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The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome

Marinos C. Dalakas, MD; Mavis Fujii, MD; Mian Li, MD; and Beverly McElroy, RN

Article abstract—*Objective:* To evaluate the clinical spectrum of anti-GAD-positive patients with stiff-person syndrome (SPS) and provide reproducible means of assessing stiffness. *Background:* SPS can be difficult to diagnose. Delineation of the clinical spectrum in a well defined population will increase diagnostic sensitivity. *Methods:* In 20 anti-GAD-positive patients with SPS (six men, 14 women), screened among 38 referred patients, the authors assessed symptoms and signs, degree of disability, associated conditions, and immunogenetic markers. Degree of bending, distribution of stiff areas, timed activities, and magnitude of heightened sensitivity were examined monthly for 4 months in five patients. *Results:* Average age at symptom onset was 41.2 years. Time to diagnosis was delayed from 1 to 18 years (mean 6.2). Stiffness with superimposed episodic spasms and co-contractions of the abdominal and thoracic paraspinal muscles were characteristic. All had stiff gait and palpable stiffness in the paraspinal muscles. Stiffness was asymmetric or prominent in one leg in 15 patients (stiff-leg syndrome) and involved facial muscles in 13. In one patient spasms lasted for days (status spasticus). Twelve patients needed a cane and seven a walker due to truncal stiffness and frequent falls (average three to four per month). Distribution of stiffness and degree of heightened sensitivity were two reproducible indices of stiffness and spasms. Autoimmune diseases or autoantibodies were noted in 80% and an association of with DR β_1 0301 allele in 70%. *Conclusions:* SPS is 1) frequently misdiagnosed due to multifaceted presentations and asymmetric signs, 2) disabling if untreated, and 3) associated with other autoimmune conditions.

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Stiff person syndrome (SPS) is a rare CNS disorder characterized by fluctuating muscle rigidity of truncal and proximal limb muscles with superimposed spasms.^{1–4} It is mostly a clinical diagnosis, facilitated by a high degree of suspicion, due to a lack of disease-specific neurologic signs and laboratory tests. The electromyographic signs of simultaneous voluntary contraction of the agonist and antagonist muscles, although helpful when the disease is suspected, are not specific.^{5–7} The recently identified disease variants^{8,9} and the superimposed strong functional component⁴ further complicate the diagnostic uncertainty. Because SPS, if untreatable, can be serious and lead to total body rigidity, objective clinical and laboratory means are essential for diagnosis and therapy.

To highlight the complexities in clinical presentation, define the clinical spectrum of the disease, and examine reproducible means of assessing stiffness, we studied 20 patients with SPS selected based on anti-glutamic acid decarboxylase (anti-GAD) antibody positivity. Even though autoantibodies against GAD may be present in only 60% of patients with SPS,^{10–13} their presence at high titers is expected to define a clinically more homogeneous group.

Methods. *Patient selection.* Twenty patients were selected among 38 referred to the Neuromuscular Diseases

Section of the NIH based on the following recently revised criteria⁴: 1) insidious onset of muscular rigidity in the limbs and axial (trunk) muscles, most prominent in the abdominal and thoracolumbar paraspinals, with difficulty in turning or bending; 2) continuous co-contraction of agonist and antagonist muscles with inability to relax, as confirmed clinically and electrophysiologically; 3) episodic spasms superimposed on the rigidity and precipitated by unexpected noises, tactile stimuli, or emotional upset; and 4) absence of any other neurologic disease or chronic pain syndromes that could explain stiffness and rigidity.

All patients were positive for anti-GAD antibodies assessed by immunocytochemistry on frozen sections of rat cerebellum,³ by Western blot on purified or recombinant GAD 65, as reported,¹³ and by an ELISA assay using commercially available kits (from Boehringer Mannheim, Germany). Positive samples by ELISA were those with antibody titers more than 50 ng/mL, a cut-off level 50-fold higher than the low anti-GAD antibody levels noted in patients with insulin-dependent diabetes mellitus (IDDM).¹³ The patients who fulfilled the above inclusion criteria were admitted to the NIH Clinical Center after signing an informed consent.

