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Review Article

SPS: Understanding the complexity

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ABSTRACT

Introduction: Stiff-person syndrome (SPS), first described in 1956 by Moersch and Woltman, is a progressive autoimmune disorder with core features of chronic fluctuating progressive truncal and limb rigidity and painful muscle spasms leading to gait difficulties, falls and an appearance that resembles tin soldiers. The syndrome is a rare, highly disabling disorder of the central nervous and frequently results in significant disability. Understanding of the etiology, clinical spectrum, diagnostic workup and therapeutic modalities for this painful and disabling disorder has vastly evolved over the past few years with more confidence in classifying and treating the patients. The purpose of this review is to increase the awareness, early detection, and treatment of this disabling disease.

Method: PubMed was searched, all date inclusive, using the following phrases: stiff person syndrome,anti-Glutamic acid decarboxylase (Anti-GAD) antibody syndrome, Progressive encephalomyelitis with rigidity and myoclonus (PERM), and Paraneoplastic Stiff Person syndrome. No filters or restrictions were used. A total of 888 articles were identified.

Results: The results were narrowed to 190 citations after excluding non-English and duplicate reports. Clinical presentation, laboratory testing, treatment, and prognosis were categorized and summarized.

Discussion: In this article we will discuss the epidemiology, presentation and classification. Explain the pathophysiology of SPS and the autoimmune mechanisms involved. Discuss the diagnostic approach and treatments available, as well as, the prognosis and outcome.

1. Epidemiology and presentation (Table 1)

SPS has an estimated prevalence of 1–2 cases per million with an incidence of 1 case per million per year in the general population [1]. Originally “stiff man syndrome”, this name was later replaced by the gender-neutral “stiff person syndrome” (SPS), after increasing reports of female patients [20,200]. Women were found to be affected in 70% of cases [278]. Most patients present between the ages of 20 and 50 years; however, children and older adults, have also been affected. In 1956, Moersch and Woltman described the classical phenotypic presentation of progressive muscle rigidity and intermittent painful anxiety-triggered spasms, phobias and postural instability with frequent falls [3]. Later, there was an observation of frequent comorbid diabetes mellitus (DM) in up to 35% in some series [1] and other concomitant autoimmune diseases in patients with SPS [4]. A breakthrough in the pathogenesis of SPS took place in 1988 by Solimena et al. when they identified an autoimmune link between SPS and DM through autoantibodies against glutamic acid decarboxylase (GAD), an enzyme found in both the central nervous system and in pancreatic islets of Langerhans [5,6]. Further cases of the core clinical findings of SPS were reported in association with anti-GAD (anti-GAD ab) and other autoimmune antibodies [7–11]. Reports of different distributions of the symptoms followed, as well as association with a wide array of neurological findings and with neoplasia [7–11]. The perception of SPS changed from a distinct idiopathic disorder with persistent tonic contraction of muscles based on the phenotype to that of an autoimmune disorder with a wide spectrum of presentations with the core clinical features as common factors. The range of the disorder expanded from affecting a single limb to a widespread, rapidly progressive form that also involves the brain stem and spinal cord. Classification of this autoimmune disorder is based on the phenotypic presentation, or associated disorders (Table 1).

2. Phenotypic presentation

2.1. Classic SPS

The natural history of SPS is one of slow progression over months or years. Patients have slow voluntary movements, intermittent muscle stiffness and tightness. Muscle stiffness and spasms are the hallmarks of

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Table 1
Stiff Person Syndrome (SPS) classification.

Phenotypic presentation	SPS classification based on associated disorders
1. Classic SPS	1.Paraneoplastic: patients with associated neoplasms and autoantibodies
2. SPS variants:	2. Stiff person spectrum disorder (SPSD): Ataxia, Epilepsy, Progressive encephalomyelitis with rigidity and myoclonus (PERM).
a. Focal SPS	
b. Myoclonic SPS	

the clinical presentation of SPS. Tightness progresses and evolves consecutively into objective progressive hypertonia or rigidity. It is due to co-contraction of agonist and antagonist groups of muscles which often fluctuate throughout the day and decrease or abate during sleep. Continuous muscle contraction leads to muscle hypertrophy and abnormal posturing such as in lumbar hyperlordosis and a restricted range of movement. Muscle strength is usually preserved, and no sensory deficits are demonstrable [3]. Clinical manifestations usually begin in the muscles of the trunk and then spread to the proximal and then to the distal limb muscles. Lower extremities are affected more commonly than the upper extremities, and proximal limb segments more severely. The muscles of the distal limbs and face are usually spared until late in the disease [12]. Spasms initially occur in paroxysms, vary in frequency, intensity and duration but can become continuous as the disease progresses. They are stimulus-sensitive and can occur because of or worsen during periods of physical or emotional stress, cold weather, sudden movement, auditory, tactile, emotional and traumatic stimuli, or even intercurrent infections [12]. There is no provocation by visual stimuli.

Oculomotor disturbances constitute dysconjugate gaze, horizontal and vertical supranuclear gaze palsy, hypometric and slow saccades, impaired smooth pursuit, nystagmus and abduction deficits [13–15]. Eyeball movements are very slow. Myoclonic spasms may occur and can be preceded by jerky muscle contractions. Tendon reflexes are characteristically exaggerated, and abdominal cutaneous reflexes may be unelicitable; however, plantar responses are flexor and there is no clonus.

Exaggerated startle responses, abnormally enhanced exteroceptive reflexes, and disinhibition of brainstem reflexes, such as the head-retraction reflex, are not uncommon features [16,17].

Autonomic dysfunction manifests as paroxysms consisting of tachycardia, tachypnea, hypertension, diaphoresis, pupillary dilation hyperthermia [18], and even autonomic crises [19].

The clinical severity of SPS can be graded according to the distribution of stiffness index, which records the number of stiff areas ranging from 0 (none) to 6 and the heightened sensitivity index, which records the number of stimuli that induces spasms ranging from 0 (none) to 7 [24].

2.1.1. Associated disorders and complications (Table 2)

2.1.1.1. Orthopedic. In the extreme, muscle spasms can be severe enough to cause joint subluxations and fractures of bone [13]. Increased muscle rigidity often causes axial hyperextension manifested as cervical and lumbar hyperlordosis, which can lead to fixed spinal deformities.

Table 2
Major Complications of Stiff Person Syndrome (SPS).

SPS Major complications
Orthopedic Fractures and joint dislocations.
Crises: Severe dysautonomia and painful muscle spasms.
Falls.
Respiratory Hypoxemic respiratory failure.
Gastrointestinal: Oesophageal obstruction from cricopharyngeal muscle spasm.
Psychiatric: Eating disorders, hysterical paralysis, phobias, posttraumatic stress disorder, and agoraphobia.

