Stiff-Person Syndrome Spectrum Disorders

José Fidel Baizabal-Carvallo and Marlene Alonso-Juarez

Abstract Stiff-person syndrome was first described in 1956; its further characterization as an autoimmune neurological disorder occurred more than 30 years later with the discovery of glutamic acid decarboxylase (GAD) antibodies (Abs), frequently coexisting in these patients. In the following years, clinical variants of SPS have been characterized, and a paraneoplastic presentation was also recognized, the latter mainly associated with amphiphysin antibodies. Although the presence of GAD-Abs has led to theorize that these antibodies cause disinhibition of the central nervous system through decreased production of the inhibitory neurotransmitter (GABA), the pathogenic role of GAD-Abs has not been demonstrated, although the evidence suggests that antibodies directed against amphiphysin and glycine receptor α1 are likely pathogenic. The treatment aims to attenuate the immunological response through immunotherapy, control the symptoms, mainly with GABAergic drugs, and remove an underlying tumor, if present. The course is usually chronic and the prognosis is frequently poor.

Keywords Stiff-man syndrome · Stiff-person syndrome · γ-aminobutyric acid · Glutamic acid decarboxylase · Progressive encephalomyelitis with rigidity and myoclonus · PERM · Paraneoplastic stiff-person syndrome · Amphiphysin · Myoclonus · Glycine receptor · GAD antibodies

Introduction

Stiff-man syndrome is the original name used by Moersch and Woltman in 1956 to describe a group of 14 individuals with progressive and fluctuating rigidity [1]. The disorder was latter named stiff-person syndrome (SPS) to avoid gender bias. The disorder was associated with the presence of glutamic acid decarboxylase (GAD)

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antibodies (Abs) since 1988 by Solimena and colleagues [2, 3]; however, soon after, it became clear that not all patients with SPS have positive serum GAD-Abs and some of them may show a different set of antibodies and variable clinical presentations [4]; therefore, the term SPS spectrum disorder is currently used to refer to this group of patients.

The enzyme GAD is the rate-limiting step in the synthesis of γ-aminobutyric acid (GABA), which is the main inhibitory neurotransmitter in the central nervous system (CNS) [5]. It has been theorized that GAD-Abs inhibit the activity of GAD in the central nervous system of patients with SPS spectrum disorders; however, this has not been unquestionably demonstrated in vivo, and the role of such antibodies in the pathogenesis of this group of disorders is still controversial as discussed in this chapter.

Epidemiology

SPS is an acquired disorder that usually appears between the third and sixth decades of life [6–8]. It has an estimated prevalence of 1–2 cases per million; women outnumber men (2:1); there is no ethnic predilection [9].

Children may also present with SPS, they represented 5% of patients evaluated during a 40-year period in a tertiary care center [10]. The mean age at onset was 11 years (range 1–14 years). Although classical SPS is observed in children, a literature review pointed to progressive encephalomyelitis with rigidity and myoclonus (PERM) as the most common presentation in this age group [10]. SPS is not considered a hereditary disorder, although rare family cases of SPS have been described in the literature [11].

Clinical Manifestations

Classification

There is not a universal agreement regarding the classification of SPS spectrum disorders. Classifications may use the distribution of the stiffness, the presence of associated neurological manifestations, the presence or absence of GAD-Abs and other Abs. Patients may also be classified according to the occurrence of an underlying neoplasm (Table 1). The following section describes the clinical features of different SPS presentations.

Table 1 Classification of stiff-person syndrome spectrum disorders

According to distribution of stiffness
Classical stiff-person syndrome (involves axial muscle and lower limbs)
Focal or segmental stiff-person syndrome or stiff-limb syndrome (involves limbs without axial involvement)
Axial (spinal) stiff-person syndrome (involves only axial muscles)
According to associated manifestations
Myoclonus
Jerking-stiff-person syndrome
Progressive encephalomyelitis with rigidity and myoclonus (PERM)
Epilepsy or cerebellar ataxia
Overlapping syndromes: stiff-person syndrome + cerebellar ataxia or epilepsy
Brainstem manifestations and/or encephalitis
Progressive encephalomyelitis with rigidity and myoclonus (PERM)
According to presence or absence of tumor
Paraneoplastic stiff-person syndrome (usually associated with amphiphysin Abs)
Non-paraneoplastic stiff-person syndrome (usually GAD-Abs)
According to serological response to GAD-Abs
Seropositive stiff-person syndrome (+ GAD-Abs)
Seronegative stiff-person syndrome (− GAD-Abs)

Classical Stiff-Person Syndrome

Patients with classical SPS usually have an insidious onset with aching and stiffness of axial muscles, which progress and spreads to the proximal and then to the distal muscles of the limbs [12]. Co-contraction of agonist and antagonist muscles underlies the stiffness. The axial stiffness usually may lead to a characteristic hyperlordosis affecting the lumbar spine and muscle hypertrophy (Fig. 1) [12, 13]. In some instances, patients may develop a kyphotic posture with bilateral shoulder elevation and prominent limitation for head movements [14]. When chest and abdominal muscles are prominently affected, there may be dyspnea, poor exercise tolerance, inability to swim underwater and early satiety. The distal extremities and cranial muscles may be involved particularly in untreated patients. Limb rigidity asymmetry may also be observed and should not be confused with corticobasal degeneration [15]. The stiffness is usually relieved by sleep, but such improvement may be lost in advanced stages; at that point patients require general anesthesia or neuromuscular blocking agents to relieve the muscle stiffness [16].

