched PubMed for the phrases "stiff person syndrome", "PERM", "anti-GAD antibody syndrome" and "glycine receptor antibody neurological disorders". Of note, searching for "stiff man syndrome" yielded the same results as searching for "stiff person syndrome." The resulting initial 706 citations were narrowed to 72 after excluding non-English papers, duplicate reports, and papers published before 2010. Papers with no available clinical information and reviews without individual clinical descriptions were also excluded. January 2010 was selected as a cut-off for inclusion in an attempt to guarantee that most of the published cases were using similar criteria to diagnose SPS-spectrum cases, but also to adhere to the journal's manuscript guidelines. Clinical descriptions, laboratory data, treatment strategies, and outcomes, when available, were extracted and tabulated into a Microsoft® Excel 2010 spreadsheet. Three separate spreadsheets were created, one for each subgroup (autoimmune, paraneoplastic, or cyptogenic), and cases were segregated into one of these categories according to the definitions mentioned above. Case series were treated as groups of case reports, and each of the cases within the series was classified independently into one of the tables. One case series[21] presented consolidated data for all of its cases and is presented here in a separate table (see Table 4) that includes autoimmune, paraneoplastic, and cryptogenic subtypes. Attempting to subdivide these cases into the prior three subgroups was thus not readily possible due to lack of individual data.

Pertinent positives and pertinent negatives for symptoms, examination findings, laboratory data, treatment strategies, and outcomes were coded in the tables as present (+) or absent (–), respectively. Fields were left blank when the paper did not comment on a specific datum. Once all data were entered, findings were summated within each category and percentages of prevalence were calculated. Either medians or means were calculated for all numeric data (i.e. age), depending on the sample size. The prevalence numbers for the subdivisions are based on the published diagnoses of SPS and its variants in the original reports.

## Results

Data extracted from each of the SPS-spectrum subgroups are presented in the following subsections.

### *Autoimmune SPS spectrum cases (Tables 1 and 2)*

Sixty-nine cases of autoimmune SPS-spectrum disorders were identified (Table 1), 46 (66.7%) of whom were female. Sex and age at presentation were available in all but four cases: two were female, but their age was not reported. Neither sex nor age was reported for the other two. Ages at presentation ranged from 1 to 78 years, the mean being 44 years. The median age at presentation in males was 45 years, whereas the mean age was 44.5 years in females.

In terms of their phenotypes, 48 cases (69.6%) received a diagnosis of SPS. Of these, three had concomitant ataxia, two had orthostatic tremor, two had corticobasal syndrome, one initially had stiff limb syndrome, one had epilepsy, and one had anorexia. Nine (13%) had findings consistent with PERM. Four (5.8%) received a diagnosis of SLS, and another four had ataxia alone. Two (2.9%) had only epilepsy, one of whom with behavioral changes. Finally, only one (1.4%) of the autoimmune cases had clinical signs of schizophrenia,[22] while another had isolated stiff trunk syndrome.[14]

Data on the time patients had symptoms before presentation were available for 48. It ranged from less than 1 month to about 46 years, with an average of 63.8 months (over 5 years). Forty-one (59.4%) described cramps or spasms, 45 (65.2%) had limb stiffness, 29 (42%) had difficulty walking, and 23 (33.3%) had pain. Sixteen (23.2%) had documented concomitant autoimmunity besides diabetes (only two had documented

Table 1. **Subjective and Objective Findings in Reported Cases of Autoimmune Stiff Person Syndrome and Its Variants**

| Reference | Reported Diagnoses at Presentation | Age and Sex at Presentation | Number Of Symptomatic Months Before Presentation | Symptoms: Bulbar (Excluding Taste Changes) | Symptoms: Taste Changes | Symptoms: Genitourinary Dysfunction | Symptoms: Difficulty Changing Position | Symptoms: Difficulty Moving Limb | Symptoms: Falls | Symptoms: Gait Difficulties (Including Ataxia) | Symptoms: Pain | Symptoms: Pruritus | History or Examination Findings: Axial Stiffness or Hyperlordosis | History or Examination Findings: Autonomic Instability (Besides Genitourinary Dysfunction) | History or Examination Findings: Concomitant Autoimmunity (Other Than Diabetes) | History or Examination Findings: Cramps/Spasms | History or Examination Findings: Diabetes | History or Examination Findings: Extraocular Movement Abnormalities | History or Examination Findings: Hepatitis C | History or Examination Findings: Encephalopathy or Psychiatric/Behavioral Changes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lobo et al.[44] | SP | 41F | 84 | | | | + | | | | + | | + | | | + | – | | | |
| Awad et al.[23] | SP | 66M | | | | | | | | + | | | + | | | + | + | | + | – |
| Scavone et al.[24] | A | 48F | | + | | | | | | + | | | | | P | | – | + | + | |
| Castelnovo et al.[45] | SL | 63F | 36 | | | | | | | + | + | | – | | P | + | + | | | |
| Cuturic et al.[46] | SP, ED | 35F | 24 | | | | | | | | | | + | | | + | + | | | + |
| Ehler et al.[6] | SP | 61M | <1 | + | | + | | + | | | | | + | + | | + | + | | | |
| Gnanapavan et al.[47] | SP | 45M | 60 | | | | | | + | + | | | + | | | + | + | | | |
| Goldkamp et al.[48] | SP | 27F | | | | | | | | | | | | | | + | | | | |
| Mas et al.[37] | E, PERM | 60M | <1 | + | | | | | | | + | | | + | | + | | + | | + |
| | PERM | 48M | 2 | | + | | | | | | | + | | + | | + | | | | |
| | SL, SP | 33F | 3 | + | | + | | | | + | + | | | | T | + | | + | | |
| Piotrowicz et al.[49] | PERM | 58M | >1 | | | | | | + | + | | | + | | | | | + | | |
| Turner et al.[27] | PERM | 28M | 1 | + | | + | | | | | | | | + | | | | + | | + |
| Witherick et al.[28] | SP | 69M | | | | | | | | | + | | | | MG, P | + | | | | |
| Anagnostou et al.[50] | SL | 40F | 108 | | | | | | | + | + | | | | | + | + | | | |
| Amyradakis et al.[51] | SP | F | <1 | + | | | | | | | + | | | | | + | + | + | | |
| Fekete and Jankovic[52] | SP | 12M | 84 | | | | | | | + | + | | + | + | | + | | | | |
| Fernandes et al.[53] | SP | 50F | 48 | | | | | | + | + | + | | + | | | + | | | | |
| | A, E | 52F | <1 | + | | | | | | + | | | | | | | | + | | |
| Iizuka et al.[25] | PERM | 61F | 1.5 | + | + | | | | | + | | | | | | + | | + | | |

Table 1. Continued

| Reference | History or Examination Findings | | | | | | | | Antibody Testing | | | | | | | Other Testing | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hyperekplexia | Hyperreflexia | Limb Posturing/Dystonia | Limb Stiffness/Rigidity | Malignancy | Myoclonus | Seizures | Weakness | Serum Anti-GAD Antibodies | Serum Anti-Glyr Antibodies | Other Serum Antibodies Detected | CSF Anti-GAD Antibodies | CSF Anti-Glyr Antibodies | Other CSF Antibodies Detected | CSF Oligoclonal Bands | EEG (Findings Consistent With Seizures) | Electromyography Findings Consistent With SP | MRI Brain Abnormalities | MRI Spine Abnormalities To Explain The Patient's Symptoms |
| Lobo et al.[44] | | | | + | – | | | | + | | | | | | | | + | | |
| Awad et al.[23] | + | | + | + | | | | – | + | | AT, AG | | | | | | | | |
| Scavone et al.[24] | | | | | | | | | + | | AI, ANA, AP, SSA | + | | | + | | | – | – |
| Castelnovo et al.[45] | + | | + | + | | | | | + | | | | | | – | | – | – | – |
| Cuturic et al.[46] | | | | + | | – | | | + | | | | | | | – | – | – | |
| Ehler et al.[6] | | | | + | | | | | + | | K | | | K | | – | + | – | – |
| Gnanapavan et al.[47] | | + | | | | | | | + | | | | | | | | + | | |
| Goldkamp et al.[48] | | | | | | | | | + | | | | | | | | | | |
| Mas et al.[37] | + | + | | + | | + | + | + | – | + | – | | + | | – | | + | – | – |
| | + | + | | + | | | | | – | + | – | | | | – | | | – | – |
| | | | + | + | | + | | | – | + | – | | | | – | | | – | – |
| Piotrowicz et al.[49] | + | + | | + | – | + | | + | – | + | – | | + | | + | | + | – | |
| Turner et al.[27] | + | + | | + | | + | + | | – | + | AN | | | | | + | | – | – |
| Witherick et al.[28] | + | | | + | | | | | + | | | | | | | | + | | |
| Anagnostou et al.[50] | + | | + | + | | | | | + | | | | | | | | + | – | – |
| Amyradakis et al.[51] | | | | + | | | | | + | | | | | | | | | | |
| Fekete and Jankovic[52] | + | + | | + | | + | + | | + | | – | | | | | – | | – | |
| Fernandes et al.[53] | | | | | – | | | | + | | | | | | | | + | – | – |
| | | | | | | | + | | + | | – | | | | | – | | – | |
| Iizuka et al.[25] | | + | | + | | + | | | + | + | AG, AX | + | + | | + | | + | | |