2.1.1.2. Gait. Patients have difficulty bending and twisting at the waist, and stiffness results in a slow, difficult gait. Eventually, patients may lose the ability to walk independently.

2.1.1.3. Falls. Patients may experience falls secondary to the abnormal gait. Falls can appear as 'statue-like' or 'log-like', without the usual reflexive maneuvers that can soften the impact and prevent injury [20]. Adaptive devices, such as walkers, canes, and wheelchairs are often utilized by patients to compensate for the fear of falling.

2.1.1.4. Cognitive decline. Patients with anti-GAD ab positivity are at a higher risk of cognitive decline. Interruption of hippocampal GABAergic interneuronal function and decreased GABA levels in the prefrontal lobes were found to be associated with executive dysfunction and working memory dysfunction [254–256]. Language, general intelligence and perceptual organization, were found to be impaired in GAD ab-positive patients [253].

2.1.1.5. Psychiatric disorders. Associated psychiatric disorders may be underestimated among treating physicians [23]. The most prominent psychiatric comorbidities are anxiety disorders. Specifically, SPS patients may suffer from task-specific phobias. Task-specific phobias are highly prevalent, occurring in as many as 50% of patients with SPS. These phobias encompass fear of falling and fear of free space [24]. They appear to be related to fear of unprotected falls or fear of physically challenging situations. Patients may also develop phobias related to a fear of specific stimuli that can trigger their episodic spasms [25]. The rate of specific phobias in SPS patients is at least five times greater than in the general population [26].

SPS patients also have a higher prevalence of depression, alcohol abuse [23], eating disorders and hysterical paralysis [25]. Given low levels of GABA in anxiety disorders, anti-GAD ab was proposed to lead to a general GABA deficiency that predisposes patients to develop PTSD [252]. The combination of physical and psychiatric symptoms in SPS often impairs quality of life, independence and ability to work [27].

2.1.1.6. Respiratory. Apneic episodes, which can be life-threatening and unpredictable, have been reported in SPS. These are caused by spasms of the diaphragm and thoracic paraspinal and intercostal muscles resulting in the restriction of chest expansion that can lead to dyspnea and poor exercise tolerance. Tonic rigidity of respiratory muscles occurs suddenly, which can result in apneic episodes, aspiration or even respiratory failure [21,22].

2.1.1.7. Autonomic dysfunction. Acute apnea and respiratory failure can also be caused by paroxysmal autonomic sympathetic hyperactivity. The latter can lead to paroxysmal attacks of transient arterial hypertension, hyperpyrexia, tachycardia, pupillary dilatation, agitation, and diaphoresis during painful muscle spasms (288,289).

2.1.1.8. Gastrointestinal. When patients experience restriction of chest and abdominal expansion, they may have accompanying gastrointestinal symptoms of fullness or a feeling of early satiety.

2.1.1.9. Sudden death. Although not an epidemiologically rigorous observation, sudden death has been reported in as many as 10% of

patients with SPS (262). Spasms involving the axial muscles can lead to episodes of dyspnea with cyanosis, leading to respiratory distress towards respiratory failure and sudden death [251]. Sudden death was reported to occur secondary to metabolic acidosis [250] or autonomic dysfunction crises [249]. Repeated spasms or sudden withdrawal of medicine may also lead to autonomic dysfunction, resulting in sudden death [18].

2.1.1.10. Peripheral neuropathy. There are rare cases reported of nondiabetic GAD65 ab positive patients with likely immune-mediated peripheral neuropathy [285–287]. These patients tend to have GAD65 ab values in the low positive range (< 20 nmol/L) [285]. Phenotypes reported include sensorimotor axonal peripheral neuropathy, cranial neuropathy, demyelinating motor and sensory neuropathy with conduction block, multifocal motor neuropathy with conduction block, and Miller-Fisher type syndrome with ataxia, diplopia, and distal numbness (but negative GQ1b ab) [285–287].

2.2. SPS variants

2.2.1. Focal (partial) SPS

Stiff-limb syndrome (SLS) is characterized by involvement of a single limb, usually the lower extremity. Eventual spread of stiffness to the trunk may often, but not always, occur [28]. Other isolated muscle groups, such as chest and abdomen, may be affected [29].

2.2.2. Myoclonic SPS

Previously referred to as "Jerking stiff man syndrome". Patients experience myoclonus, that occurs spontaneously with high frequency, affecting the axial and leg muscles bilaterally and synchronously. It can be triggered by auditory or other sensory stimuli. Generalized myoclonic responses followed by prolonged tonic spasms may occur. Myoclonus responds dramatically to diazepam [200].

Symptoms of SLS or myoclonus can occur with several autoantibodies, but the syndrome specificity of each antibody is unclear (301).

2.3. SPS with associated disorders

2.3.1. Stiff Person Spectrum Disorder (SPSD)

Different neurological manifestations in the context of SPS core features of fluctuating rigidity and spasms with pronounced stimulus sensitivity are linked to certain antibody serology. This constitutes the SPS spectrum [30]. Phenotypes include cerebellar ataxia, epilepsy, cognitive impairment and encephalitic syndromes [4]. Patients within the SPS spectrum have antibodies that target proteins expressed by the inhibitory synapses of the Gamma-aminobutyric acid (GABA)system: GAD (GAD65), amphiphysin; α1-subunit of the glycine receptor (GlyR) [31,32]; gephyrin and dipeptidyl peptidase-like protein 6 (DPPX) [33,34]; γ-aminobutyric acid-A receptor (GABAaR) [35] and GABA receptor associated Protein (GABARAP), [36,37]. There is no clear syndrome-immunologic specificity. Any form of SPSD can potentially occur with any of the anti-GABAergic synapse antibodies. The following sections review disorders within this entity.

2.3.1.1. Cerebellar ataxia. Cerebellar ataxia accounts for approximately 28% of neurologic presentations [38,39] associated with anti-GAD ab. It may evolve subacutely or chronically. The most common presentation is gait ataxia with or without limb ataxia, dysarthria, and nystagmus [40]. Onset is usually in late middle age, and women are affected more than men [41]. Serum titers of anti- GAD ab is similar in cerebellar ataxia and SPS, yet there is evidence suggesting greater intrathecal synthesis in cerebellar cases [42] as well as a more extensive neurological phenotype. The clinical presentation within the SPSD is characterized by SPS and idiopathic cerebellar ataxic symptoms [41,43].

