

**AUTOIMMUNE STIFF PERSON SYNDROME AND RELATED
MYELOPATHIES: UNDERSTANDING OF ELECTROPHYSIOLOGICAL AND
IMMUNOLOGICAL PROCESSES**

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Abstract

Stiff Person Syndrome (SPS) is a disabling autoimmune CNS disorder characterized by progressive muscle rigidity and gait impairment with superimposed painful spasms that involve axial and limb musculature, triggered by heightened sensitivity to external stimuli. Impaired synaptic GABAergic inhibition resulting from intrathecal B-cell-mediated clonal synthesis of autoantibodies against various presynaptic and synaptic proteins in the inhibitory neurons of the brain and spinal cord is believed to be an underlying pathogenic mechanism. SPS is most often idiopathic, but it can occur as a paraneoplastic condition. Despite evidence that anti-GAD and related autoantibodies impair GABA synthesis, the exact pathogenic mechanism of SPS is not fully elucidated. The strong association with several MHC-II alleles and improvement of symptoms with immune-modulating therapies support an autoimmune etiology of SPS. In this review, we discuss the clinical spectrum, neurophysiological mechanisms, and therapeutic options, including a rationale for agents that modulate B cell function in SPS.

Keywords

GABA, anti-GAD antibodies, stiff person syndrome, autoimmunity, paraneoplastic disorders

List of Abbreviations

Anti-RNP- Anti-Ribonucleoprotein antibody

CNS- Central Nervous System

CSF- Cerebrospinal fluid

DM1- Diabetes mellitus type I

ELISA- Enzyme-linked immunosorbent assay

EMG- Electromyography

GABA- Gamma-aminobutyric acid

GABARAP_A - GABA-A- receptor associated protein

GAD- Glutamic acid decarboxylase

GAD65- Glutamic acid decarboxylase 65 kilodalton isoform

GAD67- Glutamic acid decarboxylase 67 kilodalton isoform

HLA- Histocompatibility leukocyte antigen

ICF- Intracortical facilitation

IDDM- Insulin-dependant diabetes mellitus

IgG- Immunoglobulin class G

IVIg- Intravenous immunoglobulin

MEP – motor evoked potential

mA- Miliamperes

MUP – motor unit potential

SICI – short intracortical inhibition

Introduction

Stiff Person Syndrome (SPS) was first described in 1956 as a new clinical entity by Moersch and Woltman in a series of 14 patients.¹ It is a rare CNS disorder characterized by progressive rigidity of the truncal muscles, superimposed spasms, and an exquisite sensitivity to external stimuli.^{2-5,1,6} Co-contractions of agonist and antagonist muscles and continuous involuntary firing of motor units at rest are the clinical and electrophysiological hallmarks of the disease.^{7-9,1} SPS is commonly associated with high anti-glutamic acid decarboxylase (GAD) antibody titers and a variety of other organ-specific autoantibodies across a wide spectrum of clinical presentations.¹⁰⁻¹³ The antibodies are believed to cause primarily a functional blockade in SPS by targeting antigens expressed in neurons of the brain and spinal cord at synapses using the neurotransmitter gamma-aminobutyric acid (GABA). Although some autopsies have shown evidence of perivascular inflammation, and, in the rapidly progressive encephalomyelitis variant, structural damage in the CNS,^{16,8,17,18} autopsies of typical cases showed no inflammation and relatively little decrease in neuronal numbers.^{14,15} High titers of anti-GAD antibodies in the serum and CSF of SPS patients seem to be directed against conformational forms of GAD selectively expressed in GABAergic neurons^{19,20,2,13,21,22,11,12} and can cause a blockade of GABA synthesis.²³ The acquired malfunction of the spinal and supra-segmental inhibitory networks utilizing GABA is hypothesized to be the mechanism underlying the excessive motor neuron firing in SPS.^{9,24,25,3,26,27}

GAD is also a major autoantigen in Insulin-dependant diabetes mellitus (IDDM), which is often associated with SPS. Although anti-GAD antibodies are detected in up to 80% of newly diagnosed type I diabetes patients, the titers are usually 50- to 100-fold less than in SPS patients with or without IDDM.^{19,28,2,29} Approximately 70% of SPS patients with high-titer GAD antibody also have antibodies against a synaptic protein, GABA-receptor-associated protein (GABARAP), that is involved in the endocytosis, recycling and maintenance of synaptic vesicles and receptors.³⁰ In a subgroup of SPS patients, proximal muscle stiffness is a paraneoplastic manifestation of breast, ovarian or small-cell lung carcinomas (SCLC), associated with antibodies against amphiphysin,³¹⁻⁴¹ and gephyrin,⁴² two synaptic proteins. Paraneoplastic SPS with anti-amphiphysin antibodies is most commonly found in association with breast adenocarcinoma and SCLC.^{31,32,40,37,38,43-45} Of interest, anti-GAD antibody is conspicuously absent in these patients; in only one reported paraneoplastic SPS case with co-morbid renal carcinoma, anti-GAD, but not amphiphysin antibodies were present.⁴⁶ Currently, there are no immunoassays or 'gold-standard' diagnostic electrophysiological tests that unambiguously distinguish SPS from patients with other neurological syndromes associated with anti-GAD antibodies or IDDM.⁴⁷ Although anti-GAD and amphiphysin antibodies are presumed to be pathogenic in SPS, proof of their direct causative role is still lacking. We include in this review an update on immunological aspects and the current understanding of electrophysiological concepts in SPS as a continuum of the earlier review by Espay et al.⁴⁸

