INVITED REVIEW

ABSTRACT: Stiff-person syndrome (SPS) is a disorder characterized by progressive muscle rigidity with superimposed painful muscle spasms and gait impairment due to continuous motor activity. Evidence has accumulated in favor of SPS representing an autoimmune, predominantly encephalomyelopathic disorder resulting from B-cell–mediated clonal production of autoantibodies against presynaptic inhibitory epitopes on the enzyme glutamic acid decarboxylase (GAD) and the synaptic membrane protein amphiphysin. Recognition of the clinical spectrum of SPS is important, particularly the upper-limb, cervical, and cranial nerve involvement that occurs in paraneoplastic variants. The correlation between antibody levels and severity of disease offers evidence for a pathogenic role for the anti-GAD and anti-amphiphysin autoantibodies. The scarcity of neuropathological correlates stand in sharp contrast with the severity of the disability in affected individuals and suggests that functional impairment of inhibitory circuits without structural damage is sufficient to develop the full clinical spectrum of SPS. The rarity of this condition limits the feasibility of controlled clinical trials in the treatment of SPS, but the available evidence suggest that drugs that increase cortical and spinal inhibition such as benzodiazepines and drugs that provide immune modulation such as intravenous immunoglobulin, plasmapheresis, and prednisone are effective treatments.

Muscle Nerve **34:** 677–690, 2006

RIGIDITY AND SPASMS FROM AUTOIMMUNE ENCEPHALOMYELOPATHIES: STIFF-PERSON SYNDROME

ALBERTO J. ESPAY, MD, MSc,[1] and ROBERT CHEN, MBBChir, MSc[2]

[1] Department of Neurology, Neuroscience Institute, Movement Disorders Center, University of Cincinnati, Cincinnati, Ohio, USA
[2] Department of Medicine, 7MC–411, Toronto Western Research Institute and Division of Neurology, 399 Bathurst Street, University of Toronto, Toronto, Ontario M5T 2S8, Canada

Accepted 28 July 2006

The first description of stiff-person syndrome (SPS) dates back to 1956, when Moersch and Woltman[97] reported a series of 14 patients collected over 32 years, with unexplained fluctuating rigidity and spasms but without pyramidal or extrapyramidal dysfunction. In 1988, Solimena et al.,[139] while studying a patient with SPS associated with epilepsy and type I diabetes mellitus, found that the patient's serum and cerebrospinal fluid produced immunocytochemical staining of all gray-matter regions identical to those produced by antibodies to glutamic acid decarboxylase (GAD). This discovery launched the hypothesis of an autoimmune pathogenesis, which was confirmed by subsequent investigators. Since it is recognized that stiff-man syndrome occurs in women, the eponym Moersch–Woltman syndrome and, more commonly, stiff-person syndrome have become current-use nomenclature for this disorder.

Areas of ongoing interest and debate in SPS include cases with additional neurological findings, such as encephalomyelitis and cerebellar deficits; the association of anti-GAD antibodies with other diseases, such as diabetes mellitus and seizures; and the high risk of other autoimmune diseases, such as diabetes, hyperthyroidism, hypothyroidism, pernicious anemia, and vitiligo. These issues will be addressed in this review.

CLINICAL FEATURES OF SPS

In its typical presentation (classic SPS), muscle rigidity and superimposed episodic spasms begin insidi-

Abbreviations: AChR, acetylcholine receptor; CNS, central nervous system; CSF, cerebrospinal fluid; EMG, electromyography; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; IDDM, insulin-dependent diabetes mellitus; IPSP, inhibitory postsynaptic potential; IVIg, intravenous immunoglobulin; PERM, progressive encephalomyelitis with rigidity and myoclonus; SLS, stiff-limb syndrome; SPS, stiff-person syndrome

Key words: encephalomyelopathies; glutamic acid decarboxylase; progressive encephalomyelitis with rigidity and myoclonus; stiff-limb syndrome; stiff-person syndrome

Correspondence to: R. Chen; e-mail: robert.chen@uhn.on.ca

Published online 12 September 2006 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mus.20653

FIGURE 1. Enhanced lumbar lordosis **(A,B)**. Note the cast on the left arm was due to a fracture sustained during a recent fall. Patients have increased fear of falling, which may partly explain the board-like posture with arms extended seen during walking **(C)**.

ously over several months, affecting the lumbar and thoracic paraspinal and proximal legs muscles. In the trunk, the continuous muscle contractions produce a board-like appearance of the abdominal wall; co-contraction of abdominal and paraspinal muscles may lead to exaggeration of the normal lumbar lordosis (Fig. 1A,B). The spasms, often associated with intense pain, typically begin with an abrupt jerk followed by tonic activity that slowly subsides over seconds to, less commonly, minutes. Rarely, these spasms last days (status spasticus).[31] The initial fluctuating pattern of stiffness gradually becomes sustained and the extent of the contractions makes trunk bending and walking difficult. The gait, however, usually progresses to becoming deliberate and slow, in part due to fear of falling (Fig. 1C). The stiffness only disappears during sleep, narcosis, or after administration of neuromuscular blocking agents such as curare or intravenous diazepam.[55] More often, patients only complain of chronic low back pain.[51]

The presence of task-specific phobias should not prompt the clinician toward the consideration of a psychogenic disorder, as this error often results in missing the appropriate diagnosis.[77] Anxiety and phobias are caused by SPS rather than due to an inherent phobic neurosis.[2]

Examination Findings in Classic SPS. Although the neurological examination is typically considered normal except for the global muscle stiffness, reflex abnormalities may be present in SPS, with exaggerated muscle stretch reflexes and loss of abdominal cutaneous reflexes.[55] An important feature of the spasms is their sensitivity to stimulation. Unexpected tactile, auditory, or emotional stimulation can trigger or exacerbate the spasms and exaggerate the lumbar lordosis.[14] Cutaneous stimulation of the legs with light touch or pinprick may elicit ipsilateral flexion of the hip and knee, dorsiflexion of the foot, extension and slight abduction of the contralateral leg, and extension of the lumbar trunk.[95] Other movements during the spasm may include extension and pronation of the arms and inversion of the feet. Pyramidal (except brisk tendon reflexes), extrapyramidal, lower motor neuron, and sphincter and sensory disturbances must be absent for consideration of this diagnosis.

Atypical Presentations and Findings. Besides asymmetric limb presentations, the stiffness may spread to other body parts, including the face (in 10 of 12 patients in one series).[77] Spasms may be severe enough to cause joint subluxations, femoral fractures, or herniation of abdominal contents.[9,55,120] When spasms affect the respiratory and thoracic musculature, patients may have difficulty in breathing.[96] Fixed flexion of the limbs with frank opisthotonos have been described.[120] Oculomotor abnormalities have been reported recently, including gaze-holding nystagmus, bilateral abduction weakness, deficient smooth pursuit, impaired saccade initiation, and hypometric saccades.[41,145] Anti-acetylcholine receptor antibodies from a coexistent autoimmune disease, myasthenia gravis, may explain these

findings in some patients.[145] Paroxysmal autonomic dysfunctions such as transient hyperpyrexia, diaphoresis, tachypnea, tachycardia, pupillary dilation, and arterial hypertension are recognized.[96] Rhabdomyolysis can be a potential complication of the excessive muscle contractions in SPS.[109] Sudden death can also occur due to acute autonomic failure.[54,96]

Associated Comorbidities. Patients positive for anti-GAD autoantibodies are prone to autoimmune diseases, especially diabetes mellitus type I.[138] Indeed, pancreatic β cells, the target of autoimmunity in insulin-dependent diabetes, are among the few cell types outside the central nervous system (CNS) that contain GAD in synaptic-like microvesicles.[117] Further, anti-GAD autoantibodies are found in the majority of type I diabetes patients, although at lower titers than in patients with SPS.[10,149] A series of 13 patients collected at the Mayo Clinic over 30 years before 1989 suggested that up to 70% of patients with classic SPS have insulin-dependent diabetes mellitus (IDDM).[80] When including other autoimmune diseases or endocrinopathies (e.g., Graves' disease, pernicious anemia, and celiac disease), the estimated collective prevalence of these comorbidities reaches 80% of SPS cases.[31,95,114] Family history may be positive for IDDM, thyroid disease, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and vitiligo,[31] but the prevalence of these comorbidities in SPS is not known. Seizures are present in about 10% of SPS patients[77] and, conversely, anti-GAD antibodies have been identified in non-SPS patients with localization-related epilepsy.[106]

Paraneoplastic SPS. Specific malignancies are associated with SPS in about 5% of patients. Most of these patients are positive for autoantibodies directed against amphiphysin (see below).[37,50] This form of SPS was first reported in a case of pathology-proven focal myelopathy in the setting of small cell lung cancer, presenting with left-leg rigidity with quadriceps myoclonus.[119] Paraneoplastic SPS has been reported in association with breast cancer,[50] thymoma,[143] and Hodgkin lymphoma,[46,157] although no autoantibody was isolated in the latter two instances. Compared to patients with GAD-positive classic SPS, there appears to be a greater prevalence in patients with amphiphysin-positive paraneoplastic SPS of cervical and upper-limb involvement,[50,120] and occasional fixed deformities of an arm.[95]

CLINICAL VARIANTS OF NONPARANEOPLASTIC AUTOIMMUNE SPS

There is growing recognition of disorders with presentations beyond axial rigidity, described by Brown and Marsden as "SPS-plus syndromes,"[17] presumed to have poorer response to treatment and prognosis, and a variable relationship to malignancies. Since these entities were initially reported before their association with anti-GAD autoantibodies became established, their terminology continues to be based on clinical deficits and area of involvement. A clinical approach to the consideration of SPS and its clinical variants is shown in Figure 2.

Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM). PERM, initially reported in 1976[159] and subsequently termed the "jerking stiff-man syndrome,"[76] is a severe and rapidly progressive end of the SPS clinical spectrum. Axial and lower-limb stiffness and rigidity are followed, after several years, by the appearance of spontaneous and stimulus-sensitive myoclonus and upper motor neuron signs.[1,76] Spasms and generalized myoclonus may be accompanied by profuse sweating and other manifestations of dysautonomia.[68,90,159] Unlike SPS, brainstem signs such as nystagmus, ocular motor impairment, retinopathy, deafness, dysarthria, and dysphagia may be prominent in PERM. Furthermore, the progressive course, brainstem and cranial nerve involvement, and long-tract signs distinguish PERM from SPS.[95] Death occurring between 6 weeks and 3 years from onset of symptoms highlights the relentless speed of progression.[12,17] Although anti-GAD autoantibodies may be absent in some,[12] their presence in others suggest that PERM is related to SPS.[22,154] Indeed, when the presence of anti-GAD was ascertained in a large number of neurological patients (301), the combined prevalence of these autoantibodies in SPS and PERM (13 and 9, respectively) for GAD-65 (see Autoantibodies, below) was ~80%, compared to 5% in other neurological conditions, mainly in sporadic progressive ataxia, but not in other recognized neuroimmunological diseases.[91] The increased anti-GAD autoantibodies were interpreted as representing a pathogenic biomarker rather than a nonspecific epiphenomenon of neuronal damage.[91] After many years, SPS may evolve into a clinical picture resembling PERM, limiting the distinction between these two clinical variants.[96,142] In addition to cerebrospinal fluid (CSF) findings of lymphocytic pleocytosis with elevated IgG and oligoclonal bands,[95] serum and CSF anti-Ri antibodies have been reported in a PERM case with associated opsoclonus.[24] The clinical deficits have been postulated to result from neuronal loss in spinal central gray zones, which, by affecting spinal interneurons, presumably remove the inhibitory control of alpha-motor neu-

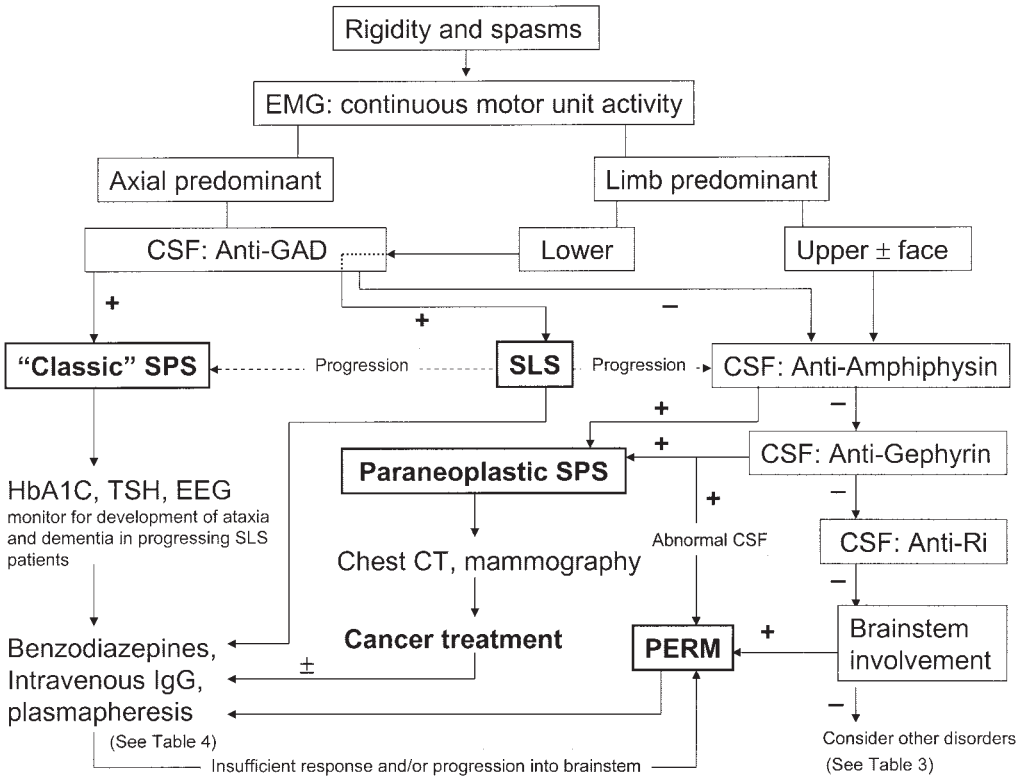

FIGURE 2. Flow diagram for the diagnosis and initial management of patients with presumed SPS. HbA1C, hemoglobin A1C; TSH, thyroid-stimulating hormone; EEG, electroencephalogram (to screen for SPS comorbidities); SLS, stiff-limb syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus. Note that PERM variant can arise in either axial or limb-predominant forms. Comorbid diabetes, thyroid disease, and epilepsy have not been reported in association with SLS.

rons,[63] and from degeneration of the long tracts in the cervical spinal cord ("spinal neuronitis").[159]

Focal Variant of SPS: Stiff-Limb Syndrome (SLS). Patients with SLS present with stiffness in one limb, usually a leg.[18,57,135] The presence of anti-GAD autoantibodies suggest that SLS is a focal variant of SPS.[126] The clinical overlap is highlighted by the progression of some patients with SLS into classic SPS (although the subsequent course may be atypical, with dementia and progressive ataxia in addition to the development of IDDM).[95] When an arm is predominantly involved, a paraneoplastic SLS should be suspected.[120,131]

EPIDEMIOLOGY OF SPS

Usually occurring between the ages of 30 and 50 years, SPS is considered rare. No clear estimates of prevalence of SPS are available in the literature, but in a single center near Heidelberg, Germany, which serves a population of 2–3 million people, 20 cases were collected over a 10-year period.[95] This suggests a prevalence of ~1:1,250,000, which may overestimate the true prevalence in other countries. Both men and women can be affected without known gender predominance. The human leukocyte antigen class II allele DRβ1 0301 was found to be present in 70% of SPS patients, but this finding is of unclear significance.[77]

Patients with SPS and anti-GAD autoantibodies often have other organ-specific autoimmune diseases, in particular type I IDDM.[138] Similar to SPS, patients with IDDM may have autoantibodies against GAD at or before diabetes onset, although usually at a lower titer. Indeed, ~72% of patients with SPS carry the DQB1*0201 allele, which is a susceptibility allele for IDDM and other autoimmune diseases.[113] The presence of the IDDM-protective DQB1*0602 allele tends to be associated with a reduced prevalence of diabetes among patients with SPS.[113] Other associated comorbidities are Graves' disease,[104] hypopituitarism,[52] and epilepsy.[86] Slater proposed the use of the term "hormonal stiff muscle syndrome"[136] to emphasize the prevalence of endocrine disorders in SPS. Symptomatic remission during pregnancy, reported in one antibody-negative case,[156] is a

phenomenon of unknown prevalence and significance.

As a paraneoplastic phenomenon, SPS is often associated with anti-amphiphysin antibodies, which are mostly associated with breast cancer. Although small cell lung carcinoma is the most common underlying malignancy in most paraneoplastic disorders (especially encephalomyelitis with sensory neuronopathy), SPS occurs in less than 3% of all possible paraneoplastic presentations for small cell lung carcinoma.[125]

PATHOGENESIS OF SPS

Circulating and intrathecal antibodies against GAD prevent the conversion by this enzyme of the excitatory neurotransmitter glutamate to the major inhibitory neurotransmitter γ-aminobutyric acid (GABA), with reduced effectiveness of GABAergic inhibition and potentially excess excitatory neurotransmission.[139,158] In the most common form of SPS, these antibodies react against the intracellular 65- and 67-kDa GAD isoforms.[137] GAD is a cytosolic enzyme and the synthesis of GABA takes place in the nerve endings of GABA-secreting neurons.[44] The GAD-65 and GAD-67 isoforms have different subcellular locations and are coded by genes on two different chromosomes.[21,43] GAD-67 has been suggested to regulate the basal levels of GABA,[83] and the corresponding knockout mice die shortly after birth.[8] By contrast, the 65-kDa form of GAD serves as a regulatory enzyme responsible for short-term changes in demand for GABA, suggesting that this isoform may provide reserve pools of GABA for regulation of inhibitory neurotransmission.[83] GAD-65–knockout mice exhibit no change in brain GABA contents, but suffer from epilepsy and stress-induced seizures.[7,67] In patients with SPS, there is marked intrathecal antibody response against the neuronal GAD-65 isoform, indicating a clonal B-cell activation in the CNS.[32] The GABA-related inhibition from anti–GAD-65 autoantibodies is presumed to affect both interneurons in the spinal gray matter and intracortical inhibitory neurons,[77] leading to continuous tonic firing of motor neurons and slow spasms. The direct pathogenic role of anti–GAD-65 autoantibodies has been questioned,[70] partly due to the intracytoplasmic location of GAD epitopes and the nonspecificity of neuropathological changes.[42,66] However, evidence of pathogenicity for the anti–GAD-65 antibodies is supported from the observation that serum from antibody-positive SPS patients, but not from patients without such antibodies, inhibit GAD activity in vitro and impair the synthesis of GABA in crude rat cerebellar extracts without causing structural changes in the GABAergic neurons.[38,65] This is, however, no confirmation that such a phenomenon occurs in vivo. Similar impairment of inhibitory neurons results from antibodies reacting against amphiphysin in paraneoplastic SPS.[158] The pathogenicity of these autoantibodies has been suggested both clinically and from animal studies. A tight correlation between amphiphysin autoantibody titers and severity of deficits was reported in a woman with SPS, opsoclonus, and encephalopathy.[158] Although not established in vivo, dose-dependent stiffness and spasms was elicited in rats injected intraperitoneally with plasma filtrates of a patient with SPS containing high titers of amphiphysin autoantibodies.[140] This is an area of active interest and ongoing research.

