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Clinical variability in stiff-person syndrome: a systematic review of atypical presentations

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Abstract

Stiff-Person Syndrome (SPS) is a rare autoimmune disorder marked by progressive muscle spasticity and spasms. Beyond the classical form, variants such as focal SPS, progressive encephalomyelitis with spasticity and myoclonus, and SPS-plus have been described. To identify the clinical diversity of SPS by systematically reviewing atypical cases and applying cluster analysis. A systematic search of PubMed, Scopus, Web of Science, and Google Scholar (inception to May 2025) identified published cases with atypical SPS features. Extracted data included demographics, clinical manifestations, antibodies, treatment, and outcomes. A cluster analysis was performed to identify clinically distinguishable subgroups. From 3,448 records screened, 30 articles were included, encompassing 36 patients. Five clusters were identified: sensory (14%), cerebellar (17%), autonomic (11%), hemiparetic (8%), and heterogeneous (50%), with diverse symptoms such as seizures, encephalopathy, rhabdomyolysis, and pseudodystonia. Antibody profiles varied, with anti-glutamic acid decarboxylase associated with widespread symptoms, while glycine receptor and amphiphysin antibodies were linked to broader phenotypic variability. This systematic review highlights the clinical heterogeneity of SPS, identifying distinct subgroups with sensory, cerebellar, autonomic, and atypical features. Recognizing these patterns may refine diagnosis and management, while providing insights into underlying immunological mechanisms and guiding more targeted therapeutic approaches.

Keywords: *Stiff person syndrome. Autoimmune neurological disorder. Progressive muscle stiffness. Atypical SPS phenotypes. Autoimmune disorder.*

Variabilidad clínica en el síndrome de la persona rígida: una revisión sistemática de presentaciones atípicas

Resumen

El síndrome de la persona rígida (SPS) es un trastorno autoinmune poco frecuente caracterizado por espasticidad y espasmos musculares progresivos. Además de la forma clásica, se han descrito variantes focales, la encefalomielitis progresiva con espasticidad y mioclonías (PERM) y el fenotipo denominado SPS-plus. Identificar la diversidad clínica del SPS mediante la revisión sistemática de casos atípicos y un análisis por conglomerados. Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science y Google Scholar desde su inicio hasta mayo de 2025. Se incluyeron artículos que reportaran casos con manifestaciones atípicas de SPS. Se extrajeron características clínicas y se aplicó un análisis de conglomerados para identificar subgrupos diferenciables. De 3,448 registros, se incluyeron 30 artículos con 36 pacientes. Se identificaron cinco

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conglomerados: sensitivo (14%), cerebeloso (17%), autonómico (11%), hemiparético (8%) y heterogéneo (50%), con síntomas como crisis epilépticas, encefalopatía, rabdomiólisis y pseudodistonía. Los perfiles de autoanticuerpos fueron variables, destacando la asociación de anti-GAD con síntomas más extensos. Esta revisión sistemática destaca la heterogeneidad clínica del SPS, identificando subgrupos con características sensitivas, cerebelosas, autonómicas y atípicas. Reconocer estos patrones puede mejorar el diagnóstico, optimizar el manejo clínico y orientar estrategias terapéuticas más específicas y efectivas.

Palabras clave: *Síndrome de la persona rígida. Trastorno neurológico autoinmune. Rigidez muscular progresiva. Fenotipos atípicos del SPS. Trastorno autoinmune.*

Introduction

Since its initial description in 1956 by Moersch and Woltman, Stiff-Person Syndrome (SPS) has been recognized as a rare autoimmune disorder characterized by progressive muscle spasticity and spasms, often triggered by minimal sensory or emotional stimuli[1]. Although originally considered a well-defined clinical entity, accumulating case reports over recent decades have revealed considerable heterogeneity, with variant forms that challenge traditional diagnostic boundaries and expand the phenotypic spectrum of the disease.

Atypical presentations of SPS include focal manifestations, dysautonomia, cerebellar dysfunction, and seronegative cases lacking canonical anti-glutamic acid decarboxylase (anti-GAD) antibodies. These variants often mimic other neurological disorders, complicating the diagnostic process and clinical decision-making. While the presence of anti-GAD antibodies has served as a key biomarker in SPS diagnosis, their detection in other neurological conditions suggests that SPS may lie within a broader immunopathological continuum[2].

Pathophysiology and classical presentation

SPS arises from a B-cell-mediated autoimmune process targeting GABAergic neurons, which leads to impaired inhibitory neurotransmission. The presence of autoantibodies, most notably anti-GAD and anti-glycine receptor (GlyR) antibodies, disrupts gamma-aminobutyric acid (GABA) signaling and results in heightened neuronal excitability, sustained muscular spasticity, and episodic spasms. Recent research has also suggested a potential association between gut dysbiosis and the development of SPS, particularly in atypical cases characterized by prominent autonomic dysfunction.

In a subset of patients, SPS emerges in a paraneoplastic context, often in association with breast carcinoma, small cell lung cancer, or lymphomas. The presence of anti-amphiphysin antibodies in such cases has made this biomarker clinically relevant in the investigation of occult neoplasms[2,3]. SPS is frequently comorbid with other autoimmune diseases, including type 1 diabetes mellitus, autoimmune thyroiditis, and myasthenia gravis. Although humoral autoimmunity has long been central to SPS pathogenesis, recent evidence suggests that seronegative patients may exhibit increased activation of monocytes and dendritic cells, raising the possibility that innate immune mechanisms may drive pathogenesis in exceptionally rare cases[4].

Moreover, a depletion of butyrate-producing gut microbiota has been observed in SPS patients, potentially disrupting immune regulation and contributing to the loss of self-tolerance[5]. While SPS has not traditionally been associated with genetic susceptibility, recent findings have identified polymorphisms in genes implicated in immune regulation, such as PRKCB, components of the HLA complex, C4A, and ATG4D, in individuals with anti-GAD-positive phenotypes. These genetic variations may modulate disease expression, particularly in rare variants with predominant sensory or cerebellar involvement[6].