Clinical features and course

SPS rigidity usually begins insidiously in the thoracolumbar paraspinal muscles in patients in their mid-to-late 30s, usually without antecedent infection or other triggering factors, and extends over time to involve proximal leg and abdominal wall muscles. As a result of the muscle rigidity, patients develop a stiff, robotic gait and hyperlordosis of the spine with 'a board-like' appearance. Muscle rigidity may fluctuate at first but gradually becomes fixed and impairs the ability to bend and walk independently. SPS patients can exhibit major fluctuations of stiffness and spasms during a week or even over the course of a day. In general, they experience more symptoms and falls during times of physical or emotional stress, cold weather, and intercurrent infections. Rigidity typically improves during sleep. Although muscle stiffness is the '*sine qua non*' in SPS, not all patients experience prominent rigidity and muscle spasms initially, but they develop the classic symptoms over time. The increasing stiffness over time results in substantial progression of functional impairment, and, in general, most patients require increasing doses or addition of new symptomatic therapies in order to achieve the same level of function.⁴⁹

The second set of pathognomonic symptoms is episodic spasms, which are sudden and sometimes painful. They are often precipitated by external stimuli and physical obstacles and may result in unprotected falls. Besides a heightened response to unexpected stimuli, SPS patients also suffer from marked anticipatory anxiety and task-specific phobias, and often from reactive depression as well.^{50,51} Much of the anxiety in SPS patients appears to be a realistic fear of falling, rather than an inherent psychiatric disorder. However,

conditioned responses and acquired dysregulation of hippocampus and amygdala circuits may play a role in the neuropsychological manifestations of SPS.^{50,52} As SPS progresses, the majority of patients have an increasing frequency of falls, require assistance for walking and activities of daily living, and frequently lose their ability to work.

Several subsets of SPS with more-or-less distinct clinical phenomenology and disease course have been described: 'Stiff-limb syndrome',⁵³⁻⁵⁵ SPS associated with myoclonus (Jerking stiff man syndrome), presumably from predominant brainstem involvement;^{56,57,26} SPS associated with epilepsy and dystonia;⁵⁷⁻⁵⁹ or SPS with neurophthalmologic manifestations such as autoimmune retinopathy.⁶⁰ Stiff person syndrome with progressive rigidity and encephalomyelitis is a much rarer form of SPS. It is characterized by a subacute encephalomyelitis that primarily affects the grey matter, resulting in widespread rigidity and rapid decline of cognitive capacities and typically leads to premature death.^{57,61,59,26} A cerebellar variant of SPS is characterized by prominent gait ataxia and dysmetria, as well as ocular findings consistent with cerebellar dysfunction without evidence of structural brain abnormalities.^{47,62-67}

The diagnosis of SPS is established by clinical findings and exclusion of pyramidal and extrapyramidal disorders, with supportive evidence from electrophysiological findings on EMG studies and serological and CSF testing that show elevated anti-GAD antibodies. Conventional MR imaging studies of the nervous system are usually normal.⁶⁸ Magnetic resonance spectroscopy has demonstrated a significant regional decrease in GABA levels in the motor cortex,^{3,68} providing supportive evidence of deficient GABAergic inhibition

as a pathophysiological mechanism in SPS. Diseases that should be differentiated from SPS include myelopathies, dystonias and other extrapyramidal diseases, neurodegenerative disorders such as spinocerebellar degenerations, primary lateral sclerosis, neuromyotonia or 'Isaacs syndrome', as well as rare forms of chronic tetanus and psychogenic disorders. Magnetic resonance imaging studies of the brain and spine are useful to exclude certain structural disorders, such as myelopathies. Electromyography plays an important role in establishing a diagnosis of SPS by demonstrating the characteristic involuntary firing of motor units.

Up to 35% of SPS patients have coexistent Type I diabetes, which may precede the onset of SPS by months to years or, more commonly, develop soon after the onset of stiffness.² Besides the relatively high prevalence of IDDM, there are several other organ-specific autoimmune diseases associated with SPS, including autoimmune thyroiditis, Graves' disease, pernicious anemia, vitiligo and celiac disease. Anti-GAD antibodies are an excellent serological marker for SPS; in addition, various other antibodies such as anti-thyroid, anti-intrinsic factor, anti-nuclear, anti-RNP, anti-gliadin and others are frequently present in serum. These likely represent a dysregulated immune system targeting different organs, as it is also observed in myasthenia gravis and other autoimmune disorders.

Physiology of SPS

The muscle stiffness in SPS is produced by involuntary firing of motor neurons resembling a normal voluntary contraction in needle EMG recordings.^{7,1} The motor unit

potentials (MUPs) have normal configurations and firing rates, and there are no findings suggestive of denervation. However, MUP firing continues when the SPS patient is at rest and during maneuvers, such as contraction of the antagonist muscle, which normally induce a reflex relaxation of the agonist muscle (**Figure 1**). Demonstrating failure of reciprocal inhibition by recording from antagonist muscle pairs can be helpful to support the diagnosis of SPS and to illustrate the involuntary nature of the contraction. In SPS, MUP firing at rest is particularly prominent in those muscles which exhibit clinical stiffness, typically the proximal leg and paraspinal muscles, and EMG recording from paraspinal muscles may be useful when limb muscle recordings are equivocal. Although the MUP activity is typically referred to as 'continuous MUP firing', the amount of activity observed in individual muscles fluctuates, and periods of relative relaxation can be appreciated in prolonged recordings made with surface EMG.⁶⁹ Sleep, treatment with benzodiazepines or baclofen, and general anesthesia reduce MUP firing as well as the stiffness and spasms.^{70-72,7,9,69} Reduction of MUP firing and spasms by diazepam has been used as one of the clinical diagnostic criteria for SPS.⁴⁻⁶