Pathology. There are few neuropathological studies in SPS and their findings are variable. A number of the initial studies showed no abnormalities or inconsistent findings.[9,26,97,147] This lack of pathological findings may be partly explained by the absence of structural changes documented in vitro in GABAergic neurons exposed to IgG anti–GAD-65 antibodies from patients with SPS,[38] suggesting that SPS is a functional rather than structural disorder.[32] Subsequently, however, anterior horn cell and spinal interneuron loss with perivascular infiltration and gliosis of the spinal cord have been reported in classic SPS.[66,86,96,127,153–155] Neuronal density of small alpha-motor neurons and gamma-motor spinal neurons is reduced, whereas the density of cerebellar Purkinje cells, known to contain high amounts of GAD, may[153] or may not[66] be decreased. The PERM variant demonstrates extension of perivascular lymphocyte cuffing in the cerebral hemispheres and brainstem.[154] It has been suggested that SLS may be due to chronic spinal interneuronitis,[18] but no pathological correlate has been identified. Similarly, and despite the involvement of cortical inhibitory interneurons,[128] no cortical pathology has been reported to date.

DIAGNOSIS

The diagnosis of SPS can be suspected based on clinical features and supported with serological (autoimmune and paraneoplastic autoantibodies) and electrophysiological testing. Diagnostic criteria for the diagnosis of SPS were proposed by Lorish et al.[80] and Brown and Marsden,[17] and are modified and updated in Table 1. A therapeutic challenge with diazepam to help confirm the diagnosis[62] is no

Table 1. Diagnostic features of SPS.

	Main characteristics	Additional characteristics
Typical features	Axial stiffness and rigidity	Proximal limb muscles may be involved
	Abnormal posture	Hyperlordosis may develop late
	Superimposed spasms	precipitated by voluntary movements, emotional upsets, and unexpected auditory and tactile stimuli
	Continuous motor-unit activity in at least one axial muscle	Enhanced exteroceptive reflexes
Supportive features	Anti-GAD autoantibodies*	If GAD-negative: amphiphysin autoantibodies (anti-gephyrin and anti-Ri are rare)
Exclusionary features	Brainstem, pyramidal, extrapyramidal or lower motor neuron signs, sphincter and sensory disturbance, cognitive impairment	Brainstem involvement is characteristic of the PERM variant.
Occasional features	Epilepsy	
	Endocrinopathy (diabetes mellitus type I, thyroiditis, pernicious anemia, Graves' disease)	
	Transient dysautonomia (hyperpyrexia, diaphoresis, tachypnea, tachycardia, pupillary dilation, and arterial hypertension)	

**Anti-GAD autoantibodies are present in 90% of SPS patients. Other autoantibodies or additional evidence of autoimmune disease may be present in anti-GAD antibody–negative SPS patients (see text).*

longer encouraged, in part due to its high false-negative rate.

Autoantibodies. The demonstration of autoimmunity has become a required element of the diagnosis of SPS. Anti-GAD and anti-amphiphysin are the most important markers of autoimmune dysfunction. Various other autoantibodies, such as antinuclear, antithyroid, antiparietal cell, antigliadin, and against RNP, Jo-1, and intrinsic factor can be identified in SPS but are believed to bear no direct pathogenic relevance, except for the associated condition to which they are related.[31]

Glutamic Acid Decarboxylase Autoantibodies. The diagnosis of SPS, formerly considered a clinical diagnosis of exclusion, can be reliably made with the aid of serological testing in more than 60% of patients.[138,139] In carefully selected series of classic SPS (i.e., after the SLS and PERM variants have been eliminated), almost 90% of patients have anti-GAD antibodies in blood and CSF.[12] Most patients have highly specific antibodies against the 65-kDa isoform of GAD (GAD-65), the rate-limiting enzyme for the synthesis of GABA at the GABAergic terminals. These antibodies can be measured by immunocytochemistry on frozen sections of rat cerebellum and confirmed by Western blot of recombinant human GAD-65. When the presence of serum and CSF titers of anti-GAD antibodies is quantified, serum (from 7.0–215 μg/ml) and CSF (from 92–2,500 ng/ml) titers are highly increased.[32] Similarly strong immunoreactions with recombinant GAD-65 on immunoblot and with GABAergic neurons on rat cerebellum increase the specificity for the diagnosis.[32] This is in contrast with IDDM patients, where the serum anti-GAD titer is low (from 200–1,760 ng/ml) and there is no reactivity to recombinant GAD-65.

Anti-GAD antibodies are not exclusive to the SPS and have been described in cases of cerebellar ataxia,[61,124] palatal myoclonus,[102] and Batten disease.[25,105] Whereas GAD-65 autoantibodies of SPS patients recognize a specific conformational C-terminal epitope (amino acids residues 4–22), autoantibodies from patients with IDDM or Batten disease recognize different epitopes.[114,116] Similarly, epitope-specific anti-GAD antibodies are likely present in patients with localization-related epilepsy.[106] Anti-GAD serology in patients with cerebellar degenerations has been positive only when IDDM or other organ-specific autoimmune disorders are present.[53,124,151] Although anti-GAD antibodies in serum and CSF are an excellent marker for SPS, their titers do not correlate with disease severity or duration.[115]

Amphiphysin Autoantibodies. The first "paraneoplastic stiff-man syndrome" was reported in 1993 in four women with breast cancer who were negative for GAD-65 autoantibodies but had autoantibodies against amphiphysin.[37] Amphiphysin is a 128-kDa synaptic membrane protein involved in synaptic-vesicle endocytosis. This protein is present only at

Table 2. Autoantibodies and clinical syndromes.

Autoantibody	Malignancy	Clinical syndromes
Anti-GAD Very high titers*	None	Classic SPS In those with SLS: Cerebellar ataxia Dementia
Amphiphysin (Am)	Breast cancer	Rostral involvement (arms > legs) in some Opsoclonus
	SCLC	Encephalomyelitis ± sensory neuronopathy Cerebellar ataxia Opsoclonus
Ri	Lung adenocarcinoma†	Rostral involvement (upper trunk, hand action tremor) PERM plus opsoclonus
Gephyrin	Mediastinal carcinoma†	Rostral (with brainstem) and caudal involvement

SPS, stiff-person syndrome; SLS, stiff-leg syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus; SCLC, small-cell lung cancer.
**Mildly increased titers of anti-GAD autoantibodies are seen in non-SPS conditions such as adult-onset epilepsy, diabetes mellitus, and other endocrinopathies.*
†Anti-Ri and anti-gephyrin-associated SPS correspond to single case reports.

very low concentration in other tissues but is often overexpressed in breast cancer cells.[48,71] Similar to GAD, amphiphysin is associated with the cytoplasmic surface of synaptic vesicles and is concentrated in nerve terminals. GAD and amphiphysin are the only two known targets of CNS autoimmunity with this distribution. Although amphiphysin autoantibodies remain restricted almost exclusively to women, they are not specific for either the clinical presentation or its underlying malignancy. Amphiphysin autoantibodies have been reported in patients with paraneoplastic encephalomyelitis, limbic encephalitis, cerebellar degeneration, and sensory neuronopathy; and have been associated with small cell lung carcinoma, thymoma, and ovarian cancer.[4,39,112,125,145] Patients with SPS due to breast carcinoma or thymoma may also have anti-GAD antibodies.[120,135,145]

Gephyrin. Gephyrin is a cytosolic protein selectively concentrated at the postsynaptic membrane of inhibitory synapses, where it is associated with receptors for GABA and glycine. Glycine is a major inhibitory neurotransmitter in the spinal cord. Gephyrin-associated SPS has been identified in one patient with gait stiffness, dysarthria, and dysphagia, due to an undifferentiated mediastinal tumor, who likely had the PERM variant.[23] Gephyrin-knockout mice exhibit stimulus-sensitive exaggerated rigidity reminiscent of SPS.[45]

Ri. There has been a single report of PERM (dysarthria, dysphagia, prominent upper-limb and cervical paraspinal muscle involvement, and no involvement of abdominal or lumbar paraspinal muscles) associated with anti-Ri autoantibodies.[89]

The various clinical syndromes reported with each of these autoantibodies are summarized in Table 2. In paraneoplastic SPS, chest computed tomography and mammography, as appropriate, are recommended for the investigation of occult malignancies. The use of ^{18}F fluorodeoxyglucose (FDG) whole-body positron-emission tomography (FDG-PET) has been suggested. However, the number of false positives and false negatives for this diagnostic modality restricts its use to those cases in which conventional imaging is negative or inconclusive or when presumably causative lesions are difficult to biopsy.[161]

Physiology of SPS. ***Continuous Motor Unit Activity.*** Electromyography (EMG) is helpful to detect the typical pattern of continuous low-frequency firing of normal motor units in agonist and antagonist muscles of the affected region simultaneously and at least in one axial muscle. This motor-unit cocontraction firing, essentially indistinguishable from voluntary muscle contraction, persists despite attempts at muscle relaxation by the patient, and lessens or disappears during sleep and after spinal or general anesthesia, indicating a central generator.[15,121] The appearance and rate of the motor unit action potential discharges, which have normal morphology, can be readily distinguished from other abnormal discharges that may be associated with stiffness, such as neuromyotonia.