The classical form of SPS is a rare disorder, with an estimated prevalence of 1-2 cases per million individuals in the general population. It shows a marked female predominance, with women affected approximately twice as often as men. This sex distribution appears consistent across populations, with no significant racial or ethnic disparities in incidence. The rarity of the condition poses substantial challenges for timely recognition and diagnosis, often resulting in delayed treatment and increased disability. The observed sex bias suggests a possible role for hormonal or sex-specific immune factors in disease pathogenesis.

The clinical course is typically characterized by progressive, fluctuating muscle spasticity that primarily involves the axial musculature and proximal limbs. Symptoms may evolve over several months or years. Painful spasms are frequent and may be spontaneous or triggered by external stimuli such as loud noises, tactile contact, emotional distress, or abrupt changes in temperature[7]. These spasms can exacerbate

spasticity, compromise gait, and significantly increase the risk of falls[8]. As the disease advances, patients often develop abnormal postural patterns, including lumbar hyperlordosis and reduced mobility, which severely affect quality of life.

Sensory hypersensitivity is another hallmark of the syndrome. Tactile and auditory stimuli can provoke exaggerated motor responses[4,5]. This heightened excitability extends beyond motor pathways, potentially compromising autonomic function and precipitating episodes of tachycardia, hypertension, or hyperthermia in response to unexpected stimuli[7].

Variants of SPS

Although originally described as a clinically uniform disorder, SPS is now recognized as a spectrum condition comprising distinct phenotypic variants. The classic form remains the most prevalent, accounting for approximately 70-80% of reported cases; however, growing clinical awareness has led to the identification of less typical subtypes that significantly broaden its clinical presentation[7,8]. Among these, stiff limb syndrome is characterized by segmental spasticity localized to a single limb, while spasmodic SPS is marked by involuntary, jerky movements that may resemble myoclonus.

Additional forms include SPS associated with epilepsy, in which seizures coexist with stiffness and other movement abnormalities. Progressive encephalomyelitis with spasticity and myoclonus (PERM) represents a particularly severe variant, characterized by rapid progression and widespread involvement of the spinal cord and brainstem structures[9,10].

To better capture the clinical heterogeneity observed in practice, the term SPS-plus has been proposed. This designation encompasses presentations that feature cognitive impairment, brainstem dysfunction (including sleep disturbances, respiratory compromise, or abnormal bulbar reflexes), cerebellar ataxia, and neuro-ophthalmologic findings such as ophthalmoparesis, nystagmus, or decreased visual acuity. While several of these features may co-occur within a single patient, they may also reflect discrete topographic patterns of central nervous system dysfunction[7,11].

Despite increasing recognition of these variants, their delineation remains complex due to substantial overlap with other autoimmune neurological syndromes. This diagnostic ambiguity can hinder accurate classification, particularly in cases that resemble dystonia, paraneoplastic syndromes, or other immune-mediated movement disorders. For example, the so-called “cerebellar variant” raises the question of whether it should be conceptualized as an extension of classical SPS or as a distinct phenotype driven by separate immunopathological processes primarily targeting cerebellar structures.

Recent evidence supports the notion that inflammatory processes in SPS may not be limited to GABAergic circuits. In patients with SPS-plus phenotypes, positron emission tomography imaging with translocator protein ligands, which are biomarkers of microglial activation, has revealed widespread neuroinflammation. This suggests that certain rare presentations may be underpinned by more diffuse involvement of the central nervous system than previously assumed[11,12].

Importantly, the clinical trajectory of SPS is not uniform, and therapeutic response varies considerably across phenotypes. While some variants respond well to immunotherapy, others exhibit partial or minimal improvement, emphasizing the need for more refined subclassification. This variability reinforces the hypothesis that SPS encompasses a broader range of autoimmune-mediated neurological dysfunction than was initially recognized[7].

Current diagnostic criteria

In light of the growing clinical heterogeneity described above, diagnostic criteria for SPS have undergone several revisions to improve specificity and sensitivity. The first formal criteria, established in the 1990s, sought to standardize diagnosis while accommodating the spectrum of clinical variability observed in affected patients[13]. Subsequent advancements in immunology during the 2000s, particularly the identification of novel autoantibodies against GlyRs, amphiphysin, and the GABA-A receptor, further expanded the diagnostic framework. These biomarkers enabled clinicians to differentiate SPS subtypes with distinct immunopathological and clinical features.

Over the past decade, diagnostic approaches have increasingly emphasized a multimodal framework incorporating clinical, immunological, and neurophysiological data. Anti-GAD65 antibodies, present in approximately 60-80% of cases, remain a cornerstone of the diagnostic process. Their detection, especially in the appropriate clinical context, provides a critical immunological marker for disease identification. Complementing this, electromyographic (EMG) findings of continuous motor unit activity at rest offer valuable neurophysiological confirmation. Moreover, symptomatic improvement with benzodiazepines, particularly oral diazepam, has emerged as a pragmatic and supportive diagnostic tool[7,12].

The frequent presence of autonomic, sensory, or cerebellar manifestations in atypical variants strengthens the view that SPS should be conceptualized as a broader spectrum of autoimmune neurological disorders rather than a single disease entity[7]. This evolving understanding underscores the necessity of refining diagnostic criteria and developing stratified therapeutic strategies tailored to the diverse phenotypes encompassed by SPS.

Rare presentations of SPS have increasingly challenged the boundaries of its conventional classification. Cases characterized predominantly by sensory, autonomic, or cerebellar symptoms, as well as those lacking anti-GAD antibodies, have prompted a critical reexamination of existing diagnostic criteria and raised the possibility of overlapping or coexisting autoimmune neurological conditions. Moreover, variability in treatment response to immunotherapy has suggested that certain variants may be driven by distinct immunopathological mechanisms. The term secondary SPS has been proposed to describe forms of the disease that occur in direct association with chronic triggers such as viral infections or malignancies[14,15].