The stiffness is accompanied by paroxysms of transient but usually intense superimposed muscle spasms. The spasms have variable duration ranging from seconds to hours and may be quite painful. The paroxysms are usually triggered by external stimuli such as noise and manipulation as well as emotional stimuli and sudden movement [4]. Spasms occurring while walking may cause falls and in extreme cases, joint dislocations and hip fractures [17]. Apneic episodes from muscle spasms may lead to acute respiratory failure [18]. Muscle spasms affecting the laryngeal muscles may lead to a spasmodic dysphonia-like presentation [19]; cricopharyngeus muscle spasms may result in total esophageal obstruction [20], whereas

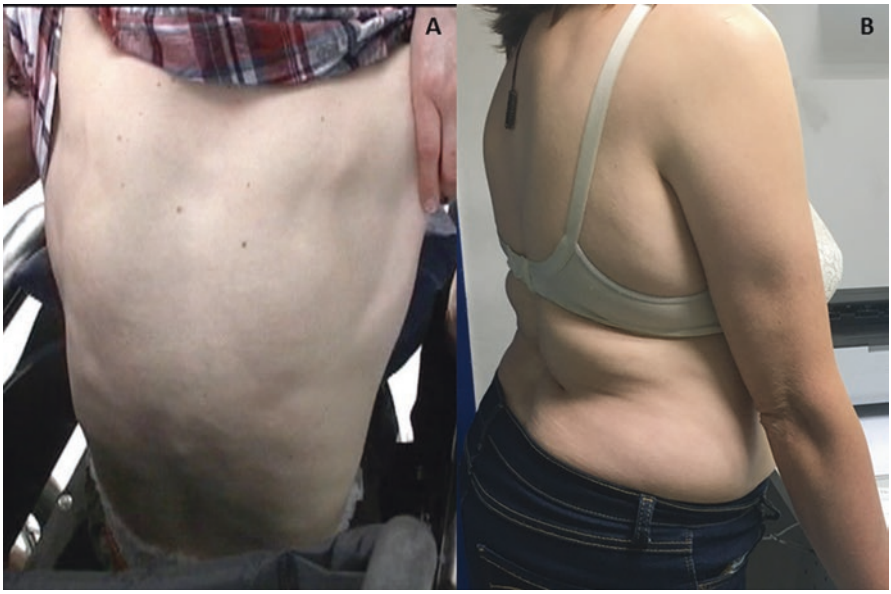

Fig. 1 (**a**) Patient with severe stiffness involving the thoracic and lumbar muscles; there is marked hypertrophy of affected muscles; (**b**) typical hyperlordosis observed in patients with classical stiff-person syndrome

dysphagia due to abnormal esophageal and gastric motility may be a more common phenomenon. Urinary retention requiring bladder catheterization, abnormal anal relaxation with anorectal spams causing constipation are recently recognized features of SPS [21].

Autonomic symptoms may accompany the paroxysms of superimposed muscle spasms with tachycardia, hypertension, hyperthermia, increased respiratory rate, pupillary dilation, profuse diaphoresis, and dysphoria [22]. Sudden death due to autonomic failure has been reported [22]. Psychiatric comorbidity is common in SPS patients and includes depression, anxiety, phobias, and chronic alcoholism [23, 24]. Phobias (particularly fear to fall) were perceived by ten patients as a realistic risk owing to motor symptoms related to SPS rather than an inherent phobic neurosis [25].

The neurological examination between spasms usually reveals “rock hard” spinal, abdominal, and proximal limb muscles [4, 12]; abnormal axial postures along with muscle hypertrophy makes possible for the examiner to bury the hand in the furrow between the paraspinal muscles in severe cases plus a paucity of movements that may resemble parkinsonism; voluntary movements are restricted in range, for example, the patient may be unable to bend at the waist to touch her or his toes or kneel. Gaze-holding nystagmus, ocular misalignment, abnormalities in ocular pursuit, and increased latency of ocular saccades may be recorded in patients with SPS [26, 27]; abnormal eye movements and vertical nystagmus may be present in some patients with positive GAD-Abs and ataxia without stiffness [28, 29]. The head

retraction reflex is hyperactive in SPS patients and may be elicited by tapping the glabella, nasal ridge, upper lip, or the chin, resulting in a backward jerk of the head sometimes with truncal retropulsion [30]; generalized hyperreflexia with plantar flexion responses is also observed. Gait may be spastic, slow, and wide-based [14]. Sensory examination is within normal limits.

Type 1 diabetes mellitus (DM1) is the most common associated autoimmune endocrine condition, present in about 35% of patients with SPS [31]; however, other autoimmune disorders may coexist with SPS, including autoimmune thyroiditis, autoimmune adrenal or ovarian failure, pernicious anemia, vitiligo, myasthenia gravis, anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis, autoimmune retinopathy, and systemic lupus erythematosus; all together these autoimmune disorders are comorbid with SPS in up to 80% of cases [31–35].

Focal or Segmental Stiff-Person Syndrome

Focal or segmental SPS (also known as stiff-leg or stiff-limb syndrome) is probably less common than classical SPS. In a series of 121 patients with SPS spectrum disorders, stiff-limb syndrome represented 20% of cases [36]. These patients usually present with stiffness and superimposed painful spasms affecting one or two legs or arms [37, 38]. Hiccup and vomiting have been reported with focal SPS, attributed to diaphragmatic spasms [39]. EMG shows the characteristic continuous motor unit activity at rest that involves agonist and antagonists muscles. Central nervous system hyperexcitability, failure of reciprocal inhibition of antagonist muscles, and altered exteroceptive reflexes can also be observed in patients with focal/segmental SPS, restricted to the affected limb [40]. The frequency of positive GAD-Abs and coexistent autoimmune syndromes seems less common than in patients with classical SPS. Amphiphysin Abs and alpha 1-glycine receptor (GlyRα1) Abs are rarely positive in individuals with focal SPS [41, 42]. Although the majority of patients with focal SPS do not have an associated cancer, an underlying malignancy is more commonly present than in patients with classical SPS. Lung cancer, breast cancer, chronic lymphocytic leukemia, and multiple myeloma are among the most common associated neoplasms [42, 43]. Unfortunately, the disorder has a protracted course with poor response to pharmacological therapy [38].

Jerking Stiff-Person Syndrome

This is a rare variant of SPS characterized by the presence of rapid and violent myoclonic jerks that may involve the axial and proximal appendicular muscles and may be nocturnal or diurnal. The myoclonus may appear years into the course of the disease and may occur either spontaneously, or it may be stimulus-sensitive, for example, following the touch of the perioral region, or stretch of head and neck

muscles [44–46]. Patients usually have symptoms that are otherwise not different to classical SPS; it is unclear whether these patients represent a continuum within the spectrum of SPS and PERM or a distinct clinical variant. Myoclonic jerks usually respond to benzodiazepines. It is uncertain why the number of reported cases of jerking SPS has dramatically decreased in the last decades, but a possible explanation is that these patients are being reclassified into another SPS spectrum disorder.