Table 1. Continued

| Reference | Reported Diagnoses at Presentation | Age and Sex at Presentation | Number Of Symptomatic Months Before Presentation | Symptoms: Bulbar (Excluding Taste Changes) | Symptoms: Taste Changes | Symptoms: Genitourinary Dysfunction | Symptoms: Difficulty Changing Position | Symptoms: Difficulty Moving Limb | Symptoms: Falls | Symptoms: Gait Difficulties (Including Ataxia) | Symptoms: Pain | Symptoms: Pruritus | History or Examination Findings: Axial Stiffness or Hyperlordosis | History or Examination Findings: Autonomic Instability (Besides Genitourinary Dysfunction) | History or Examination Findings: Concomitant Autoimmunity (Other Than Diabetes) | History or Examination Findings: Cramps/Spasms | History or Examination Findings: Diabetes | History or Examination Findings: Extraocular Movement Abnormalities | History or Examination Findings: Hepatitis C | History or Examination Findings: Encephalopathy or Psychiatric/Behavioral Changes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lorenzoni et al.[33] | SL | 10F | | | | | | | | + | + | | | + | | + | | | | |
| | SP | 40M | | | | | | | | + | + | | | | | + | + | | | |
| | SP | 42M | | | | | | | | + | + | | + | | | + | + | | | |
| Najjar, at al.[22] | S | 19F | | | | | | | | | | + | | | | | – | | | + |
| Peeters et al.[36] | PERM | 37F | 1 | + | | + | | | + | | + | | + | + | | + | | + | | – |
| Qureshi et al.[54] | SP | 56M | 72 | + | | | | | | | + | | + | | | + | + | – | | + |
| Tsai et al.[55] | SP | 66M | 4 | + | | | | | + | | | | | | | + | + | | | |
| Baroncini et al.[26] | A, LE | 44F | 36 | + | | + | | | | + | | | + | | T | + | | + | | + |
| Clardy et al.[14] | SP | 8F | <12 | | | | | | | | | | | | V | | + | | | |
| | SP | 26M | 168 | + | | | | | | | | | + | | V | | | | | |
| | SP | 51F | 552 | | | | | | | | | | + | | – | | | | | |
| | SP | 49M | 528 | + | | | | | | | | | | | G | | + | | | |
| | SL | 14F | 156 | | | | | | | | | | | | T | | + | | | |
| | ST | 17M | 36 | | | | | | | | | | + | | – | | | | | |
| | PERM | 13F | <12 | | | | | | | | | | + | | | + | + | | | |
| De la Casa-Fages et al.[56] | SP | 59F | 10 | + | | | | | | + | | | + | | P, V | + | | | | |
| | SP | 48M | 240 | | | | | | + | + | | | + | | V | + | + | | | |
| Damasio et al.[57] | PERM | 1F | <1 | + | | + | | | | + | | | + | + | | + | | + | | + |
| Marinovic et al.[58] | SP | 51F | | | | | | | | + | + | | + | | | + | | | | |
| Nakane et al.[59] | SP | | | | | | | | | | | | | | | | | | | |
| | SP | | | | | | | | | | | | | | | | | | | |
| O'Toole et al.[60] | SP | 72F | 12 | | | | | | | + | | | + | | T | + | + | | | |
| Sidransky et al.[61] | SP | 34 | 6 | – | | | | | | | + | | + | | | | | | | |
| Sengupta et al.[62] | A, SP | F | | | | | | | | | | | | | | | | | | |

Table 1. Continued

| Reference | History or Examination Findings | | | | | | | | Antibody Testing | | | | | | | | Other Testing | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hyperekplexia | Hyperreflexia | Limb Posturing/Dystonia | Limb Stiffness/Rigidity | Malignancy | Myoclonus | Seizures | Weakness | Serum Anti-GAD Antibodies | Serum Anti-Glyr Antibodies | Other Serum Antibodies Detected | CSF Anti-GAD Antibodies | CSF Anti-Glyr Antibodies | Other CSF Antibodies Detected | CSF Oligoclonal Bands | EEG (Findings Consistent With Seizures) | Electromyography Findings Consistent With SP | MRI Brain Abnormalities | MRI Spine Abnormalities To Explain The Patient's Symptoms |
| Lorenzoni et al.[33] | | + | | + | | | | | + | | | | | | | | + | | |
| | | | | + | | | | | + | | | | | | | | + | | |
| | | | | + | | | | | + | | | | | | | | + | | |
| Najjar, at al.[22] | | | | | | | | | + | | – | | | | | – | | | |
| Peeters et al.[36] | + | + | | + | – | + | | | – | + | – | | + | | + | | + | – | – |
| Qureshi et al.[54] | | – | | + | | + | | + | + | | – | | | | + | – | | | – |
| Tsai et al.[55] | + | + | + | + | –[a] | + | | + | + | | – | | | | – | | | – | |
| Baroncini et al.[26] | | | + | + | – | | + | | + | | AP, AX | + | | | + | – | + | + | |
| Clardy et al.[14] | | – | | + | | | | | + | + | – | + | | | | | – | | – |
| | | + | | + | | | | | + | – | – | + | | | | | – | | – |
| | | – | | – | | | | | + | – | – | + | | | | | – | | – |
| | | + | | + | | | | | + | – | – | + | | | | | – | | – |
| | | – | | – | | | | | + | – | – | + | | | | | – | | – |
| | | + | | + | | | | | + | – | – | + | | | | | + | | – |
| De la Casa-Fages et al.[56] | + | | | + | | | | | + | | – | | | | | | + | | |
| | + | | | + | | | | | + | | – | | | | | | + | | |
| Damasio et al.[57] | + | + | + | + | | + | | | | + | – | | + | | | – | | – | |
| Marinovic et al.[58] | | | | | | | | | + | | – | | | | | | + | | – |
| Nakane et al.[59] | | | | | | | | | + | | | | | | | | | | |
| | | | | | | | | | + | | | | | | | | | | |
| O'Toole et al.[60] | + | | | + | – | | | | + | | | | | | | | + | | |
| Sidransky et al.[61] | + | | | | | | | | + | | | | | | | | | | |
| Sengupta et al.[62] | | | | | | | | | + | | | | | | | | | | |

Table 1. Continued

| Reference | Reported Diagnoses at Presentation | Age and Sex at Presentation | Number Of Symptomatic Months Before Presentation | Symptoms: Bulbar (Excluding Taste Changes) | Symptoms: Taste Changes | Symptoms: Genitourinary Dysfunction | Symptoms: Difficulty Changing Position | Symptoms: Difficulty Moving Limb | Symptoms: Falls | Symptoms: Gait Difficulties (Including Ataxia) | Symptoms: Pain | Symptoms: Pruritus | History or Examination Findings: Axial Stiffness or Hyperlordosis | History or Examination Findings: Autonomic Instability (Besides Genitourinary Dysfunction) | History or Examination Findings: Concomitant Autoimmunity (Other Than Diabetes) | History or Examination Findings: Cramps/Spasms | History or Examination Findings: Diabetes | History or Examination Findings: Extraocular Movement Abnormalities | History or Examination Findings: Hepatitis C | History or Examination Findings: Encephalopathy or Psychiatric/Behavioral Changes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vetrugno et al. 2013[63] | OT, SP | 77F | 1 | | | | | | | | | | | | | + | | | | |
| | OT, SP | 55F | 12 | | | | | | + | + | + | | + | | T, V | + | | | | |
| Bordelon et al.[64] | SP | 60F | 108 | | | | | | + | | | | + | + | | + | | | | + |
| Emuh et al.[65] | SP | 20F | 12 | | | | | + | | + | | | | + | T | + | + | | | + |
| Fourlanos et al.[66] | SP | 78F | 300 | | | | | | | | | | + | | | + | + | | | + |
| | SP | 72F | 6 | | | | | | | | + | | | | + | + | + | | | |
| Georgieva et al.[67] | A, E | 45M | | + | | | | | | + | | | | | | | + | + | | + |
| Ho et al.[68] | SP | 43F | | + | | | | + | + | + | | | + | | | + | | + | | + |
| Jung et al.[69] | SP | 55F | 12 | | | | | | + | + | + | | | | | + | | – | | |
| | SP | 58F | 15 | | | | | | | | + | | + | | P | + | + | | | |
| | E, SP | 49F | 10 | | | | | | | | | | + | | | | | | | |
| Pagano et al.[30] | SP | 45M | | | | | | | | | | | | | | | + | | | |
| | A, SP | 65F | | | | | | | | | | | | | | | + | | + | |
| | SP | 48F | | | | | | | | | | | | | | | | | | |
| | SP | 61F | | | | | | | | | | | | | | | | | | |
| | SP | 34F | | | | | | | | | | | | | | | + | | | |
| | A, SP | 50F | | | | | | | | | | | | | | | | | | |
| Rana et al.[70] | SP | 50F | 30 | + | | | | | | | + | | + | | V | + | | | | |
| Sanders et al.[71] | SP | 48F | | | | | | | + | + | | | | | | | | | | + |
| | SP | 30F | 24 | + | | | | | | | | | | | | | | | | |
| Stern et al.[72] | PERM | 40M | <1 | + | | | | | | | | | | + | | + | | + | | + |
| Wuerfel et al.[73] | B, E | 2M | 12 | + | | | | | | | | | | + | | | | | | + |
| Bowen et al.[29] | C, SP | 49F | 24 | | | | | + | + | + | | | + | | | + | | – | | |
| | C, SP | 68F | 84 | | | | | + | + | + | | | + | | | | + | – | | |
| Farooqi et al.[74] | E | 23F | 48 | | | | | | | – | | | | | | | | – | | – |

Table 1. Continued

| Reference | History or Examination Findings | | | | | | | Antibody Testing | | | | | | | | Other Testing | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hyperekplexia | Hyperreflexia | Limb Posturing/Dystonia | Limb Stiffness/Rigidity | Malignancy | Myoclonus | Seizures | Weakness | Serum Anti-GAD Antibodies | Serum Anti-Glyr Antibodies | Other Serum Antibodies Detected | CSF Anti-GAD Antibodies | CSF Anti-Glyr Antibodies | Other CSF Antibodies Detected | CSF Oligoclonal Bands | EEG (Findings Consistent With Seizures) | Electromyography Findings Consistent With SP | MRI Brain Abnormalities | MRI Spine Abnormalities To Explain The Patient's Symptoms |
| Vetrugno et al. 2013[63] | + | | | + | – | | | | + | | – | | | | | | | – | – |
| | + | | | + | – | | | | + | | – | | | | | | | | |
| Bordelon et al.[64] | | + | | + | | | | | + | | | | | | | – | + | – | |
| Enuh et al.[65] | | | + | | | + | – | + | | | | + | | | | | + | – | – |
| Fourlanos et al.[66] | + | + | | + | | | | | + | | | + | | | | | | – | – |
| | + | | + | + | | | | | + | | | | | | – | | | – | – |
| Georgieva et al.[67] | | + | | | | | + | | + | | | + | | | + | | | – | |
| Ho et al.[68] | + | – | | | | | | – | + | | – | | | | | – | + | – | – |
| Jung et al.[69] | + | + | | + | | | | – | + | | | | | | | | + | | |
| | + | | | + | | | | | + | | – | | | | | | – | | – |
| | | + | | + | | | + | – | + | | | | | | | + | + | – | |
| Pagano et al.[30] | | | | | – | | | | + | | | | | | | | | | |
| | | | | | – | | | | + | | AA | | | | | | | | |
| | | | | | – | | | | + | | | | | | | | | | |
| | | | | | – | | | | + | | | | | | | | | | |
| Rana et al.[70] | | | | | | | | | + | | | | | | | | | | |
| Sanders et al.[71] | + | + | | + | | | | – | + | | | | | | | | – | – | – |
| | + | | | + | | | | | + | | | | | | | | + | | |
| Stern et al.[72] | + | | | + | – | + | | | – | + | – | | + | | – | | | – | |
| Wuerfel et al.[73] | – | | + | – | – | – | + | | – | + | – | | – | | – | + | | – | |
| Bowen et al.[29] | + | | – | + | | – | | – | + | | | + | | | + | | | – | – |
| | | | | + | | | | | + | | | | | | + | | | + | – |
| Farooqi et al.[74] | | | | – | | | + | | + | | | | | | | + | | + | |