In this context, this systematic review aims to identify the clinical diversity of SPS by systematically reviewing atypical cases and applying cluster analysis. It seeks to delineate the boundaries of the SPS spectrum, recognize emerging phenotypic patterns, and determine whether these presentations represent variations within a unified disorder or distinct entities within the broader autoimmune neurological landscape.

Methods

Search strategy

This systematic review was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[16]. A systematic search was conducted across the PubMed, Scopus, Web of Science, and Google Scholar databases from inception to May 9, 2025, without language restriction. The search strategy was designed and conducted by one author (R.S.-G.), using controlled vocabulary with keywords “stiff-person syndrome or stiff-man syndrome or anti-glutamic acid decarboxylase syndrome or glutamic acid decarboxylase-negative or rare or mimic or chameleon” and “autoimmune encephalitis or neurophysiology or treatment response” “case report or clinical case” to search for case reports describing the clinical course and outcomes of patients with SPS with an initially atypical presentation.

Eligibility

Inclusion criteria

Studies were eligible if they reported patients diagnosed with SPS presenting atypical clinical manifestations. Eligible articles had to provide clearly defined clinical characteristics, diagnostic approaches, neuroimaging findings, therapeutic interventions, and reported outcomes. To ensure broad representativeness, no restrictions were applied regarding publication year, geographic location, patient sex, or ethnicity. Both historical and contemporary reports were included to allow comparison of evolving diagnostic and therapeutic paradigms, as well as to assess the global distribution of atypical presentations.

Exclusion criteria

Reports were excluded if the clinical presentation lacked diagnostic consistency with SPS or if insufficient evidence was provided to substantiate the case as atypical. Studies that did not include individual patient-level data or lacked adequate clinical documentation were also excluded.

Data extraction and screening

The initial screening of titles and abstracts was independently conducted by two authors (H.R.-A. and U.A.G.-V.) using Microsoft Excel spreadsheets (Microsoft Corp., Redmond, Washington, USA). For abstracts deemed eligible, full-text articles were retrieved and subsequently scrutinized by two authors (R.S.-G. and H.R.-A.) to determine the final list of included articles. Based on the predefined eligibility criteria, 3,448 records were screened after duplicate removal; 30 full-text articles met the inclusion criteria. For case series, we extracted patient-level data only for those with atypical SPS features.

Baseline patient characteristics were extracted from each article, including sex, age, clinical manifestations, autoantibodies, treatment, outcomes, and both initial and final diagnoses.

Cluster analysis

A cluster analysis was performed to explore patterns within atypical SPS presentations. The analysis was conducted using the K-means algorithm in Statistical

Package for Social Sciences, based on a dataset of 36 documented cases. Clinical variables considered atypical, including sensory, cerebellar, autonomic symptoms, hemiparesis, and sudden onset, were dichotomized before analysis. To determine the optimal number of clusters, a preliminary hierarchical analysis was performed.

Results

From our initial evaluation, a total of 3,448 studies were screened, of which 30 articles met our inclusion criteria. All the included studies were case reports or small case series; for series, we extracted only those individual patients with atypical SPS features that aligned with our focus on SPS presenting atypical manifestations, because not all patients matched these characteristics. The publication dates from the different studies ranged from 1983 to 2025. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in figure 1. The baseline study characteristics can be found in table 1[17-47].

Five distinct phenotypic groups were identified. The sensory cluster (5 cases; 14%) was characterized by paresthesia and neuropathic pain. The cerebellar cluster (6 cases; 17%) presented with ataxia, dysmetria, and scanning dysarthria. The autonomic cluster (4 cases; 11%) involved dysregulation of blood pressure, along with sudomotor and digestive disturbances. The hemiparetic cluster (3 cases; 8%) was defined by focal motor deficits resembling cerebrovascular syndromes. The remaining 18 cases (50%) formed a heterogeneous miscellaneous cluster, encompassing seizures, encephalopathy, rhabdomyolysis, and pseudodystonia.

Discussion

The recognition of atypical manifestations of SPS has become increasingly relevant in neurological practice, as these variants continue to challenge traditional conceptions of the disorder. Frequently mimicking other neuromuscular or autoimmune conditions, atypical SPS presentations pose a significant diagnostic challenge. Timely and accurate identification is essential, not only to avoid misdiagnosis and treatment delays but also to mitigate functional deterioration and improve patient quality of life. These considerations highlight the urgent need to increase awareness of non-classical SPS variants among clinicians, particularly in settings where rare autoimmune syndromes may be overlooked.

Beyond diagnostic concerns, the expanding clinical heterogeneity of SPS raises fundamental questions about its nosological boundaries. Rather than constituting a single, well-delineated disease entity, SPS may occupy a position along a broader spectrum of autoimmune neurological disorders, suggesting a shared yet variable pathophysiological substrate. The emergence of atypical phenotypes raises the possibility that such cases may not merely reflect divergent clinical expressions of the same disorder, but instead represent distinct subtypes with separate immunological underpinnings. Whether these forms constitute overlapping yet discrete conditions or differing degrees of a unifying pathological process remains an open and pressing question.

Among the defined clusters, the cerebellar variant, although previously reported, remains poorly characterized in terms of disease progression, neuroimaging correlates, and therapeutic response. Distinguishing it from immune-mediated and paraneoplastic cerebellar ataxias remains a diagnostic challenge, raising the possibility that its true incidence is underestimated. Similarly, autonomic involvement suggests more extensive GABAergic dysfunction, likely implicating the brainstem.