Progressive Encephalomyelitis with Rigidity and Myoclonus [PERM]

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is considered within the spectrum of SPS; it is also known as stiff-person plus syndrome in some cases. However, this condition differs in several clinical and immunological aspects with respect to classical SPS. The disorder was probably first described by Campbell and Garland in 1956, under the name "subacute myoclonic spinal neuronitis" [47]. PERM distributes roughly equal between men and women [48]. DM1 is much less frequent than in classical SPS.

Muscle stiffness, myoclonus, and prominent brainstem manifestations with cranial nerve involvement are cardinal manifestations in patients with PERM; other prominent features include severe dysautonomia, corticospinal signs, gait ataxia, seizures, hypersomnia, pruritus, and behavioral changes [48–51]. The disorder is more commonly associated with GlyRα1-Abs; but about 20% of patients have positive GAD-Abs [48]. Although the term "progressive" is used in the acronym of the syndrome, a substantial proportion of patients have a relapsing-remitting course that may be fatal if left untreated. Pathological samples are dominated by inflammatory infiltrates with prominent involvement of Purkinje cells, hippocampal and pyramidal neurons, with loss of ventral horn and spinal interneurons with relative spearing of the neocortex [34, 52, 53]. Non-specific hyperintensities in the MRI are observed in about one third of cases involving the brain and spinal cord [48].

A condition resembling PERM has been associated with Abs against dipeptidyl-peptidase-like protein-6 (DPPX), which is a regulatory subunit of the neuronal potassium channel (Kv4.2) [54]. The median age at onset is 53 years, with both genders equally affected. A prominent initial manifestation is gastrointestinal tract dysfunction that manifests more commonly with diarrhea, although gastroparesis and constipation have also been described [55, 56]. This is followed by a myriad of neurological manifestations, including eye-movement disturbances, tremor, myoclonus, rigidity, exaggerated startle, hyperreflexia, hyperventilation, neuropsychiatric symptoms, and seizures [55, 56]. An underlying lymphoma or leukemia has been reported in some cases [55].

Paraneoplastic Stiff-Person Syndrome

Paraneoplastic SPS is mostly observed associated with Abs directed against the presynaptic protein amphiphysin. Patients are usually females with breast cancer; other reported malignancies are small-cell lung cancer, thymoma, and ovarian cancer [57]. These patients represent about 5% of cases with SPS [58]. A predominant upper-limb distribution of the stiffness was reported in a single study of paraneoplastic SPS [57]. However this finding has not been informed in other reports. Ophthalmoplegia and opsoclonus have also been recognized in patients with paraneoplastic SPS associated with amphiphysin antibodies [59, 60]. Comorbid DM1 is uncommon in these patients [57].

Despite the well-known association between stiffness and amphiphysin Abs, these Abs are not specific for paraneoplastic SPS, as they may be present in some patients suffering limbic encephalitis, dysautonomia, neuropathy, and cerebellar dysfunction but without stiffness; some of these patients may have underlying cancer [61]. In few cases, these disorders may coexist with stiffness; for example, a case of paraneoplastic SPS and limbic encephalitis associated with amphiphysin antibodies has been described [62]. In another study, amphiphysin Abs were positive in various paraneoplastic disorders, including neuropathy and encephalopathy; however, these patients showed positivity to other antibodies such as anti-Hu [63]. Patients that show positivity only to amphiphysin Abs, but not to other onconeural antibodies, usually presented with myelitis or SPS phenomena [63]. Recognizing paraneoplastic SPS is important, as tumor removal and chemotherapy may result in marked clinical improvement.

The paraneoplastic variant of SPS may rarely be associated with high titers of GAD-Abs; whether the association of classical SPS with underlying cancer is coincidental or not is uncertain [8, 31, 64]. However, the risk of underlying malignancy in patients with SPS is higher with older age, male gender, and positive neuronal cell-surface Abs, including GABA-B Abs and GlyRα1-Abs coexisting with GAD-Abs [65]. Anti-gephyrin Abs has been described in a single patient with paraneoplastic SPS associated with a malignant thymoma, but this finding has not been reproduced in other studies [66]. Anti-Ri (also known as anti-neuronal nuclear antibodies: ANNA-2) antibodies have been observed in patients with SPS phenomena and some malignancies [67], but such association may not be specific.

Overlapping Syndromes

Some patients with SPS may present with other neurological manifestations associated with GAD-Abs. In a retrospective study of 121 patients with SPS spectrum disorders, 8.3% were diagnosed as having an overlapping syndrome, i.e., classical or focal SP syndrome with ataxia, epilepsy, or encephalitis [36]. Among these syndromes, cerebellar ataxia is probably the most commonly associated with SPS

[68, 69]. Gait ataxia is the most common manifestation followed by limb ataxia and dysarthria [70]. The so-called brainstem attacks, characterized by transient episodes of cranial nerve, cerebellar, and long tract dysfunction preceding the onset of progressive cerebellar ataxia, are observed in about 25% of cases [71, 72]. Epilepsy may occur in few cases of SPS and it is suspected to have an autoimmune pathophysiology [2].

Pathophysiology

Increased muscle tone or hypertonia is the "*sine qua non*" condition of SPS. Muscle tone can be defined as the resistance to passive stretch of a joint. The degree of stiffness is assessed by the amount of force required to get a movement. Hypertonia can result from three different mechanisms: (1) altered mechanical properties of the muscle or joint; (2) increase in reflex response to the stretch opposing the movement, and (3) co-contraction of muscles acting on the joint [73]. The latter is the main mechanism explaining stiffness in subjects with SPS.

The increased activity of agonists and antagonists muscles in SPS is probably related to CNS disinhibition. The questions are as follows: (1) What are the molecular and neurophysiological correlates underlying such disinhibition? (2) What is the role of GAD and other Abs in the pathogenesis of SPS? (3) Where does the disinhibition originate within the nervous system? and finally (4) How can the autoimmune process be attenuated and the symptoms controlled? Currently, there are not definitive answers for these questions, but established knowledge and recent advances are provided in this chapter to better understand the pathophysiology and pathogenesis in this group of disorders.