2.3.1.2. SPS with epilepsy. A subset of epilepsy patients with anti-GAD ab have an autoimmune pathogenesis for their seizures [53]. Anti-GAD-Abs were detected in 2.6% of cases in a cohort of 233 patients with all types of epilepsy [290]. Literature has emphasized to test for anti- GAD-Abs in patients with localization-related epilepsy [291], specifically temporal lobe epilepsy (TLE) of "unknown etiology" [292], where GAD-Abs were the third most commonly observed abs following antinuclear and anti -VGKC Abs [293]. On clinical grounds, features suggestive of TLE with positive serology tend to be older age and a higher frequency of autoimmune comorbidity [296,297]. In addition, certain epileptic semiology such as musicogenic reflex seizures [294] and peri-ictal autonomic features, although not specific, seem to cluster in individuals with GAD-Abs [295]. High titers of anti-GAD65 ab were also detected in limbic encephalitis (LE) cases [201–203]. Generalized epilepsy, focal epilepsy (mainly temporal lobe epilepsy) or myoclonic epilepsy, may be the main or the only clinical presentation in encephalitis associated with intra-cellular GAD ab deposition [204,49–52]. This subset of GAD-ab epilepsy patients are younger, have more temporal lobe seizures [54], and are more likely to have refractory epilepsy, and less likely to respond to methylprednisolone [54–57].

2.3.1.3. Progressive encephalomyelitis with rigidity and myoclonus (PERM). First described in 1956 by Campbell and Garland [58], PERM is considered to fall within the spectrum of SPS. It is a relapsing-remitting disease with brainstem involvement in addition to the axial or limb rigidity typical of stiff person syndrome [59,60]. Most patients affected by PERM are in their fifth or sixth decades [61]. There is prominent brainstem dysfunction and dysautonomia, prominent myoclonus, hyperekplexia and cerebellar ataxia, altered level of consciousness, axial and limb rigidity and stimulus-sensitive spasms [32,62]. Transient oculomotor manifestations can occur [63]. Histopathological findings include signs of encephalomyelitis with perivascular lymphocytic cuffing [64–66], microglial changes and cell loss in the pons, medulla, cerebellum, spinal cord and autonomic ganglia [28]. Neurophysiological studies show the classical continuous firing of normal motor unit potentials (MUP) at rest [189]. PERM is associated primarily with antibodies to glycine-α1 receptor (anti-GlyR) subunits expressed on the surface of cells, and to a lesser extend anti-GAD antibodies [32,67,68]. Anti-glycine-α1 receptor (anti-GlyR) antibodies and antibody titers correlate with disease severity [69].

The expanding spectrum of PERM was shown by the associated reported with antibodies directed against dipeptidyl peptidase-like protein 6 (DPPX), a regulatory subunit of the Kv4.2 potassium channels on the surface of neurons. Magnetic resonance imaging (MRI) shows increased T2 fluid-attenuated inversion recovery signals of spinal cord and brainstem. Patients with PERM usually respond to aggressive immunotherapy, but relapses are frequent [67,69].

2.3.2. Paraneoplastic SPS

SPS associated with anti-amphysin antibodies belongs to the immune mediated paraneoplastic neurologic syndromes associated with antibodies against neural antigens expressed by the tumor (onconeural antibodies) [70,71]. Five percent of all SPS patients have associated malignancy [72], mostly associated with neoplasms of breast, colon, lung and thymus, as well as Hodgkin's lymphoma [72]. The clinical presentation is very similar to classic SPS, but patients often exhibit a rostrocaudal spread of stiffness with more frequent neck and upper limb stiffness [73]. Paraneoplastic SPS is often associated with anti-amphiphysin antibodies [74], a well characterized onconeural antibody, and anti-Gephyrin antibodies [75]. It has also been associated with anti-GAD and anti-Ri (ANNA-2; antineuronal nuclear autoantibody type 2) antibodies [76]. Symptoms have been noted to improve or even disappear with treatment of the malignancy [77,78].

3. Autoimmunity

A major breakthrough in the understanding of the pathogenesis of SPS came with the discovery of the association between SPS and diabetes mellitus in up to 35% of patients with SPS [1], and other autoimmune disorders, such as disorders of thyroid, pernicious anemia, vitiligo, celiac disease, and rheumatologic diseases. It is believed that these antibodies target different epitopes in affected versus unaffected patients [4]. SPS demonstrates the hallmarks of an antibody-mediated B-cell dependent process. The generation of high-affinity, class-switched antibodies requires a T-cell dependent germinal center reaction. T-cells target neural antigens in the peripheral lymphoid tissue. Once T-cells cross the blood-brain barrier, macrophage/microglia, dendritic cells and B cells can support T-cell reactivation. Th2 cytokine production supports antigen-driven collaboration between T and B cells leading to a sustained intrathecal production of oligoclonal anti-GAD IgG antibodies and a perpetuation of the abnormal autoimmune response [80–82].

3.1. Autoantibodies (Fig. 1) (Table 3)

Autoantibodies targeting six main antigens in the GABAergic neurotransmission pathway were described. Glutamic acid decarboxylase 65(GAD65) is by far the most common antigen, but other antigens include α1-subunit of the glycine receptor (GlyR), amphiphysin, gephyrin, dipeptidyl peptidase-like protein 6 (DPPX) and γ-aminobutyric acid-A (GABA-A) receptor (GABAaR).

3.1.1. Anti-glutamic acid decarboxylase antibodies (anti-GAD antibodies)

3.1.1.1. Role in SPS. Twenty-five to 35% of all synapses in the CNS are GABAergic [83]. GAD is the rate limiting intracellular presynaptic enzyme in the synthesis of the inhibitory neurotransmitter GABA. Anti-GAD-induced disinhibition leads to impairment of neurons to produce, transport and release GABA into the synaptic cleft, thus undermining the entire GABAergic system throughout the CNS and resulting in excitatory overriding inhibitory neurotransmission.

3.1.1.2. Background. There are two isoforms of GAD, a cytoplasmic, active 67-kilodalton isoform (GAD67), and a synaptic membrane-associated form of 65-kilodalton isoform (GAD65) [4]. The two isoforms are encoded by different genes, GAD1 and GAD2, located on chromosome 2q31.1 and 10p12, respectively [27]. The cytoplasmic, active GAD67 isoform acts to provide a steady basal production of GABA. The synaptic membrane-associated GAD65 isoform acts to supply pulses of GABA under circumstances demanding rapid postsynaptic inhibition [4].