Although rare, hemiparesis in SPS introduces further complexity, raising the question of whether it represents a discrete variant or the convergence of overlapping autoimmune mechanisms, as seen in certain immune-mediated epilepsies. In both scenarios, cortical involvement may be relevant. Functional neuroimaging studies have demonstrated altered connectivity patterns within the motor cortex in long-standing SPS, likely reflecting compensatory adaptations to chronic hyperexcitability[11,15].

The heterogeneous cluster reflects the underlying pathophysiological diversity of atypical SPS, with cases associated with different autoantibody profiles. While anti-GAD antibodies are more often linked to widespread symptomatology, GlyR and amphiphysin antibodies have been associated with broader phenotypic variability.

A particularly important consideration is the potential overlap with PERM. The substantial symptom overlap suggests that some cases historically classified under SPS may represent incomplete or unrecognized PERM variants, particularly in the absence of comprehensive diagnostic evaluation. Although this continuum has been previously acknowledged[7], several cases in the present review diverged even from well-documented atypical phenotypes.

While the term SPS-plus has been introduced to account for presentations exceeding the classical

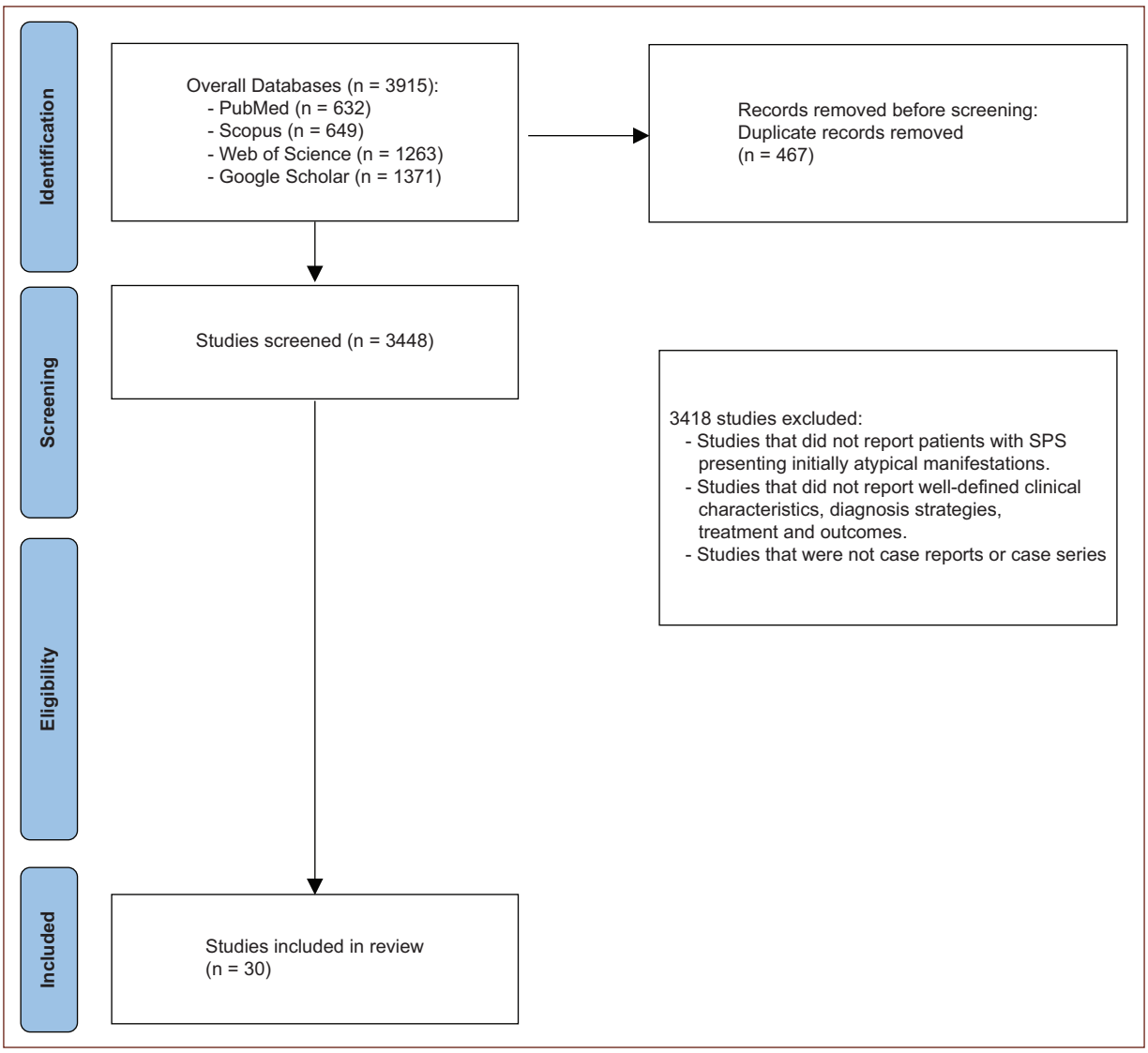


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram. SPS: stiff-person syndrome.

phenotype, its boundaries remain ill-defined. The heterogeneity of symptoms included under this label, which range from cerebellar dysfunction and autonomic instability to cognitive and neuro-ophthalmologic disturbances, suggests that SPS-plus is not a unified entity but rather a spectrum that likely encompasses multiple distinct subtypes. In the absence of formal classification criteria, it remains an umbrella term without sufficient nosological precision.

To advance clarity in this domain, future research must prioritize the development and validation of biomarkers capable of reliably distinguishing atypical SPS variants. Such tools would enhance diagnostic accuracy, particularly in specialized care settings, and enable more personalized therapeutic strategies tailored to the specific pathophysiological profile of each variant. Although several immunological and neurophysiological biomarkers have shown potential correlations with clinical subtypes, their applicability in routine practice remains limited. Well-controlled, large-scale studies are urgently needed to establish their diagnostic and prognostic utility. Identifying and understanding these phenotypic subgroups is crucial to optimize clinical management and to elucidate underlying immunological mechanisms, fostering the development of targeted treatments.