Glutamic Acid Decarboxylase Enzymes

The enzyme GAD is specifically localized within GABAergic neurons in the central nervous system. However, an immunologically identical enzyme is present in pancreatic beta cells, the epithelium of fallopian tube, and spermatozoa [74]. The enzyme GAD is the rate-limiting step in the production of GABA. The enzyme GAD exists in 2 isoforms, one of 67 kD (GAD67) and one of 65 kD (GAD65); these enzymes are codified by two different genes [75]. GAD67 is localized in the soma of neurons and is constitutively active, providing neurons with a steady supply of GABA. On the other hand, GAD65 localizes in the cytoplasmic surface of synaptic vesicles, it provides pulses of GABA in situations requiring rapid synthesis and release of the neurotransmitter [3, 5, 74]. GAD65 is the main target of Abs in patients with SPS, but GAD67 Abs are found in the serum and CSF in a proportion of patients with SPS.

Role of GAD-Abs in the Pathogenesis of SPS Spectrum Disorders, Experimental Models

As GAD has an eminent role in the production of GABA, it can be anticipated that Abs directed against these enzymes would block the production of GABA potentially leading to disinhibition. However, GAD enzymes are intracellular which limits the interaction with pathogenic Abs. Early in vitro experiments demonstrated decreased production of GABA in crude rat cerebellar extracts, exposed to Abs obtained from the serum or CSF of patients with SPS and positive GAD-Abs [76]. Moreover, a significant increase in the frequency of post-synaptic inhibitory potentials was registered in cultured hippocampal neurons of rats after being exposed to the serum of epileptic patients with positive GAD-Abs, while no effect was observed using sera from negative controls [77]. More recently, internalization of monoclonal GAD65 Abs was shown in cultured cells, and epitope-dependent pathogenic actions of GAD65 Abs were shown in slice (normal components are preserved) and in vivo preparations [78]. Although lack of GAD-Abs internalization into cultured hippocampal rat neurons was observed in another study [79], GAD-Abs have been shown to coexist with Abs that bind to the cell surface of GABAergic neurons, but the underlying antigen was not identified [80]. Passive transfer to experimental animals of Abs directed against GAD from patients suffering SPS or cerebellar ataxia has been carried out with mixed results. Continuous motor activity with repetitive muscle discharges [81], and impaired cerebellar function due to altered motor and spatial procedural behaviors has been observed following intracerebellar and/or paraspinal administration of Abs with anti-GAD activity [82] as well as an increase in glutamate levels in cerebellar nuclei and inhibition of GAD activity [83]; stiffness-like behavior with impaired walking and decreased grip strength of the upper limbs along with postural and sensory-motor dysfunction was reported in another study following intra-lateral ventricle injection of a purified IgG fraction of an SPS patient into mice [84]. Despite this evidence, other studies have not shown the core features of SPS in mice models exposed to Abs from SPS patients but rather increased activity [80], anxious behavior or agoraphobia [85].

In Vivo Evidence of GABAergic Dysfunction

Studies in humans have demonstrated evidence of CNS disinhibition from the cerebral cortex to the spinal cord in patients with SPS. Hyperexcitability of the motor cortex was recorded using transcranial magnetic stimulation (TMS) in patients with SPS, suggesting an imbalance between inhibitory and excitatory intracortical circuits; moreover, the degree of disinhibition seems to correlate with the titer of GAD-Abs [86, 87]. Brainstem hyperexcitability has also been documented by an abnormal recovery cycle in the R2 component of the blink reflex and abnormalities in the masseter and glabellar reflexes [88, 89]. Brain magnetic resonance

spectroscopy (MRS) has shown reduced levels of GABA in the sensorimotor and posterior occipital cortex in patients with SPS [90], and imaging of GABA-A receptor with PET-CT revealed large areas of decreased binding of 11C-flumazenil in the bilateral premotor cortex, motor cortex, and right supplementary motor cortex in few patients with SPS, suggesting downregulation of GABA-A receptors [91, 92]. These evidences suggest the possibility of supra-spinal disinhibition as the cause of muscle stiffness [93]. However, stimulation of peripheral nerves released myoclonic bursts in the trunk muscles after 60–70 ms, such phenomenon was called "spasmodic reflex myoclonus," and the recruitment order of the muscles suggested a spinal origin in the Renshaw cells or the gamma motor system [94].

Differences in Immunological Profile Between DM1 and SPS and Triggers of the Autoimmune Response

There are several quantitative and qualitative differences regarding the humoral response between patients with DM1 and SPS. GAD-Abs are observed in about 60–80% of patients with classical SPS but in a lower proportion in subjects with DM1. These Abs can also be positive in Batten disease, autoimmune polyendocrine syndrome type 1, and occasionally some neurodegenerative disorders [4]. GAD-Abs are increased 100–1000 times in patients with SPS, whereas in DM1 such increase is usually not beyond 10 times the reference range [93]. The distribution of GAD-Abs is also different; they can be found in the serum and CSF in patients with SPS, but only in the serum in patients with DM1 [4]. Epitope recognition also differs; patients with SPS have Abs recognizing linear epitopes in the N-terminal segment of GAD proteins that are not observed in patients with DM1 [95, 96]; this segment of GAD is exposed during synaptic transmission, but the pathogenic role of these GAD-Abs is unknown [97]. SPS patients also have conformational GAD-Abs that recognize discontinuous segments of the middle and C-terminal part of GAD65, some of these antibodies block the enzymatic activity of the protein [98]. Although patients with DM1 also have conformation Abs against the middle and C-terminal segments of GAD, they do not block the activity of the enzyme, and the epitope recognition is also different [76, 99]. GAD-Abs isotype is IgG1 in patients with DM1, whereas IgG1, IgG2, IgG3, IgG4, and IgE are detected in patients with SPS [5, 100].