Abbreviations: A, Ataxia; AA, Anti-amphiphysin Antibodies; AG, Anti-thyroglobulin; AI, Anti-intrinsic Factor; AN, Anti-N-methyl-D-aspartate Receptor Antibodies; ANA, Anti-nuclear Antibody; AP, Anti-parietal Cell Antibody; AT, Anti-thyroid Microsomal; AX, Anti-thyroid Peroxidase Antibody; B, Behavioral Changes; C, Corticobasal Syndrome; CSF, Cerebrospinal Fluid; E, epilepsy; ED, Eating Disorder; F, Female; G, Graves' Disease; K, Antibodies against Tick-borne Meningoencephalitis; LE, Limbic Encephalitis; M, Male; MG, Myasthenia Gravis; MRI, Magnetic Resonance Imaging; OT, Orthostatic Tremor; P, Pernicious Anemia; PERM, Progressive Encephalomyelitis with Rigidity and Myoclonus; T, Autoimmune Thyroid Disease; S, Schizophrenia; SL, Stiff Limb Syndrome; SP, Stiff Person Syndrome; SSA, Anti-Sjögren's-Syndrome-Related Antigen A; ST, Stiff Trunk Syndrome; V, Vitiligo.

[a]This patient had no evidence of active malignancy at the time of symptom presentation; but had a remote history of treated lymphoma

absence of concomitant autoimmunity; data were lacking for the rest), and 26 (37.7%) had documented diabetes. In descending order of frequency, other associated autoimmune conditions included five with isolated thyroid disease; four with isolated vitiligo; three with isolated pernicious anemia; one with coexisting thyroid disease and vitiligo; one with coexisting pernicious anemia and vitiligo; one with coexisting myasthenia gravis and pernicious anemia; and one with Graves' disease. Eight (11.6% of all autoimmune cases) had coexisting diabetes along with another autoimmune disease.

Serum anti-GAD antibody testing was documented for 66/69 (95.6%), 58/66 (87.9%) being seropositive. Twenty-five of the 26 patients (96.2%) with diabetes were seropositive for anti-GAD antibodies. Serum anti-GlyR antibody testing was documented for 17/69 (24.6%), and 11/69 (15.9%) were positive. Eight of these 11 had PERM. Testing for other antibodies was documented in 26/69 (37.7%), and seven were positive for the following antibodies: three for anti-thyroid antibodies; two against parietal cells; one for anti-amphiphysin; one for rheumatologic antibodies (Anti-Sjögren's-syndrome-related antigen A and anti-nuclear antibody);[23] one for non-specific immunoglobulin (Ig)M against tick-borne meningoencephalitis; and one for anti-N-methyl-D-aspartate receptor antibodies. Four of these seven patients had two or more detectable autoantibodies in serum.[23–26] Only the patient with antibodies against tick-borne meningoencephalitis had them in both serum and CSF.[6] Testing for oligoclonal bands (OCBs) was reported in 17 patients (24.6%), and they were detected in nine. Electromyography (EMG) findings were reported in 36 patients (52.2%), with findings consistent with SPS in 26.

As shown in Table 2, the two most commonly used treatments were benzodiazepines and intravenous immunoglobulin, which were used in 45/69 cases (65.2%). Baclofen followed as the third most commonly used agent (26/69 cases, or 37.7%). Fifty-eight patients (84.1%) received either intravenous immunoglobulins, plasmapheresis, rituximab, steroids, or a steroid-sparing immunosuppressant. In terms of outcomes, 54 reported improvement (78.3%), nine (13%) remained stable, and three (4.3%) either worsened or died (one of these had PERM; the other two had SPS, one of which was also had concomitant corticobasal syndrome).[27–29] Eighteen of the 54 (33.3%) patients who improved experienced at least one relapse at some point in the course of their disease.

### *Paraneoplastic SPS-spectrum cases (Table 3)*

There were 19 paraneoplastic SPS-spectrum cases. Thirteen were females. The median age at presentation was 59 (range 21–81) years. Eleven had SPS, four of whom also had other neurologic disorders (two with limbic encephalitis; one with ataxia; and one with opsoclonus–myoclonus). Three cases were consistent with SLS and two with PERM. One had West Nile encephalitis with positive anti-GAD antibodies; another had a "paraneoplastic centrally mediated disorder with central planning" but had no detectable antibody; and the remaining case had isolated opsoclonus–myoclonus with serum anti-GAD antibodies.[30,31] Ten cases documented the time between symptom onset and presentation with a median of 3 months and ranging from weeks up to 13 years. Fifteen patients described gait difficulties, 11 reported pain, 12 had cramps or spasms, and 13 had limb stiffness.

All cases had a documented malignancy, the most common being breast cancer (eight cases). Malignancies of the following organs were also reported: thymus (three cases); colon (two); and lung (two). The remaining four cases had either Hodgkin's lymphoma, leukemia, mesothelioma, or melanoma. In terms of comorbidities, only one had pre-existent diabetes (another four were documented not to be diabetic) and screening for autoimmunity was documented in only one case (and not detected).

The antibody profile was varied. Seventeen cases were tested for anti-GAD antibodies, of which eight were positive. Anti-GlyR antibodies were tested in two cases, one was positive. Thirteen cases were tested for other antibodies, and the following were identified: four were seropositive for anti-amphiphysin antibodies (two cases had antibodies also in CSF) and one was positive for anti-Ri antibodies in both serum and CSF. No antibodies were detected in five. Oligoclonal bands were tested in eight, and four were positive. Seven had EMGs, with six having features consistent with SPS.

Benzodiazepines and cancer treatment (chemo- or radiotherapy) were employed in 13 cases. Nine cases underwent oncologic surgery, and 16 patients received some kind of cancer treatment, including chemotherapy, radiotherapy, and/or oncologic surgery. Despite all of these patients having a malignancy, 16 improved neurologically (one of them deteriorated eventually). Two remained stable and two others worsened, one of whom succumbed to mesothelioma after having previously improved from a neurologic standpoint. Four of the 16 patients who improved experienced at least one relapse.

### *Cryptogenic SPS-spectrum cases (Table 4)*

There were 13 cryptogenic cases. Four were female, nine were male. The ages ranged from 7 to 75 years, with a median age of 44 years. Of these 13, 11 had SPS, including a patient who initially presented with SLS.[32] Among the two remaining cases, one had SLS and the other had PERM. Data for 11/13 patients regarding the time between symptom onset and presentation ranged from less than 1 month to 14 years, with the median being 9 months. All of the cases had either cramps or spasms, and nine had limb stiffness. Other common symptoms were pain (reported in 11 cases) and gait difficulties (nine). Only one case had concomitant autoimmunity (thyroid disease and vitiligo),[33] and absence of concomitant autoimmunity was only reported in another case.[14] Eleven of 13 reported testing for commonly associated antibodies, and all of them were negative for either anti-GAD or anti-GlyR antibodies. Of these 11, one reported positive OCBs[34] while another documented absence of this finding (the patient with PERM).[35] EMG findings consistent with SPS were reported in seven. The most commonly used medication was a benzodiazepine (12 cases). Treatment outcomes in this cohort were overwhelmingly positive. Twelve reported improvement and the thirteenth stabilized, but there was no mention of worsening or death. Among the 12 who improved, only the PERM case relapsed.[35]

Table 2. **Treatments and Outcomes in Reported Cases of Autoimmune Stiff Person Syndrome and Its Variants**

| | | | | Treatment | | | | | | | | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Reported Diagnoses at Presentation | Age and Sex At Presentation | Number of Symptomatic Months Before Presentation | Antibiotics | Antiepileptics | Antipsychotics | Baclofen | Benzodiazepines | Botulinum Toxin Injections | Intravenous Immune Globulin | Other Agents Or Interventions | Plasmapheresis | Rituximab | Steroids | Steroid–Sparing Immunosuppression | Surgery: Spinal Cord Stimulator | Improvement or Resolution | Stabilization Without Improvement | One or More Relapses Mentioned | Worsening and/or Death |
| Lobo et al.[44] | SP | 41F | 84 | | | | | + | + | | | | + | | | | + | | | |
| Scavone et al.[24] | SP | 66M | | | | | | | | + | | | | | | | + | | | |
| Awad et al.[23] | A | 48F | | | | | | | | + | | | + | + | | | | + | | |
| Castelnovo et al.[45] | SL | 63F | 36 | | | | | + | | + | | | | | | | + | | | |
| Cuturic et al.[46] | SP, ED | 35F | 24 | | | | + | + | | + | + | | | | | | + | | | |
| Ehler et al.[6] | SP | 61M | <1 | | | | + | + | | | | + | | + | + | | + | | + | |
| Gnanapavan et al.[47] | SP | 45M | 60 | | | | + | + | | + | + | | + | | + | | + | | + | |
| Goldkamp et al.[48] | SP | 27F | | | | | + | + | | + | + | | | + | | | + | | | |
| Mas et al.[37] | E, PERM | 60M | <1 | | | | | | | | | | | | | | | + | | |
| | PERM | 48M | 2 | | | | | + | | + | + | | | + | | | + | | | |
| | SL, SP | 33F | 3 | | | | + | + | | + | | | | + | | | + | | + | |
| Piotrowicz et al.[49] | PERM | 58M | >1 | | | | | + | | | | + | | + | + | | + | | + | |
| Turner et al.[27] | PERM | 28M | 1 | | + | | | | | | | | | | | | | | | + |
| Witherick et al.[28] | SP | 69M | | | | | | | | + | + | | | | + | | + | | + | + |
| Anagnostou et al.[50] | SL | 40F | 108 | | | | | + | + | | | | | | | | + | | | |
| Amyradakis et al.[51] | SP | F | <1 | | | | | + | | | + | | | | | | + | | + | |
| Fekete and Jankovic[52] | SP | 12M | 84 | | + | | + | + | | + | + | | + | | | | + | | | |
| Fernandes et al.[53] | SP | 50F | 48 | | | | + | + | | + | | | | | | | + | | | |
| | A, E | 52F | <1 | | + | | | + | | + | | | | + | + | | | | | |
| Iizuka et al.[25] | PERM | 61F | 1.5 | | | | | + | | + | | | | + | + | | + | | + | |
| Lorenzoni et al.[33] | SL | 10F | | | | | | + | | + | | | | | | | + | | | |
| | SP | 40M | | | | | + | + | | + | | | | | | | + | | | |
| | SP | 42M | | | | | + | + | | + | | | | | | | + | | | |
| Najjar, et al.[22] | S | 19F | | | | + | | | | + | | + | | + | | | + | | + | |
| Peeters et al.[36] | PERM | 37F | 1 | | | | + | + | | | | + | | + | | | + | | + | |
| Qureshi et al.[54] | SP | 56M | 72 | | + | | | + | | + | + | + | + | + | | | + | | | |
| Tsai et al.[55] | 66M | SP | 4 | | | | + | + | | + | | | | + | + | | + | | + | |
| Baroncini et al.[26] | A, LE | 44F | 36 | | + | | | | | + | | + | + | + | | | + | | | |