The spasms that occur in SPS can occur spontaneously or be triggered by external stimuli such as touch or loud sounds. Spasms typically begin abruptly, involve co-contraction of multiple muscles, are often bilateral, and may last for minutes or recur over several hours.^{7,26,69,9} Spasms can be strong enough to produce posturing of the limbs or spine and cause bone fractures.^{70,26} When spasms are elicited by cutaneous or acoustic stimuli, the timing and pattern of the initial muscle activation may resemble an exaggerated segmental or brainstem reflex, although there is abnormal spread of activity to additional

muscles, particularly the clinically stiff muscles. However, following the normal reflex, a prolonged muscle activation with co-contraction of antagonist muscles typically occurs, and is clinically observed as a spasm.^{9,26} This excessive spread of reflexes and spasms occurs with stimulation of cutaneous nerves at non-noxious intensities, as shown for the leg flexor reflex in an example from one patient (**Figure 2A**) and for blink reflexes⁷³ from another patient (**Figure 2B**). Demonstrating that stimulation of a cutaneous or mixed nerve produces EMG activity in distant limbs or paraspinal muscles can provide supportive evidence for the clinical impression of SPS. Acoustic startle responses are also abnormal in SPS, with spread to limb muscles and prominent spasms in leg or axial muscles where stiffness predominates.^{74,25} The disinhibition of startle responses and other brainstem reflexes in SPS is also seen in hereditary hyperekplexia, a disorder of glycinergic transmission, leading to the proposal that the excessive responsiveness to stimuli may reflect loss of inhibition at brainstem as well as spinal levels.^{25,73,75} The prolonged spasms following acoustic stimuli that occur in SPS are not seen, however, in hereditary hyperekplexia.

The involuntary motor neuron firing observed in SPS is not a primary abnormality of the motor neuron or of the monosynaptic stretch reflex arc. The MUPs fire at normal rates, and volitional recruitment is normal – except for co-contraction of antagonists. There is notable absence of the doublets, multiplets or repetitive discharges that are commonly seen with peripheral nerve hyperexcitability syndromes such as Isaacs disease.⁷⁶ Motor nerve conduction velocities, F-waves, T-waves, and H-reflexes are normal, as are the silent periods induced by mixed nerve stimulation and muscle stretch,^{77,7} which contrasts

to findings in patients with tetanus.⁷⁸ Despite the patient's muscle rigidity, stretch reflexes are brisk, and untreated SPS patients may exhibit clonus, but without abnormal plantar responses. Following the discovery of anti-GAD antibodies in SPS patients, several studies investigated the actions of interneuron circuits believed to use GABA as a neurotransmitter, with an initial focus on the inhibitory spinal cord interneuron circuits. Several studies reported enhanced H-reflex recovery and reduced vibration-induced H-reflex inhibition, phenomena which are believed to be mediated by GABAergic interneurons that produce presynaptic inhibition of stretch reflex afferents.^{24,79,9} One study that examined additional spinal inhibitory reflexes found a complex pattern of disinhibition, with sparing of some presumptive GABAergic spinal reflex circuits, and impairment of some presumptive glycinergic inhibitory circuits.²⁴ The authors speculated that these findings could result from previously unrecognized GABAergic contributions to presumed glycinergic reflexes, differential susceptibility of interneuron populations, or from impaired descending modulation of spinal inhibitory circuits by descending supraspinal systems.

Because the corticospinal system is known to modulate inhibitory spinal interneurons, Sandbrink and colleagues examined the excitability of the motor cortex in seven SPS patients using transcranial magnetic stimulation (TMS).²⁷ A paired-pulse TMS paradigm with subthreshold conditioning stimulation was used to assess short intracortical inhibition (SICI) and intracortical facilitation (ICF). In this paradigm, a subthreshold conditioning stimulus is given that activates cortical interneurons without producing a motor evoked potential (MEP), followed by a second "test" stimulus at an intensity

sufficient to produce a small MEP. At short interstimulus intervals, less than 5 ms, the MEP is inhibited, whereas at longer intervals, from 8-30 ms, the MEP is facilitated.⁸⁰

Sandbrink and colleagues found that SPS patients had markedly increased ICF compared to healthy controls; conditioning TMS stimuli did not produce similar facilitation of H-reflexes, demonstrating that the facilitation was not due to increased motor neuron excitability. Short intracortical inhibition is thought to be mediated by cortical GABAergic interneurons, but the mechanism of ICF is not entirely clear. Drugs that enhance GABAergic transmission or block the glutamatergic NMDA receptor reduce ICF.⁸¹⁻⁸³ Because ICF does not produce changes in spinal motor neuron excitability, as measured by its effects on H-reflexes,⁸⁴ it has been inferred that the facilitation is generated by intracortical circuits. It should be noted, however, that a recent study in patients with implanted epidural electrodes failed to find an increase in the number or amplitude of descending volleys associated with the facilitated MEP, raising the question whether facilitation occurred through unidentified subcortical circuits, undetected dispersed descending volleys, or changes in the composition of corticospinal neurons firing in the volley.⁸⁵

Sandbrink and colleagues also found that cortical silent periods following MEPs were shortened and that paired suprathreshold stimulation, which reflects cortical and spinal excitability, produced greater facilitation in SPS patients than healthy controls. SPS patients had normal thresholds for activating MEPs and normal central motor conduction times, providing evidence that interneurons, and not corticospinal neurons, were responsible for the increased excitability.²⁷ In a larger study, Koerner and colleagues

extended these findings to show that the magnitude of ICF was greater in untreated than treated SPS patients, that it was associated with high levels of anti-GAD antibody in the CSF, and that ICF was reduced by GABAergic medications.⁸⁶ In one SPS patient who underwent physiological and serological testing before and throughout immunosuppressive treatment, treatment was associated with a concurrent decline in excessive ICF, serum anti-GAD antibody titers, and clinical symptoms.⁸⁷ A reduction in intracortical inhibition would be consistent with magnetic resonance spectroscopy findings of reduced levels of GABA in the sensory-motor cortex.^{3,68} However, as GABAergic neurons are widespread in the brain and spinal cord, reduced inhibition at multiple levels in the neuraxis is likely to contribute to the excessive excitatory drive upon the motor neurons that produces muscle stiffness and spasm. The relative contributions from cortical, brainstem and spinal circuits to the generation of clinical symptoms are difficult to ascertain and could differ among individual patients.