The role of T cells in the pathogenesis of SPS has not been clarified, but activation outside the CNS followed by crossing the blood-brain barrier is possible [4]. The stimuli that trigger the T-cell response are unclear, but viral infections, including West Nile virus, coxsackievirus, and cytomegalovirus, may precede the onset of SPS [101]. Clonal CD4(+) T cells can recognize a derived epitope of the human cytomegalovirus (hCMV) processed by dendritic cells, and show cross-reactivity

with GAD65 and hCMV major DNA-binding protein [102]. This evidence indicates that T cells are involved in the loss of tolerance to GAD enzymes possibly through molecular mimicry, but this remains to be confirmed. T cells are activated in peripheral lymphoid organs, and although some of these cells cross the blood-brain barrier, it is likely that only those T cells reactivated in the CNS remain intrathecal (Fig. 2); patients with SPS and DM1 have T cells showing overlap reactivity to diverse GAD65 epitopes [103–105]; but only lymphocytes from SPS patients seem to produce a mixed Th1 and Th2 response contrasting with the Th1 response in patients with DM1 [104, 106]; Th1 response leads to cell-mediated immunity, whereas the Th2 response through interleukin-4, driven by a group of T-cell clones, facilitates switching of B-cell isotype, which seems to sustain the secretion of oligoclonal bands in the CSF of patients with SPS [104, 107]. Whether T cells mediate damage to the nervous system is unclear in classical and focal/segmental SPS, and it seems more likely to occur in patients with PERM; mice possessing monoclonal T cells against GAD65 can develop encephalomyelitis-like manifestations [108].

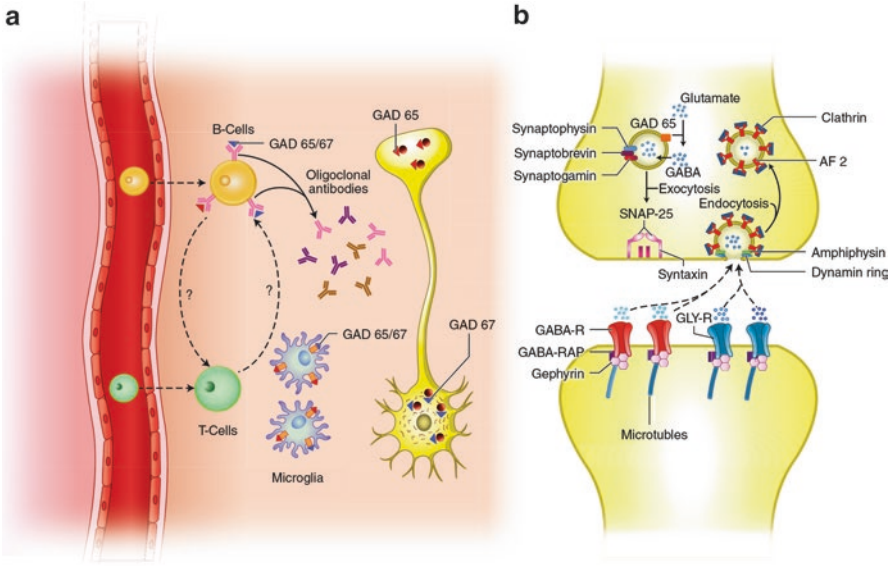

Fig. 2 (**a**) Cellular events occurring in patients with stiff-person syndrome; a set of oligoclonal GAD antibodies is produced, although how the autoimmune response is sustained within the central nervous system is unclear; (**b**) synapsis of inhibitory neurons shows the main molecular targets for antibodies found in patients with stiff-person syndrome spectrum disorders. (From Baizabal-Carvallo J.F. & Jankovic J. Reproduced with permission of BMJ Publishing Group Limited.)

Pathogenic Roles of Other Antibodies: Amphiphysin, Glycine Receptor, and DPPX

Despite the ongoing controversy about the pathogenic role of GAD-Abs, other Abs observed in SPS seem to have a more definitive role in its pathogenesis. Amphiphysin is a presynaptic protein involved in clathrin-mediated endocytosis. These Abs can be internalized into neurons by an epitope-specific mechanism and colocalize with presynaptic vesicular proteins [109]. Experimental studies have demonstrated that exposure to human anti-amphiphysin Abs provokes a depletion of the resting pool vesicles, trapping of releasable vesicular pool proteins at the presynaptic plasma membrane of GABAergic neurons with activation of alternative endocytic pathways [110]. Moreover stiffness and spasms have been induced following intraperitoneal injection of purified IgG Abs against amphiphysin from a patient with SPS and breast cancer, along with encephalitogenic T-helper lymphocytes to disrupt the blood-brain barrier, allowing Abs reaching the CNS [111]. Intrathecal passive transfer of the same type of Abs can also induce anxious behavior in rats [112]; a similar phenomenon has been documented with GAD-Abs (see above section).

By means of cell-based assays, binding of GlyRα1 IgG Abs was shown at 4 °C in controls, whereas antigen endocytosing (modulation) at 37 °C was observed in patients with SPS spectrum disorders [113]. Moreover, immunotherapy has been reported more effective in patients with positive serology to GlyRα1 IgG Abs than in seronegative patients supporting a direct pathogenic role of such Abs [114]. Abs directed against DPPX increase the excitability and action potential frequency of guinea pig and human enteric nervous system neurons; this may explain the typical diarrhea observed in patients with positive DPPX Abs; moreover decreased expression of DPPX and Kv4.2 has been observed in hippocampal neuron exposed to DPPX Abs [54–56]. Other Abs have been detected in patients with SPS spectrum disorders. Abs directed against the postsynaptic GABA-A receptor-associated protein were detected in about 70% of patients with SPS spectrum disorders in a single study [115]. However, this finding has not been yet replicated by other investigators. Abs directed to the GABA-A receptor have been associated with SPS spectrum disorders, some patients with positivity to such Abs, may present with seizures or limbic encephalitis [116]. Patients with SPS-like phenotype have low titers of GABA-A receptor Abs, whereas high titers are related to severe encephalitis [116]. Antibodies against the enzyme 17β-hydroxysteroid dehydrogenase type 4 have been identified in few patients with SPS, but their pathogenic role is unknown [117].