Table 2. Continued

| Reference | Reported Diagnoses at Presentation | Age and Sex At Presentation | Number of Symptomatic Months Before Presentation | Treatment | | | | | | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Antibiotics | Antiepileptics | Antipsychotics | Baclofen | Benzodiazepines | Botulinum Toxin Injections | Intravenous Immune Globulin | Other Agents Or Interventions | Plasmapheresis | Rituximab | Steroids | Steroid–Sparing Immunosuppression | Surgery: Spinal Cord Stimulator | Improvement or Resolution | Stabilization Without Improvement | One or More Relapses Mentioned | Worsening and/or Death |
| Clardy et al.[14] | SP | 8F | <12 | | | | + | + | | + | | + | | | + | | + | | | |
| | SP | 26M | 168 | | | | + | + | | | | | | + | | | | + | | |
| | SP | 51F | 552 | | | | + | + | | + | | | | | + | | | + | | |
| | SP | 49M | 528 | | | | | | | | | | + | | | | | + | | |
| | SL | 14F | 156 | | | | | + | | + | | | | | | | + | | + | |
| | ST | 17M | 36 | | | | + | + | + | | + | + | | | | | + | | | |
| | PERM | 13F | <12 | | | | | + | | + | | + | + | | | | | + | | |
| De la Casa-Fages et al.[56] | SP | 59F | 10 | | + | | + | + | + | + | | + | | + | + | | + | | | |
| | SP | 48M | 240 | | | | | + | | + | | + | | + | + | | + | | | |
| Damasio et al.[57] | PERM | 1F | <1 | + | + | | | + | | + | | | | | | | | | + | |
| Marinovic et al.[58] | SP | 51F | | | | | | + | | | + | | | | | | | + | | |
| Nakane et al.[59] | SP | | | | | | | + | | + | | | | | + | | | | | |
| | SP | | | | | | | + | | | | + | | + | + | | + | | + | |
| O'Toole et al.[60] | SP | 72F | 12 | | | | | | | | | | | | | | | | | |
| Sidransky et al.[61] | SP | 34 | 6 | | | | + | + | | + | + | | | | | | + | | | |
| Sengupta et al.[62] | A, SP | F | | | | | | | | | | | + | | + | | + | | + | |
| Vetrugno et al.[63] | OT, SP | 77F | 1 | | | | | + | | + | | | | | | | + | | + | |
| | OT, SP | 55F | 12 | | | | | + | | + | | | | | | | + | | | |
| Bordelon et al.[64] | SP | 60F | 108 | | | | + | + | | + | + | | | + | | | + | | | |
| Enuh et al.[65] | SP | 20F | 12 | | | | + | + | | + | + | | | | | | + | | | |
| Fourlanos et al.[66] | SP | 78F | 300 | | | | | | | + | | + | | | | | + | | | |
| | SP | 72F | 6 | | | | + | | | + | | | | | | + | + | | | |
| Georgieva et al.[67] | A, E | 45M | | | | | | | | + | | + | | | + | | + | | + | |
| Ho et al.[68] | SP | 43F | | | | | + | + | | | | | | + | | | | | | |
| Jung et al.[69] | SP | 55F | 12 | | | | | + | | | | | | | | | + | | + | |
| | SP | 58F | 15 | | | | + | + | | | | | | | | | + | | | |
| | E, SP | 49F | 10 | | | | + | + | | | | | | + | | | + | | | |

Table 2. Continued

| Reference | Reported Diagnoses at Presentation | Age and Sex At Presentation | Number of Symptomatic Months Before Presentation | Treatment | | | | | | | | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Antibiotics | Antiepileptics | Antipsychotics | Baclofen | Benzodiazepines | Botulinum Toxin Injections | Intravenous Immune Globulin | Other Agents Or Interventions | Plasmapheresis | Rituximab | Steroids | Steroid–Sparing Immunosuppression | Surgery: Spinal Cord Stimulator | Improvement or Resolution | Stabilization Without Improvement | One or More Relapses Mentioned | Worsening and/or Death |
| Pagano et al.[30] | SP | 45M | | | | | | | | | | + | | | | | + | | | |
| | A, SP | 65F | | | | | | | | + | | + | | | | | | + | | |
| | SP | 48F | | | | | | | | + | | + | | | | | + | | | |
| | SP | 61F | | | | | | | | + | | + | | | | | + | | | |
| | SP | 34F | | | | | | | | + | | + | | | | | + | | | |
| | A, SP | 50F | | | | | | | | | | + | | | | | + | | | |
| Rana et al.[70] | SP | 50F | 30 | | | | | | | | | | | | | | | | | |
| Sanders et al.[71] | SP | 48F | | | + | | + | + | | + | + | + | | | + | | + | | | |
| | SP | 30F | 24 | | | | + | + | | + | + | + | | | | | + | | | |
| Stern et al.[72] | PERM | 40M | <1 | | | | + | + | | + | | + | | + | | | + | | + | |
| Wuerfel et al.[73] | B, E | 2M | 12 | | + | | | | | | | | | + | | | + | | | |
| Bowen et al.[29] | C, SP | 49F | 24 | | | | | | | | | | | | | | | | | |
| | C, SP | 68F | 84 | | | | | | | + | | | | | | | | | | + |
| Farooqi et al.[74] | E | 23F | 48 | | + | | | | | + | | + | | + | + | | | + | + | |

Abbreviations: A, Ataxia; B, Behavioral Changes; C, Corticobasal Syndrome; E, Epilepsy; ED, Eating Disorder; F, Female; LE, Limbic Encephalitis; M, Male; OT, Orthostatic Tremor; PERM, Progressive Encephalomyelitis with Rigidity and Myoclonus; S, Schizophrenia; SL, Stiff Limb Syndrome; SP, Stiff Person Syndrome; ST, Stiff Trunk Syndrome.

### *Case series of patients with anti-GAD antibodies and cerebellar ataxia (Table 5)*

Ariño et al.[21] described 34 cases of cerebellar ataxia with anti-GAD antibodies. Data are consolidated for the cohort, as individual details for each of these 34 are not available. Twenty-eight of the 34 patients were female. Gait difficulty was the most common symptom in this cohort (91.2%). Concomitant autoimmunity was reported for well over half, with thyroid disease being the most prevalent (52.9%). Cancer was detected in four cases (11.8%). Different immunosuppressant agents were the treatment of choice, and outcomes varied considerably with a subacute course and early medical treatment being good prognostic indicators.

## Discussion

Segregation of SPS-spectrum cases based on likely etiology allowed detecting similarities and differences between categories. It also allowed identifying themes within each group. Perhaps the most evident observation is the phenotypical variability present within each group. The data demonstrate that SPS, SLS, or PERM can all be found in autoimmune, paraneoplastic, or cryptogenic SPS-spectrum disease. This lack of specificity hinders the examiner's ability to predict an etiology based solely on clinical features.

By definition, the presence of anti-GAD antibodies includes a condition within the SPS spectrum. However, these antibodies do not differentiate between paraneoplastic and autoimmune causes as they are present in both. In this review over 80% of autoimmune SPS-spectrum cases were positive for anti-GAD antibodies, but close to 50% of paraneoplastic cases were also seropositive. Additional antibodies (anti-amphiphysin antibodies) can increase specificity, particularly when multiple antibodies are present, in which case anti-amphiphysin antibody seropositivity should encourage an investigation for an underlying malignancy. The presence of multiple antibodies further supports the notion that anti-GAD antibodies are not the sole pathogenic cause but that the GABA synthesis apparatus along with its associated pathways are disrupted. It also suggests that it is important to obtain CSF in these patients with multiple antibodies as some are predominantly found in the CNS, such as GAD67,[21] particularly when clinical findings or preliminary serum tests are inconclusive.

Anti-GlyR antibodies were the second-most commonly observed after anti-GAD antibodies. In this review, 11 autoimmune SPS-spectrum cases had anti-GlyR antibodies in serum (15.9%), nine had them in CSF (13%), seven had antibodies in both CSF and serum (10.1%), and two only in CSF but not in serum (2.9%). The phenotypes included PERM, three with SPS, one with stiff trunk syndrome, and one with behavioral changes and epilepsy. Interestingly, among the patients who had antibodies in both CSF and serum, one had prodromal reduction in taste,[25] one had prodromal pruritus,[36] and a last one had both.[37] All of them were eventually diagnosed with PERM. We find this observation clinically relevant, since changes in taste and pruritus may be specific enough to predict a diagnosis of PERM in the right clinical context. This could ultimately translate into prompt initiation of immunosuppressive treatment. In contrast to autoimmune cases, anti-GlyR antibodies were only found in one paraneoplastic case: a case of SLS in the setting of leukemia.[38] Thus, the presence of anti-GlyR antibodies despite the clinical phenotypic variation may strongly suggest a more autoimmune pathology rather than a paraneoplastic variation, unlike anti-GAD antibodies, which are present in both.