Clinical examination and search for stiffness-related factors. Detailed neurologic examination was performed on all patients. History regarding symptomatology, factors influencing daily fluctuations, frequency and conditions of falling, ability to work or carry out daily activities, history of concurrent medical or psychiatric illnesses, and family

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history of autoimmune diseases were explored. The degree of disability was determined by the patient's need for assistive devices such as a walker or cane. Forced discontinuation from work due to SPS symptomatology was also noted.

Immunologic and immunogenetic studies. A search for the following autoantibodies was performed: antithyroid, antiparietal cell, anti-intrinsic factor, antinuclear antibody, rheumatoid factor, anti-RNP, anti-SSA (RO), anti-SSB (La), anti-SM, antistriated muscle, antimicrosomal, anti-Jo-1, antimitochondrial, and GM1. Total serum immunoglobulins and immunofixation electrophoresis were also examined.

Human leukocyte antigen (HLA) class II allele-specific oligonucleotide typing was performed in genomic DNA extracted from peripheral blood by the NIH clinical laboratory in 18 patients, using PCR sequence-specific primer mixture for 71 alleles contained in the DQ β 1 and DR β 1, DR β 3, DR β 4, and DR β 5 loci, based on the method of Park and Tonai.¹⁵

Sequential measurements of stiffness. To assess reproducibility of various indices that may best capture stiffness and episodic spasms, we used the data collected monthly for 4 consecutive months in five patients randomized to placebo during their participation in a controlled clinical trial. The following indices were examined, as close as possible to the same time of day.

Degree of stiffness. Bending at the waist. With the patients standing against the wall and their palms rested on the anterior or lateral aspect of each thigh, we measured the distance from the top of the middle finger to the floor before (A) and after bending at the waist and laterally on each side trying to touch the floor (B). The ratio of B/A defined the degree of flexibility.

Chest expansion. The difference during deep inhalation (B) and full exhalation (A) at the nipple line was measured.

Distribution of stiffness. This was rated by the physician according to the number of stiff areas as follows: 0, no stiff areas; 1, stiffness of the lower trunk; 2, stiffness of the upper trunk; 3, stiffness of both legs; 4, stiffness of both arms; 5, stiffness of the face; and 6, stiffness of the abdomen and back.

Heightened sensitivity: spasms and falls. The distribution of muscle spasms, their frequency, and sensitivity to stimuli were recorded by the examining physician in each monthly visit. Stimuli that trigger or increase stiffness, such as open spaces, anxiety, crowds, unexpected noises, approaching cars, and sense of a hurry, were recorded. The frequency of falls and the events predisposing to falls were also noted. The magnitude of *heightened sensitivity* was measured according to the induction of stiffness and spasms by the following factors: noise (1); visual stimuli (2); somatosensory stimuli (3); voluntary activities (4); emotional upset or stress (5); untriggered (6); and awakenings due to nocturnal spasms (7). The maximum score of 7 was the total score of heightened sensitivity.

Timed activities. The time needed to perform the following tasks as quickly as possible was recorded with a stopwatch: 1) rising from a chair; 2) walking a 30-foot length of corridor three times; 3) turning 180° with feet together, clockwise and counterclockwise; and 4) going up and down four standard stairs.

Results. Clinical observations. Symptoms. The average age at diagnosis was 41.2 years and the average time from symptom onset to diagnosis was 6.2 years (range 1 to 18 years). The patients were 6 white men and 14 women (three African American); hence the more appropriate term "stiff-person syndrome." The number of falls averaged three to four per month. One patient had become bedridden. Two sets of symptoms predominated, muscular rigidity (stiffness) and episodic spasms superimposed on the rigidity.