Pathology

There are a relative small number of pathological studies in patients with SPS spectrum disorders. It was initially suggested that neuropathological changes were scarce in patients with SPS, and the clinical features were related to functional impairment of neurons. However, more recent pathological studies have demonstrated loss of cerebellar GABAergic cells, anterior horn cells, and spinal interneurons (Renshaw cells), in some cases associated with perivascular inflammatory changes with cytotoxic T-cell infiltration, microglia infiltration, and gliosis [118, 119]. A reduction up to 70% in the spinal cord density of neurons with central chromatolytic changes has been reported in patients with SPS [120]. Vacuolation of motor neurons in the caudal segments of the spinal cord was demonstrated in a 69-year-old man with SPS and positive GAD-Abs; such vacuoles were lined by a membrane and contained invaginations with cytoplasmic matter [121]. Lipofuscin-containing lysosomes observed by electron microscopy were common in affected cells [121]. Macrophage infiltration along with neuronal cell loss in the dorsal root ganglion was also observed [121]. Affected muscles may show neurogenic atrophy [120]. Perivascular lymphocytic cuffing and parenchymal infiltrates of CD8+ lymphocytes were observed in a patient with paraneoplastic SPS and positive amphiphysin Abs [122].

Diagnosis

Diagnostic Criteria

The diagnosis of classical SPS is based on the presence of insidious onset and progressive course of muscle stiffness in the spinal and proximal lower limbs muscles secondary to co-contractions of agonist and antagonist muscles, with superimposed muscle spasms and increased exteroceptive reflexes, [123]. The diagnosis is supported by neurophysiological demonstration of continuous motor activity in the involved muscles at rest demonstrated by EMG that is usually abolished during sleep, except in advanced cases, as well as other neurophysiological features plus the absence of other neurological disorder that can explain the symptoms (Table 2). The diagnosis is also supported by the presence of high serum titers of GAD-Abs; however, negative serology does not rule out the diagnosis, particularly in patients with focal/segmental SPS; on the other hand, patients with DM1 may have low levels of GAD-Abs that should not be considered supportive of the diagnosis of SPS. In case of suspicion of paraneoplastic SPS or PERM, assessment of amphiphysin or GlyRα1 Abs should be considered, unfortunately the latter is carried out mainly in research laboratories. Secretion of GAD-Abs within the central nervous system strongly supports the diagnosis of SPS spectrum disorders.

Table 2 Criteria for the diagnosis of stiff-person syndrome

Clinical
Gradual onset and slow progression of muscle stiffness
Stiffness is related to persistent contraction of paraspinal, abdominal, and limb muscles
Abnormal postures, including hyperlordosis of the lumbar spine
Stiffness is usually abolished by sleep
Superimposed stimulus-sensitive painful spasms
Dysautonomia
Neurophysiology
Continuous motor unit activity at rest demonstrated by EMG
EMG activity abolished by sleep, peripheral nerve block, spinal or general anesthesia
Altered exteroceptive reflexes and reciprocal inhibition
Exaggerated startle reflex
Normal peripheral nerve conduction
Immunological
High serum titers of GAD65 antibodies
Intrathecal production of GAD65 antibodies

Diagnosis Workup

As previously discussed, the cornerstone of the diagnostic workup in patients with SPS spectrum disorders is the electromyographic (EMG) demonstration of continuous motor unit activity that can be abolished with the administration of benzodiazepine or anesthetics. EMG shows no signs of denervation and peripheral motor and sensory nerve conduction velocity are usually within normal limits. Ultrasonography may be used as a non-invasive method to assess for impaired relaxation of involved muscles but its specificity for the diagnosis of SPS spectrum disorders is probably low [124]. Other abnormalities that can be recorded in neurophysiologic tests include brainstem myoclonus, exaggerated startle reflex, and non-habituating exteroceptive or cutaneomuscular reflexes [125].

For detection of GAD-Abs, radioimmunoassay has 96% sensitivity and 95% specificity when compared with immunocytochemistry [126]. A newly sensitive proximity ligation assay can detect GAD levels as low as 0.65 pg/ml and GAD-anti-GAD immune complexes [127]. Detection of GAD-Abs in the CSF may be important when low levels of serum GAD-Abs are present in a patient with unclear neurological diagnosis and autoimmune endocrine disorder. CSF may show positive oligoclonal bands, but this finding is not specific. It can be assessed with the following formula, GAD-Abs CSF/GAD-Abs serum/albumin (mg/L) CSF/albumin (mg/l) serum, and a result of ≥ 1 supports intrathecal production of GAD-Abs.

Patients with SPS may show positivity for other organ- and non-organ-specific Abs, including antinuclear, anti-smooth muscle, anti-mitochondrial, antithyroid microsomal, anti-thyroglobulin, anti-parietal cell Abs, etc. [128, 129]. Systematic evaluation for underlying cancer is not indicated in patients with classical SPS; however, in male patients or those with predominant upper limb and cervical stiffness, and coexistent neuronal cell-surface Abs, a search for underlying malignancy should be considered [65]. Neuroimaging studies are usually unnecessary in patients with SPS, except in cases displaying signs of encephalomyelitis, where a proportion of cases may show non-specific MRI abnormalities.

Differential Diagnosis

The stiffness observed in patients with SPS spectrum disorders should be differentiated from other forms of hypertonic muscles, such as spasticity, parkinsonian rigidity, tetanus, or dystonia. Spasticity has a different distribution of increased muscle tone, with velocity-sensitive resistance to muscle stretch, not observed in SPS; there is absence of superimposed muscle spasms, lack of associated weakness and pathological reflexes. Moreover patients with spasticity do not show exaggerated, non-habituating exteroceptive or cutaneomuscular reflexes or increased startle reflex as patients with SPS.

Parkinson's disease and other extrapyramidal disorders present with muscle rigidity, a form of hypertonia that is not velocity-sensitive to muscle stretch, and it usually does not lead to abnormal fixed postures as observed in patients with SPS. In patients with early progressive supranuclear palsy (PSP), rigidity predominates in the axial muscles, but the characteristic hyperlordosis of SPS is not seen; other neurological manifestations such a supranuclear ophthalmoplegia and cognitive decline distinguish PSP from SPS. Members of a family affected by spinocerebellar ataxia type 3 have been described with progressive trunk and abdominal muscle stiffness, along with myokymia, painful spasms, and EMG showing continuous motor unit activity [130]. Chronic tetanus can be confused with SPS; however, trismus is more common in the former and the spasms are abrupt in onset and resolution, the syndrome lasts weeks to months, rather than years as it occurs in SPS [131]. Interestingly, a lockjaw has been reported in a patient with SPS and positive GlyRα1-Abs [132].