Paraneoplastic SPS-spectrum cases too present with a myriad of different phenotypes. Because of this, it may be prudent to screen for malignancy in all patients with symptoms consistent with the SPS-spectrum, although, admittedly, it may not be cost-effective. Thus, we recommend a step-wise approach, first with brain and spine MRI, routine blood work, including complete blood count, comprehensive metabolic panel, and B12 level, EMG/nerve conduction studies, and lumbar puncture assessing for autoimmune and infectious causes before a malignancy screen. If this preliminary work-up and subsequent serum and CSF paraneoplastic antibody panels are negative, whole-body positron emission tomography is recommended to assess for occult malignancy. The possible scenario in which this intervention may be most cost-effective is in patients with opsoclonus–myoclonus. We identified the opsoclonus–myoclonus phenotype to be specific for paraneoplastic cases, as seen in two out of 19 paraneoplastic cases, as opposed to none of the 69 autoimmune or the 13 cryptogenic cases. However, if serum anti-amphiphysin antibodies are detected, a specific search for breast malignancy should be undertaken as previous reports[19,39] and our current analysis show a high likelihood of associated breast cancer.

Among ancillary testing, EMG is particularly useful. Although not consistently reported, EMG was positive in 72.2% of all EMG-tested autoimmune cases, 85.7% of paraneoplastic cases, and 87.5% of the cryptogenic EMG-tested cases. Given this apparent high probability of a confirmatory finding, we advocate for routine EMG testing in all suspected SPS-spectrum cases featuring rigidity, dystonic posturing, or cramping. However, there were no specific EMG findings to differentiate among the subgroups. One important consideration based on both our literature review and experience is that the pathognomonic EMG findings may take some time to develop.[33] Thus, in cases where an initial EMG is negative, a repeat EMG should be performed in at least 3 months' time if the clinical suspicion is high.

Thus, the constellation of commonalities within groups is most helpful when attempting to identify the cause of a SPS-spectrum condition, rather than relying solely on clinical features or a single antibody. Thus, the presence of a concomitant autoimmune condition, anti-GAD antibodies, and symptoms of a SPS-spectrum disorder suggests an autoimmune pathomechanism. However, anti-amphiphysin antibodies in the presence of these symptoms and a malignancy suggest a paraneoplastic etiology. Although this may not be absolute, it can provide a guide to quickly diagnose and appropriately treat these patients. For example, in patients with paraneoplastic disease, treatment of the underlying malignancy with chemo/radiotherapy and oncologic surgery should be the focus of care.

Whereas we are confident of our autoimmune and paraneoplastic classifications, we have reservations with the cryptogenic category. We believe that this category can potentially include autoimmune cases for which a known antibody is either present in titers that evade detection, or are positive for antibodies that are yet to be recognized. The response to

Table 3. **Reported Cases of Paraneoplastic Stiff Person Syndrome and Its Variants**

| | | | | Symptoms | | | | | | | | | History or Examination findings | | | | | | | | | | | Antibody Testing | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Reported Diagnoses | Age And Sex At Presentation | Number Of Symptomatic Months Before Presentation | Bulbar Dysfunction | Falls | Gait Difficulties (Including Ataxia) | Pain | Axial Stiffness Or Hyperlordosis | Autonomic Instability | Concomitant Autoimmunity (Other Than Diabetes) | Cramps/Spasms | Diabetes | Extraocular Movement Abnormalities | Encephalopathy Or Psychiatric/Behavioral Changes | Hyperekplexia | Hyperreflexia | Limb Posturing/Dystonia | Limb Stiffness/Rigidity | Malignancy | Myoclonus | Seizures | Weakness | Serum Anti-GAD Antibodies | Serum Anti-Glyr Antibodies | Other Serum Antibodies Detected | Other CSF Antibodies Detected | CSF Oligoclonal Bands |
| Agarwal et al.[75] | SL | 55F | 2 | | | + | + | | | | + | | | | + | – | + | + | B | | | | + | | – | | – |
| Kosseifi et al.[76] | SP | 29M | <1 | + | | + | + | | | | + | | | | | | | + | T | | | + | – | | – | | |
| Schmidt et al.[77] | PERM | 21M | 18 | | + | + | | | + | | | | + | + | + | | + | + | H | + | + | | – | | – | | – |
| Thumen et al.[78] | OM,SP | 66F | 36 | + | + | + | | + | | | | | + | + | + | + | + | + | B | | | | – | | AR | AR | + |
| Chamard et al.[79] | SL | 65F | <1 | | | + | + | | + | | + | + | | + | + | | + | + | B | | | | | | AA | AA | + |
| Lemieux et al.[80] | PERM | 30F | | + | + | + | + | | | | + | | + | – | | + | | + | B | | | | – | | – | | |
| Byrne et al.[81] | LE,SP | 60F | 4 | | + | + | + | | + | | + | | | + | | + | + | + | B | | | + | – | | AA | | + |
| Krishna et al.[82] | LE,SP | 54F | 2 | | | | + | – | | | + | | – | + | + | – | | + | B | | + | – | – | | AA | | + |
| Aghajanzadeh et al.[83] | SP | 32M | | | | | | + | | | + | – | | | | | | + | T | | – | | + | | | | |
| Badzek et al.[84] | SP | 55F | | | | + | | + | | | | | | | | | | + | C | | | | – | | – | | |
| Derksen et al.[38] | SL | 66M | 1 | | | + | + | | + | – | + | – | | | + | + | + | + | K | + | | | – | + | – | | – |
| Rakcevic et al.[85] | SP | 57F | | | | + | + | + | | | + | | | | + | | | | L | | | | | | | | |
| Kelly et al.[86] | SP | 64F | | | + | | + | | – | | + | | | + | + | | | + | B | | | | + | | AA | AA | |
| Kobayashi et al.[87] | SP | 81F | 156 | + | | + | + | + | | | + | – | | | + | | | | T | | | | + | | | | |
| Koca et al.[88] | SP | 58F | | + | | + | + | + | | | + | – | – | | + | – | | + | ME | | – | – | + | | | | – |
| Laroumagne et al.[31] | OM | 65M | | | | + | | | | | | | + | | | | | | L | + | | | | | – | | |
| Pagano et al.[30] | WNE | 72M | | | | | | | | | | | | | | | | | C | | | | + | | | | |
| | PN | 54F | | + | | + | | | | | | | | | | | | | B | | | | – | | | | |
| | A,SP | 70F | | + | | + | | | | | | | | | | | | | N | | | | + | | | | |

Table 3. Continued

| Reference | Other Testing | | | Treatment | | | | | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Electroencephalographic Abnormalities | Electromyography Findings Consistent With SP | MRI Brain Abnormalities (Incidental Findings Excluded) | Antibiotics | Antiepileptics | Baclofen | Benzodiazepines | Botulinum Toxin Injections | Chemotherapy Or Radiotherapy | Intravenous Immune Globulin | Other Agents Or Interventions | Plasmapheresis | Rituximab | Steroids | Steroid-Sparing Immunosuppression | Surgical Intervention | Improvement Or Resolution | Stabilization Without Improvement | 1 Or More Relapses Mentioned | Worsening And/Or Death |
| Agarwal et al.[75] | – | + | – | | | + | + | | + | | | | | + | | + | + | | + | |
| Kosseifi et al.[76] | | | | | | | + | | + | | + | | | | | | + | | | |
| Schmidt et al.[77] | – | + | – | + | + | | + | | + | | + | | | + | | | + | | | |
| Thumen et al.[78] | | + | – | | | + | + | | | | | | | + | | + | + | | | |
| Chamard et al.[79] | | + | – | | | + | + | | + | | + | | | + | | + | + | | + | |
| Lemieux et al.[80] | – | – | – | | | + | + | | + | + | + | + | | | | + | + | | + | |
| Byrne et al.[81] | + | | + | | | + | + | | + | + | + | | + | + | | + | + | | + | + |
| Krishna et al.[82] | | | + | | + | + | + | | + | | | | | | | | + | | | |
| Aghajanzadeh et al.[83] | | | | | | + | + | | | | + | | | | | + | + | | | |
| Badzek et al.[84] | | | | | | | + | | + | | | | | | | + | + | | | |
| Derksen et al.[38] | | + | – | | | + | + | | + | + | | | + | + | | | | + | | |
| Rakcevic et al.[85] | | | | | | + | + | | + | | | | + | + | + | | + | | | |
| Kelly et al.[86] | | | | | | + | | + | + | + | + | + | + | + | + | + | + | | | |
| Kobayashi et al.[87] | | | | | | | | | | | | | | + | + | + | + | | | |
| Koca et al.[88] | | + | – | | | + | + | | + | | + | | | + | | | + | | | + |
| Laroumagne et al.[31] | – | | – | | | | | | + | | | | | + | | | | | | + |
| Pagano et al.[30] | | | | | | | | | | + | | + | | | + | | | + | | |
| | | | | | | | | | | - | | + | | | - | | + | | | |
| | | | | | | | | | | + | | + | | | - | | + | | | |

Abbreviations: A, ataxia; AA, anti-amphiphysin antibodies; AR, anti-Ri antibodies; B, breast cancer; C, colon cancer; CSF, cerebrospinal fluid; F, female; H, Hodgkin lymphoma; K, leukemia; L, lung cancer; LE, limbic encephalitis; M, male; ME, mesothelioma; MRI, magnetic resonance imaging; N, melanoma; OM, opsoclonus-myoclonus; PERM, progressive encephalomyelitis with rigidity and myoclonus; PN, paraneoplastic centrally mediated disorder with central planning impairment; SL, stiff limb syndrome; SP, stiff person syndrome; T, thymic malignancy; V, vitiligo; WNE, west Nile encephalitis