Monosynaptic Reflexes. The monosynaptic reflex arc is also hyperexcitable in SPS, as shown not only by brisk muscle stretch reflexes but also by the loss of

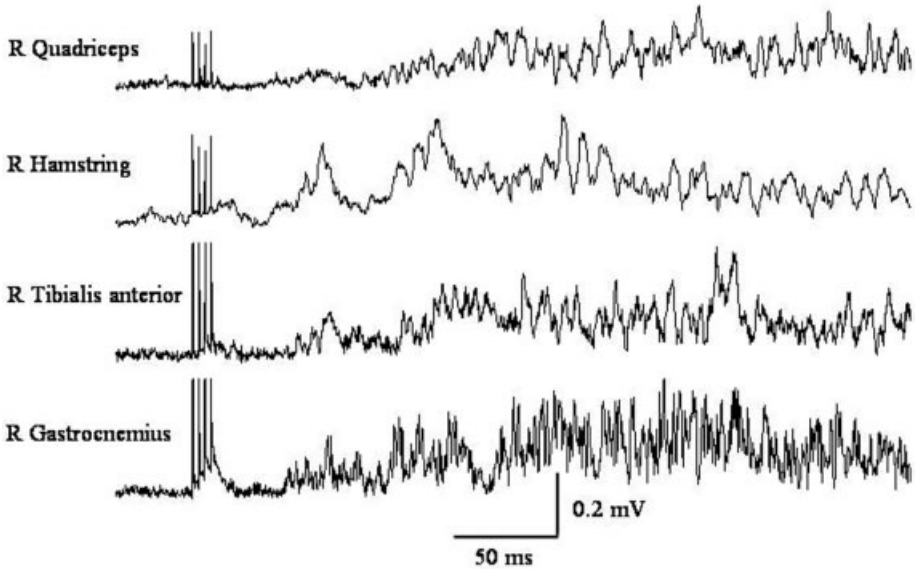

FIGURE 3. Exteroceptive reflexes shown by surface electromyographic recordings from the muscles of the right leg after stimulation of the right tibial nerve at the ankle in a 55-year-old woman with SPS. Rectified, averaged record from six trials is shown. Stimuli were delivered as a train of 4 pulses of 0.2 ms duration, 3 ms apart, at an intensity of 5.85 mA (sensory threshold, 1.95 mA). Note that there are two phases of EMG response: a brief first phase (latency of 50 ms in tibialis anterior) followed by a second phase of longer latency and duration.

vibration-induced inhibition of forearm and soleus H reflexes. Vibration induced inhibition of the H reflexes may result from presynaptic inhibition mediated by GABAergic spinal interneurons and by the presynaptic phenomenon of postactivation depression. Either or both of these mechanisms may be depressed in SPS.[47,85,94,121]

Exteroceptive Reflexes. Exteroceptive reflexes, elicited from peripheral stimulation (tactile, auditory, or electrical), including blink reflexes, are enhanced excessively in SPS.[56,93] These reflexes can be readily elicited in an electrophysiology laboratory by delivering median or tibial nerve stimulation, usually in train of 4 or 5 pulses, at intensities of 2 to 3 times the sensory threshold (Fig. 3). These exaggerated polysynaptic reflexes from nonpainful stimuli habituate poorly and spread as reflex spasms into muscles not normally involved in the reflex in both upper and lower limbs as well as to the axial muscles.[93] These enhanced exteroceptive reflexes show an initial EMG burst at a short latency (50–80 ms) followed by a period of tonic activity and large-amplitude bursts of gradual, "tonic decrescendo" activity.[94,95] The recruitment order of muscles along the neuraxis shows a slow spread up and down from spinal cord entry, similar to that observed for propriospinal myoclonus.[94] Although both propriospinal myoclonus and SPS predominantly affect truncal muscles, propriospinal myoclonus has little or no stimulus sensitivity and flexor preponderance, whereas SPS is highly sensitive to stimuli and affects both flexor and extensor muscles.[94] The short latency and stereotypical motor responses in the trunk in SPS has led to the suggested name of "spasmodic reflex myoclonus." Since they are not present in any other causes of muscle hypertonia, their presence represents an important diagnostic feature of SPS.[95]

Startle Reaction. It should be noted that exaggerated startle reactions can superficially resemble enhanced exteroceptive reflexes in SPS. Compared to the enhanced exteroceptive reflexes, however, a startle reaction has a shorter latency and is short-lasting (20–400 ms). In a startle reaction, the muscle recruitment after auditory stimulation follows a stereotypical sequence from the fifth and seventh cranial nerve nuclei (orbicularis oculi, sternocleidomastoid, masseter, biceps brachii, and occasionally lower limb muscles), and the reflex rapidly habituates.[19] The startle reaction is generated in the nucleus reticularis pontis caudalis and is transmitted via the reticulospinal system.[35] SPS patients have a normal startle response in cranial muscles but are exaggerated in truncal and lower-limb muscles, where it habituates poorly.[88] This finding suggests that the brainstem generator for startle reaction is normal in SPS but it projects to hyperexcitable spinal circuitries.[88] In contrast, in hyperekplexia or startle disease, exaggerated and nonhabituating startle occurs in all muscles involved in the startle reaction, suggesting that there is hyperexcitability of the brainstem gen-

erator for startle.[19,87] The physiological differences between hyperekplexia and SPS may be related to the finding that hyperekplexia is due to deficiency of glycine-mediated fast inhibitory postsynaptic potentials (IPSPs),[133] whereas SPS, with less abrupt spasms, may result from deficiency of GABA-mediated slow IPSP. However, hyperexcitability in other brainstem reflex pathways has been observed in both SPS and hyperrekplexia.[69,98]

Head Retraction Reflex. This vestigial withdrawal reflex of the face is elicited by gentle taps to the glabella or nose bridge and is suppressed in healthy subjects. It is exaggerated in hereditary and acquired hyperekplexia[146] and in a considerable proportion of SPS patients,[13] although it is not specific to these conditions. It consists of short-latency (11–13 ms) reflex activity in the orbicularis oculi and trapezius muscles, followed shortly thereafter by the sternocleidomastoid.[13] This reflex may be helpful in distinguishing SPS from other conditions with focal or generalized stiffness.

Cortical Involvement of SPS. Brain and spinal computed tomography (CT) and magnetic resonance imaging (MRI) are generally normal, with rare exceptions.[92,131] However, magnetic resonance spectroscopy (MRS) demonstrates a reduction in brain levels of GABA, predominantly in the sensorimotor cortex and, to a lesser extent, in the posterior occipital cortex.[77,78] Transcranial magnetic stimulation (TMS) studies in SPS patients have also shown impaired cortical inhibition and increased cortical facilitation.[72,128] Specifically, short-interval intracortical inhibition, which is likely mediated by $GABA_A$ receptors,[130,164] and the silent period, which likely involves $GABA_B$ receptors,[130,164] are both decreased[72,128] and intracortical facilitation is increased[72,128] in SPS patients. Furthermore, in untreated patients the level of intracortical facilitation is correlated with the level of GAD-65 antibodies in the CSF.[72] Brainstem hyperexcitability is identified by the enhanced recovery of the R2 component of electrically evoked blink reflexes.[98]