SPS spectrum disorders should also be differentiated with disorders associated with continuous muscle activity such as myotonia and Isaac's and Morvan's syndrome. Myotonia characterizes by delayed muscle relaxation following a voluntary contraction and it is not present at rest. Moreover, myotonia may be observed with a number of hereditary muscle disorders including dystrophies. Isaac's syndrome is characterized by the presence of spontaneous and continuous motor unit discharges with a high intraburst frequency known as neuromyotonia, often accompanied by stiffness, cramps, fasciculations, and myokymia (irregular wave-like rippling of

muscles or motor unit discharges in doublets or triplets). The latter are not observed in patients with SPS. EMG shows continuous motor activity that persists during sleep (contrasting with SPS) [73]. The distribution of muscle contraction is mostly distal, in contrast with the axial and proximal muscle involvement of SPS. Morvan's syndrome is characterized by the presence of neuromyotonia plus neuropsychiatric features, dysautonomia, and neuropathic pain; it occurs almost exclusively in males, and it is frequently associated with an underlying thymoma [133]. The disorder is caused by the presence of CASPR2 (contactin-associated protein 2) Abs and less commonly due to LGI11 (leucine-rich glioma inactivated 1) Abs, rather than Abs directed to the voltage-gated potassium channel (VGKC) [8, 134].

Treatment

Treatment of SPS spectrum disorders is divided into four main lines of action: (1) suppression of the autoimmune process with immunotherapy, (2) symptomatic control of rigidity, spasms and other neurological, psychiatric and dysautonomic manifestations, (3) tumor removal in case of underlying neoplasm, and (4) rehabilitation and support. As SPS is an uncommon disorder, there are few randomized controlled trials comparing different therapies used in SPS. Therapeutic decisions are mostly based on previous experience coming from isolated cases, small case series, and expert opinion (Fig. 3).

Immunotherapy

Immunotherapy is divided into "first line," used to achieve a relative rapid immunosuppression in order to induce remission, but it can be continued as a maintenance therapy, and "second line," which includes drugs with slower onset of action and possibly less efficacy compared to first-line therapies; however they are easier to administer providing a more sustained benefit.

First-line therapy includes intravenous immune globulin (IVIg), plasma exchanges, and steroids. In a randomized, placebo-controlled crossover study of IVIg vs. placebo in 16 patients with SPS with each therapy provided during 3 months, a significant improvement in stiffness and heightened-sensitivity scale was observed when patients were receiving IVIg, accompanied by a decrease in GAD-Abs titer [135]. This effect may result in improvement in quality of life [136, 137]. The mechanism of action of IVIg may include suppression or neutralization of Abs, inflammatory cytokines, and activated complement; blockade of leukocyte adhesion proteins; restoration of idiotypic-anti-idiotypic networks; and modulation of dendritic cell activity, among others [138]. Potential drawbacks of chronic use of IVIg are side effects (anaphylaxis) and high costs. IVIg has also provided benefit in

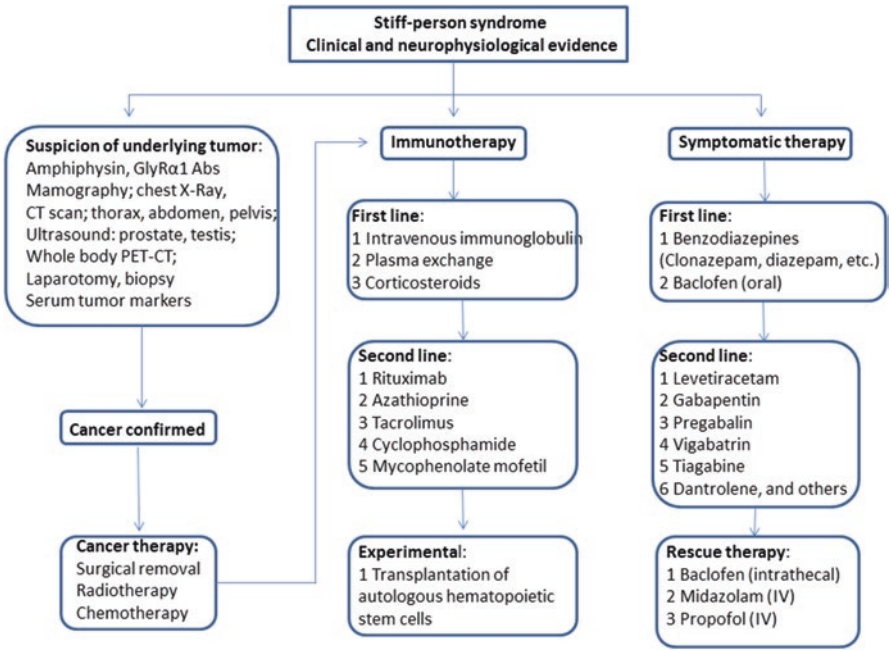

Fig. 3 Algorithm for treatment of stiff-person syndrome spectrum disorders

open trials and isolated reports [139, 140]. Plasma exchange has been used with variable success in patients with SPS spectrum disorders with transient improvements of neurological symptoms observed in 42% of cases in a meta-analysis of 26 patients treated with this therapy [141]. Monthly use of plasmapheresis has been used to maintain initial clinical benefit, but high costs and potential side effects limit this therapeutic strategy [142]. Corticosteroids (oral or pulse IV therapy) can provide variable benefit, but their use should be very cautious in patients with DM1, which is a frequent comorbid disorder in patients affected with SPS.

Second-line therapy includes rituximab, cyclophosphamide, and other immunosuppressants. Rituximab has been used as rescue therapy in patients with SPS with respiratory failure due to severe stiffness of thoracic muscles [143, 144]. However, a randomized placebo-controlled trial in 24 patients with SPS showed lack of improvement of pre-specified 50% in stiffness scores and heightened sensitivity at 6 months [145]. Quality of life improved in both groups at 3 months but not at 6 months suggesting a placebo effect [145]. Relapses are possible following initial response of rituximab [146]. Other immunosuppressants such as azathioprine, tacrolimus, cyclophosphamide, mycophenolate mofetil, and methotrexate have proved benefit in some cases [4, 147]. Transplantation of autologous hematopoietic stem cells provided sustained clinical remission on two patients with SPS, although titers of GAD-Abs remained positive and long-term benefit is unknown [148].

