**Stiff-Person Syndrome**

Mandar S. Jog, Colin D. Lambert and Anthony E. Lang

**ABSTRACT:** The stiff-person syndrome is a disorder of persistent, painful muscle contractions predominately affecting the axial musculature. We describe a patient with this disorder and review its pathophysiology. Molecular biologic and immunologic techniques have recently added to the understanding of the mechanism of this disorder. Association with diseases such as diabetes, vitiligo and hypothyroidism have strengthened the auto-immune nature of this syndrome. Auto-antibodies against glutamic acid decarboxylase (GAD), an intraneuronal enzyme, have been implicated in the etiology of this unique disease. Therapeutic intervention with agents such as benzodiazepines that modify central GABAergic activity have demonstrated significant benefit in patients with stiff-person syndrome.

**RÉSUMÉ:** Le syndrome de l’individu raide. Le syndrome de l’individu raide est caractérisé par des contractions musculaires persistantes, douloureuses, prédominant à la musculature axiale. Nous décrivons un patient atteint de cette affection et nous revoyons sa physiopathologie. Les techniques de biologie moléculaire et d’immunologie ont contribué récemment à la compréhension du mécanisme de cette affection. L’association avec des maladies telles le diabète, le vitiligo et l’hypothyroïdie ont renforcé la nature auto-immune de ce syndrome. Des auto-anticorps contre la décarboxylase de l’acide glutamique (GAD), une enzyme intraneuronale, ont été impliqués dans l’étiole de cette maladie unique. Une intervention thérapeutique avec des agents tels les benzodiazépines, qui modifient l’activité GABAergique centrale, a démontré un net bénéfice chez les patients atteints du syndrome de l’individu raide.

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The stiff-person syndrome (previously “stiff-man syndrome”) is a rare neurologic disease characterized by paroxysmal, fluctuating, muscle spasms and rigidity predominantly affecting axial musculature.\(^1\)\(^2\) The disorder is not infrequently associated with systemic disease. Recent work has shed new light on this poorly understood entity. We describe an illustrative case, followed by a review of the topic.

**CASE REPORT**

A 47-year-old woman was admitted to hospital, in January 1991, for evaluation of a progressive gait disorder. In December 1989 she developed episodes of unprovoked spasms in the lower back which increased in frequency, so that assistance was required for walking. By March 1990 it had become necessary to use two canes. In April 1990 paroxysmal curling of the toes occurred and by September 1990 sustained plantar flexion of both ankles developed. By November the patient was wheelchair bound. The back spasms were accompanied by generalized shaking, profuse sweating and pain that could last for several hours.

**Back symptoms** first occurred about 15 years earlier. While shoveling snow she suddenly found that her legs were locked and she was unable to move. She required assistance into the house and subsequently recovered. Episodes continued in which the legs would suddenly become stiff. On one occasion the patient had to be carried from the grocery store. Investigations including a myelogram, were normal. Muscle relaxants in the form of benzodiazepines in low doses were prescribed. Over subsequent years the patient reported intermittent problems, with back spasms and difficulty walking. Over about three to five years the symptoms improved but occasionally recurred especially with prolonged walking, or at the time of her menses.

At age 32 she had two unprovoked generalized tonic clonic seizures. Treatment had been instituted with phenytoin but because of gum hypertrophy this was replaced by phenobarbital. Seizure control had not been a problem with the last episode 4 or 5 years prior to assessment. Past health was additionally notable for insulin-dependent diabetes mellitus (IDDM) of 10 years duration and for hypothyroidism. Current medications were: insulin, phenobarbital, diazepam p.r.n., and eltroxin. Family history included a paternal cousin with multiple sclerosis, a maternal cousin with epilepsy, and another with orthopedic problems involving the feet.

Examination revealed a middle-aged female who sweated excessively. A hyperdynamic precordium and soft mitral regurgitant murmur were present. Cranial nerves were normal. Motor exam revealed decreased bulk in both calves with fixed plantar flexion deformities of both feet. Tone and power were normal. Reflexes were normal except for absent ankle jerks. Plantar responses were flexor. Pin prick was reduced to the knees, and vibration was lost to above the ankles. The patient required support to stand, and was unable to walk unaided because of marked stiffness in the back and the fixed flexion deformity at her ankles.

