



Stiff-person syndrome and systemic lupus erythematosus: A cross-disease examination of autoimmunity and neurological involvement

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Keywords

Stiff-Person Syndrome; Systemic Lupus Erythematosus; Autoimmunity; Immunosuppression Therapy

Abstract

Background: Stiff-person syndrome (SPS) is a rare autoimmune neurological disorder characterized by progressive muscle rigidity and spasms, while systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease. Despite having different clinical presentations, both conditions share underlying immunological mechanisms including antibody production, B-cell dysfunction, and cytokine dysregulation. The rare co-occurrence of SPS and SLE is explored in this review, analyzing shared pathophysiology, overlapping neurological features, diagnostic challenges, and therapeutic implications.

Methods: A comprehensive literature search was conducted in PubMed, Scopus, and Cochrane up to June 2025 using the keywords "stiff person syndrome",

"systemic lupus erythematosus", "autoimmune overlap", and "case report" in various combinations. Additional sources were identified through manually screening the relevant articles. Inclusion criteria were articles describing SPS, SLE, or their overlap, including case reports, case series, retrospective studies, and reviews. Exclusion criteria were conference abstracts without full texts and studies not directly addressing SPS and SLE. In total, 120 publications were screened, of which 53 met the inclusion criteria and were analyzed in detail.

Results: A total of 53 studies were included, comprising case reports, case series, and reviews. These reports suggested a rare but clinical overlap between SPS and SLE.

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The main themes identified were shared autoimmune mechanism, overlapping clinical manifestations, diagnostic challenges, and implications for therapy, underscoring the need for improved recognition and management.

Conclusion: Early diagnosis and an interdisciplinary approach are crucial for optimal outcomes. Improving the prognosis for individuals with overlapping autoimmune disorders requires increased awareness, integrated care approaches, and further research into common biomarkers and treatments.

Introduction

Stiff-person syndrome (SPS) is an uncommon autoimmune neurological disorder, occurring at a rate of 1-2 cases per million and mainly affecting women, with the onset of age being forty to fifty.^{1,2} It is predominantly characterized by progressive axial muscle stiffness, central nervous system (CNS) hyperexcitability, and stimulus-sensitive painful muscle spasms.² The classic signs of SPS are stiffness and spasms in the lumbar and proximal lower limb muscles that exacerbate over time.¹

Systemic lupus erythematosus (SLE), on the other hand, is a chronic, multisystem autoimmune disorder marked by periods of flare-ups and remission. The annual incidence of this disease ranges from 0.3 to 31.5 per 100000, with most of the cases occurring in women.³ SLE is distinguished by the presence of antibodies targeting nuclear and cytoplasmic antigens, affecting various molecules, organelles, cell types, plasma proteins, or tissues.⁴ Along with that, various environmental and genetic factors interact to trigger immune responses, leading to excessive production of autoantibodies by B cells and cytokine dysregulation, which further cause tissue and organ damage.⁵

Neurological and muscular symptoms from SPS and SLE can be clinically indistinguishable due to their shared autoimmune bases. Reports of the uncommon simultaneous presence of these conditions support the involvement of mutual risk elements.⁶

Although SPS and SLE are clinically distinct diseases with limited overlap, both share fundamental autoimmune mechanisms, including the involvement of B cells, autoantibodies, and cytokine dysregulation. Details of specific autoantibody mechanisms have been consolidated into the "Etiology and Pathogenesis" subsection. The aim of this study is to explore the rare but clinically relevant co-occurrence of SPS and SLE,

examining possible overlapping immunological pathways, diagnostic challenges, and implications for clinical management. This review aims to enhance diagnostic clarity and provide suitable therapy options when both diseases are suspected in a single patient by comprehending the shared mechanisms and unique features. This comprehensive approach could enhance the clinical management of both SPS and SLE, providing deeper insights into their shared pathophysiology. Understanding the distinct yet intersecting clinical backgrounds of SPS and SLE provides a foundation for examining their etiological and pathogenic mechanisms, which highlight where the conditions may converge. This narrative review explores the available evidence on the overlap between SPS and SLE with a focus on shared pathophysiology, clinical manifestations, diagnostic challenges, and therapeutic implications.

Materials and Methods

Study design: This study is a narrative review of published literature on the association between SPS and SLE. A narrative design was chosen due to the rarity of cases and heterogeneity of evidence, precluding systematic review or meta-analysis. This review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA).

Search strategy: We searched PubMed, Scopus, and Cochrane up to June 2025 using the terms "stiff person syndrome", "systemic lupus erythematosus", "autoimmune overlap", and "case report" in various combinations.

Eligibility criteria: Studies were eligible for inclusion if they were case reports, case series, retrospective studies, or reviews describing SPS, SLE, or their clinical overlap. We excluded conference abstracts without available full text and studies that did not directly address the association between SPS and SLE.