The rigidity, characterized by tightness and stiffness, began insidiously in the axial muscles (trunk) and caused limitation in bending and walking in nine patients. Fear of dropping an object because they could not bend to pick it up if alone was common. Asymmetric onset with predominance of stiffness in one leg and superimposed spasms on the same leg causing limping (stiff-leg syndrome)^{8,9} was noted in 15 of 20 patients. The rigidity was at first fluctuating but then became fixed, resulting in abdominal wall rigidity, hyperlordosis, and frequent falls. Falls averaged 3 to 4/month especially when patients were anxious or stressed. Ten patients had breathing difficulty, precipitated by fear and anxiety, due to chest restriction and stiffness in the thoracic muscles.

Signs. On examination, increased tone in the paraspinal muscles (a hallmark diagnostic sign) was noted in all patients. Hyperlordosis and co-contractions of the abdominal and thoracic paraspinals (figure 1) was prominent. On palpation, these muscles were very tight. In several patients, lumbar puncture could be done only under fluoroscopy due to severe tightness. In one patient it could not be done even under fluoroscopy. Stiffness in the legs was usually asymmetric (table 1). In three patients, the stiffness was present only in one leg (stiff-leg syndrome). In 13 of 20 patients there was stiffness in the facial muscles causing, at times, a mask-like appearance. One patient had prominent stiffness in the cervical paraspinal muscles that spread upward and downward after stress or unexpected noises. The strength was normal. The tone was increased throughout the extremity in a global fashion. There was no cogwheel rigidity or spasticity, as seen with extrapyramidal or pyramidal tract involvement. The reflexes were increased 2 to 3+ in eight patients; Babinski was intermittently present in two. The gait was stiff, deliberate, and slow. Some patients could not initiate gait and others were afraid to walk without a cane or walker. Despite normal strength, stiffness was disabling. Twelve patients need a cane to walk, and seven a walker (see table 1). Assistive devices were necessitated by 1) fear initiating a gait without holding on to something; 2) truncal stiffness that precipitated sudden falls "en bloc"; 3) fear of falling on sudden and unexpected stimuli, such as when crossing a street unprotected in front of an oncoming car, or walking across a long hall; and 4) fear of falling caused by sudden or reflex spasms in trunk and legs.

Spasms. The episodic spasms were sudden or reflex, varied in severity, and were provoked by unexpected tactile stimuli, sudden noises, emotional upset, or fear of open spaces. Spasms were painful in eight and very painful in one. Marked anxiety, obsession with details, and task-specific phobias were noted in 10 patients. Some patients had experienced severe spasms for which they had to visit an emergency room for IV therapy with diazepam. One of

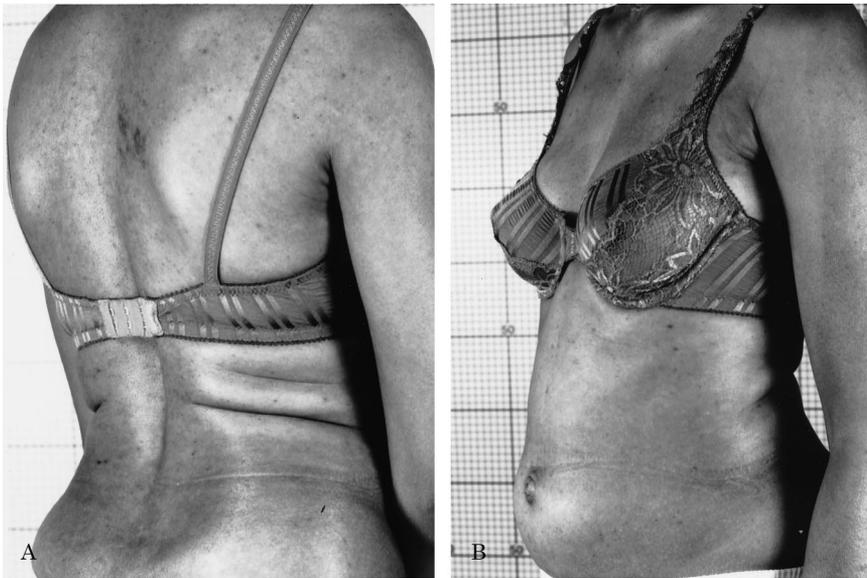


Figure 1. Prominent hyperlordosis with co-contraction of the thoracolumbar paraspinals (A) and abdominal muscles (B) is characteristically seen in a woman with stiff-person syndrome.