During spasms her axial musculature (back and abdomen) became markedly rigid but the legs themselves did not show an increase in tone. Spasms were painful, and lasted several hours at a time. Routine blood tests showed two abnormalities: creatinine kinase was elevated at 1500 (normal up to 90 \(\mu\)L) and blood sugars ranged between 12 and 20 mmol/L. The following antibodies were present at the titres indicated: anti-microsomal antibody 1:6400, antiparietal cell antibody 1:640 and islet cell antibody 1:640. Anti-mitochondrial, anti-smooth muscle, and anti-thyroglobulin antibodies were negative. HLA typing is shown in Table 1.

A myelogram showed no abnormality in the cervical, thoracic or lumbar regions. A CT scan of the head, with contrast, was normal. A previous MRI study, of the entire spine, was also reported to have been normal.

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Nerve conduction studies (Table 2) demonstrated evidence of a generalized sensory motor neuropathy, predominantly of axonal type, with greater involvement in the lower extremities. Concentric needle electromyography showed continuous motor unit activity in the right vastus medialis, soleus, tibialis anterior and paraspinal muscles. This activity, examined in the right soleus muscle, waxed and waned synchronizing at a burst frequency of about 16 Hz. No fasciculations or fibrillations were seen. Supramaximal stimulation of the posterior tibial nerve produced an M response. No clear H-reflex was obtained. A favorable response to intravenous diazepam was seen with significant reduction in the abnormal muscle activity. Triple evoked potentials (VEPs, BAERs, and SSEPs) were normal except for changes attributable to the peripheral neuropathy. An electroencephalogram was normal.

Spinal fluid examination was normal for cell count, glucose, and protein. CSF and serum samples were strongly positive for antibodies directed against GABA-ergic neurons (Dr. Solimena, Yale University). Details of antibody detection technique are available through Dr. Solimena at Yale University.

Therapy was initiated by the addition of 200 mg a day of phenytoin and subsequently with diazepam 40 mg o.d. in divided doses. This produced a substantial improvement in the frequency and severity of spasms over the next three months. Corticosteroid therapy could not be used due to the patient’s brittle diabetes mellitus. Permanent motor point blocks of soleus, flexor digitorum longus and both heads of the gastrocnemius muscles were attempted with 2cc of 2% xylocaine each, but persistent dystonic posturing of the feet required surgical correction. However, less frequent spasms returned particularly involving the legs, despite an increase in diazepam dosage to 80 mg daily. Valproic acid, baclofen and clonidine were not tolerated or had no effect. The patient is currently undergoing further therapeutic trials.

### Table 1. Results of HLA Typing

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DR</th>
<th>DQ</th>
<th>DRw</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>w7</td>
<td>17</td>
<td>2</td>
<td>52</td>
</tr>
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<td>29</td>
<td>44</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td>53</td>
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### Table 2. Sensory Nerve Conduction

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Record</th>
<th>Stimulate</th>
<th>Latency</th>
<th>Distance</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Median</td>
<td>wrist</td>
<td>palm</td>
<td>2.8 msec</td>
<td>7.5 cm</td>
<td>8 µV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>index</td>
<td>4.3</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>middle</td>
<td>4.4</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>R. Ulnar</td>
<td>wrist</td>
<td>little</td>
<td>2.2</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>L. Median</td>
<td>wrist</td>
<td>palm</td>
<td>2.4</td>
<td>7.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>index</td>
<td>3.9</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Conduction Velocity</td>
<td>57 m/sec</td>
<td>2.7</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Record</th>
<th>Conduction Velocity</th>
<th>Distal Lat.</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Median</td>
<td>thenar</td>
<td>40 m/sec</td>
<td>5.3 msec</td>
<td>9 mV</td>
</tr>
<tr>
<td>R. Ulnar</td>
<td>thenar</td>
<td>57</td>
<td>2.9</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table 3. Motor Nerve Conduction

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Fibrillation</th>
<th>Fasculation</th>
<th>Voluntary Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Soleus</td>
<td>0</td>
<td>0</td>
<td>Continuous motor unit activity as above, with synchronization at about 16Hz.</td>
</tr>
<tr>
<td>R. Tib. Ant.</td>
<td>0</td>
<td>0</td>
<td>Motor unit activity as above.</td>
</tr>
</tbody>
</table>

### Discussion

The stiff-person syndrome was first described by Moersch and Woltman in 1956 in a report of 14 cases collected over a 32 year period between 1924 and 1956 at the Mayo clinic. Howard described effective treatment with the use of benzodiazepines in 1963. Diagnostic criteria were published by Gordon et al., in 1967 and with modification remain valid today. Recent work by Solimena et al., has shed new light on the mechanism and immunopathology of this disorder.