Study selection: A total of 120 publications were screened; 53 met the inclusion criteria and were analyzed.

Data extraction: Data were extracted from the included studies, focusing on study type, patient characteristics, clinical presentation, diagnosis, and treatment. Findings were narratively synthesized to highlight patterns and clinical implications.

Etiology and Pathogenesis

Autoantibody-mediated mechanisms: SPS is a rare autoimmune disease with an unclear etiology

that causes a rigid appearance of muscles.⁷ Though glutamic acid decarboxylase (GAD) antibodies are linked to SPS and support its autoimmune origin, it is unclear what role GAD antibodies play in SPS.^{1,8} However, it has been shown that other autoantibodies and variables may contribute to the disease progression.¹ On the other hand, patients with SLE develop various autoantibodies with anti-nuclear antibodies (ANAs) as their most common type. The cause of SLE remains unclear, mainly because of the complex and diverse nature of the disease, both of which can be attributed to the numerous interrelated genetic, hormonal, and environmental factors and susceptibility sources.⁷

Shared immunological pathways: SLE and SPS both are heavily influenced by the presence of autoantibodies and can be hypothesized to share immunological dysregulation. While diseases such as antiphospholipid syndrome (APS) or SLE may present as chorea, autoimmunity to GAD in SPS frequently causes movement impairments, including cerebellar ataxia.⁹ Among the case reports reviewed, we identified a patient with SPS and anti-GAD antibodies who developed SLE symptoms such as myalgia, highlighting a potential link between the two diseases.⁴ Furthermore, much like the SPS, SLE can also cause CNS involvement.¹⁰ Since both conditions are driven by immune dysregulation and overlapping antibody responses, their clinical presentations may also intersect, creating diagnostic challenges that merit closer examination. The shared and distinct autoimmune pathways implicated in SPS and SLE are illustrated in figure 1.

Clinical manifestations: SPS primarily causes a

gradual stiffening of the limbs, beginning in the trunk before spreading to the extremities. The disorder produces different expressions, including high muscle tone combined with numerous spasms or milder movement challenges related to posture.¹¹ In later stages, facial muscle weakness may cause difficulties with facial expressions, swallowing, and speech. In rare cases, respiratory muscle impairment can lead to breathing difficulties.¹² SLE is a systemic autoimmune disease that can affect nearly any organ or tissue. Cutaneous symptoms include the characteristic malar (butterfly) rash and photosensitivity. Hematological complications, such as anemia, leukopenia, and thrombocytopenia increase the risk of infections and bleeding. Renal involvement, known as lupus nephritis, may lead to proteinuria and elevated creatinine levels, potentially resulting in renal failure.

Pulmonary complications, including pleuritis and interstitial lung disease, can cause significant respiratory impairment. Patients commonly experience joint pain as well as arthritis that spreads across small joints, such as the bones in the fingers, with migratory characteristics. Avascular necrosis (AVN) may also develop due to impaired blood circulation in the bones, leading to extreme pain and functional limitations.¹³ Given this symptomatic overlap, establishing an accurate diagnosis requires careful use of clinical criteria, serological markers, and imaging, which can help distinguish between the two conditions or identify their co-occurrence. A comparison of the major clinical manifestations of SPS and SLE is presented in table 1.

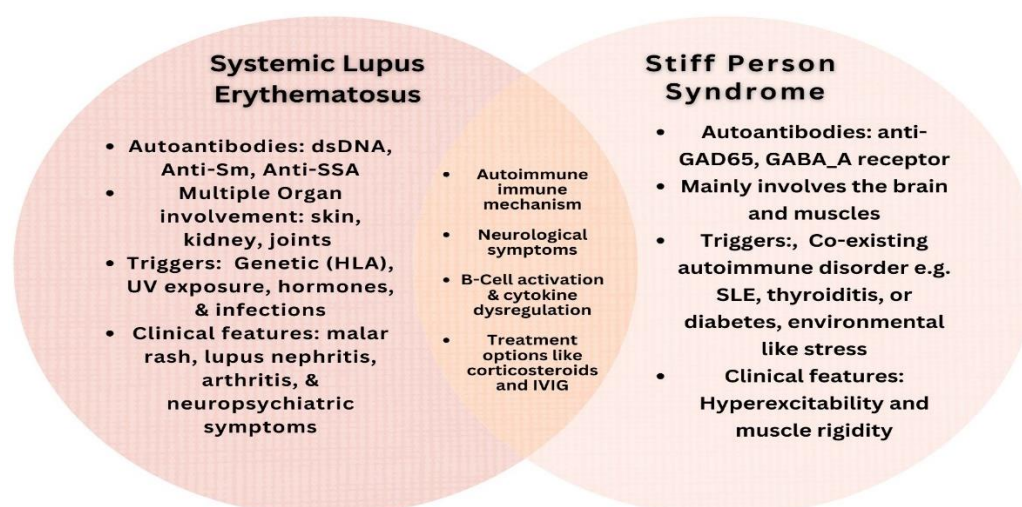


Figure 1. Visual representation of shared and distinct autoimmune pathways in stiff-person syndrome (SPS) and systemic lupus erythematosus (SLE)