3.1.1.3. Antigenicity. GAD65 possesses an increased protein flexibility and charge that are associated with augmented protein antigenicity [4]. Anti-GAD65 ab are found in around 1.7% of the general population with or without neurologic disorders [84,85], but they are found in approximately 60 to 80% of SPS patients [86,87]; and antibodies against GAD67 are reported in approximately 60% of SPS patients [206]. In SPS, GABA-mediated synaptic transmission is thought to be functionally impaired by the production of autoantibodies to GAD65 and GAD67 [35–37]. Intrathecal oligoclonal bands of total Immunoglobulin G anti-GAD65 ab synthesis in cerebrospinal fluid occurs in over 85% of SPS [38,88,89,90]. Production is estimated to be 10-fold higher in the CNS than in peripheral tissues [91], supporting a strong intrathecal production by active B cells with an intact blood-brain barrier [92,93]. There has been no correlation found between CSF anti-GAD intrathecal production and SPS clinical severity [94]. The persistence of GAD intrathecal synthesis without immunotherapy was thought as reflective of continuous disease progression [94].

3.1.1.4. Specificity towards SPS. Anti-GAD ab are not specific for SPS. Cerebellar ataxia is the second most common association with anti-GAD ab [95,96], and accounts for approximately 28% of neurologic presentations [38,39]. Values usually have higher titers in Classic SPS compared to SPS variants. Epilepsy, limbic encephalitis, palatal

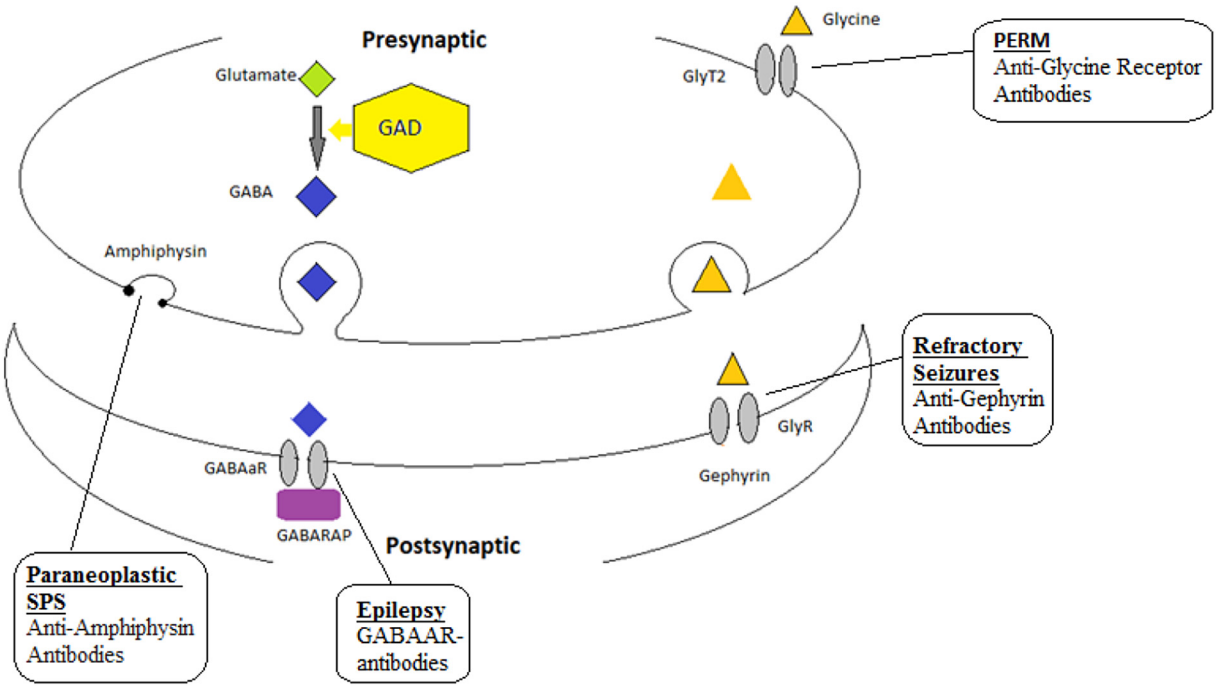

Fig. 1. Pathophysiology in Stiff-Person Syndrome – demonstration of antibody targets.
Diagram demonstrating antibody targets in inhibitory synapse.
Abbreviations GABAaR, gamma-aminobutyric acid type A receptor; GABARAP, gamma-aminobutyric acid type A receptor associated protein; GAD, glutamic acid decarboxylase; GlyR, glycine receptor; GlyT2, Glycine Transporter

Table 3
Stiff-Person Syndrome most common antibody-clinical association.

Antibody	Clinical association
Anti-GAD Antibodies	Classic SPS
Anti-Amphiphysin Antibodies	Paraneoplastic SPS
Anti-Glycine Receptor Antibodies (GlyRα1-IgG)	PERM
Anti-Gephyrin Antibodies and	Encephalitis and refractory seizures.
Anti-dipeptidyl peptidase-like protein antibodies (DPPX)	Trunk stiffness, prominent cerebellar ataxia, striking hyperekplexia and stiffness. Dysautonomia, somatosensory disturbances, and cognitive decline.
GABA***a***R-antibodies	Epilepsy with early age of onset (below 20 years) in most reported cases.

SPS: Stiff person syndrome; PERM: Progressive encephalomyelitis with rigidity and myoclonus.

myoclonus, neurodegenerative diseases and non-neurological autoimmune diseases, such as Batten disease, autoimmune polyendocrine syndrome type 1, type 1 diabetes mellitus, autoimmune thyroid disease, and pernicious anemia [38,92] are associated with anti-GAD antibodies.

3.1.2. Anti-Gephyrin Antibodies and GABARAP-antibodies

Both antigens are located intracellularly in the postsynaptic neuron. Gephyrin is a tubulin-binding protein needed for clustering the receptors of both inhibitory neurotransmitters, glycine and GABA-A [207]. GABA receptor-associated-protein (GABARAP) interact with gephyrin to facilitate the assembly of the GABA-A receptors into plasma membrane [1,97]. Antibodies to Gephyrin were described in a single patient with SPS and mediastinal cancer [207]. Antibodies to GABARAP were described in 70% of a cohort of 27 patients with SPS and GAD65-ab [97,98].

When found in CSF or at high titers in serum, anti-GABARAP ab are often associated with encephalitis and refractory seizures, including status epilepticus [98].

3.1.3. Anti-Amphiphysin Antibodies

Anti-Amphiphysin Antibodies are paraneoplastic autoantibodies associated with SPS, especially breast cancer [99,100]. Amphiphysin is an intracellular, cytoplasmic pre-synaptic vesicle protein which promotes endocytosis at synapses. In paraneoplastic SPS, anti-amphiphysin antibodies are likely to affect the anchoring of GABA (and glycine) receptors [101] and recycling of synaptic vesicles and receptors [100]. Phenotypically, patients usually demonstrate neck and upper limb stiffness [73]. Other neurologic disorders that have also been associated with antiamphiphysin antibodies include peripheral neuropathies, encephalopathies, myelopathy and cerebellar ataxias [73].