This study not only documents rare SPS variants but also proposes a classification approach grounded in clinical and pathophysiological clustering. The use of cluster analysis provides a structured method to

Table 1. Summary of characteristics of patients analyzed with a rare SPS presentation

Case	Author	Sex/Age	Clinical manifestations	Key findings	Autoantibodies	Treatment	Outcome	Diagnosis
1	Siddiqui et al., 2017[17]	M/84	Atypical: edema in the right hemicranium Typical: spasticity in the lower limbs	NR	GAD positive	IGIV, benzodiazepines	Reduction of symptoms, decreased spasms, but poor control over disease progression	Initial: SPS Final: SPS
2	Siddiqui et al., 2017[17]	F/26	Atypical: infranuclear facial paralysis Typical: pain and dystonia in the lower limbs	NR	GAD positive	IGIV	Complete improvement	Initial: common variable immunodeficiency Final: SPS
3	Hassin-Baer et al., 2004[18]	M/41	Atypical: cruciate spasticity (left arm and right leg). Typical: lower back pain, spasticity	Repetitive nerve stimulationand electromyography were normal, except that the patient took longer to relax and suspend voluntary recruitment of motor unit potentials.	GAD positive	Five PLEX sessions, benzodiazepines	Three months after the onset of his symptoms, the pyramidal signs were no longer present, and the spasticity in his right leg was nearly resolved.	Initial: West nile fever Final: SPS
4	Cabrera et al., 2017[19]	F/71	Atypical: dysautonomia (Peripheral cyanosis) Typical: spasticity in the lower limbs and lumbar region	Axonal sensorimotor neuropathy in the pelvic limbs revealed in EMG	GAD positive	Benzodiazepines	Improvement of symptoms and reduction of progression	Initial: chronic fatigue syndrome Final: SPS
5	Sabatino and Newsome, 2017[20]	F/53	Atypical: hemiparesis Typical: lumbar spasticity	Normal EMG	GAD positive	Immunosuppressant	Clinical improvement	Initial: multiple sclerosis Final: SPS
6	Sabatino, and Newsome, 2017[20]	F/46	Atypical: hemisensory syndrome Typical: hyperlordosis	Normal EMG	GAD positive	Immunosuppressant	Clinical improvement	Initial: multiple sclerosis Final: SPS
7	Sabatino and Newsome, 2017[20]	F/64	Atypical: ataxia Typical: axial spasticity	NR	GAD positive	Immunosuppressant	Clinical improvement	Initial: multiple sclerosis Final: SPS
8	Roman-Filip et al., 2013[21]	F/42	Atypical: Sudden-onset paravertebral contracture Typical: Painful neck spasticity, gait disturbances	EMG revealed continuous, highly acute tetaniform activity in the sternocleidomastoid muscle, less pronounced in the trapezius muscle, with relaxation failure	GAD negative	Methylprednisolone, benzodiazepines	Clinical improvement	Initial: SPS Final: SPS

(Continues)

Table 1. Summary of characteristics of patients analyzed with a rare SPS presentation *(continued)*

Case	Author	Sex/Age	Clinical manifestations	Key findings	Autoantibodies	Treatment	Outcome	Diagnosis
9	Fakhari et al., 2023[22]	M/66	Atypical: dysautonomia (Febrile episodes and retrograde amnesia) Typical: spasticity in the lower limbs	Gray matter tumor	Amphiphysin positive	Levetiracetam	Clinical improvement	Initial: cerebral tumoration Final: paraneoplastic SPS
10	Belém et al., 2021[23]	M/26	Atypical: right ophthalmoparesis Typical: postural instability	Decreased presynaptic release of GABA, partilarly in Purkinje cells	GAD positive	IGIV	Improvement in ophthalmoparesis and resolution of ataxia	Initial: ataxia and ophthalmoparesis associated with anti-GAD Final: SPS
11	Degeneffe et al., 2018[24]	F/62	Atypical: myoclonus in the lower limbs Typical: lumbar muscle contractures and back spasticity	EMG showed continuous rhythmic motor activity in axial muscles	GAD positive	Levetiracetam	Admission to the ICU due to respiratory failure, followed by a relapse of myoclonus.	Initial: neuroleptic malignant syndrome Final: progressive encephalomyelitis with spasticity and myoclonus
12	Balint et al., 2014[25]	M/69	Atypical: ataxia (severe abasia) Typical: marked spasticity in the right leg with extension posture	Exaggerated exteroceptive reflexes along with continuous motor unit activity	GAD positive	Diazepam, tizanidine, corticosteroid pulse	Clinical improvement	Initial: corticobasal syndrome Final: SPS
13	Balint et al., 2014[25]	M/71	Atypical: monoarticular arthritis and ataxia Typical: left foot spasticity	Increased exteroceptive reflexes	GAD positive	Levodopa, baclofen, diazepam, corticosteroid pulse, IGIV	Response only to diazepam, corticosteroid pulse, and IVIG	Initial: parkinsonism Final: SPS
14	Diaz and Ratliff, 2019[26]	F/44	Atypical: progressive dysarthria and hemibody spasticity Typical: lumbar pain	Full saccadic and pursuit movements	GAD positive	NR	NR	Initial: chronic Parkinson's Final: SPS
15	Nakanishi and Kenzaka, 2021[27]	F/52	Atypical: rhabdomyolysis Typical: episodic spasticity of the back and thighs	NR	GAD positive	PLEX, IGIV, diazepam	Gait improvement	Initial: neuroleptic malignant syndrome Final: SPS
16	Nguyen et al., 2022[28]	F/25	Atypical: dysautonomia (Severe emesis and fever) Typical: spasticity in the lower limbs	Babinski sign could not be assessed due to hypersensitivity to touch	GAD positive	IGIV	Clinical improvement	Initial: functional neurological disorder Final: SPS