DIFFERENTIAL DIAGNOSIS

Possibly the closest related disease is tetanus because both conditions affect central GABA mechanisms. Tetanus toxin selectively blocks release of the inhibitory neurotransmitters glycine and GABA into synapses in the spinal cord.[27,28] Other infectious or toxic disorders that may produce an SPS-like picture are borreliosis,[84] encephalomyelitis lethargica,[152] and strychnine poisoning.[59] The latter is due to competitive postsynaptic antagonism of glycine receptors in the spinal cord.[162] Neuromyotonia, a peripheral nerve disease, may cause rippling, painful muscle spasms that, unlike those of SPS, persist after nerve block, anesthesia, and sleep and appear more in distal than proximal muscle groups.[20,118] Satoyoshi disease, although largely a disorder of the first two decades of life, may present in adults with generalized painful muscle cramps and endocrine disturbances in addition to alopecia and intractable diarrhea, but none of the bone and joint deformities seen in the young-onset cases.[64] Importantly, both neuromyotonia and Satoyoshi disease, like SPS, are autoimmune disorders and may respond to the suppression or removal of specific antibodies.[6] Indeed, voltage-gated potassium channel antibodies in neuromyotonia[103] and, surprisingly, anti-GAD antibodies in Satoyoshi disease,[40] have been identified. Interestingly, both of these antibodies have been reported in the same individual with thymoma-associated neuromyotonia.[5] An important caveat, however, is that thymoma can be associated with other (non-neuromyotonia) autoimmune neuromuscular hyperexcitable disorders such as cramp–fasciculation syndrome and acquired rippling muscle syndrome due to nicotinic acetylcholine receptor (AChR) autoantibodies.[106] Finally, rare focal lesions of the spinal cord have been reported to cause an SPS-like picture. These are intrinsic neoplasms,[82,123] syringomyelia,[144] trauma,[108] and spinal cord ischemia.[36]

It should be noted that the stiff-baby syndrome is the neonatal form of hyperekplexia, a condition that presents at birth with hypertonia, exaggerated startle reflex, and pronounced brainstem reflexes, including head retraction reflex.[3] The muscle stiffness typically recedes during the first year of life, but a marked startle reflex, sometimes accompanied by transient hypertonia, can persist throughout adulthood. Notably, some cases of hyperekplexia were originally reported as congenital forms of SPS.[129] Lastly, a childhood-onset SPS-like presentation was reported in a boy with mutation of an autosomal dominant dystonia gene (*DYT1*) and no anti-GAD antibodies.[160] His asymptomatic sister has diabetes mellitus and anti-GAD antibodies but no *DYT1* mutation. *DYT1* accounts for 90% of early limb-onset generalized primary dystonia among Ashkenazi Jews and in 40%–60% of similar non-Jewish cases.[73,74] The investigations suggested for SPS-like conditions are listed in Table 3.

TREATMENT

Enhancing GABA neurotransmission and removing pathogenic antibodies are the aims of the current

Table 3. Investigations in SPS-like disorders.

Investigations	Finding	Disorder
Additional history	Laceration or open wound	Suspect tetanus
	Exposure to rat pesticide	Suspect strychnine poisoning
EMG	Neuromyotonic discharges	Neuromyotonia
Laboratory studies	Strychnine (urine or serum)	Strychnine poisoning
	VGKC antibodies	Neuromyotonia
	AChR antibodies	Cramp-fasciculation syndrome
		Acquired rippling muscle syndrome
	GLAR1 gene mutation	Hyperekplexia
	DYT1 gene mutation	Hereditary dystonia
CSF	Lymphocytic pleocytosis	Encephalomyelitis lethargica
		PERM variant
	Borrelia burgdorferi titers	Neuroborreliosis (Lyme disease)

VGKC, voltage-gated potassium channel; AChR, acetylcholine receptor; GLAR1, gene encoding the α1 subunit of the glycine receptor.

treatment strategies (Table 4). In general, drugs that promote GABAergic inhibition, such as benzodiazepines (diazepam and clonazepam) and baclofen, and those reducing monoaminergic effects, such as clonidine and tizanidine, diminish the severity of spasms and stiffness.[26,75,93] High-dose benzodiazepines are known to abolish the excessive motor unit activity.[15,26] Oral baclofen provides relatively modest relief of clinical symptoms[111] compared to intrathecal administration.[107] The latter improved electrophysiological measures (decreased mean EMG activity in exteroceptive reflexes, prolonged latency to onset of response) in all of three patients but led to clinical improvement in only one.[134] Benefit has been reported from the use of antiepileptic drugs such as valproate,[141] levetiracetam,[122] vigabatrin,[150] tiagabine,[99] and gabapentin.[148]

The presence of pathogenic autoantibodies provides the rationale to consider immunosuppressants, plasmapheresis, or intravenous immunoglobulin (IVIg). Prednisone has brought benefits to selected SPS patients.[52,110] A randomized, placebo-controlled cross-over design study demonstrated safety and efficacy of IVIg in 16 SPS patients with anti-GAD antibodies.[29,30] Several case reports have shown that plasmapheresis lowers antibody titers, reduces motor unit activity, decreases exteroceptive reflex responses, and results in marked clinical improvement in SPS patients.[16,58,60,101] Antibody-negative patients, however, are less likely to respond[132] but patients with the PERM variant may derive lasting remission with this treatment modality.[49] A dramatic response with lasting clinical remission to Rituximab, an anti-CD20 monoclonal antibody that specifically binds

Table 4. Treatment options in SPS.

Intervention	Doses used	Level of recommendation*
IVIg	2 g/kg IV in 2 daily doses	One class I study
Plasmapheresis	4 double filtration plasma exchanges of 3,000 ml each in an 8-day period	Two consistent class III studies
Prednisone	25–80 mg daily	Several class IV studies
Baclofen	50 μg intrathecally	One class I study
	10–100 mg per day orally	One class IV study
Rituximab	375 mg/m^2 IV	One class IV study
Diazepam	Up to 100 mg daily	Several class IV studies
Clonazepam	2.5–18 mg daily	One class IV study
Valproate	600 mg to 2 g daily	Several class IV studies
Levetiracetam	2,000 mg daily	One class IV study
Vigabatrin	2–3 g daily	Several class IV studies
Tiagabine	6 mg daily	One class IV study
Clonidine	0.0025 mg/kg daily	One class IV study
Botulinum toxin type A	500–1,000 U in L1–L5 paraspinal muscles	Two class IV studies
Gabapentin	300–3,600 mg daily	Expert opinion

**Class of studies[163]: I, prospective, randomized, controlled clinical trial; II, prospective matched group cohort study; III, all other controlled trials where outcome is independently assessed or independently derived by objective outcome measurement; IV, evidence from uncontrolled studies, case series, case reports, or expert opinion. Most of the above treatments were administered to patients with SPS associated with anti-GAD antibodies, with exceptions noted in the text.*

and destroys mature B lymphocytes, was recently reported in a 41-year-old woman with anti–GAD-positive SPS.[11] Anti-GAD antibodies became undetectable with this treatment, providing further support for SPS to represent a B-cell–mediated autoimmune disease. This report is sufficiently promising to warrant confirmation through a controlled clinical trial.

Injections of botulinum toxin have been reported to reduce the tone of paraspinal and thigh muscles and result in marked improvement of ambulation and a cessation of pain.[34] This observation was confirmed in two bedridden SPS patients who had bilateral improvement of rigidity and spasm following injections in one limb (argued to result from hematogenous spread).[79] The benefits lasted about 4 months. The use of tricyclic antidepressants may worsen stiffness. Rapid withdrawal from therapy may be life-threatening and should be avoided.[93,100]

Finally, the recognition of the neurological symptoms and signs of paraneoplastic SPS and their specific serum autoantibodies allow earlier identification and treatment of the underlying cancer and, potentially, a reduction in morbidity and mortality derived from both the malignancy and the neurological manifestation.[81] For paraneoplastic SPS, after removal of cancer, if one can be identified, immunotherapy is accompanied by a significant improvement of the neurological symptoms.[33,50]