3.1.4. Anti-Glycine Receptor Antibodies (GlyRα1-IgG ab)

Anti-Glycine Receptor Antibodies (GlyRα1-IgG ab) are associated most commonly with PERM. However, they are found in 10–15% of patients with classic SPS [102,103], and can also be seen in SPS variants such as stiff limb and stiff trunk syndrome [64]. Anti-GAD65 ab coexist in approximately 30% [64]. Titers are high in serum and CSF and are associated with a severe form of disease [104] and seizures [102,105,106]. A chronic disease course is typical [103]. Approximately 10–20% have an underlying malignancy [73,103]. Glycine receptors are neuronal cell-surface, and mediate chloride influx, membrane hyperpolarization and reduction in neuronal excitation. GlyRα1-IgG predicts immunotherapy responsiveness in patients with SPS spectrum, although a chronic disease course is typical [[69,64,208].

3.1.5. Anti-dipeptidyl peptidase-like protein antibodies (DPPX ab)

DPPX is a membrane glycoprotein, widely expressed throughout the CNS and works as an auxiliary subunit of Kv4.2 Channels [114,115]. One third of patients with DPPX ab show SPS-core features of heightened exteroceptive reflexes, hyperekplexia and stiffness [107,108]. Further case reports shed light on further features comprising somatosensory disturbances, cognitive decline, prominent cerebellar ataxia [107], dysautonomic signs, sleep disturbance [110,111] and even paraneoplastic etiology [108,110]. The CSF shows lymphocytosis and intrathecal IgG synthesis [111]. The disease runs a progressive course and the severity ranges from moderate disability to intensive care needs. The response to immunotherapy is good [111]. The pathophysiological mechanism implied is increased CNS hyperexcitability [112,113]. DPPX-ab titers correlate with the disease course [109].

3.1.6. Gamma-aminobutyric acid type A receptor antibodies (GABAαR ab)

The antibodies target GABAaR α1 and β3 subunits and disrupt their role in endocytosis, recycling and maintenance of synaptic vesicles and receptors [35,157]. The main phenotype associated with GABAaR-ab is preeminent epilepsy [116,117]. The early age of onset (below 20 years) in most reported cases is noteworthy [35]. Patients have other antibodies, like neuronal antibodies or thyroid antibodies in the context of an autoimmune predisposition [35]. The antibodies have been proposed as paraneoplastic when reported in associated with Hodgkin's lymphoma [35]. Brain MRI show cortical and subcortical T2 hyperintensities. The CSF may contain raised protein and/or pleocytosis.

4. Pathophysiology

Pathophysiology of classic SPS remains to be fully elucidated. The hallmark manifestations of stiffness and spasms are attributed to loss of inhibition by interneurons because of a widespread dysfunction of central inhibitory mechanisms [257]. GABA is the major central nervous system (CNS) inhibitory neurotransmitter, and GAD catalyzes the rate-limiting step in its synthesis. The decreased GABA-ergic inhibition at brainstem and spinal cord level is responsible for enhanced motor excitability [122,123]. This results in increased excitation and spontaneous firing of lower motor neurons [258]. GABA is also involved in brain circuits controlling autonomic responses, fear, arousal and behavior [124].

This may partly explain why emotional distress can trigger spasms in patients with SPS. In SLS, it has been suggested that the underlying pathophysiology is that of local interneuronitis, and selective destruction of spinal interneurons in the gray matter without long-tract damage [28]. The associated reflexive spasms result from an excessive response to descending reticulospinal activity at the segmental level [28]. There are several publications which describe the familial occurrence of neurologic conditions associated with GAD65-ab [125,126,127]. Genetic basis for susceptibility to the development of GAD ab autoimmunity was studied and immunogenic associations were investigated by HLA-I and II allele-specific oligonucleotide typing in DNA extracted from peripheral blood and compared to age, ethnicity, and Type-I diabetes-matched healthy controls [190]. HLA genetic predisposition to SPS was found to be linked with the DRB1*0301 and DQB1*0201 alleles [16,24,128]. Associations were also noted with the DRB* 3*0101 locus and the 3*0202 locus. In contrast, DQB1*0602 may be somewhat protective against diabetes mellitus among SPS patients [129].

5. Pathology

While initial reports failed to identify any abnormalities [130], subsequent reports from pathological tissue examination from patients with SPS have described selective loss of GABAergic neurons within the cerebellum and spinal cord and paucity of inflammatory changes. In some cases, there is chromatolysis of anterior horn cells [131,132] and loss of α-motor neurons, γ-motor neurons and spinal interneurons with gliosis [18,133]. Neuronal degeneration with macrophage/microglia infiltrates in the dorsal-root ganglia has also been documented [132]. Pathologic findings in PERM include encephalitis with perivascular lymphocytic cuffing at different levels of the CNS [134]. Paraneoplastic SPS is associated with inflammatory infiltrates, predominantly in the mesial temporal lobes, brainstem, and spinal cord and dorsal-root ganglia [74,135]. These findings suggest that, at least in the later stages of the disease, the functional GABAergic deficit results from frank neuronal loss.

6. Diagnosis (Table 4)

SPS remains a clinical diagnosis that relies heavily on the recognition of the cardinal clinical manifestations of rigidity together with the typical electromyography (EMG) findings of sustained involuntary firing of normal motor unit potentials (MUPs), together with positive autoantibody serology. The average time from symptom onset to diagnosis has been reported to be 6.2 years (range 1–18 years) [136]. A high index of clinical suspicion is crucial to making the diagnosis. In 1967, Gordon et al. [137] proposed diagnostic criteria for SPS based on the clinical phenotype and the EMG findings. These criteria have subsequently been updated and expanded by Dalakas.

6.1. Testing for other relevant antibodies

Testing for other antibodies is useful and should be considered when feasible. This includes testing for anti-amphiphysin, and anti-gephyrin antibodies in cases of paraneoplastic SPS and anti-glycine receptor antibodies in patients with PERM. Anti-GABARAP antibodies and other tissue-specific autoantibodies, like anti-gastric parietal cell antibodies and anti-thyroid microsomal antibodies, may be tested to confirm an autoimmune diathesis. None of the antibodies is considered a specific diagnostic tool.

6.2. Intrathecal antibodies

Intrathecal synthesis of GAD-antibody occurs in over 85% of SPS and has been suggested as a requirement when relating a neurologic presentation to the GAD ab [210]. The higher intrathecal GAD-specific IgG production was found to be four-fold higher than serum levels [212] and was found to correlate with continuous disease progression. No correlation was found with clinical severity [212]. Anti-GAD ab were 10-fold higher in SPS patients with cerebellar disease compared to Classic SPS [213]. Oligoclonal IgG bands were found in 28% of patients with elevated IgG index [212].