(Continues)

Table 1. Summary of characteristics of patients analyzed with a rare SPS presentation *(continued)*

Case	Author	Sex/Age	Clinical manifestations	Key findings	Autoantibodies	Treatment	Outcome	Diagnosis
17	Maludzińska et al., 2016[29]	F/32	Atypical: cerebellar ataxia, vertigo, and diplopia Typical: progressive muscle spasticity of axial and limb muscles of unknown origin	Neurosensory testing was normal. EMG revealed continuous motor unit activity in both agonist and antagonist muscles at rest	GAD positive	Diazepam	Rigidity improvement	Initial: SPS Final: SPS
18	Yong and Lo, 2019[30]	M/66	Atypical: compartment syndrome, left leg Typical: acute bilateral hip pain	EMG showed continuous motor unit activity at rest despite voluntary relaxation	GAD positive	Clonazepam, baclofen, prednisone, IGIV	Gradual improvement of symptoms, including spasticity and spasms	Initial: compartment syndrome Final: SPS
19	Ozer et al., 2009[31]	M/41	Atypical: Paresthesias in the abdominal area, elbows, and posterior knees Typical: Gait difficulty	Normal EMG	GAD negative	Citalopram, clonazepam	Global improvement	Initial: multiple sclerosis Final: SPS
20	Zhang et al., 2019[32]	M/53	Atypical: sudden-onset progressive myoclonus in the left lower limb Typical: muscle spasticity	Positive patellar reflex (++++) and bilateral positive babinski	GAD negative	IGIV, baclofen, clonazepam	Clinical improvement	Initial: SPS Final: SPS
21	Herbulot et al., 2022[33]	F/14	Atypical: Anterograde amnesia Typical: SPS symptoms	NR	GAD positive	Immunosuppressant, rehabilitation	Global improvement	Initial: SPS Final: SPS
22	Quintal-Medina et al., 2021[34]	F/52	Atypical: sudden-onset right leg spasticity Typical: gait difficulty	Deep tendon reflexes	GAD positive	Baclofen	Gait improvement	Initial: partial SPS Final: SPS
23	Gogia et al., 2021[35]	F/83	Atypical: Pseudo-dystonia (clubfoot) Typical: Painful distal limb spasticity	NR	Amphiphysin positive	Diazepam	The patient was bedridden within 3 months and passed away within 6 months from symptom onset	Initial: paraneoplastic Sjögren-Larsson syndrome Final: SPS
24	Kosseifi et al., 2010[36]	M/29	Atypical: presence of chylothorax Typical: trunk spasticity	NR	NR	Diazepam, opioids	NR	Initial: secondary SPS Final: SPS
25	Shah et al., 2025[37]	M/45	Atypical: subacute vision loss Typical: bilateral weakness in the lower limbs	NR	GAD positive	NR	Development of bilateral retinopathy	Initial: SPS Final: SPS

(Continues)

Table 1. Summary of characteristics of patients analyzed with a rare SPS presentation *(continued)*

Case	Author	Sex/Age	Clinical manifestations	Key findings	Autoantibodies	Treatment	Outcome	Diagnosis
26	Jones et al., 2019[38]	F/50	Atypical: cerebellar ataxia and tremor in the right upper limb Typical: postural instability	NR	GAD positive	IGIV, infliximab, rituximab)	Rigidity improvement	Initial: SPS Final: SPS
27	Stephan et al., 2029[39]	NR	Atypical: cervicothoracic hyperkyphosis Typical: cervical spasticity	NR	NR	Cervical surgery	Improvement after surgery	Initial: SPS Final: SPS
28	Gao et al., 2020[40]	F/34	Atypical: anterograde amnesia Typical: persistent spasticity in the legs	NR	GAD positive	IGIV	NR	Initial: SPS Final: SPS
29	Taneda et al., 2022[41]	M/65	Atypical: hyperalgesia Typical: painful muscle spasms	NR	GAD negative	Hydrocortisone	The condition improved rapidly, and the patient became asymptomatic	Initial: isolated ACTH deficiency Final: SPS
30	Bernardo et al., 2020[42]	M/78	Atypical: focal motor seizures Typical: axial and limb spasticity	Normal EMG	GlyR positive	Methylprednisolone	Clinical improvement	Initial: minor depression Final: SPS
31	Bernardo et al., 2020[42]	M/85	Atypical: sudden-onset lower limb spasticity and encephalopathy Typical: progressive spasticity	NR	Amphiphysin positive	NR	The patient died of cardiac arrest a few days after admission.	Initial: SPS Final: SPS
32	Moustafa et al., 2013[43]	F/48	Atypical: seizures and hallucinations Typical: spasticity in the neck and back muscles	EMG showed continuous motor unit activity in both agonist and antagonist muscles	GAD positive	Methylprednisolone, IGIV	The patient showed significant improvement in cognitive and behavioral symptoms	Initial: SPS Final: SPS
33	O'Sullivan et al., 2009[44]	M/41	Atypical: celiac disease and dermatitis herpetiformis Typical: progressive spasticity in the lumbar region	NR	GAD positive	NR	NR	Initial: previous celiac disease, dermatitis herpetiformis Final: added SPS
34	Orija et al., 2005[45]	F/52	Atypical: hemibody spasm Typical: muscle spasticity in the limbs	NR	NR	Immunosuppressant	Severe neurological deterioration	Initial: previous Graves' disease Final: SPS

(Continues)

Table 1. Summary of characteristics of patients analyzed with a rare SPS presentation *(continued)*

Case	Author	Sex/Age	Clinical manifestations	Key findings	Autoantibodies	Treatment	Outcome	Diagnosis
35	Louis-Jean et al., 2023[46]	M/58	Atypical: nausea with emesis and dysautonomia Typical: abdominal muscle spasms	NR	GAD positive	Insulin therapy	Persistent	Initial: diabetic ketoacidosis Final: SPS
36	Jamil et al., 2019[47]	M/57	Atypical: focal pain in the right groin Typical: muscle spasms	Neurological examination with diffusely increased muscle tone and generalized hyperreflexia	NR	IGIV, primary right total hip replacement, uncemented	Functional improvement after surgery	Initial: SPS Final: SPS and hip fracture