REFERENCES

1. Alberca R, Romero M, Chaparro J. Jerking stiff-man syndrome. J Neurol Neurosurg Psychiatry 1982;45:1159–1160.
2. Ameli R, Snow J, Rakocevic G, Dalakas MC. A neuropsychological assessment of phobias in patients with stiff person syndrome. Neurology 2005;64:1961–1963.
3. Andrew M, Owen MJ. Hyperekplexia: abnormal startle response due to glycine receptor mutations. Br J Psychiatry 1997;170:106–108.
4. Antoine JC, Absi L, Honnorat J, Boulesteix JM, de Brouker T, Vial C, et al. Antiamphiphysin antibodies are associated with various paraneoplastic neurological syndromes and tumors. Arch Neurol 1999;56:172–177.
5. Antozzi C, Frassoni C, Vincent A, Regondi MC, Andreetta F, Bernasconi P, et al. Sequential antibodies to potassium channels and glutamic acid decarboxylase in neuromyotonia. Neurology 2005;64:1290–1293.
6. Arimura K. Isaacs' syndrome, stiff person syndrome and Satoyoshi disease: pathomechanisms and treatment. Rinsho Shinkeigaku 2004;44:805–807.
7. Asada H, Kawamura Y, Maruyama K, Kume H, Ding R, Ji FY, et al. Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. Biochem Biophys Res Commun 1996;229:891–895.
8. Asada H, Kawamura Y, Maruyama K, Kume H, Ding RG, Kanbara N, et al. Cleft palate and decreased brain gamma-aminobutyric acid in mice lacking the 67-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci U S A 1997;94:6496–6499.
9. Asher R. A woman with the stiff-man syndrome. Br Med J 1958;14:265–266.
10. Baekkeskov S, Aanstoot HJ, Christgau S, Reetz A, Solimena M, Cascalho M, et al. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature 1990;347:151–156.
11. Baker MR, Das M, Isaacs J, Fawcett PR, Bates D. Treatment of stiff person syndrome with rituximab. J Neurol Neurosurg Psychiatry 2005;76:999–1001.
12. Barker RA, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 1998;65:633–640.
13. Berger C, Meinck HM. Head retraction reflex in stiff-man syndrome and related disorders. Mov Disord 2003;18:906–911.
14. Blum P, Jankovic J. Stiff-person syndrome: an autoimmune disease. Mov Disord 1991;6:12–20.
15. Boiardi A, Crenna P, Bussone G, Negri S, Merati B. Neurological and pharmacological evaluation of a case of stiff-man syndrome. J Neurol 1980;223:127–133.
16. Brashear HR, Phillips LH. Autoantibodies to GABAergic neurons and response to plasmapheresis in stiff-man syndrome. Neurology 1991;41:1588–1592.
17. Brown P, Marsden CD. The stiff man and stiff man plus syndromes. J Neurol 1999;246:648–652.
18. Brown P, Rothwell JC, Marsden CD. The stiff leg syndrome. J Neurol Neurosurg Psychiatry 1997;62:31–37.
19. Brown P, Rothwell JC, Thompson PD, Britton TC, Day BL, Marsden CD. The hyperekplexias and their relationship to the normal startle reflex. Brain 1991;114:1903–1928.
20. Brown TJ. Isaacs syndrome. Arch Phys Med Rehabil 1984;65:27–29.
21. Bu DF, Erlander MG, Hitz BC, Tillakaratne NJ, Kaufman DL, Wagner-McPherson CB, et al. Two human glutamate decarboxylases, 65-kDa GAD and 67-kDa GAD, are each encoded by a single gene. Proc Natl Acad Sci U S A 1992;89:2115–2119.
22. Burn DJ, Ball J, Lees AJ, Behan PO, Morgan-Hughes JA. A case of progressive encephalomyelitis with rigidity and positive antiglutamic acid decarboxylase antibodies. J Neurol Neurosurg Psychiatry 1991;54:449–451.
23. Butler MH, Hayashi A, Ohkoshi N, Villmann C, Becker CM, Feng G, et al. Autoimmunity to gephyrin in stiff-man syndrome. Neuron 2000;26:307–312.
24. Casado JL, Gil-Peralta A, Graus F, Arenas C, Lopez JM, Alberca R. Anti-Ri antibodies associated with opsoclonus and progressive encephalomyelitis with rigidity. Neurology 1994;44:1521–1522.
25. Chattopadhyay S, Ito M, Cooper JD, Brooks AI, Curran TM, Powers JM, et al. An autoantibody inhibitory to glutamic acid decarboxylase in the neurodegenerative disorder Batten disease. Hum Mol Genet 2002;11:1421–1431.
26. Cohen L. Stiff-man syndrome. Two patients treated with diazepam. JAMA 1966;195:222–224.
27. Curtis DR, De Groat WC. Tetanus toxin and spinal inhibition. Brain Res 1968;10:208–212.
28. Curtis DR, Felix D, Game CJ, McCulloch RM. Tetanus toxin and the synaptic release of GABA. Brain Res 1973;51:358–362.
29. Dalakas MC. The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. J Neurol 2005;252(Suppl 1):I19–I25.
30. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med 2001;345:1870–1876.
31. Dalakas MC, Fujii M, Li M, McElroy B. The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. Neurology 2000;55:1531–1535.

32. Dalakas MC, Li M, Fujii M, Jacobowitz DM. Stiff person syndrome: quantification, specificity, and intrathecal synthesis of GAD65 antibodies. Neurology 2001;57:780–784.
33. David C, Solimena M, De Camilli P. Autoimmunity in stiff-man syndrome with breast cancer is targeted to the C-terminal region of human amphiphysin, a protein similar to the yeast proteins, Rvs167 and Rvs161. FEBS Lett 1994;351:73–79.
34. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. Mov Disord 1993;8:371–373.
35. Davis M, Gendelman DS, Tischler MD, Gendelman PM. A primary acoustic startle circuit: lesion and stimulation studies. J Neurosci 1982;2:791–805.
36. Davis SM, Murray NM, Diengdoh JV, Galea-Debono A, Kocen RS. Stimulus-sensitive spinal myoclonus. J Neurol Neurosurg Psychiatry 1981;44:884–888.
37. De Camilli P, Thomas A, Cofiell R, Folli F, Lichte B, Piccolo G, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man syndrome with breast cancer. J Exp Med 1993;178:2219–2223.
38. Dinkel K, Meinck HM, Jury KM, Karges W, Richter W. Inhibition of gamma-aminobutyric acid synthesis by glutamic acid decarboxylase autoantibodies in stiff-man syndrome. Ann Neurol 1998;44:194–201.
39. Dropcho EJ. Antiamphiphysin antibodies with small-cell lung carcinoma and paraneoplastic encephalomyelitis. Ann Neurol 1996;39:659–667.
40. Drost G, Verrips A, Hooijkaas H, Zwarts M. Glutamic acid decarboxylase antibodies in Satoyoshi syndrome. Ann Neurol 2004;55:450–451.
41. Economides JR, Horton JC. Eye movement abnormalities in stiff person syndrome. Neurology 2005;65:1462–1464.
42. Ellis TM, Atkinson MA. The clinical significance of an autoimmune response against glutamic acid decarboxylase. Nat Med 1996;2:148–153.
43. Erlander MG, Tillakaratne NJ, Feldblum S, Patel N, Tobin AJ. Two genes encode distinct glutamate decarboxylases. Neuron 1991;7:91–100.
44. Erlander MG, Tobin AJ. The structural and functional heterogeneity of glutamic acid decarboxylase: a review. Neurochem Res 1991;16:215–226.
45. Feng G, Tintrup H, Kirsch J, Nichol MC, Kuhse J, Betz H, et al. Dual requirement for gephyrin in glycine receptor clustering and molybdoenzyme activity. Science 1998;282:1321–1324.
46. Ferrari P, Federico M, Grimaldi LM, Silingardi V. Stiff-man syndrome in a patient with Hodgkin's disease. An unusual paraneoplastic syndrome. Haematologica 1990;75:570–572.
47. Floeter MK, Valls-Sole J, Toro C, Jacobowitz D, Hallett M. Physiologic studies of spinal inhibitory circuits in patients with stiff-person syndrome. Neurology 1998;51:85–93.
48. Floyd S, Butler MH, Cremona O, David C, Freyberg Z, Zhang X, et al. Expression of amphiphysin I, an autoantigen of paraneoplastic neurological syndromes, in breast cancer. Mol Med 1998;4:29–39.
49. Fogan L. Progressive encephalomyelitis with rigidity responsive to plasmapheresis and immunosuppression. Ann Neurol 1996;40:451–453.
50. Folli F, Solimena M, Cofiell R, Austoni M, Tallini G, Fassetta G, et al. Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. N Engl J Med 1993;328:546–551.
51. Gallien P, Durufle A, Petrilli S, Verin M, Brissot R, Robineau S. Atypical low back pain: stiff-person syndrome. Joint Bone Spine 2002;69:218–221.
52. George TM, Burke JM, Sobotka PA, Greenberg HS, Vinik AI. Resolution of stiff-man syndrome with cortisol replacement in a patient with deficiencies of ACTH, growth hormone, and prolactin. N Engl J Med 1984;310:1511–1513.
53. Giometto B, Nicolao P, Macucci M, Tavolato B, Foxon R, Bottazzo GF. Temporal-lobe epilepsy associated with glutamic-acid-decarboxylase autoantibodies. Lancet 1998;352:457.
54. Goetz CG, Klawans HL. On the mechanism of sudden death in Moersch-Woltman syndrome. Neurology 1983;33:930–932.
55. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. Am J Med 1967;42:582–599.
56. Guilleminault C, Sigwald J, Castaigne P. Sleep studies and therapeutic trial with L-dopa in a case of stiffman syndrome. Eur Neurol 1973;10:89–96.
57. Gurol ME, Ertas M, Hanagasi HA, Sahin HA, Gursoy G, Emre M. Stiff leg syndrome: case report. Mov Disord 2001; 16:1189–1193.
58. Hao W, Davis C, Hirsch IB, Eng LJ, Daniels T, Walsh D, et al. Plasmapheresis and immunosuppression in stiff-man syndrome with type 1 diabetes: a 2-year study. J Neurol 1999; 246:731–735.
59. Hardin JA, Griggs RC. Diazepam treatment in a case of strychnine poisoning. Lancet 1971;2:372–373.
60. Hayashi A, Nakamagoe K, Ohkoshi N, Hoshino S, Shoji S. Double filtration plasma exchange and immunoadsorption therapy in a case of stiff-man syndrome with negative anti-GAD antibody. J Med 1999;30:321–327.
61. Honnorat J, Saiz A, Giometto B, Vincent A, Brieva L, de Andres C, et al. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. Arch Neurol 2001;58:225–230.
62. Howard FM Jr. A new and effective drug in the treatment of the stiff-man syndrome: preliminary report. Mayo Clin Proc 1963;38:203–212.
63. Howell DA, Lees AJ, Toghill PJ. Spinal internuncial neurones in progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 1979;42:773–785.
64. Ikeda K, Satoyoshi E, Kinoshita M, Wakata N, Iwasaki Y. Satoyoshi's syndrome in an adult: a review of the literature of adult onset cases. Intern Med 1998;37:784–787.
65. Ishida K, Mitoma H, Song SY, Uchihara T, Inaba A, Eguchi S, et al. Selective suppression of cerebellar GABAergic transmission by an autoantibody to glutamic acid decarboxylase. Ann Neurol 1999;46:263–267.
66. Ishizawa K, Komori T, Okayama K, Qin X, Kaneko K, Sasaki S, et al. Large motor neuron involvement in stiff-man syndrome: a qualitative and quantitative study. Acta Neuropathol (Berl) 1999;97:63–70.
67. Kash SF, Johnson RS, Tecott LH, Noebels JL, Mayfield RD, Hanahan D, et al. Epilepsy in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci U S A 1997;94:14060–14065.
68. Kasperek S, Zebrowski S. Stiff-man syndrome and encephalomyelitis. Report of a case. Arch Neurol 1971;24:22–30.
69. Khasani S, Becker K, Meinck HM. Hyperekplexia and stiff-man syndrome: abnormal brainstem reflexes suggest a physiological relationship. J Neurol Neurosurg Psychiatry 2004; 75:1265–1269.
70. Kissel JT, Elble RJ. Stiff-person syndrome: stiff opposition to a simple explanation. Neurology 1998;51:11–14.
71. Kocak E, Abdessalam S, Walker MJ, Nuovo GJ, Kissel JT. Stiff-person syndrome: a rare presentation for breast cancer. Breast J 2004;10:552–553.
72. Koerner C, Wieland B, Richter W, Meinck HM. Stiff-person syndromes: motor cortex hyperexcitability correlates with anti-GAD autoimmunity. Neurology 2004;62:1357–1362.
73. Kramer PL, de Leon D, Ozelius L, Risch N, Bressman SB, Brin MF, et al. Dystonia gene in Ashkenazi Jewish population is located on chromosome 9q32–34. Ann Neurol 1990;27: 114–120.
74. Kramer PL, Heiman GA, Gasser T, Ozelius LJ, de Leon D, Brin MF, et al. The DYT1 gene on 9q34 is responsible for most cases of early limb-onset idiopathic torsion dystonia in non-Jews. Am J Hum Genet 1994;55:468–475.
75. Kuhn WF, Light PJ, Kuhn SC. Stiff-man syndrome: case report. Acad Emerg Med 1995;2:735–738.