Table 4
Dalakas-modified criteria for diagnosis of Stiff-Person Syndrome.

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.
5) Positive serology: GAD autoantibodies, confirmed by immunocytochemistry, Western blot, or radioimmunoassay.
6) Response to diazepam.

6.3. Neurophysiological studies

EMG in SPS patients shows 1) continuous firing of normal-appearing motor unit potentials despite the patient's continuous efforts at relaxation in affected muscle groups. There are superimposed bursts during muscular spasms. The muscle activity is not dependent on stretch or shortening of muscle, rather it disappears during sleep, and after iv Diazepam [259]. 2) superimposed intermittent generalized contractions while awake, which continued into drowsiness and interfered with onset of sleep, 3) abnormal co-contractions of antagonistic muscles [258]. EMG could also show myoclonic jerks at a short latency and short intervals that are synchronous in antagonistic muscle pairs, followed by prolonged tonic muscle activation. No distinct findings were found to be characteristic of any of the SPS subgroups. The pathognomonic EMG findings may take some time to develop [211], thus absence of relevant findings on EMG in the presence of clinical suspicion does not rule out SPS and mandates repeating the study in 3–6 months. Response to Diazepam should be evaluated by EMG. Exaggerated and Poorly Habituating Acoustic Startle Reflex has been noted [260]. On Blink reflex, there is enhanced R2 recovery, suggestive of hyperexcitability of brainstem interneuronal circuits in SPS [257].

6.4. Muscle biopsy

Mild lymphocytic infiltrates and up-regulation of MHC-I was found in 2 out of 57 SPS patients, indicative of an indolent inflammatory autoimmune process also affecting the muscle [212].

7. Differential diagnosis (Table 5)

Several neurologic disorders with similar clinical presentation, including focal and generalized dystonia, ankylosing spondylitis, Parkinsonian syndromes, tetanus, neuromyotonia, hereditary spastic paraparesis, motor neuron disease, myelopathies and psychogenic movement disorders should be considered when diagnosing SPS. In addition, an autoimmune pathologic process may cause limbic encephalitis acutely and epilepsy chronically.

8. Treatment (Table 6)

Treatment of SPS is based on the triad of symptomatic treatment, immunotherapy, and tumor treatment in the appropriate scenario.

8.1. Symptomatic therapy

First reported to significantly reduced muscle stiffness and rigidity in SPS in 1963, Benzodiazepines with their GABA A agonist activity are the first line of treatment for SPS [148,149,152]. They have muscle relaxant, anticonvulsant and anxiolytic effects. There are no randomized trials to support the choice of the initial drug; however, diazepam, lorazepam, clonazepam, alprazolam, and tetrazepam have all been found effective [153]. A suggested dose for diazepam is 5–100 mg/day progresses [184,261], in divided doses [18,155]. 3.Patients with PERM respond less well to diazepam as compared to those with SPS (270). Adverse effects to be considered with benzodiazepines include sedation, fatigue, addiction, depression, dysarthria, vertigo, or ataxia. In patients who are refractory to benzodiazepine monotherapy or who suffer dose-limiting adverse effects, baclofen, a synthetic agonist of GABA B receptors is used concomitantly or independently [156,271,272]. Oral baclofen is administered first. Dose escalation can be limited by adverse effects, such as sedation. If ineffective or untolerated, intrathecal baclofen (ITB) via an intrathecal pump is used for medically intractable hypertonia and spasms [157,155,158] and a s a rescue therapy for severe symptoms of SPS and PERM [273–275].

Complications associated with ITB include pump failure, spasm-induced rupture and dislocation of the intrathecal catheter [159–161].

Table 5
Stiff-Person Syndrome differential diagnosis.

Autoimmune encephalitis: limbic and extra-limbic subtypes [138,139]. High titers of anti-GAD-antibody [38]. Memory loss, seizures, and psychiatric manifestations.
Epilepsy: 10% of patients with SPS or cerebellar ataxia [144,145]. Most are focal intractable seizures associated with mesial temporal sclerosis [79,144]. GAD-ab [79] in refractory cases.
Extrapyramidal and Parkinsonian disorders: generally manifest with bradykinesia, tremor and rigidity.
Basal ganglia disease: Axial torsion dystonia. Not associated with exteroceptive and startle reflex abnormalities.
Generalized dystonia manifests with twisting postures in youth.
Tardive dystonia of the spine can cause hyperlordosis and truncal extension, but less frank rigidity.
Myotonia: typical in distal musculature, presents as stiffness, focal cramps, and delayed muscle relaxation after voluntary contraction.
Isaac syndrome: limb and trunk stiffness. Peripheral motor hyperexcitability, neuromyotonia, myokymia that persistence during sleep and are more prominent distally.
Myopathies: Rigid spine syndrome, myositis fibrosa and Emery-Dreifuss dystrophy: paraspinal myopathy and spinal contracture mimicking hyperlordosis. Predominantly proximal muscle groups. Weakness rather than stiffness and spasms. Magnetic resonance imaging (MRI) of the paraspinal muscles: atrophy and fatty infiltration. EMG: absence of continuous, normal MUP discharges at rest.
Physiological benign cramps: painful muscle contractions affecting mostly distal muscles that occur after exercise or at rest, relieved by stretching. SPS spasms are more widespread in limb and trunk muscles.
Psychogenic movement disorder: distractible, improves without interventions [146]. SPS shows profound influence of emotion on symptoms and profound benefit derived from minor assistance [147].
Hereditary hyperekplexia: Present from infancy. Exaggerated paroxysmal startle and stiffening, especially after auditory startle.
Sclerosing connective tissue disorders: limb stiffness, restriction of movement, and pain. Prominent skin involvement in addition to joint abnormalities.
Tetanus: associated with focal or generalized spasms worsened by startle, acute to subacute in onset, often associated with trismus.
Progressive multiple sclerosis, motor neuron diseases, and atypical hereditary spastic paraplegias: hyperreflexia and spasticity that may be progressive, but does not include the axial muscles.

IVIg (intravenous immunoglobulin), Plasma exchange (PE).

Tizanidine, an α2-adrenergic receptor agonist, or Dantrolene, an agent that reduces excitation-contraction coupling, have also been used to control symptoms in SPS. Major possible side effects include cognitive dysfunction and hepatotoxicity. Other agents like methocarbamol and Vigabatrin, tiagabine, gabapentin and valproic acid, enhance GABA activity and may reduce muscle stiffness and spasm in SPS. Levetiracetam and botulinum toxin A injections are also sometimes used to reduce muscle stiffness and spasms.

Other oral agents have been reported in isolated case reports as effective for symptomatic relief of SPS with a benzodiazepine sparing effect.

8.2. Immunotherapy

In line with the autoimmune etiology, and in addition to immunomodulation, immunotherapy was shown to favor GABA over glutamate balance at the cortical level [162].