M: male; F: female; NR: not reported; SPS: stiff-person syndrome; IGIV: immune globulin intravenous; GAD: glutamic acid decarboxylase; GlyR: glycine receptor; ACTH: adrenocorticotropic hormone, EMG: electromyographic, PLEX: plasma exchange

evaluate whether these variants represent discrete entities within the autoimmune neurology spectrum or reflect varying degrees of GABAergic impairment. These findings underscore the need to reconceptualize SPS as a continuum of immune-mediated disorders, in which certain phenotypes may benefit from individualized diagnostic and therapeutic strategies. Identifying such subgroups may facilitate the development of targeted biomarkers and improve clinical management in patients with rare or diagnostically ambiguous presentations.

Limitations

Although we think this study represents a valuable contribution to the literature, it comes with certain limitations. The analysis relied exclusively on published case reports and small case series, which are inherently prone to reporting bias and lack standardized data. The heterogeneity in diagnostic criteria, antibody testing, and treatment strategies across reports limit the comparability of cases. In addition, the small number of patients in each cluster reduces the generalizability of the findings. The absence of longitudinal follow-up in most cases also restricted the ability to assess long-term outcomes or disease progression. Finally, the lack of uniform neuroimmunological testing precludes definitive conclusions regarding underlying mechanisms.

Conclusion

This systematic review highlights the clinical heterogeneity of SPS, identifying distinct subgroups with sensory, cerebellar, autonomic, and atypical features. These findings expand the boundaries of the SPS spectrum and underscore the limitations of current diagnostic criteria, particularly the ambiguous category of SPS-plus. Recognizing emerging phenotypic patterns may facilitate earlier diagnosis, refine nosological definitions, and guide the development of tailored therapeutic strategies. Further studies integrating biomarkers and long-term outcomes are essential to determine whether these atypical cases represent true variants of SPS or separate autoimmune neurological disorders.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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References