Immunogenetics

Genetic risk for SPS and overlapping autoimmune diseases includes genes within the major histocompatibility complex (MHC) such as the human leukocyte antigens (HLA) DR and DQ alleles.^{88,89} In both idiopathic and paraneoplastic SPS, there is a strong association with several DQB1 and DRB1 MHC-II alleles. It appears that the HLA class II locus confers most of the shared susceptibility for these diseases; the DQB1*0201 allele is present in approximately 70 % of patients with SPS,⁸⁹ which is also a prevalent allele in IDDM without SPS and other autoimmune disorders. The DQB1*0602 allele

seems to have a protective property, and it associated with a reduced occurrence of IDDM in SPS patients.⁸⁹

Antibodies against components of inhibitory synapses

Circulating antibodies against several of the components of inhibitory synapses have been found in SPS (**Figure 3**)^{90,91} The best serological marker for SPS is an antibody directed against GAD, a protein that catalyzes the decarboxylation of L-glutamate to GABA and is widely expressed in presynaptic GABAergic terminals in the CNS. GAD is a cytoplasmic enzyme present in two isoforms that are encoded by genes on different chromosomes.⁹² These isoforms mostly differ in the amino-terminal region that accounts for their sub-cellular localization; GAD65 is attached to the surface of synaptic vesicles in GABAergic neurons or microvesicles in the pancreatic beta-cells, while GAD67 is a soluble form detectable only in the CNS.^{93,20} GABA is the main inhibitory neurotransmitter in the forebrain, whereas both GABA and glycine serve as inhibitory neurotransmitters in the brainstem and spinal cord⁹⁴⁻⁹⁶. GABARAP is a postsynaptic protein that stabilizes and modulates the conductance of GABA-A receptors in the postsynaptic membranes of GABAergic synapses.^{97,98} The protein gephyrin is found at both glycinergic and GABAergic synapses, where it plays a role in clustering glycine receptors and GABA-A receptors in the brain and the spinal cord.⁹⁶

Anti-GAD antibodies were first reported by Solimena and colleagues in a patient afflicted by SPS, diabetes mellitus and epilepsy.¹² Anti-GAD antibodies have also been found in the serum of patients affected by insulin-dependent diabetes mellitus (IDDM) without

associated neurological disorders, but in much lower titers.^{28,11,47,99} Anti-GAD antibodies are also reported in 1% of the normal population and in 5% of patients with other neurological syndromes.¹⁰⁰ However, the recognized GAD epitopes differ between patients with diabetes mellitus and those with SPS. In IDDM, the antibodies are found to recognize conformational epitopes, while in SPS they mostly recognize linear and denatured epitopes in the -NH₂ terminal region of the GAD antigen.^{19,20,101,21,22} A recent study points toward the decarboxylase catalytic site as a particularly antigenic motif.¹⁰² Differences in epitope fidelity and specificity may explain the low incidence of stiff person syndrome in patients with diabetes mellitus (about 1 in 10,000 persons).^{21,103}

Anti-GAD antibodies have been measured in the serum and CSF using ELISA and more sensitive RIA methods.^{104,105} Anti-GAD65 antibodies are present in the serum of 80% of SPS patients, while antibodies against the GAD67 isoform occur in less than 50% of patients and at much lower levels.^{23,90} When GAD-titers were compared to the disease severity, as measured by the Stiffness Index and Heightened Sensitivity scores, no consistent correlation was found between the serum and CSF titers and the clinical fluctuations of the disease; the titers were high in some patients with mild disease and low in some others with severe disease as previously reported.^{13,52} In the CSF, antibodies against GAD65 are detected in 75% of patients at titers 50-fold lower than in the serum, but with a 10-fold higher rate of synthesis and binding avidity.^{52,47,90} It is suggested that this is due to intrathecal synthesis of GAD-specific IgG by clonally restricted B-cells within the CSF compartment and driven by local antigens. The different epitope specificity noted between paired serum and CSF specimens further suggests local

stimulation of B cells within the confines of the blood-brain barrier.¹⁰⁶ A potential role of infection in the loss of immune tolerance on the basis of molecular mimicry has also been implicated, especially since GAD65 is expressed in thymus and was also localized in antigen-presenting cells.¹⁰⁷ In a patient who developed SPS following West Nile virus infection, a stretch of 12 amino acids homologous between the virus and GAD65 suggested that loss of tolerance after the infection may have been responsible for autoimmune SPS.¹⁰⁸

The exact mechanism by which these autoantibodies interact with intracellular antigens in the brain parenchyma remains unknown, since GAD, gephyrin and amphiphysin are cytosolic and not readily recognized by the immune system. One hypothesis is that, during GABA exocytosis, GAD65 peptide fragments may be exposed on the neuronal surface and become the target of autoantibodies. It has been postulated that intrathecally produced immunoglobulins may target antigens expressed in the brain and spinal cord by recognizing different epitopes than those in the serum, and may exert a change of synaptic transmission at the neuronal level by blocking either function or synthesis of GAD.^{85,101} Arguably, the lack of neurological symptoms in infants who acquire high GAD65 titers through passive transfer from mothers with SPS and failed experiments to induce SPS symptoms in mice using patients' GAD sera suggest that these antibodies may not be pathogenic.^{85,115}