Patients with PERM and GlyRα1-Abs usually benefit with immunotherapy, although relapses are not uncommon [48]; if DPPX-Abs are implicated, a robust response following immunotherapy has been reported [55]. Cerebellar ataxia related to GAD-Abs may benefit from immunotherapy; in this regard corticosteroids and IVIg have shown the best results [69]. Improvement has been reported in one third of cases; subacute onset and rapid treatment initiation are the most accurate clinical predictors of response [71].

Symptomatic Control

Medications with GABAergic effect are the mainstay of symptomatic therapy aimed to decrease the rigidity and superimposed muscle spasms. Benzodiazepines are considered the first-line therapy; among these drugs, diazepam and clonazepam are among the most frequently used and possibly some of the most effective drugs to treat stiffness and spasms in patients with SPS, but clinical trials are lacking [14, 149]. The dose of benzodiazepines can be progressively escalated but are usually limited by side effects such as drowsiness or sedation. Oral baclofen is another potentially effective drug with less side effects that can be used alone or with benzodiazepines in order to achieve a combined effect on GABA receptors: type A (benzodiazepines) and type B (baclofen) [150].

Other medications with GABAergic effect or muscle relaxants have been reported useful in single case reports or small case-series of patients with SPS. Levetiracetam showed benefit in a small blinded crossover trial, but confirmation of its efficacy is needed [151, 152]. Valproic acid, clonidine, vigabatrin, tiagabine, gabapentin, and pregabalin can also be considered [153–156]. Dantrolene, tetrahydrocannabinol, cannabidiol, and other cannabis derivatives available in spray have also been reported useful [157, 158]. The role of all these drugs is not established, but they can be used as "add-on" medications in patients with incomplete response to muscle relaxants or in substitution of benzodiazepines or baclofen in case of prominent side effects from these medications, although they are probably less effective than the former. Evaluation of therapy is usually difficult in patients with SPS due to the fluctuating nature of the disorder and lack of well-validated clinical scales showing reproducibility.

In case of severe nonresponsive muscle spasms, intrathecal baclofen has been used as rescue therapy [159]. Small trials and retrospective studies demonstrated that intrathecal baclofen provides improvement in muscle stiffness evaluated by EMG or clinical assessments [160–163]. The therapy is useful for patients with SPS and PERM, although complete remissions are unlikely [161]. However, several complications may be observed with this therapy, including spasm-induced rupture of the catheter, catheter dislocation causing radicular symptoms, and inaccurate dosage administration due to pump malfunction; catheter dysfunction can be associated with severe symptomatic withdrawal and death [160, 161, 164]. Propofol and

midazolam administered intravenously are other drugs that can be used as rescue therapy in cases of frequent or prolonged muscle spasms (spasmodic storm) and dysautonomia complicated with respiratory failure, rhabdomyolysis, and myoglobinuria with acute renal lesion [165, 166]. Botulinum toxin injections may be helpful particularly in patients with focal SPS that show a lack of response to oral pharmacological therapies or to control pain in cervical muscles and reduce stiffness in facial muscles [167, 168]. Spinal cord stimulation has been reported to improve the spasms observed in cases of stiff-limb syndrome, but confirmatory studies are lacking [169].

Psychiatric manifestations, particularly anxiety, panic attacks, and phobias, can improve with the use of benzodiazepines; clinicians should be aware that medications commonly used for depression and anxiety such as serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants may potentially aggravate the motor symptoms of SPS and they should be avoided whenever possible in patients with SPS [170].

Tumor Removal

Treatment of underlying cancer is of paramount importance in cases where such condition is detected. In patients with paraneoplastic SPS, tumor removal is usually mandatory before starting immunotherapy. Dramatic improvement has been documented in patient with positive GlyRα1-Abs following removal of underlying thymoma and immunotherapy [171, 172].

Special Situations, Anesthesia, and Pregnant Patients

There is concern that patients with SPS exposed to inhalational (volatile) agents and neuromuscular blockers may suffer prolonged and severe hypotonia following anesthesia which may lead to respiratory failure with prolonged intubation. Although some patients are anesthetized with volatile agents and neuromuscular blockers develop this side effect [173], it is believed that this side effect results from the enhancement of GABA action on synapsis by medications with agonist GABAergic effect [174]. Due to this potential side effect, the TIVA technique which does not require neuromuscular blockage has been proposed for SPS patients [175]. Regional anesthetic techniques may also be used to avoid exposure to muscle relaxants [174]. Total intravenous anesthesia instead of inhalation anesthetics with close monitoring of respiratory drive and use of electrical nerve stimulator when neuromuscular blockers are used are also recommended [176].

There are few reports of patients with SPS during pregnancy, for these patients, medication adjustments to use low levels of benzodiazepines or baclofen can be tried to reduce side effects [177, 178], while immunotherapy should be withheld.

Some patients may experience transitory improvement during pregnancy [179]. Cesarean section is the preferred method of delivery but there are reports of successful vaginal delivery [178, 179]. Although newborn babies may have positive GAD-Abs until the age of 24 months, they do not seem to develop SPS phenomenology [180].

Prognosis

Patients with SPS spectrum disorders have a chronic evolution despite treatment with immunotherapy and muscle relaxants. The quality of life has been investigated in 24 patients with SPS through the Short-Form Health Survey (SF-36) showing decreased (worse) scores compared with normal controls; a strong correlation of SF-36 scores with the extent of the disease and degree of depression was observed [181].

Conclusions

SPS spectrum disorders are a group of conditions characterized by CNS disinhibition that causes muscle stiffness, spasms, and enhanced exteroceptive reflexes. Although major advances have shown that amphiphysin and GlyRα1 Abs are likely pathogenic in patients with paraneoplastic SPS and PERM, respectively, this has not been the case with GAD-Abs, and the pathogenesis of classical and focal/segmental SPS is still to be clarified; as the disorders partially respond to IVIg, plasmapheresis, and rituximab, an autoimmune humoral response is likely. Further studies should help to elucidate the pathogenesis of this group of disorders to develop better treatment strategies.

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