Table 4. **Reported Cases of Cryptogenic Stiff Person Syndrome and Its Variants.**

| | | | | Symptoms | | | | | | | | History or Examination Findings | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Reported Diagnosis** | **Age And Sex at Presentation** | **Number Of Symptomatic Months Before Presentation** | **Bulbar Dysfunction** | **Genitourinary Dysfunction** | **Difficulty Moving Limb** | **Falls** | **Gait Difficulties (Including Ataxia)** | **Pain** | **Axial Stiffness Or Hyperlordosis** | **Autonomic Instability (Besides Genitourinary Dysfunction)** | **Concomitant Autoimmunity** | **Cramps/Spasms** | **Encephalopathy Or Psychiatric/Behavioral Changes** | **Hyperekplexia** | **Hyperreflexia** | **Limb Posturing/Dystonia** | **Limb Stiffness/Rigidity** | **Myoclonus** | **Seizures** | **Weakness** |
| Ughratdar et al.[32] | SL, SP | 44M | 168 | | | | | | + | | | | + | | + | | + | + | | | |
| Hegyi.[40] | SP | 24F | 9 | | | + | | + | + | – | | | + | + | | | + | + | | | + |
| Iwata et al.[34] | SL | 29M | 24 | | | | | + | + | | | | + | | + | + | + | + | | | |
| Prasad[89] | SP | 51M | 6 | | | | + | | + | | – | | + | + | + | | | | | + | |
| Sanefuji et al.[90] | SP | 7F | <1 | | | | | + | + | | | | + | + | + | – | | | – | | |
| Schreiber et al.[41] | SP | 75F | 36 | | | | + | + | + | + | | | + | – | + | + | | + | | | |
| Lorenzoni et al.[33] | SP | 43M | | | | | | + | + | + | | T, V | + | | + | + | | + | | | |
| Clardy et al.[14] | SP | 13M | 2 | | | | | | | + | | – | + | | | – | | | | | |
| Newton et al.[42] | SP | 48M | | + | | | | + | + | + | | | + | | | – | | + | | | |
| Vicente–Valor et al.[43] | SP | 40M | 72 | | | + | | + | + | + | + | | + | | + | + | | + | | | |
| Sharma et al.[91] | SP | 65M | 6 | | | | | + | + | + | | | + | + | | – | | + | | | |
| Pakeerappa et al.[92] | SP | 48M | 17 | | | | | | | + | | | + | | | | | + | | | |
| Ueno et al.[35] | PERM | 48F | <1 | | + | | + | + | + | + | + | | + | + | | | | | | | |

Table 4. Continued

| Reference | Testing | | | | | | Treatment | | | | | | | | Outcome | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Documentation Of Autoantibody Testing | Serum Anti–Gad Or Anti–Glyr Antibodies | CSF Oligoclonal Bands | Electroencephalographic Abnormalities | Electromyography Findings Consistent With SP | MRI Brain Abnormalities (Incidental Findings Excluded) | Antiepileptics | Baclofen | Benzodiazepines | Botulinum Toxin Injections | Intravenous Immune Globulin | Other agents or interventions | Plasmapheresis | Steroids | Steroid–sparing immunosuppression | Surgical intervention | Improvement or resolution | 1 or more relapses | Stabilization without improvement |
| Ughratdar et al.[32] | | | | | | | | | | | | | | | | | | | |
| Hegyi.[40] | – | | | | | | | | + | | | + | | | | | + | | |
| Iwata et al.[34] | | | | | | | | | | | | | | | | | | | |
| Prasad[89] | – | | | – | | – | | + | + | | | + | | | | | | | + |
| Sanefuji et al.[90] | | | | | | | | | | | | | | | | | | | |
| Schreiber et al.[41] | + | – | | | – | – | | + | + | | | + | | | | | + | | |
| Lorenzoni et al.[33] | | | | | | | | | | | | | | | | | | | |
| Clardy et al.[14] | + | – | | | | | | | | | | + | + | + | | | + | | |
| Newton et al.[42] | | | | | | | | | | | | | | | | | | | |
| Vicente–Valor et al.[43] | + | – | | | + | | + | + | + | | + | + | | + | + | | + | | |
| Sharma et al.[91] | | | | | | | | | | | | | | | | | | | |
| Pakerappa et al.[92] | + | – | | | | | | + | + | + | | + | | | | | + | | |
| Ueno et al.[35] | | | | | | | | | | | | | | | | | | | |

Abbreviations: CSF, Cerebrospinal Fluid; F, Female; M, Male; MRI, Magnetic Resonance Imaging; PERM, Progressive Encephalomyelitis with Rigidity and Myoclonus; SL, Stiff Limb Syndrome; SP, Stiff Person Syndrome; T, Thyroid Disease; V, Vitiligo.

Table 5. **Case Series of Patients with Anti-GAD Antibodies in the Setting of Cerebellar Ataxia with or without Stiff Person Symptoms**

| | Number of Patients Reporting the Following Symptoms | | | | Number of Patients with the Following history of Examination Findings | | | | | | | | | | Number of Patients with the Following Work-up Findings | | | Number of Patients Treated with the Following Medications | | | Number of Patients with the Following Outcome to Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Reported Diagnoses at Presentation (n)** | **Age Range and Sex Distribution** | **Number of Symptomatic Months Before Presentation (n)** | **Bulbar** | **Gait Difficulties (Including Ataxia)** | **Concomitant Autoimmunity (Except Diabetes) (N)** | **Cramps/Spasms** | **Diabetes** | **Extraocular Movement Abnormalities** | **Hyperekplexia** | **Malignancy** | **Seizures** | **Serum Anti-GAD Antibodies** | **CSF Oligoclonal Bands** | **Electromyography Findings Consistent With SP** | **Intravenous Immune Globulin** | **Rituximab** | **Steroids** | **Improvement or Resolution** | **Stabilization Without Improvement** | **Worsening and/or Death** |
| Arino et al.[21] | A (6)<br>A,SP (28) | 33–80<br>28F, 6M | <1 (13) | 24 | 31 | T (18)<br>P (7)<br>V (2) | 9 | 13 | 2<br>0 | 1 | 4 | 4 | 34 | 16 | 4 | 10 | 1 | 10 | 10 | 5 | 3 |

Abbreviations: A, Ataxia; CSF, Cerebrospinal Fluid; F, Female; GAD, glutamic acid decarboxylase; M, Male; MRI, Magnetic Resonance Imaging; n, Number of Cases; P, Pernicious Anemia; T, Autoimmune Thyroid Disease; SP, Stiff Person Syndrome; V, Vitiligo.

immunosuppression (plasmapheresis, steroids) in five out of 13 cases argues in favor of this theory. Of note, these patients also received other interventions, and it is impossible to ascertain which agent(s) was responsible for the symptomatic response. In addition, the presence of a microscopic malignancy in some of these cases cannot be completely excluded, and patients with cryptogenic SPS-spectrum disease may eventually declare themselves as paraneoplastic, granted a sufficient follow-up period is allowed. Finally, the absence of both antibodies and EMG evidence to support a diagnosis of SPS-spectrum disease opens the possibility for cramping syndromes or other conditions featuring rigidity to be misclassified within the SPS spectrum. The differential diagnosis of SPS is vast and includes myelopathy, myopathy, Isaac's syndrome, Parkinson's disease and atypical parkinsonian syndromes, primary lateral sclerosis, ankylosing spondylitis, neuroleptic malignant syndrome, serotonin syndrome, hereditary or tropical spastic paraparesis, spinal interneuronitis with rigidity, dystonia, neuromyotonia, and tetanus.[6,37] With this differential in mind, in seronegative patients with inconclusive EMGs, a comprehensive work-up can include a complete blood cell count, a comprehensive metabolic panel, thyroid function tests, creatine kinase, erythrocyte sedimentation rate, C-reactive protein, serum B12 level, human T-cell lymphotropic virus-1, rheumatoid factor, antinuclear antibody, computed tomography (CT) chest screening for a mediastinal mass, CT abdomen and pelvis, MRI brain, and CSF analysis including oligoclonal bands and IgG index.[15]

With these caveats in mind, the great majority of cryptogenic cases were diagnosed with SPS. Interestingly, unlike autoimmune and paraneoplastic cases, the majority of cryptogenic cases were male. This may be an indication of a different pathophysiology within this group, but the significance of this finding is unclear. The majority of cryptogenic cases in this review reported symptomatic improvement. However, some of the success was with novel interventions for SPS (including spinal cord stimulation,[32] physical therapy,[40] dantrolene,[41] intrathecal baclofen,[42] and cannabis[43]). We find this likely constitutes a reporting bias, since it is possible that cases in which novel interventions were unsuccessful may not have been published. Thus, we wonder whether the prognosis of these patients is as favorable as the data in this review suggested.

There are certain limitations to consider regarding our data. To start, the prevalence estimates of SPS, PERM, and other variants among the three subdivisions were based on the original published descriptions. It was difficult for us to ensure that the specific criteria established by Dalakas were met, as clinical descriptions were often incomplete. We are thus relying on the original author's clinical judgment in diagnosing these patients with the said conditions. It is possible that those diagnosed with classical SPS may in fact have been a variant and vice versa. In addition, both the paraneoplastic and the cryptogenic groups had fewer than 20 cases each, making inferences from these groups difficult to generalize. Furthermore, many of the cases reported describe treatment successes, and it is possible that this overestimates the response rates of patients with these conditions. In addition, it is impossible to demonstrate the complete absence of cancer in all of the autoimmune cases, just as it is impossible to guarantee that an autoimmune (and not a paraneoplastic) etiology is not responsible for SPS symptoms in some of the paraneoplastic cases. Finally, it is unclear whether the data acquired would vary significantly should our search be expanded to include cases in other languages, or cases reported before 2010.

Overall, this review supports the idea that, unlike the original descriptions, SPS encompasses a spectrum of diseases related by their clinical symptoms, the presence of autoantibodies, EMG findings, and its response to immunomodulation and muscle relaxants. Despite these commonalities, different causative mechanisms are likely among the disorders, and their classification based on likely etiology can guide treatment and provide useful prognostic information. As new associated antibodies and associated clinical features are discovered, it is possible that the spectrum will continue to expand. Ultimately, a high degree of clinical suspicion is necessary to initiate the work-up and select appropriate treatment that can be initiated in a timely fashion. Future directions in the management of these conditions may emerge as we better understand the role, if any, that these antibodies play in the emergence of symptoms. This could lead to the development of targeted therapies that minimize systemic side effects.

## References


1. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome); report of a case and some observations in 13 other cases. *Proc Staff Meet Mayo Clin* 1956;31:421–427.

2. Ali F, Rowley M, Jayakrishnan B, Teuber S, Gershwin ME, Mackay IR. Stiff-person syndrome (SPS) and anti-GAD-related CNS degenerations: Protean additions to the autoimmune central neuropathies. *J Autoimmun* 2011; 37:79–87. doi: 10.1016/j.jaut.2011.05.005.

3. Blum P, Jankovic J. Stiff-person syndrome: An autoimmune disease. *Mov Disord* 1991;6:12–20. doi: 10.1002/mds.870060104.

4. Asher R. A woman with the stiff-man syndrome. *Br Med J* 1958;1:265–266. doi: 10.1136/bmj.1.5065.265.

5. Dalakas MC. Stiff person syndrome: Advances in pathogenesis and therapeutic interventions. *Curr Treat Options Neurol* 2009;11:102–110. doi: 10.1007/s11940-009-0013-9.