### Classification

Continuous muscle spasms occur predominately in three situations, namely Isaacs syndrome, stiff-person syndrome (SPS), and jerking stiff-person syndrome.

Clinically, Isaacs syndrome is characterized by generalized stiffness as well as weakness and is subacute in onset. The jerking stiffman syndrome may be associated with encephalitis, is acute and exhibits cerebral and bulbar stiffness as well as stimulus sensitive myoclonus. Nerve blocks, anesthesia and sleep appear to have minimal effect in reducing the abnormal muscle activity. In contrast, SPS is a chronic disorder with primarily truncal muscle stiffness which is greatly reduced by sleep, general anesthetic and nerve block. Features of these disorders are summarized in Table 3. This paper is restricted to discussion of SPS.

### Clinical Manifestations

SPS is more common in men (men:women = 3:2) and is diagnosed at a mean age of 45 years. Diagnostic features listed in Table 4 rely on the signs and symptoms of the disorder together with supplementary tests.

Disease onset and progression is insidious, with involvement of the neck, abdominal and paraspinal muscles symmetrically. Facial and distal musculature remains unaffected; however,
many patients have exhibited severe abnormal posturing (dystonia) of their feet. Rigidity is associated with co-contraction of axial antagonistic muscles resulting in restricted mobility. Dull aching discomfort due to rigidity is common. Super-imposed intermittent forceful and painful spasms lasting up to minutes can be precipitated by sudden movement, noises, or even touch. Spasms predispose to falling and may be severe enough to fracture bones even in absence of a fall. Paroxysmal hyperhidrosis can also occur with other signs of autonomic dysregulation such as tachycardia.

Pathophysiology

The etiology of stiff-person syndrome remains unclear. Proposed mechanisms for SPS include increased alpha-motor neuron activity, possibly due to a disorder of Renshaw cells, or dysfunction of the descending inhibitory brainstem pathways leading to increased muscle tone. Increased levels of MHPG (3-methoxy-4-hydroxyphenylglycol) have been noted in the urine of patients with stiff-person syndrome, especially during periods of spasm, suggesting over-reactivity of this catecholamine system. Other untenable proposed mechanisms include a metabolic myopathy and a primary psychiatric disorder.

Recently, an auto-immune origin has been suggested. Antibodies directed against glutamic acid decarboxylase (GAD) have been found in the CSF of a high proportion of SPS patients. Studying samples from 32 patients from various countries, Solimena and his colleagues found that 60% had anti-GAD antibodies in both serum and CSF using a mouse brain assay. It has been proposed that these antibodies are capable of reducing the levels of gamma-amino-butyric-acid (GABA) in the central nervous system (CNS). This could then result in a decrease of the inhibitory input to anterior horn cells accounting for the increased muscle tone. Similar alterations in cerebral GABA inhibitory function may account for the occurrence of seizures seen in 10 percent of patients with SPS including the present case.

The intermedio-lateral column as well as the ventro-lateral medulla receive input from the periventricular nuclei of the hypothalamus. These are innervated densely by GABA-ergic neurons. The intermedio-lateral column output is also GABA-ergic and inhibitory to the pre-ganglionic sympathetic neurons.

Autonomic dysregulation with increased catecholaminergic outflow and respiratory dysfunction due to sudden spasm of respiratory and diaphragmatic muscles are possible causes of sudden death in SPS.

GAD is specific for GABAergic neurons in the CNS. It is a hydrophilic enzyme that catalyses conversion of glutamic acid to GABA. It is now accepted that GAD exists as a protein coupled with a molecular weight of each protein between 55 kDa and 67 kDa.