Anti-GAD antibodies are also found in association with neurological conditions other than SPS, such as cerebellar ataxia, limbic encephalitis with myoclonus, temporal lobe

epilepsy and others.^{109,63} GAD-associated cerebellar ataxia is often accompanied by polyendocrine autoimmunity including IDDM and is manifested by prominent cerebellar dysmetria, nystagmus and dysarthria.⁴⁷ These patients may respond favorably to steroid treatment.^{110,111} Cerebellar symptoms in SPS patients with prominent cerebellar findings seem not to respond to immunotherapies,⁶⁷ despite observations that their anti-GAD antibody titers and immunoreactivity are not significantly different from patients with cerebellar ataxia only.^{63,47} Drug-refractory temporal lobe epilepsy patients may also have high-titers of anti-GAD antibodies, which could be acting to lower the seizure threshold through decreased inhibition by hippocampal GABAergic neurons.¹¹²⁻¹¹⁴

Amphiphysin and SPS

In the paraneoplastic variant of SPS (5% of all SPS patients), there are anti-amphiphysin and anti-gephyrin antibodies (n = 1),⁴² most commonly found in association with breast adenocarcinoma and small-cell lung carcinoma.^{31,33,115,40,116,45} Amphiphysin is a widely expressed presynaptic protein that supports endocytosis by formation of dynamin rings around clathrin vesicles^{117,118} and regulates the density of receptors, particularly GABA-A, at the axon membrane.¹¹⁹ It is possible that antibodies to amphiphysin interfere with the expression of GABA-A receptors at synapses on the membranes of spinal and other motor neurons. Such a mechanism could be related to the signs and symptoms of SPS as shown in the experiments using passive transfer of amphiphysin-specific IgG from a patient with breast cancer and SPS into rats with induced blood-brain barrier leakage.^{120,121} These animals developed dose-dependent motor signs of SPS including typical EMG findings, and IgG binding was demonstrated in their CNS. These

experiments support the hypothesis of a direct pathogenic role of amphiphysin antibodies as shown in other landmark passive transfer experiments in myasthenia gravis and Lambert-Eaton myasthenic syndrome.¹²²⁻¹²⁴ Also, clinical improvement correlates with lowering of amphiphysin antibody titers by plasmapheresis.¹²⁵ Nevertheless, the induction of an autoimmune SPS by active immunization with GAD and amphiphysin antigens, as shown for nicotinic acetylcholine receptors in myasthenia gravis, has not been demonstrated.¹²¹ Furthermore, SPS is not transmissible by passive transfer of anti-GAD and amphiphysin antibodies in the setting of an intact blood-brain barrier, such as through maternal transfer of antibodies.^{126,127}

Since anti-amphiphysin and gephyrin antibodies target the antigens expressed in tumor tissue as well as the CNS, this raises the possibility of cross-reactive binding of antibodies that leads to disruption of the functioning of GABAergic neurons. There appears to be a close link between amphiphysin and SPS associated with breast and lung cancer, since anti-amphiphysin antibodies are not typically present in SPS without cancer, or in cancer patients without SPS. GAD antibodies were notably absent in most previously described cases of amphiphysin antibody-positive paraneoplastic SPS; there has been only one case report with both anti-GAD and anti-amphiphysin antibodies in association with breast cancer.⁴⁴ Cancer patients with paraneoplastic disorders are prone to develop a complex state of autoimmunity due to ectopic expression or over-expression of neuronal antigens. This can lead to simultaneous production of several autoantibodies, which may be specific for neuronal tissue and may or may not be clinically relevant.¹²⁸ Enhanced expression of amphiphysin in breast cancer tissue and its potential role in the

neoplastic transformation of normal cells through an impairment of growth regulatory mechanisms has also been described.³⁸ The degree of molecular mimicry at the tumor site may be more important in the pathogenesis of immune-mediated manifestations rather than the actual titers of paraneoplastic antibodies. This hypothesis is supported by the observation that high titers of anti-neuronal antibodies directed against putative antigens of neuroectodermal tumors, such as SCLC, are less commonly associated with paraneoplastic SPS than with adenocarcinoma.^{115,116,128}

SPS patients who develop cancer cannot be distinguished from idiopathic cases on clinical or electrodiagnostic grounds. Different patterns of stiffness and phenotypes in cryptogenic and paraneoplastic SPS are likely to represent a clinical continuum with a similar underlying mechanism in which a dysregulated immune system allows autoantibodies to target GABAergic pathways in the CNS.¹²⁹⁻¹³¹ Nevertheless, prominent trunk muscle involvement together with a poor response to standard SPS therapy, as well as symptoms of primary tumor, should raise the possibility of a paraneoplastic SPS. A comprehensive screen is indicated to look for occult malignancy in the setting of unusual and progressive neurological syndromes such as SPS, with a high suspicion for commonly encountered breast and lung carcinoma. Although not specific, amphiphysin antibodies may be useful in pointing to an undiscovered cancer as the etiology of the neurological syndrome. In paraneoplastic SPS, cross-reactive binding of serum antibodies with malignant cells expressing neuronal antigens such as GAD and amphiphysin may be responsible for triggering the autoimmune response. Management of the primary tumor is central to neurological outcome in patients with paraneoplastic disease.¹³² When specific

antibodies are identified and clinical suspicion is high, in addition to full body CT scans, Fluoro-2-deoxy-glucose (FDG)-positron emission tomography scanning is important to increase the sensitivity of tumor detection.^{133,132,134}