6. Ehler E, Latta J, Mandysova P, Havlasova J, Mrklovsky M. Stiff-person syndrome following tick-borne meningoencephalitis. *Acta Medica (Hradec Kralove)* 2011;54:170–174.

7. Solimena M, Folli F. Stiff-man syndrome and type I diabetes mellitus: A common autoimmune pathogenesis? *Ann Ist Super Sanita* 1988;24:583–586.

8. Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. *N Engl J Med* 1988;318:1012–1020. doi: 10.1056/NEJM198804213181602.

9. Grimaldi LM, Martino G, Braghi S, et al. Heterogeneity of autoantibodies in stiff-man syndrome. *Ann Neurol* 1993;34:57–64. doi: 10.1002/ana.410340111.

10. Holmoy T, Geis C. The immunological basis for treatment of stiff person syndrome. *J Neuroimmunol* 2011;231:55–60. doi: 10.1016/j.jneuroim.2010.09.014.

11. Rakocevic G, Raju R, Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person

syndrome: Correlation with clinical severity. *Arch Neurol* 2004;61:902–904. doi: 10.1001/archneur.61.6.902.

12. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. *Am J Med* 1967;42:582–599. doi: 10.1016/0002-9343(67)90057-5.

13. Barker RA, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome: Clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry* 1998;65:633–640. doi: 10.1136/jnnp.65.5.633.

14. Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. *JAMA Neurol* 2013;70:1531–1536.

15. Hadavi S, Noyce AJ, Leslie RD, Giovannoni G. Stiff person syndrome. *Pract Neurol* 2011;11:272–282. doi: 10.1136/practneurol-2011-000071.

16. Alexopoulos H, Dalakas MC. A critical update on the immunopathogenesis of stiff person syndrome. *Eur J Clin Invest* 2010;40:1018–1025. doi: 10.1111/j.1365-2362.2010.02340.x.

17. Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: Distinctive features of a rare disease. *Neurology* 2008;71:1955–1958. doi: 10.1212/01.wnl.0000327342.58936.e0.

18. Carvajal-Gonzalez A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: Characteristics, clinical features and outcomes. *Brain* 2014;137:2178–2192. doi: 10.1093/brain/awu142.

19. Folli F, Solimena M, Cofiell R, et al. Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. *N Engl J Med* 1993;328:546–551. doi: 10.1056/NEJM199302253280805.

20. Helfgott SM. Stiff-man syndrome: From the bedside to the bench. *Arthritis Rheum* 1999;42:1312-1320. doi: 10.1002/1529-0131(199907)42:7<1312::AID-ANR2>3.0.CO;2-W.

21. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: Immunologic profile and long-term effect of immunotherapy. *JAMA Neurol* 2014;71:1009–1016. doi: 10.1001/jamaneurol.2014.1011.

22. Najjar S, Pearlman D, Zagzag D, Golfinos J, Devinsky O. Glutamic acid decarboxylase autoantibody syndrome presenting as schizophrenia. *Neurologist* 2012;18:88–91.

23. Awad A, Stuve O, Mayo M, Alkawadri R, Estephan B. Anti-glutamic Acid decarboxylase antibody-associated ataxia as an extrahepatic autoimmune manifestation of hepatitis C infection: A case report. *Case Rep Neurol Med* 2011; 2011:975152.

24. Scavone G, Zaccardi F, Manto A, Caputo S, Pitocco D, Ghirlanda G. A case of chronic hepatitis C developing insulin-dependent diabetes, thyroid autoimmunity and stiff-person syndrome as complications of interferon therapy. *Diabetes Res Clin Pract* 2010;89:e36–38. doi: 10.1016/j.diabres.2010.05.006.

25. Iizuka T, Leite MI, Lang B, et al. Glycine receptor antibodies are detected in progressive encephalomyelitis with rigidity and myoclonus (PERM) but not in saccadic oscillations. *J Neurol* 2012;259:1566–1573. doi: 10.1007/s00415-011-6377-2.

26. Baroncini D, Spagnolo F, Sarro L, Comi G, Volonte MA. A complex case of anti-GAD antibody-related syndrome treated with Rituximab. *Neurol Sci* 2013;34:1847–1849. doi: 10.1007/s10072-013-1327-7.

27. Turner MR, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: Glycine and NMDA receptor antibodies. *Neurology* 2011;77:439–443. doi: 10.1212/WNL.0b013e318227b176.

28. Witherick J, Highley JR, Hadjivassiliou M. Pathological findings in a case of stiff person syndrome with anti-GAD antibodies. *Mov Disord* 2011;26: 2138–2139. doi: 10.1002/mds.23784.

29. Bowen LN, Subramony SH, Heilman KM. Apraxia in anti-glutamic acid decarboxylase-associated stiff person syndrome: Link to corticobasal degeneration? *Ann Neurol* 2015;77:173–176. doi: 10.1002/ana.24245.

30. Pagano MB, Murinson BB, Tobian AA, King KE. Efficacy of therapeutic plasma exchange for treatment of stiff-person syndrome. *Transfusion* 2014;54:1851–1856. doi: 10.1111/trf.12573.

31. Laroumagne S, Elharrar X, Coiffard B, et al. "Dancing eye syndrome" secondary to opsoclonus-myoclonus syndrome in small-cell lung cancer. *Case Rep Med* 2014;2014:545490.

32. Ughratdar I, Sivakumar G, Basu S. Spinal cord stimulation to abort painful spasms of atypical stiff limb syndrome. *Stereotact Funct Neurosurg* 2010;88: 183-186. doi: 10.1159/000313871.

33. Lorenzoni PJ, Scola RH, Kay CS, Teive HA, dos Santos LH, Werneck LC. Electrophysiological characteristics in four patients from Brazil with stiff person syndrome. *J Clin Neurosci* 2012;19:889–891. doi: 10.1016/j.jocn.2011.08.034.

34. Iwata T, Shigeto H, Ogata K, et al. Hyperexcitability restricted to the lower limb motor system in a patient with stiff-leg syndrome. *J Clin Neurosci* 2011;18:1720–1722. doi: 10.1016/j.jocn.2011.03.021.

35. Ueno S, Miyamoto N, Shimura H, et al. Successful immune moderation treatment for progressive encephalomyelitis with rigidity and myoclonus. *Intern Med* 2015;54:219–221. doi: 10.2169/internalmedicine.54.3760.

36. Peeters E, Vanacker P, Woodhall M, Vincent A, Schrooten M, Vandenberghe W. Supranuclear gaze palsy in glycine receptor antibody-positive progressive encephalomyelitis with rigidity and myoclonus. *Mov Disord* 2012;27:1830–1832. doi: 10.1002/mds.25239.

37. Mas N, Saiz A, Leite MI, et al. Antiglycine-receptor encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry* 2011;82:1399–1401. doi: 10.1136/jnnp.2010.229104.

38. Derksen A, Stettner M, Stocker W, Seitz RJ. Antiglycine receptor-related stiff limb syndrome in a patient with chronic lymphocytic leukaemia. *BMJ Case Rep* 2013;2013. doi: 10.1136/bcr-2013-008667.

39. De Camilli P, Thomas A, Cofiell R, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man syndrome with breast cancer. *J Exp Med* 1993;178:2219–2223. doi: 10.1084/jem.178.6.2219.

40. Hegyi CA. Physical therapist management of stiff person syndrome in a 24-year-old woman. *Phys Ther* 2011;91:1403–1411. doi: 10.2522/ptj.20100303.

41. Schreiber AL, Vasudevan JM, Fetouh SK, Ankam NS, Hussain A, Rakocevic G. Atypical clinically diagnosed stiff-person syndrome response to dantrolene—a refractory case. *Muscle Nerve* 2012;45:454–455. doi: 10.1002/mus.22331.

42. Newton JC, Harned ME, Sloan PA, Salles SS. Trialing of intrathecal baclofen therapy for refractory stiff-person syndrome. *Reg Anesth Pain Med* 2013; 38:248–250. doi: 10.1097/AAP.0b013e318288b8f9.

43. Vicente-Valor MI, Garcia-Llopis P, Mejia Andujar L, et al. Cannabis derivatives therapy for a seronegative stiff-person syndrome: A case report. *J Clin Pharm Ther* 2013;38:71–73. doi: 10.1111/j.1365-2710.2012.01365.x.

**44.** Lobo ME, Araujo ML, Tomaz CA, Allam N. Stiff-person syndrome treated with rituximab. *BMJ Case Rep* 2010;2010. doi: 10.1136/bcr.05.2010.3021.

**45.** Castelnovo G, Renard D, Bouly S, Labauge P. Isolated hypertrophy of the tibialis anterior muscle in the stiff leg syndrome. *Muscle Nerve* 2011;44:306. doi: 10.1002/mus.22152.

**46.** Cuturic M, Harden LM, Kannaday MH, Campbell NN, Harding RK. Stiff-person syndrome presenting as eating disorder: A case report. *Int J Eat Disord* 2011;44:284–286. doi: 10.1002/eat.20794.

**47.** Gnanapavan S, Vincent A, Giovannoni G. Surviving stiff-person syndrome: A case report. *J Neurol* 2011;258:1898–1900. doi: 10.1007/s00415-011-6015-z.

**48.** Goldkamp J, Blaskiewicz R, Myles T. Stiff person syndrome and pregnancy. *Obstet Gynecol* 2011;118:454–457. doi: 10.1097/AOG.0b013e318216196b.

**49.** Piotrowicz A, Thumen A, Leite MI, Vincent A, Moser A. A case of glycine-receptor antibody-associated encephalomyelitis with rigidity and myoclonus (PERM): Clinical course, treatment and CSF findings. *J Neurol* 2011;258:2268–2270. doi: 10.1007/s00415-011-6078-x.

**50.** Anagnostou E, Zambelis T. Botulinum toxin A in anti-GAD-positive stiff-limb syndrome. *Muscle Nerve* 2012;46:457–458. doi: 10.1002/mus.23416.

**51.** Amyradakis G, Carlan SJ, Bhullar A, Eastwood J. Pregnancy and stiff person syndrome. *Am J Med* 2012;125:e1–2. doi: 10.1016/j.amjmed.2011.10.012.

**52.** Fekete R, Jankovic J. Childhood stiff-person syndrome improved with rituximab. *Case Rep Neurol* 2012;4:92–96. doi: 10.1159/000339446.