Conversion of glutamic acid to GABA is an intra-cellular process and hence the GAD molecule is not directly exposed to the immune-system. However, fragments of intra-cellular cytoplasmic proteins can be expressed at the neuronal membrane. Recognition of such antigenic molecules occurs in the presence of the major histocompatibility complexes co-expressed on the cellular surface. This association then enables the antigens to be recognized by the T-lymphocyte-macrophage system.

Although this phenomenon has been studied with other neuronal antigens, in vitro analysis of humoral and cell-mediated immune mechanisms in the GAD system has not yet been completed.

Table 3. Diagnostic Features of SPS

<table>
<thead>
<tr>
<th>Description</th>
<th>SPS</th>
<th>Jerking Stiff-Man</th>
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<tbody>
<tr>
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<td>(2) proximal muscle involvement — difficulty with volitional movement*</td>
<td>(± encephalomyelitis with rigidity)</td>
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<td>(2) fixed spinal deformity</td>
<td>(3) fixed spinal deformity (most often lordosis)*</td>
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</tr>
<tr>
<td>(4) spasms precipitated by movement*</td>
<td>(5) normal intellect*</td>
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<td>(6) normal motor and sensory examination</td>
<td>(7) associated investigations: EMG-NCS serology</td>
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<td>(8) favorable EMG response to IV diazepam</td>
<td>(9) anti-GAD antibody activity</td>
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*signifies criteria essential for diagnosis of SPS

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There is evidence that the GAD antibody is polyclonal.\textsuperscript{6,7} Antigenic molecules may take the form of macromolecular complexes against which antibodies may be directed.\textsuperscript{34} Hence, the GAD antigen could co-localize with the above macromolecular protein complex presenting a combined target for the immune-mediated attack. The antibody is probably of the IgG type. These data may be supported by the occurrence of oligoclonal bands (primarily IgG) in the CSF of these patients.\textsuperscript{7,8}

In patients with anti-GAD-antibody and SPS, a varying percentage of other auto-antibodies has also been seen. Gastric parietal cell antibody has been found in 80% and microsomal fraction antibody in 45% of cases.\textsuperscript{6,7} Hypothyroidism, pernicious anemia, and vitiligo have also been reported in patients with SPS.\textsuperscript{5,7,13,35}

The autoimmune hypothesis is further strengthened by the association of SPS with IDDM \textsuperscript{6,7,13,28,36} as seen in our patient. The frequency of occurrence of IDDM in the general population is 0.25% compared to 8% in patients with SPS.\textsuperscript{1,16,37} A 64 kDa dimeric protein in pancreatic B-cells has long been recognized as a major auto-antigen in IDDM.\textsuperscript{11} This protein has recently been identified as glutamic-acid-decarboxylase.\textsuperscript{39}

Solimena and colleagues\textsuperscript{6-8} found that the anti-GAD antibody present in serum and CSF of SPS patients also labelled beta-islet-cells of the rat pancreas in all except one case. Sera from these patients were also positive for islet-cell antibodies further supporting an association between SPS and IDDM. On the other hand, it has recently been suggested\textsuperscript{17} that presence of the anti-GAD-antibody in SPS is an accidental finding entirely related to the presence of the anti-islet-cell antibody rather than to the primary pathophysiological disturbance of SPS. It is of note that only 17% of patients with SPS in this latter study had positive serologic evidence of anti-GAD-antibody as compared to the 60% in the studies of Solimena and his colleagues.\textsuperscript{6-8}

Similarly, 95% of patients with IDDM have HLA DR4 and/or DR3 histocompatibility complexes which may imply mediation by regulatory HLA molecules.\textsuperscript{13,36} Alterations of HLA determined regulatory protein configurations that have been implicated in the pathogenesis of IDDM may also be responsible for development of autoimmunity in SPS. HLA DR3/DR4 were the alleles found in all three patients that were typed and had both anti-GAD antibodies and IDDM.\textsuperscript{6,7,39} HLA B4, which is in linkage disequilibrium with HLA DR4, was found in 80% of patients (4/5) reported by Williams et al.\textsuperscript{16} However, HLA typing in our case did not correspond with these observations.

Hence, although a reasonably strong association between the anti-GAD-antibody and presence of SPS has been noted, a true cause-effect mechanism remains to be confirmed. Determination of anti-GAD-antibody is therefore only relevant with the associated clinical picture of SPS and only helps to support the diagnosis.