Experimental studies of antibody pathogenesis

The proposed pathogenic role of anti-GAD antibodies in SPS was initially inferred from the immunostaining pattern against GABAergic neurons using SPS patient sera.¹² Two mechanisms have been proposed to explain how anti-GAD and amphiphysin antibodies impair GABAergic neurotransmission: 1) inhibition of GABA synthesis and 2) interference with the exocytosis of vesicles containing GABA.^{23,65,120} Meinck and colleagues showed that anti-GAD antibodies inhibited the synthesis of GABA in extracts of rat cerebellum; inhibition occurred in a dose-dependent manner with IgG from the serum and cerebrospinal fluid of several patients with SPS with anti-GAD antibodies, but not from IDDM patients with anti-GAD antibodies or patients without anti-GAD antibodies.²³ Such studies support the mechanism of impaired synthesis of GABA. However, patch clamp recordings from intact neurons in slices of rat cerebellum or hippocampus that were perfused with anti-GAD antibodies from patients with various CNS syndromes showed changes consistent with decreased presynaptic GABA release.^{65,135,113} The mechanism by which antibodies impair synaptic transmission has been studied in greater detail for anti-amphiphysin antibodies than for anti-GAD antibodies. Using calcium imaging to measure postsynaptic potentials in cultured embryonic motor neurons, anti-amphiphysin IgG from a patient with paraneoplastic SPS was shown to reduce GABA-induced calcium influx, consistent with reduced presynaptic

release of GABA.¹³⁶ Intrathecal administration of the purified antibodies from this same patient into a rat produced stiffness, muscle spasms, and reduced postactivation depression of H-reflexes,¹²⁰ paralleling the clinical and electrophysiological findings in patients with SPS.^{24,7,77,26} It has also been shown that anti-amphiphysin antibodies were internalized by mouse hippocampal neurons and that synaptic activity produced progressive reduction of induced GABAergic postsynaptic currents.¹²⁰ The antibodies co-localized with other presynaptic proteins associated with synaptic vesicles and vesicle recycling. The internalization of antibodies occurred to a greater extent in GABAergic terminals than in excitatory terminals, and it was proposed that the high rate of vesicle turnover in GABAergic terminals was a factor in the preferential internalization. To date, there is no evidence for similar internalization of anti-GAD antibodies, however.

Physiological studies have found that the functioning of some presumptive GABAergic inhibitory circuits of the brain and spinal cord are less affected than others.²⁴ This may reflect the complexity of the networks at multiple levels that use GABA and are also modulated by GABAergic neurons. Other explanations for this heterogeneity might be differences in the antigenic determinants among GABAergic neurons or in the accessibility of antibodies to GAD to different terminal fields. Additionally, in some neurons or circuits, inhibitory transmitters such as glycine may be able to compensate for the loss of GABA, as some classes of spinal interneurons have been shown to contain both GABA and glycine in the same synaptic vesicle during development.¹³⁷ In paraneoplastic SPS, GABAergic synapses appear more vulnerable than glutamatergic synapses to defective endocytosis induced by anti-amphiphysin antibodies. Whole-cell

patch-clamp experiments on hippocampus granule cells have demonstrated a decrease in the amplitude of evoked inhibitory postsynaptic currents *in vivo* when the brain slices were treated with antibodies against amphiphsin.¹²⁰

Therapeutic considerations in patients with SPS

Based on the presumed pathogenesis of SPS, the two main therapeutic approaches are: 1) GABA-enhancing drugs and 2) immunomodulating or immunosuppressant agents. As the reduced level of GABAergic tone appears to be responsible for muscle stiffness, medications that increase GABA activity alleviate SPS symptoms. Howard initially observed that the spasms dramatically improve with use of diazepam⁷¹ and this has been used to help confirm the clinical diagnosis of SPS, although not always reliably. At the onset of SPS symptoms and the time of establishing the appropriate diagnosis, diazepam or other benzodiazepines (GABA_A agonists) are usually the first choice and the mainstay of therapy.^{70,71,138} Most patients respond favorably to diazepam, baclofen or similar drugs¹³⁹⁻¹⁴¹ for some period of time, although they eventually require higher doses, which invariably cause drowsiness and other undesirable effects. Other, less commonly used approaches have included various muscle relaxants, botulinum toxin injections and some centrally acting agents. Botulinum toxin and intrathecal baclofen administration have been used sporadically but seem not to confer long-term benefit. They also have the potential for serious complications and are inconvenient to administer.^{142,143} Several reports have described substantial beneficial effect of immunotherapies such as prednisone, plasmapheresis¹⁴⁴⁻¹⁴⁶ and high-dose IVIg¹⁴⁷⁻¹⁵⁰ in the treatment of SPS. Intravenous immunoglobulin has been shown to be an efficacious and safe therapy for

SPS patients in a controlled clinical trial,¹⁵¹ although not all the patients experienced a sustained benefit. Some patients are not able to tolerate intravenous immunoglobulin secondary to infusion-related headache, nausea and vomiting, as well as flu-like symptoms, rash, fatigue, or, less often, serious complications such as aseptic meningitis and stroke, which are rarely life-threatening.^{152,153} More recently, anti-B cell therapies using humanized monoclonal antibodies directed against CD20 + cells have been proposed as a rational approach to modulating autoreactive and clonally expanded B cells in the CNS in SPS.¹⁵⁴ Several case reports have indicated that rituximab, a B-cell depleting monoclonal antibody, was well-tolerated and appeared to exert long-lasting clinical remissions,¹⁵⁵⁻¹⁵⁸ although circulating antibody titers did not decline.^{155,158} In a placebo-controlled trial, although muscle stiffness and spasms improved considerably in several treated patients, rituximab was found to be ineffective overall.¹⁵⁹ It has been proposed that the immune response has rituximab-sensitive and -resistant components, with persistent antibody secretion, possibly from long-lived plasma and memory B cells.¹⁶⁰

Concluding Remarks

The diagnosis of SPS requires a high degree of clinical suspicion in addition to diagnostic testing, with emphasis on specific serological markers such as anti-GAD, GABARAP and amphiphysin antibodies. Anti-GAD antibodies are produced intrathecally, presumably by B cells that have crossed the blood-brain barrier.^{13,106,161} There is evidence that clonal expansion of B cells, either *in situ* or intrathecally, and circulating autoantibodies play a causative or contributory role in the pathophysiology of many

neurological diseases that overlap with SPS, some of which are associated with GAD antibodies such as subacute cerebellar ataxia, drug-refractory temporal epilepsy, brainstem encephalitis, and various forms of organ-specific autoimmune diseases.⁴⁷ The occurrence of multiple neurological symptoms and signs in SPS patients, as well as the association of coexisting nuclear and cytoplasmic autoantibodies, may reflect evolving immune responses to multiple CNS and other tissue-specific antigens similar to the phenomenon of 'intermolecular epitope spreading' described in the paraneoplastic setting.⁴¹