Table 1. Clinical manifestations of stiff-person syndrome (SPS) and systemic lupus erythematosus (SLE)

System	SPS	SLE
Musculoskeletal	Progressive axial/proximal muscle rigidity, spasms, hyperlordosis	Osteonecrosis arthralgia, arthritis
Immune/autoimmune	Anti-GAD65, anti-amphiphysin, glycine receptor antibodies	ANA, anti-dsDNA, antiphospholipid antibodies
Renal	No significant involvement	Lupus nephritis, hypertension
Neurological	Reflex or stimulus-sensitive spasms, co-contraction, gait disturbances	Neuropsychiatric involvement: seizures, mood/cognitive disorders
Severity/frequency	Variable; risk of status spasticus and progressive functional disability	Chronic, fluctuating, involving multiple systems, with flare-ups and remissions

SPS: Stiff-person syndrome; SLE: Systemic lupus erythematosus; GAD: Glutamic acid decarboxylase; ANA: Anti-nuclear antibody; dsDNA: Double-stranded deoxyribonucleic acid

Diagnosis: There are several criteria for making a diagnosis of SPS. Electromyography (EMG) results are imperative; they indicate continuous motor unit activity in agonist and antagonist muscles, most often in the paraspinal muscles. This activity is characterized by normal morphology along with no myotonic potential.¹⁴ Dalakas modified criteria was used for diagnosis of SPS, as outlined in table 2.¹⁵ In brief, these criteria require: (1) stiffness in axial and limb muscles, especially the paraspinal region; (2) painful spasms precipitated by stimuli; (3) continuous motor unit activity on EMG; (4) exclusion of other neurologic or psychiatric disorders; and (5) supporting findings such as anti-GAD65 or anti-amphiphysin antibodies.¹⁶ Diagnosis relies on serological confirmation of disease-specific antibodies (e.g., anti-GAD65).

Magnetic resonance spectroscopy (MRS) can show a focal change in gamma-aminobutyric acid (GABA) levels in the motor area of the brain in SPS. In patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), magnetic resonance imaging (MRI) might show hyperintense signals in the spinal cord and the brainstem.¹⁷

Healthcare professionals use the 2019 European League Against Rheumatism/ American College of Rheumatology (EULAR/ ACR) criteria to diagnose SLE and maintain uniform patient evaluation, as

outlined in figure 2.

These criteria are based on a positive ANA ($\geq 1:80$) as an entry requirement, followed by additive weighted domains across clinical and immunologic systems, with a total score ≥ 10 confirming classification. This structured scoring system ensures both sensitivity and specificity, and standardizes patient evaluation across studies. Lupus nephritis (Class III/IV on biopsy) plus ANA positivity is enough to classify a patient as having SLE due to its strong disease association. Unexplained fever was added as an early indicator, and criteria like neuropsychiatric symptoms, pericarditis, and complement levels were refined. Importantly, each symptom must be attributable to SLE and not better explained by another condition.¹⁸ Other conventional serological markers, including ANA and anti-double stranded deoxyribonucleic acid (dsDNA), do not offer adequate sensitivity and specificity when used in isolation. Kidney biopsy, used practically in assessing renal involvement, is invasive and has extra risks associated with the procedure.¹⁹ Given the heterogeneity of SLE and the complexity of overlap syndromes, clinical follow-up is frequently required to assess comorbid conditions and infections, which may present like disease activity. The key diagnostic criteria, sensitivity, and specificity of diagnostic markers for SPS and SLE are summarized in table 3.

Table 2. Dalakas modified diagnostic criteria for stiff-person syndrome (SPS)

1) Increased tone of axial muscles, especially of the abdominal or thoracolumbar paraspinal areas resulting in hyperlordosis
2) Painful spasms occurring on top of the existing ones due to contact or sound
3) Electromyographic evidence of continuous agonist-antagonist muscle co-contraction
4) Lack of any other neurological signs suggestive of an alternative diagnosis
5) Positive serology: Presence of GAD autoantibodies supported by subsequent immunocytochemistry, Western blotting, or radioimmunoassay
6) Response to diazepam

GAD: Glutamic acid decarboxylase



Figure 2. 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE)

There remains a significant paucity of data regarding the natural progression of these overlap syndromes.²⁰ One published case report described a patient presenting with acute-onset SLE, followed by the development of SPS within several months. SLE has probably not been caused by the treatment prescribed for SPS since the drugs cannot lead to drug-induced lupus or raise ANA titers. Moreover, no anti-histone antibodies were detected in the serum and urine, as well as in the skeletal muscle. Hence, the detection of anti-GAD antibodies during the manifestation of SPS should raise the clinical suspicion of co-occurring SLE, necessitating vigilant monitoring.²¹ Once diagnostic clarity is achieved, attention naturally shifts toward therapeutic strategies, which often

require balancing symptomatic relief with immunomodulation in both SPS and SLE.