76. Leigh PN, Rothwell JC, Traub M, Marsden CD. A patient with reflex myoclonus and muscle rigidity: "jerking stiff-man syndrome." J Neurol Neurosurg Psychiatry 1980;43:1125–1131.
77. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann Intern Med 1999; 131:522–530.
78. Levy LM, Levy-Reis I, Fujii M, Dalakas MC. Brain gamma-aminobutyric acid changes in stiff-person syndrome. Arch Neurol 2005;62:970–974.
79. Liguori R, Cordivari C, Lugaresi E, Montagna P. Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. Mov Disord 1997;12:1060–1063.
80. Lorish TR, Thorsteinsson G, Howard FM Jr. Stiff-man syndrome updated. Mayo Clin Proc 1989;64:629–636.
81. Lorusso L, Hart IK, Giometto B, Pezzani R, Broome JC, Gritti D, et al. Immunological features of neurological paraneoplastic syndromes. Int J Immunopathol Pharmacol 2004;17:135–144.
82. Lourie H. Spontaneous activity of alpha motor neurons in intramedullary spinal cord tumor. J Neurosurg 1968;29:573–580.
83. Martin DL, Rimvall K. Regulation of gamma-aminobutyric acid synthesis in the brain. J Neurochem 1993;60:395–407.
84. Martin R, Meinck HM, Schulte-Mattler W, Ricker K, Mertens HG. Borrelia burgdorferi myelitis presenting as a partial stiff man syndrome. J Neurol 1990;237:51–54.
85. Martinelli P, Nassetti S, Minardi C, Macri S, Ippoliti M. Electrophysiological evaluation of the stiff-man syndrome: further data. J Neurol 1996;243:551–553.
86. Martinelli P, Pazzaglia P, Montagna P, Coccagna G, Rizzuto N, Simonati S, et al. Stiff-man syndrome associated with nocturnal myoclonus and epilepsy. J Neurol Neurosurg Psychiatry 1978;41:458–462.
87. Matsumoto J, Fuhr P, Nigro M, Hallett M. Physiological abnormalities in hereditary hyperekplexia. Ann Neurol 1992;32:41–50.
88. Matsumoto JY, Caviness JN, McEvoy KM. The acoustic startle reflex in stiff-man syndrome. Neurology 1994;44:1952–1955.
89. McCabe DJ, Turner NC, Chao D, Leff A, Gregson NA, Womersley HJ, et al. Paraneoplastic "stiff person syndrome" with metastatic adenocarcinoma and anti-Ri antibodies. Neurology 2004;62:1402–1404.
90. McCombe PA, Chalk JB, Searle JW, Tannenberg AE, Smith JJ, Pender MP. Progressive encephalomyelitis with rigidity: a case report with magnetic resonance imaging findings. J Neurol Neurosurg Psychiatry 1989;52:1429–1431.
91. Meinck HM, Faber L, Morgenthaler N, Seissler J, Maile S, Butler M, et al. Antibodies against glutamic acid decarboxylase: prevalence in neurological diseases. J Neurol Neurosurg Psychiatry 2001;71:100–103.
92. Meinck HM, Ricker K. Long-standing "stiff-man" syndrome: a particular form of disseminated inflammatory CNS disease? J Neurol Neurosurg Psychiatry 1987;50:1556–1557.
93. Meinck HM, Ricker K, Conrad B. The stiff-man syndrome: new pathophysiological aspects from abnormal exteroceptive reflexes and the response to clomipramine, clonidine, and tizanidine. J Neurol Neurosurg Psychiatry 1984;47:280–287.
94. Meinck HM, Ricker K, Hulser PJ, Solimena M. Stiff man syndrome: neurophysiological findings in eight patients. J Neurol 1995;242:134–142.
95. Meinck HM, Thompson PD. Stiff man syndrome and related conditions. Mov Disord 2002;17:853–866.
96. Mitsumoto H, Schwartzman MJ, Estes ML, Chou SM, La Franchise EF, De Camilli P, et al. Sudden death and paroxysmal autonomic dysfunction in stiff-man syndrome. J Neurol 1991;238:91–96.
97. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome); report of a case and some observations in 13 other cases. Mayo Clin Proc 1956;31:421–427.
98. Molloy FM, Dalakas MC, Floeter MK. Increased brainstem excitability in stiff-person syndrome. Neurology 2002;59:449–451.
99. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. Neurology 2001;57:366.
100. Murinson BB, Vincent A. Stiff-person syndrome: autoimmunity and the central nervous system. CNS Spectr 2001;6:427–433.
101. Nakamagoe K, Ohkoshi N, Hayashi A, Hisahara S, Shoji S. Marked clinical improvement by plasmapheresis in a patient with stiff-man syndrome: a case with a negative anti-GAD antibody. Rinsho Shinkeigaku 1995;35:897–900.
102. Nemni R, Braghi S, Natali-Sora MG, Lampasona V, Bonifacio E, Comi G, et al. Autoantibodies to glutamic acid decarboxylase in palatal myoclonus and epilepsy. Ann Neurol 1994; 36:665–667.
103. Newsom-Davis J, Buckley C, Clover L, Hart I, Maddison P, Tuzum E, et al. Autoimmune disorders of neuronal potassium channels. Ann N Y Acad Sci 2003;998:202–210.
104. Orija IB, Gupta M, Zimmerman RS. Graves' disease and stiff-person (stiff-man) syndrome: case report and literature review. Endocr Pract 2005;11:259–264.
105. Pearce DA, Atkinson M, Tagle DA. Glutamic acid decarboxylase autoimmunity in Batten disease and other disorders. Neurology 2004;63:2001–2005.
106. Peltola J, Kulmala P, Isojarvi J, Saiz A, Latvala K, Palmio J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology 2000;55:46–50.
107. Penn RD, Mangieri EA. Stiff-man syndrome treated with intrathecal baclofen. Neurology 1993;43:2412.
108. Penry JK, Hoefnagel D, Van den Noort S, Denny-Brown D. Muscle spasm and abnormal postures resulting from damage to interneurones in spinal cord. Arch Neurol 1960;3:500–512.
109. Petzold GC, Marcucci M, Butler MH, van Landeghem FK, Einhaupl KM, Solimena M, et al. Rhabdomyolysis and paraneoplastic stiff-man syndrome with amphiphysin autoimmunity. Ann Neurol 2004;55:286–290.
110. Piccolo G, Cosi V, Zandrini C, Moglia A. Steroid-responsive and dependent stiff-man syndrome: a clinical and electrophysiological study of two cases. Ital J Neurol Sci 1988;9:559–566.
111. Piovano C, Piattelli M, Spina T, Iervese G, Bosco G. The stiff-person syndrome. Case report. Minerva Anestesiol 2002; 68:861–865.
112. Pittock SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 2005;58:96–107.
113. Pugliese A, Solimena M, Awdeh ZL, Alper CA, Bugawan T, Erlich HA, et al. Association of HLA-DQB1*0201 with stiff-man syndrome. J Clin Endocrinol Metab 1993;77:1550–1553.
114. Raju R, Foote J, Banga JP, Hall TR, Padoa CJ, Dalakas MC, et al. Analysis of GAD65 autoantibodies in stiff-person syndrome patients. J Immunol 2005;175:7755–7762.
115. Rakocevic G, Raju R, Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. Arch Neurol 2004;61:902–904.
116. Ramirez-Montealegre D, Chattopadhyay S, Curran TM, Wasserfall C, Pritchard L, Schatz D, et al. Autoimmunity to glutamic acid decarboxylase in the neurodegenerative disorder Batten disease. Neurology 2005;64:743–745.
117. Reetz A, Solimena M, Matteoli M, Folli F, Takei K, De Camilli P. GABA and pancreatic beta-cells: colocalization of glutamic acid decarboxylase (GAD) and GABA with synaptic-like microvesicles suggests their role in GABA storage and secretion. EMBO J 1991;10:1275–1284.
118. Requena I, Arias M, Pardo J, Portela M, Alvarez JA. Syndromes of continuous muscular activity: report of a central case (stiff-man) and a peripheral case (neuromyotonia) associated with neuroborreliosis. Rev Neurol 1995;23:129–133.
119. Roobol TH, Kazzaz BA, Vecht CJ. Segmental rigidity and spinal myoclonus as a paraneoplastic syndrome. J Neurol Neurosurg Psychiatry 1987;50:628–631.
120. Rosin L, DeCamilli P, Butler M, Solimena M, Schmitt HP, Morgenthaler N, et al. Stiff-man syndrome in a woman with