1. Cullinane PW, Carr AS, Irani SR, Warner TT. Stiff person syndrome. Handb Clin Neurol. 2024;203:211-33.
2. Alexopoulos H, Dalakas MC. Immunology of stiff person syndrome and other GAD-associated neurological disorders. Expert Rev Clin Immunol. 2013;9:1043-53.
3. Baizabal-Carvallo JF, Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. J Neurol Neurosurg Psychiatry. 2015;86:840-8.
4. Burton AR, Baquet Z, Eisenbarth GS, Tisch R, Smeyne R, Workman CJ, et al. Central nervous system destruction mediated by glutamic acid decarboxylase-specific CD4+ T cells. J Immunol. 2010;184:4863-70.
5. Baj A, Moro E, Bistoletti M, Orlandi V, Crema F, Giaroni C. Glutamatergic signaling along the microbiota-gut-brain axis. Int J Mol Sci. 2019;20:1482.
6. Strippel C, Herrera-Rivero M, Wendorff M, Tietz AK, Degenhardt F, Witten A, et al. A genome-wide association study in autoimmune neurological syndromes with anti-GAD65 autoantibodies. Brain. 2023;146:977-90.
7. Bose S, Jacob S. Stiff-person syndrome. Pract Neurol. 2025;25:6-17.
8. Ciccotto G, Blaya M, Kelley RE. Stiff person syndrome. Neurol Clin. 2013;31:319-28.
9. Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol. 2009;11:102-10.
10. Werner C, Pauli M, Doose S, Weishaupt A, Haselmann H, Grünewald B, et al. Human autoantibodies to amphiphysin induce defective presynaptic vesicle dynamics and composition. Brain. 2016;139 Pt 2:365-79.
11. Levy LM, Levy-Reis I, Fujii M, Dalakas MC. Brain gamma-aminobutyric acid changes in stiff-person syndrome. Arch Neurol. 2005;62:970-4.
12. Wiessler AL, Talucci I, Piro I, Seefried S, Hörlin V, Baykan BB, et al. Glycine receptor β-targeting autoantibodies contribute to the pathology of autoimmune diseases. Neurol Neuroimmunol Neuroinflamm. 2024;11:e200187.
13. McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012;69:230-8.
14. Thaler FS, Bangol B, Biljecki M, Havla J, Schumacher AM, Kümpfel T. Possible link of genetic variants to autoimmunity in GAD-antibody-associated neurological disorders. J Neurol Sci. 2020;413:116860.
15. Sandbrink F, Syed NA, Fujii MD, Dalakas MC, Floeter MK. Motor cortex excitability in stiff-person syndrome. Brain. 2000;123:2231-9.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
17. Siddiqui MZ, Tohid H, Brown R, Qazi S. The stiff people: two rare cases of stiff-person syndrome. Cureus. 2017;9:e1602.
18. Hassin-Baer S, Kirson ED, Shulman L, Buchman AS, Bin H, Hindiyeh M, et al. Stiff-person syndrome following West Nile fever. Arch Neurol. 2004;61:938-41.
19. Cabrera Espinosa ES, Enríquez Coronel G. Síndrome de la persona rígida. Caso clínico y revisión de la literatura. Rev Mex Neuroci. 2017;18:86-94.
20. Sabatino JJ Jr., Newsome SD. Stiff person syndrome masquerading as multiple sclerosis. J Neurol Sci. 2017;372:297-9.
21. Roman-Filip C, Radu D, Ungureanu A, Deaconu A, Pereanu M. Stiff person syndrome with negative anti-gad65 antibodies. Case report. Rom J Neurol. 2013;12:156-9.
22. Fakhari MS, Poorsaadat L, Mohammad Talebi H, Kosari F. Stiff-person syndrome revealing an occult gray zone lymphoma: a diagnostic challenge. Clin Case Rep. 2023;11:e8328.
23. Belém AD, Vasconcelos TM, Paula RC, Costa FB, Rodrigues PG, Pereira IS, et al. Stiff-eye síndrome-anti-GAD ataxia presenting with isolated ophthalmoplegia: a case report. Brain Sci. 2021;11:932.
24. Degeneffe A, Dagonnier M, D'hondt A, Elosegi JA. A case report of spasticity and recurrent lower limb myoclonus: progressive encephalomyelitis spasticity and myoclonus syndrome, a chameleon. BMC Neurol. 2018;18:173.
25. Balint B, Mahant N, Meinck HM, Fung V. Stiff limb syndrome mimicking corticobasal syndrome. Mov Disord Clin Pract. 2014;1:354-6.
26. Diaz M, Ratliff J. Stiff Person Syndrome as a Mimic of Parkinsonism (P3.8-026). Neurology. 2019;92(15 Suppl):P3.8-026. doi: 10.1212/WNL.92.15_supplement.P3.8-026.
27. Nakanishi T, Kenzaka T. Stiff-person syndrome with rhabdomyolysis. BMJ Case Rep. 2021;14:e246147.
28. Nguyen PM, Vu DD, Vu KD, Nguyen HT, Nguyen DV. Stiff person syndrome: a case report with sudden onset and coexistence of sero-positive antibodies to glutamic acid decarboxylase and anti-SOX1 antibodies. Case Rep Neurol. 2022;14:237-44.
29. Maludzińska E, Rudzińska M, Stępień A, Szczudlik A. Cerebellar variant of stiff person syndrome: a case report. Neurol Neurochir Pol. 2016;50:59-62.
30. Yong KP, Lo YL. Stiff person syndrome associated with compartment syndrome. Case Rep Neurol. 2019;11:217-21.
31. Ozer S, Ozcan H, Dinç GS, Ertuğrul A, Rezaki M, Uluğahin A. Two stiff person cases misdiagnosed as conversion disorder. Turk Psikiyatri Derg. 2009;20:392-7.
32. Zhang CG, Li LL, Feng YY, Chen J. Stiff limb syndrome with lower limb myoclonus: a case report. Medicine (Baltimore). 2019;98:e18160.
33. Herbulot L, Bost C, Viguier A, Faure-Marie N, Baudou E, Cheuret E. Stiff person syndrome and encephalitis with gad antibodies with severe anterograde amnesia in an adolescent: a case study and literature review. Neuropediatrics. 2022;53:136-9.
34. Quintal-Medina IA, Gómez-Pérez FJ, Almeda-Valdés P. Stiff person syndrome and brittle type 1 diabetes: report of 2 cases. AACE Clin Case Rep. 2024;10:198-201.
35. Gogia B, Shanina E, Fang X, He J, Li X. Case report: amphiphysin antibody-associated stiff-limb syndrome and myelopathy: an unusual presentation of breast cáncer in an elderly woman. Front Neurol. 2021;12:735895.
36. 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;103:43-7.
37. Shah RM, Maloney MH, Gilbert AL, Patel AP, Vora RA. Autoimmune retinopathy in a patient with stiff-person syndrome: a case report. Retin Cases Brief Rep. 2025;19:139-44.
38. Jones LA, Baber W, Wardle M, Robertson NP, Morris HR, Church A, Llewelyn JG, Peall KJ. A Case of Treatment Resistance and Complications in a Patient with Stiff Person Syndrome and Cerebellar Ataxia. Tremor Other Hyperkinet Mov (N Y). 2019;9:677. doi: 10.7916/tohm.v0.677.
39. Stephan SR, Ju DG, Ross LB, Naruse RT, Kim TT, Johnson JP. Severe Chin-on-Chest Cervical Spine Deformity in the Setting of Stiff-Person Syndrome: A Case Report. JBJS Case Connect. 2020;10(4):e20.00378. doi: 10.2106/JBJS.CC.20.00378.
40. Gao SY, Lu J, Zhao CB. Stiff-person syndrome associated with anti-Glutamic Acid Decarboxylase autoimmune encephalitis in a young woman: a case report. Chin Med Sci J. 2020;35:387-90.
41. Taneda T, Okawara S, Namekawa M, Umeda Y, Oyake M, Fujita N. Isolated ACTH deficiency clinically presented as stiff-person syndrome, successfully treated by hormonal replacement: a case report. Rinsho Shinkeigaku. 2022;62:736-9.
42. Bernardo F, Rebordão L, Rêgo A, Machado S, Passos J, Costa C, et al. Stiff person spectrum disorders: an illustrative case series of their phenotypic and antibody diversity. J Neuroimmunol. 2020;341:577192.
43. Moustafa A, Alsamman MA, Fernandes D. Rare association of autoimmune limbic encephalitis and stiff person syndrome. R I Med J (2013). 2023;106:7-9.
44. O'Sullivan EP, Behan LA, King TF, Hardiman O, Smith D. Stiff-person syndrome with type 1 diabetes, celiac disease and dermatitis herpetiformis. Clin Neurol Neurosurg. 2009;111:384-6.
45. Orija IB, Gupta M, Zimmerman RS. Graves' disease and stiff-person (stiff-man) syndrome: case report and literature review. Endocr Pract. 2005;11:259-64.
46. Louis-Jean S, Agrawal N, Chaudhry S, Mazer A. Biliary dyskinesia in stiff person syndrome: an association between reduced GABA production and gastroenteric dysmotility. J Community Hosp Intern Med Perspect. 2023;13:94-6.
47. Jamil M, Saleem M, Habib A, Khan S, Qahir M. Femur neck fracture in a patient with stiff person syndrome: a case report. JBJS Case Connect. 2019;9:e0049.