Treatment: There are both symptomatic and disease-modifying treatments for SPS and SLE, but they differ depending on the condition. In the case reports and studies included in this review, the first-line treatment is benzodiazepines. If dyskinesia persists, a dose of levetiracetam or pregabalin is further suggested. For the second-line therapy, oral baclofen is preferred over rituximab and tacrolimus. Several included reports describe the use of intrathecal baclofen plus intravenous immunoglobulin (IVIG) (recognized immunotherapy for SPS) along with plasmapheresis to help patients resistant to other treatment options.

Table 3. Diagnostic criteria

Criteria	SPS	SLE
Primary diagnostic criteria	Anti-GAD65 antibodies, clinical presentation, and electromyography for continuous motor unit activity	Kidney biopsy for lupus nephritis, anti-dsDNA, anti-Ro/La, and antiphospholipid antibodies
Sensitivity	Moderate; anti-GAD65 positive in ~ 30%-65%	ANA: ~95% sensitivity; anti-dsDNA for disease activity
Specificity	Anti-GAD65 relatively specific but may overlap with other autoimmune disorders	Anti-dsDNA highly specific, especially in nephritis

SPS: Stiff-person syndrome; SLE: Systemic lupus erythematosus; GAD: Glutamic acid decarboxylase; dsDNA: Double-stranded deoxyribonucleic acid; ANA: Anti-nuclear antibody

Patients with SPS under treatment with IVIG and intrathecal baclofen experience better outcomes compared to those treated with plasmapheresis.²² Nevertheless, propofol demonstrates efficacy in patients with refractory symptoms; however, its use is restricted to short-term therapy.²³

Treatment is aimed at alleviating a key sign of spasticity, muscle rigidity. This often involves drugs that act to increase the amount of GABA present in the body, for instance, benzodiazepines (such as diazepam), baclofen, gabapentin, and vigabatrin.²⁴ Other drugs, such as intrathecal baclofen and other muscle relaxants like dantrolene and tizanidine, could be useful. In reviewed cases where autoimmune components were assumed, disease-modifying agents, including IVIG, were used to provide lasting relief. Plasma exchange and corticosteroids have partial efficacy, and rituximab has been demonstrated to be effective. Some human immunomodulation agents that have received varying levels of success include mycophenolate mofetil (MMF) and azathioprine.¹⁷ Subsequently, the GABA receptor-associated protein (GABARAP) – a 14-kilodalton (kD) protein located at the postsynaptic area of the GABAergic axon terminal – suppresses the GABA type A (GABAA) receptor in approximately 65% of patients with SPS. Therapeutic choices may be influenced by the specific antibody profile: amphiphysin-positive patients often show improvement with steroids, plasmapheresis, or treatment of underlying malignancy, while those with anti-GAD antibodies may respond more favorably to IVIG, diazepam (37 mg/day), and clonazepam (4 mg/day).²⁵

Managing SPS in the long term is a challenge, mainly due to the differences between individual communities. To manage these symptoms, early commencement of IVIG therapy and supportive interventions, which include homeschooling, unrestricted physical activity, and bracing, is recommended.²⁶ Similarly, women who are planning to conceive must transition from GABA enhancers to IVIG to prevent possible harm to the fetus, although the symptoms may improve during pregnancy due to immunomodulation changes.²⁷ The therapeutic landscape, again, has several weaknesses. Managing symptoms without causing too much sedation remains a challenge, and while the frequency and intensity of the symptoms can be documented, better evaluation tools that measure the efficacy of the treatments are

warranted. Long-term IVIG therapy is helpful, but it is not sufficient to arrest the progression of the disease in approximately 30% of the patients after four years of treatment.²⁶

Treatments for SLE target the immune system to decrease swelling and reduce harmful antibodies. According to published SLE guidelines and included reports, the treat-to-target model has emerged as a primary strategy, targeting remission or low disease activity as well as glucocorticoid sparing. Antimalarial medications are a cornerstone of SLE management which are prescribed to all diagnosed patients due to their efficacy in reducing inflammation and preventing flare-ups. While quinacrine is applied for skin lesions, glucocorticoids are used only for exacerbations since their usage has several side effects in the long run. Other immunosuppressive agents that are used but are not corticosteroids include cyclophosphamide, MMF, and azathioprine for severe manifestations, including lupus nephritis. Additional choices include B-cell depletion therapies such as rituximab and other different anti-CD20 antibodies. Anti-interferon alpha (IFN α) and Janus kinase (JAK) inhibitors have emerged as novel therapeutic strategies.²⁸ Both conditions have similar approaches toward management. The main treatment for SLE depends on corticosteroids, which show potential benefits for autoimmune SPS. Motor imagery-based trunk training may be useful in treating both SPS and SLE; specifically, it may mitigate muscle rigidity and spasms in SPS, while simultaneously preserving joint mobility in SLE. This means that education is crucial for both SPS and SLE patients to ensure compliance with the directed treatment and proper symptom management. Patients should be monitored regularly, maintain a stable lifestyle, minimize stress, follow a balanced diet, and engage in physical exercise. These reported strategies show an integration point in the view of the management of chronic conditions, irrespective of the disparate methods needed to cater to each disease.^{22,29} Another important aspect that affects the management of SLE is its association with an increased prevalence of comorbidities such as cardiovascular, renal, and psychiatric disorders. It is evident from the published literature that patients with SLE are prone to acquiring new comorbidities and have a higher mortality index than controls.³⁰ Furthermore, a significant prevalence of psychiatric comorbidities, most notably depressive