A criticism against the pathogenic role of anti-GAD65, GABARAP, amphiphysin and gephyrin antibodies has been that they recognize cytoplasmic antigens. One possible explanation for how antibodies come to recognize GAD and other intracellular antigens is that certain peptide fragments could be transiently expressed at the cell surface during exocytosis and are presented to T-cell receptors by the antigen-presenting cells. For example, T-cell mediated mechanisms are evident in patients with IDDM, where a Th-1 response is seen with upregulation of interleukin-1 and interferon-gamma, and generation of cytotoxic T cells against the GAD of the pancreatic beta cells. In patients with SPS, however, the very high anti-GAD titers may be consistent with a Th-2 response, in which relevant cytokines, such as interleukin- 4 and interleukin- 6, suppress a T-cell-mediated cytotoxicity.^{162,103} However, a recent study using a mouse model demonstrated that GAD65CD4 + response caused SPS-like encephalomyelitis by disrupting the function of GABAergic neurons.¹⁶³ An active T-cell response, especially in the early stages of SPS, appears to play an important role in driving humoral autoimmune processes,¹⁶⁴ but

significant T-cell infiltration is rarely observed in the brain and spinal cord of SPS patients post-mortem.¹⁶⁵ Additional supportive evidence for the humoral autoimmune process is the clinical response to immunomodulatory therapies.⁹¹ Further advances in understanding the neurobiology and pathophysiology of SPS through emerging B-cell and T-cell depleting therapies will likely provide additional insight into the complex immune pathways involved in this autoimmune disorder.

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Figure Legends

Figure 1. Reciprocal inhibition between antagonist muscles. The upper pair of traces shows needle EMG recordings from a pair of antagonist muscles in a patient with SPS, with involuntary MUP firing in the agonist muscle (top trace). Volitional contraction of the antagonist muscle (arrow) does not silence the agonist MUP firing (asterisk). In contrast, in the lower pair of traces, contraction of the antagonist muscle (arrow) silences the voluntary contraction (asterisk) in a healthy control subject voluntarily contracting the agonist muscle.

Figure 2. Increased reflex excitability in SPS patients. **A.** Flexor reflex of the leg. Stimulation of the sural nerve with 4 pulses elicits contraction of the two flexor muscles (tibialis anterior, hamstrings) and spreads abnormally to extensor (quadriceps) and paraspinal muscles. **B.** Hyperexcitability of the blink reflex in an SPS patient following paired stimulation of the contralateral supraorbital nerve at 16 mA with an interstimulus interval of 160 ms. Four stimulation trials are shown. The first stimulus of each pair elicits a response (R2a) with normal latency, although the first trial produced a prolonged response. The R2 response (R2b) to the second stimulus of the pair should normally be fully inhibited at this interval, but instead a robust and prolonged blink occurs.

Figure 3. Components of the inhibitory synapse recognized by known antibodies in Stiff Person Syndrome. The pre-synaptic glutamic acid decarboxylase (GAD) (1) is the rate-limiting enzyme in GABA synthesis; amphiphysin (2) is a cytosolic, pre-synaptic vesicle-

associated protein responsible for endocytosis of vesicle plasma membranes following GABA release. The post-synaptic target antigens in SPS are gephyrin (3), and GABA-A-receptor-associated protein (GABARAP) (4). Gephyrin is a cytosolic, tubulin-binding protein involved in clustering the glycine and GABA-A receptors in the spinal cord and the brain. GABARAP is a linker protein between gephyrin and GABA-A receptors and promotes recycling and organization of the GABA receptors. The most common autoantigen in SPS is GAD, which is seen in 85 % of patients, followed by GABARAP, which is found in 65 % of patients. Amphiphysin is detected in 5 % of patients, while gephyrin has been seen only in one case. (From reference ⁹¹ with permission).