8.3. Corticosteroids

Immunomodulation with steroids was found to reduce stiffness and spasms and improve other neurological symptoms in SPS [163].

It is given orally or intravenously as monotherapy or in combination with other immunomodulatory agents. Oral prednisone dose is 60 mg daily and can then be tapered according to patient's response. Recommended IV methylprednisolone treatment is 1000 mg daily for 5 consecutive days [163,263]. It was reported to cause a good response in PERM despite a delayed diagnosis [269].

8.4. Intravenous imunoglobulin (IVIg)

High-dose IVIg is the primary immune therapy for SPS and the only immunomodulatory treatment shown to provide significantly reduced stiffness compared with placebo in randomized, double-blinded, placebo-controlled crossover trials [78,164–169]. The duration of IVIg efficacy ranges from about 6 weeks to 1 year. Anti-GAD65 ab titers did not correlate with disease severity and were unrelated to the magnitude

Table 6
Summary of therapeutic options in patients with Stiff-Person Syndrome.

Class	Agent	Dose	Route of administration
Symptomatic therapy: Benzodiazepines [18]	Diazepam [240]	5-100 mg/day	Oral
	Clonazepam [241,242]	2.5–6 mg/day	Oral
	Alprazolam	2–4 mg/day	Oral
	Lorazepam	6 mg/day	Oral
Muscle relaxants	Tizanidine [244]	6–36 mg/day	Oral
	Baclofen [243]	10–60 mg/day	Oral
	ITB [237]	50–150 μg/day	Intrathecal
	Dantrolene	200–400 mg/day	Oral
	Botulinum toxin A [228,277]	Variable	IM
Cannabis	THC-CBD [227]	Variable	Oromucosal spray
Antiepileptic drugs	Levetiracetam [221]	500–1000 mg twice a day	Oral
	Pregabaline	75–150 mg twice a day	
	Gabapentin [236]	300–900 mg three times day	
	Tiagabine [234]	4–8 mg once or twice a day	
	Valproate [233]	300–600 mg twice daily	
	Vigabatrin [235]	500–1500 mg twice daily	
Immunotherapy	IVIg [220,223]	1 g/kg body weight/month. See text for details.	IV
	Rituximab [225]	2 infusions of 1 g each, every two weeks. See text for details.	IV
	Plasma exchange [178,224]	5 PE in 1–2 weeks	
	Corticosteroids [238,239]	50-60 mg/day	Oral
	Mycophenolate mofetil [248]	2 g/day	
	Tacrolimus [229]	3 mg/day	
	Cyclophosphamide [245]	1-5 mg/kg/day	
	Azathioprine [246]	1–2.5 mg/kg/day	
	Methotrexate	15-20 mg/day	
Interventional therapy	Anesthesia [230,247]		
	Spinal cord Stimulation [232]		

of the clinical response [164,165]. IVIg can be given 0.4 g/kg/day daily for 5 consecutive days, repeated monthly for three consecutive months [165]. The subsequent dose is 1 g/kg per infusion every 2–4 weeks [164].

8.5. Plasma exchange (PE)

The association of specific autoantibodies with SPS is the rationale for studying PE as a treatment for SPS [173,174]. PE can effectively deplete antibodies of the IgG class when sufficient plasma volumes are exchanged over a brief time. In a study where first-line treatment failed, about half of the SPS patients treated with PE experienced clinically significant improvement [175]. PE has been shown to be well tolerated with adverse effects seen in just 4.75% of patients receiving it [176–178]. It is given every other day for 10–14 days [266,279].

8.6. Rituximab

Rituximab binds to the CD20 antigen on mature B-cells, leading to B-cell lysis, while sparing the precursor B-cells. In an antibody-mediated B-cell dependent autoimmune disease, it seems logical that therapeutic use of rituximab would deplete CD20 B cells and diminish anti-GAD65 production and mitigate disease. However, a large controlled trial conducted on anti-GAD ab positive SPS patients demonstrated no statistically significant difference in the efficacy measures between rituximab and placebo [170]. PERM or patients with SPS with anti-amphiphysin antibodies who lack response to other immunotherapies, may benefit from a trial of rituximab [282–284].

Currently, there is limited evidence for proving the effectiveness of rituximab use in SPS [171,172].

8.7. Physical therapy

SPS patients receiving physical therapy intervention in the form of massage, relaxation, ROM exercise, ultrasound, hydrotherapy, heat therapy, and stretching, experienced reduction of pain, spasm, and stiffness, improved the joint ROM, were able to maintain upright stance, functional mobility, ability to ambulate with assistance devices, were less dependent for their ADLs and showed increased self-confidence [179–184,300].

8.8. Cognitive behavioral therapy

About 44% of the patients develop severe motor symptoms such as stiffness, that is exaggerated due to their anxiety, in the context of underlying SPS [26]. Cognitive behavioral therapy was shown to cause substantial decrease in anxiety, upliftment of the self-confidence, and lessening stiffness and rigidity [226].

8.9. Recommendation for treatment protocol (Fig. 2)

There are no strong evidence-based treatment guidelines; most recommendations are based on retrospective series and expert opinion.

Treatments were classified as (1) symptomatic (eg, GABAergic drugs), (2) first-line immunotherapies (intravenous corticosteroids, intravenous immunoglobulin, or plasma exchange alone or combined), (3) second-line immunotherapies (cyclophosphamide), and (4) long-term oral immunotherapy (prednisone, azathioprine, mycophenolate mofetil, cyclosporine) (267).

Baseline evaluations (clinical, radiologic, and electrophysiologic) are used to monitor treatment response based on objective baseline parameters.

Benzodiazepines and Baclofen are symptomatic treatments [148,149,150] and can be used concomitantly [151].

As it was shown in a large longitudinal study that in SPS patient with anti-GAD ab and anti-glycine receptor antibodies, is a steadily progressive disease that leads to physical disability without immunotherapy [263], it is recommend that immunotherapy be employed early on, in highly suspicious cases, while awaiting results of antibody tests or cancer tests [266].

Thus first-line immunotherapy is implied in the form of high-dose intravenous (IV) corticosteroids therapy, IVIg, or PE.

Initial treatment effect is maintained by repeated IV methylprednisolone once weekly for 6–12 weeks. There is no recommendations for long-term corticosteroid treatment or weaning protocols in literature except tailoring dose and frequency according to patient's response [298,299].

IVIg infusions can be given monthly. PE is given every other day for 10–14 days [266,279].

No studies are available to suggest a preferred agent. IVIg is preferable in patients with DM.

After the initial trial of therapy, the patient should be re-evaluated for objective evidence of improvement.