disorders, has been observed in both SLE and SPS populations; these conditions substantially impair health-related quality of life (HRQoL).^{31,32} Therefore, it is important to diagnose and treat these conditions to ensure patients receive holistic care. While SPS and SLE demand different treatment methods, certain aspects of the treatment of both conditions complement each other in terms of focusing on the necessity of controlling symptoms, immunosuppression, physiotherapy, and comprehensive patient education, underscoring the need for an interprofessional approach to the management of such patients.³³ Although conventional therapies remain central, emerging biologics and cell-based treatments offer new directions for managing complex autoimmune conditions.

Recent advances in treatment: Regarding the management of SPS and SLE, it deserves to be mentioned that the treatment of these two diseases in moderate-to-severe cases depends on the individual characteristics of the patient. According to the recent reports and trials, survival rates in the SLE have improved gradually over the past few years, with an enhanced impact on management that has occurred with the development and use of biological agents and immunomodulatory therapies.³⁴ For instance, B-cell inhibitors, including belimumab and rituximab, are accepted and utilized in treating SLE, especially where the symptoms are severe.³⁵ However, chimeric antigen receptor (CAR)-T cell therapies were reported to be effective in the recent clinical trials of both SPS and SLE. A phase 1 trial of a dual-target CAR-T cell therapy in thirteen patients with SLE demonstrated a profound capacity to eliminate B-cells and autoantibodies, achieving remission in most cases.³⁶ This finding represents one of the biggest developments in SLE treatment, suggesting that CAR-T cell therapy may facilitate prolonged remission while reducing reliance on conventional medications. Likewise, treatment-refractory SPS has also been treated using the first-in-class CAR-T cell therapy, such as Kyverna Therapeutics' KYV-101, which targets CD19. Early outcomes suggested that this therapy might help to lessen the symptoms' severity and could be viewed as a new approach to treating such patients when other treatments fail.³⁷ For SPS, treatment options center on immunomodulatory therapy to downregulate autoantibodies while at the same time gaining control over neurological manifestations. These include IVIG and rituximab,

used especially in cases where patients present anti-GAD antibodies. IVIG has been used in the early stages of the disease, and has helped prevent the worsening of the condition and preserve the quality of life (QoL) of the affected individuals. Several recent investigations point out that rituximab might minimize the clinical manifestations of refractory SPS cases and could be used in cases with difficult management outcomes.³⁷ By targeting specific molecular processes, these treatments minimize side effects, thereby improving patient prognosis.³⁸ It is further envisioned that future research will address aspects of autoimmunity dealing with B-cells and T-cells where cross-prevalent treatment modalities may be used for various forms of autoimmune diseases.³⁸ The inclusion of CAR-T cell therapy in the treatment regimens used for treating SPS and SLE represents a significant therapeutic advancement and offers potential for providing effective remission and more favorable control over such disorders.³⁶ These findings are synthesized from the most recent clinical studies, and they have significant implications for long-term outcomes and prognosis, which remain guarded in many patients despite therapeutic progress.

Prognosis: The predicted outcome of SPS depends on symptom severity, disease duration, the presence of underlying neoplasia, and therapeutic response. Many patients show improvement with medications but may experience fluctuating symptoms often related to stress. However, some patients with SPS continue to have progression of the disease even with available treatments, which results in permanent orthopedic complications, including lumbar hyperlordosis, joint deformity, and muscle atrophy, among others. One longitudinal study suggested that only 19% of patients with SPS were able to work after four years, implying a poor QoL due to limitations in physical and social functioning.¹⁷