Laboratory Evaluation

Electrophysiological assessment of SPS includes EMG and sleep studies. Surface recordings of electrical potentials show continuous muscle activity varying with posture, passive and active movement, with superimposed generalized paroxysmal muscle contractions comprised of co-contraction of antagonist muscles. Needle electromyography reveals normal motor unit potentials.\textsuperscript{42,44} The ratio between the maximum amplitude of the H-response and the compound muscle potential (M) (the H-M ratio) may be increased. As well, the H-reflex amplitude can be increased if it is preceded by a conditioning stimulus.\textsuperscript{43} Neuropharmacological effects on the EMG are summarized in Table 5.

Routine EEG is often normal or contaminated with muscle artifact. Sleep studies show abnormally long latencies with fluctuations between stage 1 and wakefulness due to muscle spasms. These disappear when stage 2 sleep is reached.\textsuperscript{10,12,44}

<table>
<thead>
<tr>
<th>Table 5. Pharmacologic Effects on EMG in SPS</th>
</tr>
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<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>L-Dopa</td>
</tr>
<tr>
<td>Sleep G.A.</td>
</tr>
</tbody>
</table>

Therapy

Diazepam has become the mainstay of therapy, with a large daily divided dosage required, ranging from 40 to 300 mg per day. There is considerable evidence indicating that benzodiazepines act via activation of GABA receptors.\textsuperscript{55,56} Two main types of GABA receptors have been identified. GABA\textsubscript{A} postsynaptic receptors mediate their actions by opening chloride channels. Two sub-types of the GABA\textsubscript{A} receptor exist. The type I receptor is picrotoxin sensitive but benzodiazepine insensitive while the type II receptor is benzodiazepine sensitive but picrotoxin insensitive. Activation of both of these subtypes will open the GABAergic chloride channel. The effects of benzodiazepines therefore appear to be mediated via action upon type II GABA\textsubscript{A} receptors. Valproic acid\textsuperscript{47} is believed to facilitate GABA receptor-mediated chloride channel activation by acting at the picrotoxin binding site. The GABA\textsubscript{A} receptor is benzodiazepine insensitive. This receptor is pre-synaptic and appears to work by opening calcium channels. Baclofen, a GABA\textsubscript{B} receptor agonist, has been tried in SPS with variable success.\textsuperscript{48,49} Clonidine, a central alpha agonist, has also been reported to be useful.\textsuperscript{50}

There have been reports of use of immuno-therapy in SPS.\textsuperscript{39,41,51} Plasmapheresis has been favoured by Vicari et al.,\textsuperscript{52} who described improvement with alternate day treatment for 10 days. A recent case report by Brashear et al.,\textsuperscript{53} showed clinical, EMG and serological improvement in one patient with a diagnosis of SPS. However Gordon et al.,\textsuperscript{54} failed to show any response in another case. Similarly, Harding et al.,\textsuperscript{55} obtained no benefit when azathioprine and prednisone were added to the regimen. Three other patients with SPS showed no improvement after six total plasma exchanges over two weeks followed by 60 mg per day of prednisone for two months and then an alternate day tapering regimen.\textsuperscript{56} Blum and Jankovic\textsuperscript{15} have shown benefit with use of 100 mg of prednisone daily in two cases of SPS, resulting in a significant reduction in axial stiffness. Remarkable response with 10 days of steroid therapy has also been shown by Piccolo.\textsuperscript{51} If indeed neurological symptoms are secondary to the
action of anti-GAD antibodies, the lack of response to plasma exchange is not surprising since GAD auto-antibody synthesis is thought to primarily occur intra-thecally and hence this intervention would not be expected to effectively remove the antibody. Further study of immuno-suppressive treatment is clearly indicated. It should be noted that, as in our patient, brittle IDDM is a contraindication to use of prednisone in patients with SPS.

The pathophysiologic and pharmacological mechanisms underlying the foot postures (dystonia-like) present in our patient and occasionally in others described in literature remain a problem. With control of axial spasms, the symptoms in our patient’s feet and legs became the major source of disability as has been reported by Blum et al. Thus adjunctive use of physical therapy is an important part of symptomatic management in these patients. Use of gait aides, range of motion exercises as well as surgical correction of foot deformities should be considered when appropriate.

ACKNOWLEDGEMENTS

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REFERENCES