**53.** Fernandes M, Munhoz RP, Carrilho PE, et al. Neurological disorders associated with glutamic acid decarboxylase antibodies: A Brazilian series. *Arq Neuropsiquiatr* 2012;70:657–661. doi: 10.1590/S0004-282X2012000900002.

**54.** Qureshi A, Hennessy M. Stiff person syndrome (SPS) complicated by respiratory failure: Successful treatment with rituximab. *J Neurol* 2012;259:180–181. doi: 10.1007/s00415-011-6123-9.

**55.** Tsai T, McGrath R. Lymphoma, thymoma and the wooden man: Stiff-person syndrome post-thymoma excision and non-Hodgkin lymphoma remission. *Intern Med J* 2012;42:205–207. doi: 10.1111/j.1445-5994.2011.02688.x.

**56.** De la Casa-Fages B, Anaya F, Gabriel-Ortemberg M, Grandas F. Treatment of stiff-person syndrome with chronic plasmapheresis. *Mov Disord* 2013;28:396–397. doi: 10.1002/mds.25167.

**57.** Damasio J, Leite MI, Coutinho E, et al. Progressive encephalomyelitis with rigidity and myoclonus: The first pediatric case with glycine receptor antibodies. *JAMA Neurol* 2013;70:498–501. doi: 10.1001/jamaneurol.2013.1872.

**58.** Marinovic I, Pivalica D, Aljinovic J, Vlak T, Skoric E, Martinovic Kaliterna D. Extremely rare coincidence of non-radiographic axial spondyloarthropathy HLA-B27 positive and stiff person syndrome – rheumatologist point of view. *Mod Rheumatol* 2013. doi: 10.3109/14397595.2013.857837.

**59.** Nakane S, Fujita K, Shibuta Y, et al. Successful treatment of stiff person syndrome with sequential use of tacrolimus. *J Neurol Neurosurg Psychiatry* 2013;84:1177–1180. doi: 10.1136/jnnp-2013-305425.

**60.** O'Toole O, Murphy R, Tracy JA, McKeon A. Teaching NeuroImages: PET-CT hypermetabolism paralleling muscle hyperactivity in stiff-person syndrome. *Neurology* 2013;80:e109.

**61.** Sidransky MA, Tran NV, Kaye AD. Anesthesia considerations in stiff person syndrome. *Middle East J Anaesthesiol* 2013;22:217–221.

**62.** Sengupta S, Tarsy D, Joyce R, Jeyapalan S. Novel use of dual immunomodulation for treating stiff-person syndrome, cerebellar variant. *Mov Disord* 2013;28:1905–1906. doi: 10.1002/mds.25574.

**63.** Vetrugno R, Fabbri M, Antelmi E, D'Angelo R, Rinaldi R. Orthostatic tremor heralding the onset of stiff-person syndrome. *Neurology* 2013;81:1361–1362. doi: 10.1212/WNL.0b013e3182a8254f.

**64.** Bordelon S, Brett Lloyd R, Rosenthal LJ. Serotonin syndrome and stiff-person syndrome: Diagnostic challenges in psychosomatic medicine. *Psychosomatics* 2014;55:506–511. doi: 10.1016/j.psym.2013.08.001.

**65.** Enuh H, Park M, Ghodasara A, Arsura E, Nfonoyim J. Stiff man syndrome: A diagnostic dilemma in a young female with diabetes mellitus and thyroiditis. *Clin Med Insights Case Rep* 2014;7:139–141. doi: 10.4137/CCRep.S16941.

**66.** Fourlanos S, Neal A, So M, Evans A. Latent autoimmune diabetes in Stiff-Person Syndrome. *Diabetes Care* 2014;37:e214–215.

**67.** Georgieva Z, Parton M. Cerebellar ataxia and epilepsy with anti-GAD antibodies: Treatment with IVIG and plasmapheresis. *BMJ Case Rep* 2014;2014. doi: 10.1136/bcr-2013-202314.

**68.** Ho CS, Ho RC, Wilder-Smith EP. Stiff person syndrome masquerading as panic attacks. *Lancet* 2014;383:668.

**69.** Jung YJ, Jeong HG, Kim R, Kim HJ, Jeon BS. Stiff-person syndrome: Case series. *J Mov Disord* 2014;7:19–21. doi: 10.14802/jmd.14004.

**70.** Rana AQ, Masroor MS, Ismail B. Spasmodic dysphonia like presentation of stiff person syndrome. *J Neurosci Rural Pract* 2014;5:322–323. doi: 10.4103/0976-3147.133659.

**71.** Sanders S, Bredeson C, Pringle CE, et al. Autologous stem cell transplantation for stiff person syndrome: Two cases from the Ottawa blood and marrow transplant program. *JAMA Neurol* 2014;71:1296–1299. doi: 10.1001/jamaneurol.2014.1297.

**72.** Stern WM, Howard R, Chalmers RM, et al. Glycine receptor antibody mediated Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM): A rare but treatable neurological syndrome. *Pract Neurol* 2014;14:123–127. doi: 10.1136/practneurol-2013-000511.

**73.** Wuerfel E, Bien CG, Vincent A, Woodhall M, Brockmann K. Glycine receptor antibodies in a boy with focal epilepsy and episodic behavioral disorder. *J Neurol Sci* 2014;343:180–182. doi: 10.1016/j.jns.2014.05.014.

**74.** Farooqi MS, Lai Y, Lancaster E, Schmitt SE, Sachais BS. Therapeutic plasma exchange and immunosuppressive therapy in a patient with anti-GAD antibody-related epilepsy: Quantification of the antibody response. *J Clin Apher* 2015;30:8–14. doi: 10.1002/jca.21342.

**75.** Agarwal PA, Ichaporia NR. Glutamic acid decarboxylase antibody-positive paraneoplastic stiff limb syndrome associated with carcinoma of the breast. *Neurol India* 2010;58:449–451. doi: 10.4103/0028-3886.65704.

**76.** Kosseifi SG, Mehta JB, Roy T, Byrd R, Jr., Farrow J. The occurrence of stiff person syndrome in a patient with thymoma: Case report and literature review. *Tenn Med* 2010;103:43–47.

**77.** Schmidt C, Freilinger T, Lieb M, et al. Progressive encephalomyelitis with rigidity and myoclonus preceding otherwise asymptomatic Hodgkin's lymphoma. *J Neurol Sci* 2010;291:118–120. doi: 10.1016/j.jns.2009.12.025.

**78.** Thumen A, Moser A. An uncommon paraneoplastic Ri-positive opsoclonus-myoclonus-like syndrome and stiff-person syndrome with elevated glutamate/GABA ratio in the cerebrospinal fluid after breast cancer. *J Neurol* 2010;257:1215–1217. doi: 10.1007/s00415-010-5501-z.

**79.** Chamard L, Magnin E, Berger E, Hagenkotter B, Rumbach L, Bataillard M. Stiff leg syndrome and myelitis with anti-amphiphysin antibodies: A common physiopathology? *Eur Neurol* 2011;66:253–255.

**80.** Lemieux J, Provencher L, Brunet D, Hogue JC. Paraneoplastic encephalomyelitis, stiff person syndrome and breast carcinoma. *Can J Neurol Sci* 2011;38:790–792. doi: 10.1017/S0317167100018011.

**81.** Byrne TN, Isakoff SJ, Rincon SP, Gudewicz TM. Case records of the Massachusetts General Hospital. Case 27–2012. A 60-year-old woman with painful muscle spasms and hyperreflexia. *N Engl J Med* 2012;367:851–861. doi: 10.1056/NEJMcpc1114036.

**82.** Krishna VR, Knievel K, Ladha S, Sivakumar K. Lower extremity predominant stiff-person syndrome and limbic encephalitis with amphiphysin antibodies in breast cancer. *J Clin Neuromuscul Dis* 2012;14:72–74. doi: 10.1097/CND.0b013e31826f0d99.

**83.** Aghajanzadeh M, Alavi A, Aghajanzadeh G, Massahania S. Stiff man syndrome with invasive thymic carcinoma. *Arch Iran Med* 2013;16:195–196.

**84.** Badzek S, Miletic V, Prejac J, et al. Paraneoplastic stiff person syndrome associated with colon cancer misdiagnosed as idiopathic Parkinson's disease worsened after capecitabine therapy. *World J Surg Oncol* 2013;11:224. doi: 10.3109/02841860903443175.

**85.** Rakocevic G, Hussain A. Stiff person syndrome improvement with chemotherapy in a patient with cutaneous T cell lymphoma. *Muscle Nerve* 2013;47:938–939. doi: 10.1002/mus.23706.

**86.** Kelly PA, Kuberski C. Stiff person syndrome: A case report. *Clin J Oncol Nurs* 2014;18:465–467. doi: 10.1188/14.CJON.465-467.

**87.** Kobayashi R, Kaji M, Horiuchi S, Miyahara N, Hino Y, Suemasu K. Recurrent thymoma with stiff-person syndrome and pure red blood cell aplasia. *Ann Thorac Surg* 2014;97:1802–1804. doi: 10.1016/j.athoracsur.2013.07.103.

**88.** Koca I, Ucar M, Kalender ME, Alkan S. The horses are the first thought but one must not forget the zebras even if they are rare: Stiff person syndrome associated with malignant mesothelioma. *BMJ Case Rep* 2014;2014. doi: 10.1136/bcr-2013-203455.

**89.** Prasad V. A perplexing consult for pseudoseizures: Stiff-man syndrome. *J Neuropsychiatry Clin Neurosci* 2010;22:451-k e420–451 e421. doi: 10.1176/jnp.2010.22.4.451.e20.

**90.** Sanefuji M, Torisu H, Kira R, et al. A case of childhood stiff-person syndrome with striatal lesions: A possible entity distinct from the classical adult form. *Brain Dev* 2013;35:575–578. doi: 10.1016/j.braindev.2012.08.003.

**91.** Sharma B, Nagpal K, Prakash S, Gupta P. Anti-GAD negative stiff person syndrome with a favorable response to intravenous methylprednisolone: An experience over evidence. *Neurol India* 2014;62:76–77. doi: 10.4103/0028-3886.128332.

**92.** Pakeerappa PN, Birthi P, Salles S. Botulinum toxin a injection to facial and cervical paraspinal muscles in a patient with stiff person syndrome: A case report. *PM R* 2015;7:326–328. doi: 10.1016/j.pmrj.2014.10.013.