A 2018 Japanese nationwide mail survey provided critical insights into the long-term outcomes, QoL, and survival rates of the patients with SPS. Of all 30 patients with GAD65-positive SPS, the median age at SPS onset was 51 years, and 76% of the cases were women. The point prevalence of GAD65-positive SPS in Japan was calculated at 0.11 per 100000 populations, making it a rare condition. Looking at the end-point measures, the Modified Rankin Scale (mRS) score, a measure of disability, was reduced from a median of 4 at baseline to a median of 2 at the last

follow-up. For patients with worse outcomes (mRS ≥ 3), other risk factors, including coexisting type 1 diabetes mellitus (DM) and a lack of long-term immunotherapy, were found to be relevant. Notably, the patients who did not undergo long-term immunotherapy had poor prognosis and a significantly higher probability [odds ratio (OR): 19.8] of death. Notwithstanding the relatively favorable prognosis observed in GAD65-positive patients with SPS, this study underscores the importance of more intensive, long-term immunotherapies to enhance patients' QoL and survival. These results highlight that case outcomes in SPS hinge on antibody titers, comorbidities, and immunotherapy access.² Despite significant advancements in the management of SLE, patients continue to face substantial risks of morbidity and mortality. These include the ten-year survival rate, which ranges from 85% to 90%. Some of the major causes of mortality in SLE comprise cardiovascular diseases (CVDs), infections, and renal diseases. Clinical outcomes are optimized through early detection of disease progression, followed by prompt intervention using organ-protective and infection-preventive methods. Specific predictors of poor prognosis in SLE include Black ethnicity, male sex, extreme age at presentation, hypertension (HTN), renal disease (particularly diffuse proliferative glomerulonephritis), low socioeconomic status, and anti-phospholipid antibodies or anti-phospholipid syndrome.³⁹

The prognosis of SPS and SLE depends mainly on the severity of the disease, treatment effectiveness, and the presence of neurological symptoms. In SPS, long-standing cases are associated with progressive disability, and in SLE, patients with severe organ damage, including lupus nephritis or neuropsychiatric SLE, have a worse prognosis. Antibodies bear a significant implication in the etiology of both diseases; while anti-GAD65 antibodies are prevalent in SPS, anti-dsDNA or antiphospholipid antibodies are linked with aggravated disease and complications in patients with SLE. Early diagnosis and full compliance with prescribed medications can greatly enhance the prognosis in both SPS and SLE and can prevent the development of the more severe forms of the diseases. Neurological involvement is also very detrimental in both conditions, often leading to long-term disability and profound reductions in QoL. In SLE, the history of neuropsychiatric involvement is a poor

prognosticator, with features from cognitive impairment to seizures. A wide variety of neurological events may develop in both diseases, and these are associated with increased morbidity and mortality; therefore, early recognition and subsequent intervention would benefit patients.¹⁶ Beyond survival and physical disability, both SPS and SLE profoundly affect QoL, underscoring the need for holistic management approaches.

QoL: SPS and SLE both cause considerable physical, psychological, and social disability for patients. The muscle rigidity along with dystonia from SPS leads to severe mobility problems, which bring about social isolation. Just like patients with SLE, SPS cases also suffer from chronic fatigue,⁴⁰ and many patients get depression, anxiety, and frustration with the unpredictability of symptom flares.¹⁷ Besides, they often run into difficulties with concentration and understanding, and these difficulties impact academic or professional performance.³³ Beyond the immediate physical symptoms, financial stress also impedes the QoL, with long-term care, disability, and a high frequency of medical visits imposing a major financial burden on patients and their families. Many patients struggle with employment retention, which subsequently compromises their financial independence.⁴¹ Moreover, a lack of public awareness and social understanding of SPS and SLE further contributes to the psychosocial burden, leaving patients susceptible to the misconception that they are incapable or inappropriate for certain things. To improve the overall QoL of individuals affected by these conditions, it is imperative to implement enhanced patient education, community support systems, and appropriate accommodations.

Case Reports

A literature search was performed to collect case reports that investigated the simultaneous occurrence of SPS and SLE, the results of which are summarized in table 4.

The presented cases^{7,42} provide important insights into patients with SPS symptoms that continue after regular treatment and need a medical examination for autoimmune syndromes, including SLE. Patients with refractory SPS might benefit from immunosuppressive therapies designed for SLE. The early identification and proper medical intervention lead to improved patient outcomes.

Both SPS and SLE are chronic and difficult-to-manage diseases, and their association is an area of two significant case reports.

Table 4. Summary of case reports

Author	Country	Symptoms	Diagnosis	Treatment	Data extraction	Study quality assessment	Risk of bias
Gómez-Bañuelos et al. ⁴	USA	Severe muscle stiffness, spasms in back and limbs	Suspected autoimmune condition involving SPS with SLE	Symptoms improved with azathioprine and mycophenolate mofetil (immunosuppressive treatment)	Extracted data including patient history, clinical findings, and therapeutic response	High quality; clear case details and treatment outcome documented	Low – comprehensive clinical information provided
Munhoz et al. ⁴³	UK	Progressive muscle stiffness, painful spasms, malar rash, arthritis	Initial SPS diagnosis later confirmed as SLE	Improvement in SPS and SLE symptoms with immunosuppressive treatment	Extracted clinical notes, symptom progression, and diagnostic confirmation	Moderate quality; some details on long-term follow-up missing	Moderate – increased potential bias due to incomplete follow-up data