This is followed by gradual lengthening of the intervals between IVIg treatments, if tolerated. IV methylprednisolone can be switched to oral prednisone [269]. Monthly use of PE was advocated for short- term maintenance therapy [276,279].

If early trials of steroids, IVIg, or PE do not prove beneficial, second-line immunotherapy is cyclophosphamide [266].

Long-term oral immunotherapy is attempted to reduce glucocorticoid or IVIg dependence with a suggested overlap period of 6–8 months [268].

Patients who relapse during the weaning process, and thus are dependent on corticosteroid or IVIg therapy are maintained on low dose of oral prednisone (10–20 mg/day or every other day) or once monthly IVIg infusion [266].

PE was shown beneficial for the management of patients both for acute exacerbations and long-term maintenance [266,279].

Azathioprine or mycophenolate mofetil, having been used in a wide range of autoimmune neurological diseases, and thus would be the agents of choice [264,265].

Alternatives include methotrexate, hydroxychloroquine, and oral cyclophosphamide [266].

Treatment of SPS with a paraneoplastic cause, both removes the source of antigen driving the autoimmune response as well as suppress the immune response with chemotherapy.

If no neurological improvement occurs with treatment, the patient may benefit from a trial of immunotherapy [266].

Monitoring:

The antibody titers do not correlate with clinical severity or with response to treatment [1,91].

9. Prognosis

In general, the disease shows diurnal fluctuations of stiffness and spasms with worsening during periods of physical or emotional stress. As SPS progresses, stiffness often spreads and what was initially, for example SLS, may progress over time to classical SPS and from that to PERM [185]. Patients may eventually lose the ability to walk independently despite therapies. The variant of SPS and the presence of associated diseases like cancer, is an independent predictor of outcome. This is portrayed in the better response to steroids, plasmapheresis, or successful resection of the tumor in patients with amphiphysin and paraneoplastic SPS antibodies [186]. To elaborate yet more on this, patients with GlyRα1antigen respond better to immunotherapies than patients with GAD65 immunoglobulin [188]. Patients with anti-GAD respond well to IVIg, diazepam and clonazepam [187]. SPS with GABARAP have shown to respond better to IVIg as opposed to high doses of GABA-enhancing drugs [1].

Although treatment of SPS is usually suboptimal, most patients show improvement in stiffness and spasms. Most treated patients will remain ambulatory but be sufficiently disabled to require assistance.

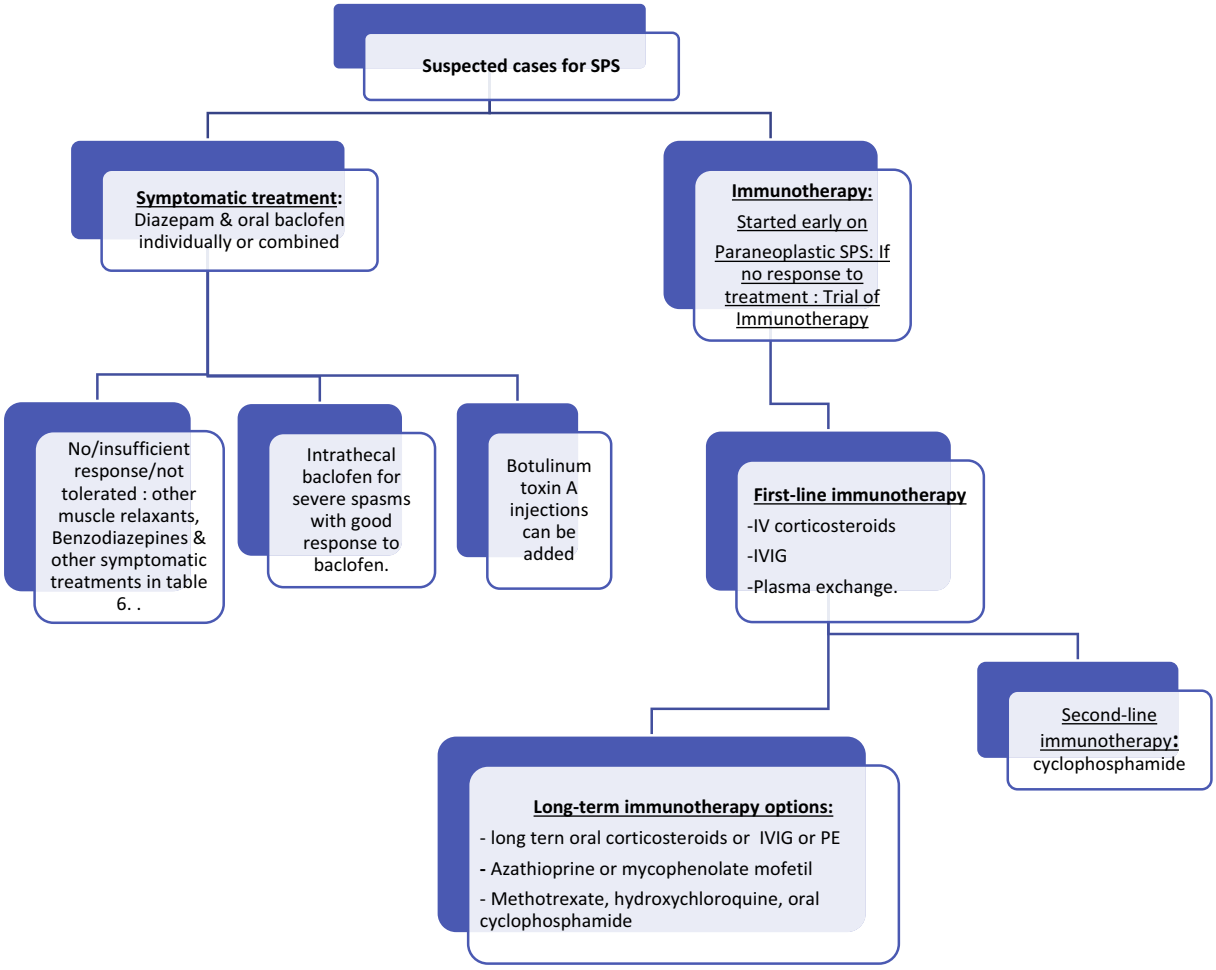

Fig. 2. Suggested Guidelines for Stiff-Person Syndrome Treatment.1.
GABA: Gamma amino butyric acid. IVIG: Intravenous immunoglobulins.

Prompt treatment of patients with SPS is very important as untreated patients usually develop disability and may become increasingly refractory to therapy as the disease progresses [212]. SPS disorder is an ever-expanding spectrum of immune-mediated disorders, mostly related to the discovery of novel antibodies and new phenotypes. It is an emerging field where autoimmunity occurs in the context of genetic susceptibility.

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