breast cancer: an uncommon central nervous system paraneoplastic syndrome. Neurology 1998;50:94–98.
121. Rossi B, Massetani R, Guidi M, Mondelli M, Rossi A. Electrophysiological findings in a case of stiff-man syndrome. Electromyogr Clin Neurophysiol 1988;28:137–140.
122. Ruegg SJ, Steck AJ, Fuhr P. Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. Neurology 2004;62:338.
123. Rushworth G, Lishman WA, Hughes JT, Oppenheimer DR. Intense rigidity of the arms due to isolation of motoneurones by a spinal tumour. J Neurol Neurosurg Psychiatry 1961;24:132–142.
124. Saiz A, Arpa J, Sagasta A, Casamitjana R, Zarranz JJ, Tolosa E, et al. Autoantibodies to glutamic acid decarboxylase in three patients with cerebellar ataxia, late-onset insulin-dependent diabetes mellitus, and polyendocrine autoimmunity. Neurology 1997;49:1026–1030.
125. Saiz A, Dalmau J, Butler MH, Chen Q, Delattre JY, De Camilli P, et al. Anti-amphiphysin I antibodies in patients with paraneoplastic neurological disorders associated with small cell lung carcinoma. J Neurol Neurosurg Psychiatry 1999;66:214–217.
126. Saiz A, Graus F, Valldeoriola F, Valls-Sole J, Tolosa E. Stiff-leg syndrome: a focal form of stiff-man syndrome. Ann Neurol 1998;43:400–403.
127. Saiz A, Minguez A, Graus F, Marin C, Tolosa E, Cruz-Sanchez F. Stiff-man syndrome with vacuolar degeneration of anterior horn motor neurons. J Neurol 1999;246:858–860.
128. Sandbrink F, Syed NA, Fujii MD, Dalakas MC, Floeter MK. Motor cortex excitability in stiff-person syndrome. Brain 2000;123:2231–2239.
129. Sander JE, Layzer RB, Goldsobel AB. Congenital stiff-man syndrome. Ann Neurol 1980;8:195–197.
130. Sanger TD, Garg RR, Chen R. Interactions between two different inhibitory systems in the human motor cortex. J Physiol (Lond) 2001;530:307–317.
131. Schmierer K, Valdueza JM, Bender A, DeCamilli P, David C, Solimena M, et al. Atypical stiff-person syndrome with spinal MRI findings, amphiphysin autoantibodies, and immunosuppression. Neurology 1998;51:250–252.
132. Shariatmadar S, Noto TA. Plasma exchange in stiff-man syndrome. Ther Apher 2001;5:64–67.
133. Shiang R, Ryan SG, Zhu YZ, Hahn AF, O'Connell P, Wasmuth JJ. Mutations in the alpha 1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperekplexia. Nat Genet 1993;5:351–358.
134. Silbert PL, Matsumoto JY, McManis PG, Stolp-Smith KA, Elliott BA, McEvoy KM. Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. Neurology 1995;45:1893–1897.
135. Silverman IE. Paraneoplastic stiff limb syndrome. J Neurol Neurosurg Psychiatry 1999;67:126–127.
136. Slater JD. Muscle 'contractures' and the 'stiff-man' syndrome. Clin Rheum Dis 1986;12:791–809.
137. Solimena M, De Camilli P. Autoimmunity to glutamic acid decarboxylase (GAD) in stiff-man syndrome and insulin-dependent diabetes mellitus. Trends Neurosci 1991;14:452–457.
138. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322:1555–1560.
139. Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 1988;318:1012–1020.
140. Sommer C, Weishaupt A, Brinkhoff J, Biko L, Wessig C, Gold R, et al. Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. Lancet 2005;365:1406–1411.
141. Spehlmann R, Norcross K, Rasmus SC, Schlageter NL. Improvement of stiff-man syndrome with sodium valproate. Neurology 1981;31:1162–1163.
142. Steffen H, Menger N, Richter W, Nolle B, Krastel H, Stayer C, et al. Immune-mediated retinopathy in a patient with stiff-man syndrome. Graefes Arch Clin Exp Ophthalmol 1999;237:212–219.
143. Tanaka H, Matsumura A, Okumura M, Kitaguchi M, Yamamoto S, Iuchi K. Stiff man syndrome with thymoma. Ann Thorac Surg 2005;80:739–741.
144. Tarlov IM. Rigidity in man due to spinal interneuron loss. Arch Neurol 1967;16:536–543.
145. Thomas S, Critchley P, Lawden M, Farooq S, Thomas A, Proudlock FA, et al. Stiff person syndrome with eye movement abnormality, myasthenia gravis, and thymoma. J Neurol Neurosurg Psychiatry 2005;76:141–142.
146. Tijssen MA, Voorkamp LM, Padberg GW, van Dijk JG. Startle responses in hereditary hyperekplexia. Arch Neurol 1997; 54:388–393.
147. Trethowan WH, Allsop JL, Turner B. The "stiff-man" syndrome. A report of two further cases. Arch Neurol 1960;3:448–456.
148. Vasconcelos OM, Dalakas MC. Stiff-person Syndrome. Curr Treat Options Neurol 2003;5:79–90.
149. Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, et al. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. Diabetes 1998;47:1857–1866.
150. Vermeij FH, van Doorn PA, Busch HF. Improvement of stiff-man syndrome with vigabatrin. Lancet 1996;348:612.
151. Vianello M, Tavolato B, Giometto B. Glutamic acid decarboxylase autoantibodies and neurological disorders. Neurol Sci 2002;23:145–151.
152. Walshe FMR. On the symptom-complexes of lethargic encephalitis with special reference to involuntary muscular contractions. Brain 1920;43:197–219.
153. Warich-Kirches M, Von Bossanyi P, Treuheit T, Kirches E, Dietzmann K, Feistner H, et al. Stiff-man syndrome: possible autoimmune etiology targeted against GABA-ergic cells. Clin Neuropathol 1997;16:214–219.
154. Warren JD, Scott G, Blumbergs PC, Thompson PD. Pathological evidence of encephalomyelitis in the stiff man syndrome with anti-GAD antibodies. J Clin Neurosci 2002;9:328–329.
155. Watanabe K, Shimizu T, Mannen T, Toyokura Y, Nagashima K. [An autopsy case with unusual muscle rigidity resembling the stiff-man syndrome]. Rinsho Shinkeigaku 1984;24:839–847.
156. Weatherby SJ, Woolner P, Clarke CE. Pregnancy in stiff-limb syndrome. Mov Disord 2004;19:852–854.
157. Werbrouck B, Meire V, De Bleecker JL. Multiple neurological syndromes during Hodgkin lymphoma remission. Acta Neurol Belg 2005;105:48–50.
158. Wessig C, Klein R, Schneider MF, Toyka KV, Naumann M, Sommer C. Neuropathology and binding studies in anti-amphiphysin-associated stiff-person syndrome. Neurology 2003;61:195–198.
159. Whiteley AM, Swash M, Urich H. Progressive encephalomyelitis with rigidity. Brain 1976;99:27–42.
160. Wong VC, Lam CW, Fung CW. Stiff child syndrome with mutation of DYT1 gene. Neurology 2005;65:1465–1466.
161. Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, et al. FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. Brain 2004;127:2331–2338.
162. Young AB, Snyder SH. Strychnine binding associated with glycine receptors of the central nervous system. Proc Natl Acad Sci U S A 1973;70:2832–2836.
163. Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005;64: 2008–2020.
164. Ziemann U. TMS and drugs. Clin Neurophysiol 2004;115: 1717–1729.