SPS: Stiff-person syndrome; SLE: Systemic lupus erythematosus

Gómez-Bañuelos et al. documented a 39-year-old female patient presenting with symptoms characteristic of SPS, particularly severe muscle stiffness and spasms in her back and lower limbs. She continued to have symptoms even after the treatment with high-dose corticosteroids and plasmapheresis. An additional assessment and workup showed that she had another autoimmune disease, namely SLE. When she started immunosuppressive therapy with azathioprine and MMF for SLE, her SPS improved, suggesting a shared autoimmune etiology and highlighting the patient's responsiveness to SLE-directed management.⁴

In the case reported by Munhoz et al., a male patient was diagnosed with SPS, especially when accompanied by progressive muscle stiffness and painful spasms that failed to respond to existing treatment options, including benzodiazepines and baclofen. Eventually, the patient began to exhibit signs of SLE, such as malar rash and arthritis. Significantly, SPS developed before SLE by several months, which is quite rare and may suggest a relationship between autoimmunity and these pathologies. After being diagnosed with SLE and starting immunosuppressive therapy for SPS, his condition significantly improved, which supports the autoimmune etiology of SPS, especially in cases who fail to achieve remission with conventional SPS therapies. These cases demonstrate that other autoimmune processes, such as SLE, must be considered in SPS cases, as early detection and treatment of such associations produce excellent clinical outcome.⁴³

Several valuable clinical insights can be learned from these cases, which can contribute to the art of practicing clinical medicine and surgery. The chronicity of SPS symptoms and their refractory nature to conventional therapies should prompt clinical consideration of an underlying autoimmune etiology, such as SLE. Furthermore, the cases discussed highlight necessity of expanding the differential diagnosis in patients with refractory SPS, mainly due to other autoimmune symptoms or the appearance of such symptoms in the course of the disease. Finally, improvement of SPS symptoms following immunosuppressive therapy for SLE indicates that shared autoimmune pathways may contribute to both conditions.

This highlights the importance of investigating overlapping immune mechanisms instead of viewing the diseases as completely separate

entities. Additionally, these reports demonstrate that early identification of autoimmune disorders like SLE results in major positive changes in SPS signs, which stresses the importance of adequate examinations in such complicated circumstances. Clinicians need to be careful to identify new-onset SPS presentations that might suggest a multisystem autoimmune disease, as the relationship between neurological and systemic autoimmune diseases might be more complicated than currently established. Moreover, this recognition is vital for optimizing the immunosuppressive therapies, given the well-documented efficacy of such interventions in modulating disease processes and improving patient outcomes.

Public Health Implications

Surveillance of SPS is important for developing an understanding of the epidemiology of this rare neurological disease and for the establishment of healthcare policies and interventions.

A few neurological diseases, including SPS, represent significant diagnostic and therapeutic challenges, frequently characterized by suboptimal responses to conventional treatment modalities. Consequently, delayed or inadequate therapeutic intervention often results in significant clinical complications including but not limited to the following: permanent neurological damage, disability, and, in some cases, death.⁴⁴ These outcomes not only profoundly affect the individuals' QoL but also impose substantial socioeconomic burdens. This chronic disability resulting from SPS and SLE leads to job loss, productivity cutbacks, and increased healthcare costs; these factors create a compounding effect that overwhelms the financial, social, and personal resources of affected patients and the health systems. Solving these problems presupposes the fortification of registries as well as the development of early detection measures. Therefore, the main steps in healthcare policy cannot be overemphasized in the management of such impacts. Strengthening public health frameworks is essential to enhancing awareness about this disease, improving diagnostic accuracy, and ensuring timely therapeutic intervention. Raising awareness among healthcare providers concerning SPS and SLE is critical for determining effective diagnosis and management.

In addition to optimizing therapeutic efficacy, early diagnosis facilitates access to educational materials, patient support groups, and other

services that address the QoL issues related to the disease.⁴⁵ Public education campaigns have been stated to greatly influence the lives of those affected.⁴⁶ However, policies regarding research funding and healthcare accessibility can minimize the total cost incurred for these diseases, which emphasizes the reactive as well as conscious healthcare approach.

Results

A PubMed search was performed using the terms 'Stiff Person Syndrome' and 'Systemic Lupus Erythematosus'. Only peer reviewed case reports minimize the possibility of selective inclusion bias. To ensure transparency, the selection process specifically for SPS-SLE overlap case reports is summarized in table 5, while the broader narrative review included 53 publications, as detailed in the "Methods" section.