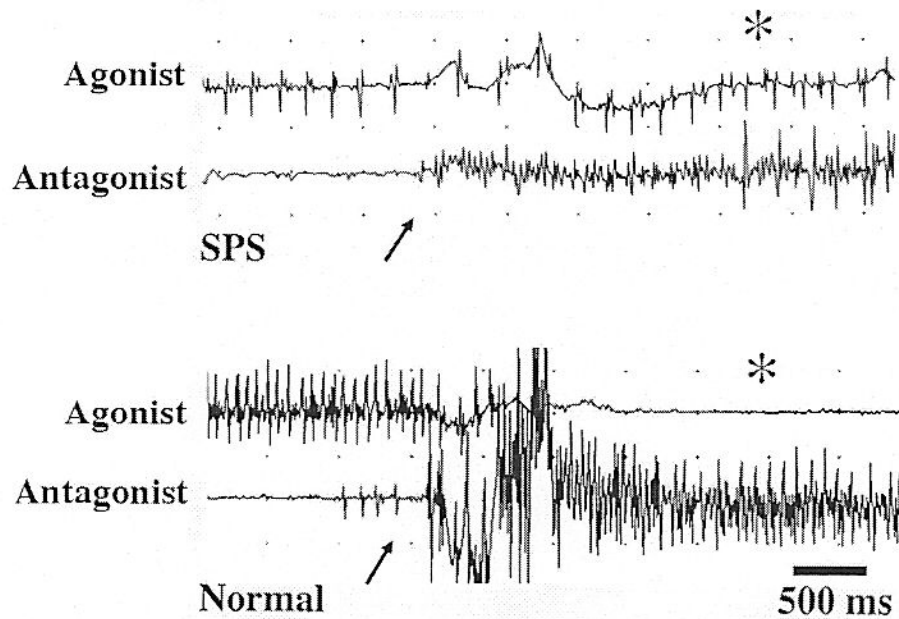


Figure 1
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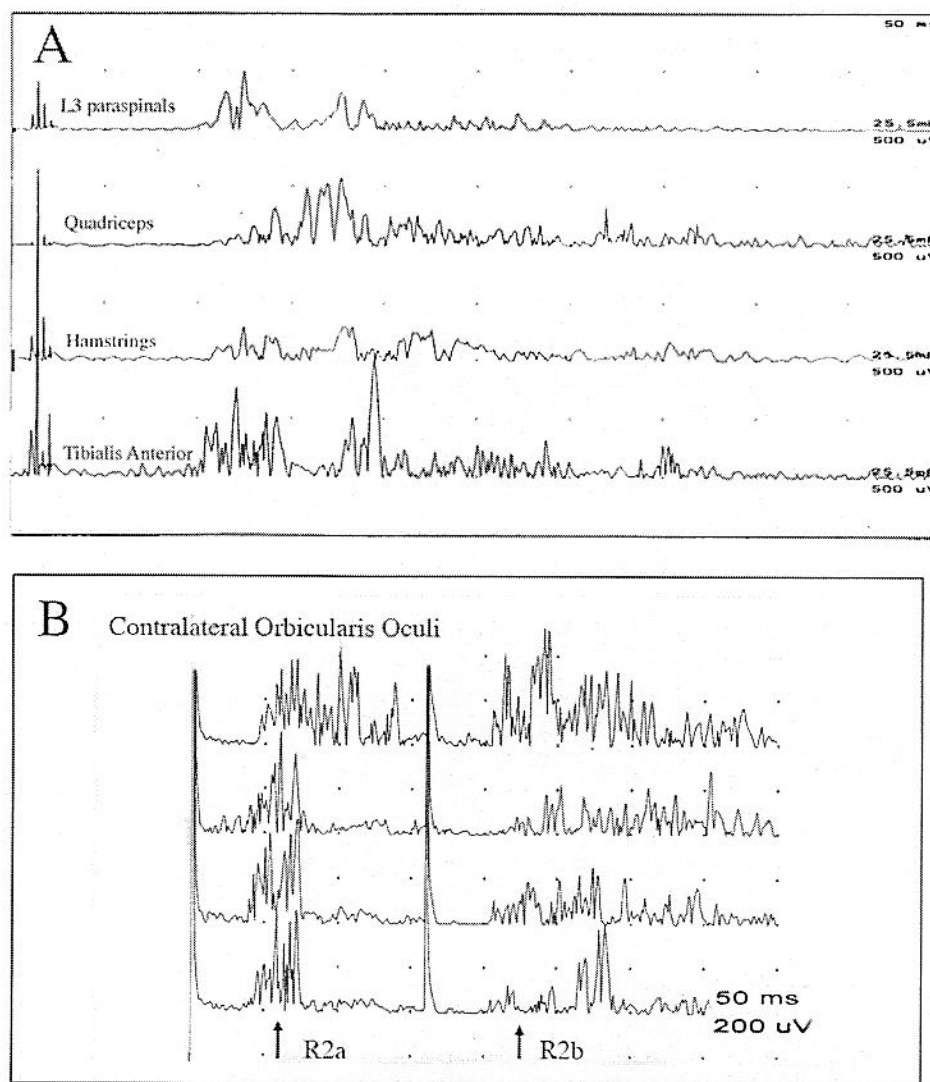


Figure 2A and 2B
76x89mm (300 x 300 DPI)

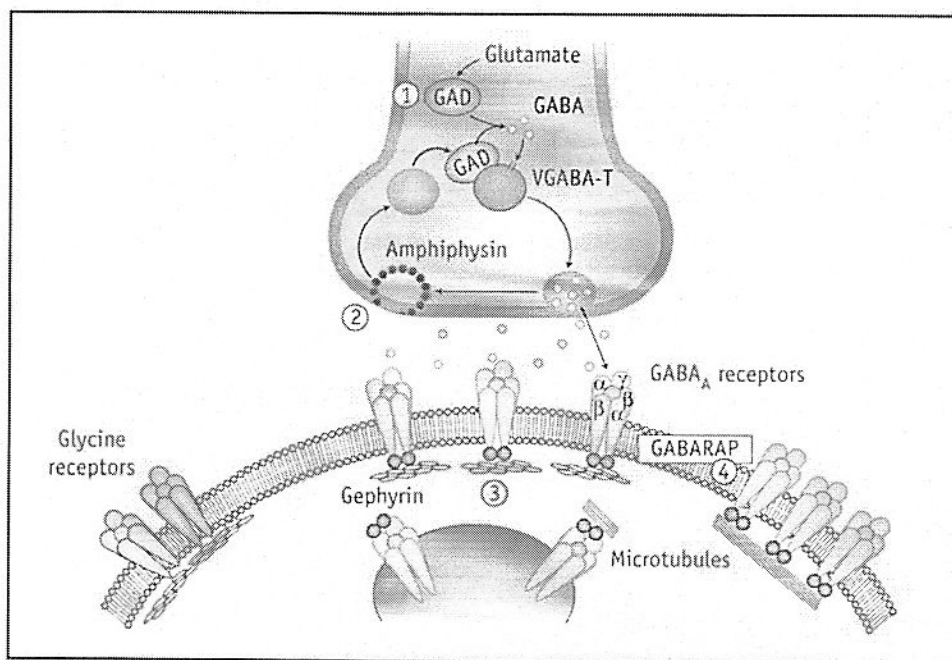


Figure 3
80x54mm (300 x 300 DPI)