Both reports described patients with the rare overlap of SPS and SLE. Taken together, these reports suggest that while immunotherapies may provide symptomatic benefit, the evidence remains limited and fragmented. This co-occurrence raises important questions regarding shared autoimmune mechanisms; furthermore, the overlap underscores the diagnostic complexity in clinical settings and necessitates controlled studies to guide long-term therapeutic management.¹⁶

Limitations: Publications on SPS and SLE show that both diseases involve intricate autoimmune processes that require further investigation. While the role of anti-GAD antibodies is well-established in SPS, their exact mechanism in driving neurological symptoms remains unclear.⁴⁸

The variability in the symptoms further complicates the interpretation of pathogenesis. Similarly, in SLE, different mechanisms produce an autoimmune response, including key biomarkers such as anti-dsDNA and antiphospholipid antibodies. Although there is evidence connecting antibodies to neurological symptoms, the underlying mechanisms driving these manifestations remain largely uncharacterized. Variations in socioeconomic

circumstances, environmental exposures, and population demographics all contribute to the vast range of reports on the incidence and prevalence of SLE around the world. Such case definitions and methods inevitably lead to gaps in knowledge about the illness.⁴⁷ Moreover, the diagnosis of SPS and SLE is challenging due to the lack of laboratory tests, similar neurological symptoms with other disorders, and a wide range of manifestations; consequently, SPS is typically verified through a clinical diagnosis. In contrast, clinical and immunological criteria must be satisfied independently to obtain an exact diagnosis for SLE.⁴⁸ Currently used diagnostic methods depend on laboratory markers, which can be unspecific. To provide accurate diagnoses and improve the quality of treatment, there is an urgent necessity for specific laboratory tests and imaging methods for SPS and SLE separately. Furthermore, SPS is strongly linked with other autoimmune diseases such as DM, thyroid, and SLE.⁴⁸ Most of the studies carried out in the context of these diseases are conducted separately and have no relation to each other. It must also be acknowledged that the existing evidence for SPS-SLE overlap is limited largely to isolated case reports and retrospective descriptions, making it difficult to determine whether this association represents a true pathogenic overlap or merely a coincidental co-occurrence of two rare autoimmune conditions. In addition, the scarcity of systematic data underscores the urgent need for larger multicenter cohort studies, prospective registries, and natural history investigations to validate these preliminary observations and provide more definitive insights into prevalence, mechanisms, and optimal management. Importantly, the scarcity and heterogeneity of available cases preclude the possibility of performing a quantitative synthesis or meta-analysis, which weakens the overall evidence base. While this represents a significant limitation, our narrative review, nevertheless, provides value by consolidating scattered case reports, identifying recurring clinical themes, and highlighting important gaps in knowledge.

Table 5. Selection process for stiff-person syndrome (SPS) and systemic lupus erythematosus (SLE) overlap case reports

Step	Number of records	Notes
Initial PubMed search	12	All publication types
Screened titles/abstracts	5	Case reports and reviews considered
Excluded	3	Not describing SPS-SLE overlap
Finally included	2	Eligible case reports

SPS: Stiff-person syndrome; SLE: Systemic lupus erythematosus

These insights may serve as a foundation for future systematic studies and as prospective data collections that could eventually support meta-analytical approaches. Thus, future cross-disease studies and autoimmune research should integrate immunological, environmental, genetic, and pathophysiological mechanisms to elucidate the link between different autoimmune diseases, ultimately enabling better clinical intervention.

In addition to the limitations of the primary literature, the present review itself has methodological constraints. Although a comprehensive search was conducted across PubMed, Scopus, and Cochrane, it is possible that some relevant studies were missed, especially those published in other databases or as gray literature. In addition, only English-language publications were included, which introduces the risk of language bias. Moreover, no formal quality appraisal of the included reports was performed, as this was a narrative review rather than a systematic review. Finally, given the descriptive nature of the synthesis, the possibility of subjective interpretation cannot be entirely excluded.

Conclusion

This review focuses on the possibility of using somatostatin analogs for SPS treatment and explores the relationship between SPS and autoimmune overlap syndromes, including SLE. The somatostatin analogs proved useful for enhancing QoL and decreasing neurological

symptoms in patients with SPS. Given the documented association between SPS and SLE, an integrated clinical assessment approach is essential. Future research should be directed at other immunotherapies for refractory SPS and SLE cases, and more emphasis should be placed on identifying new biomarkers for both patient triage and the prediction of disease activity in overlapping autoimmune diseases. At the same time, current evidence for SPS-SLE overlap remains largely limited to case reports, and in some instances, the association may represent coincidence rather than a true mechanistic link.

The novelty of our review lies in consolidating scattered case reports to underscore the importance of recognizing this rare overlap. This synthesis highlights the need for heightened clinical vigilance and a more systematic approach to diagnosis and treatment. Future research should prioritize the development of prospective multicenter registries, the identification of reliable biomarkers indicative of overlap syndromes, and the exploration of targeted immunotherapeutic strategies tailored to the dual pathology of SPS-SLE overlap.

Conflict of Interests

The authors declare no conflict of interest in this study.

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