our patients, 24 hours before admission, developed intense generalized muscle spasms lasting over 1 hour each. He became markedly diaphoretic, hypertensive, and tachycardic, with a drop in pulse oxygen. He was in a “status spasticus” for several days with intermittent generalized spasms involving initially the left leg followed by the truncal and appendicular muscles that necessitated IV boluses of diazepam every 1.5 hours, reaching up to 90 mg daily. Decreased sensory input (dark room, quiet nursing care, attention to avoid unexpected stimuli) and decreased voluntary movements terminated these life-threatening spasms only after 2 weeks of hospitalization. Although very closely monitored, he was not transferred to the in-

tensive care unit because the noises and foreign environment of the unit could have worsened the spasms and made them more difficult to control.

Assessment of stiffness. Data for reproducibility and validation of stiffness and spasms, collected blindly monthly for 4 months in five patients, had a very wide range among patients and within patients in reference to timed activities, degree of bending, and chest expansion. Two elements of stiffness and spasms, however—the heightened sensitivity and distribution of stiffness—gave reproducible scores with minimal SD. The mean heightened sensitivity scores during the 3-month period were 5.2 ± 0.49 and the number of stiff areas 5.4 ± 0.25 (figure 2). The validity of these parameters is strengthened by the fact that their assessment was made blindly while the patients were randomized to placebo.

Associated conditions and autoantibodies. Eight patients had IDDM, eight others thyroid disease, three pernicious anemia, one celiac disease, and one other notalgia paresthetica. Four patients had seizures. Transient CK elevation (two- to fourfold) was noted in 5 of 20 patients; one of them had mild muscle weakness. Muscle biopsy in two patients with persistent CK elevation showed histologic features suggestive of polymyositis with CD8+ T cells invading MHC-I-expressing muscle fibers (data not shown). Seven patients had family history of IDDM, four had thyroid disease, and one each had family history of systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and vitiligo. Except for anti-GAD antibodies at high titers as described,⁴ various autoantibodies were also present, including antinuclear (1:80 to 1:12800) in six; antithyroid in six others; antiparietal cell in four; and against RNP, Jo-1, intrinsic factor, and anti-gliadin in four others. One patient had a monoclonal IgG_k gammopathy of unknown significance.

Immunogenetics. The most frequent alleles were associated with DR haplotypes (table 2); the DRβ1 0301 allele was noted in 8 of 18 patients (44%), which is higher than the frequency of this allele in the white populations of 1,331 examined white subjects (13%, $p < 0.01$). No significant HLA-DR association was found for the other alleles. When the three African American patients were excluded

Table 1 Neurologic signs in 20 patients with stiff-person syndrome

Symptoms	n (%)
Increased tone	
Paraspinal muscles	20 (100)
Face	13 (65)
Asymmetry with 1 leg predominant	15 (70)
Asymmetry with 1 arm predominant	7 (41)
Only in one leg (stiff-limb)	3 (17)
Prominent stiffness in the cervical paraspinal region	1
Mild proximal muscle weakness with coexisting signs of myopathy	1 (6)
Functional impairment resulting in:	
Stiff gait	20 (100)
Hyperlordosis	14 (65)
Need for cane	12 (65)
Need for walker	7 (35)
Inability to work	12 (65)
Shortness of breath	10 (50)
Task-specific phobias	10 (50)

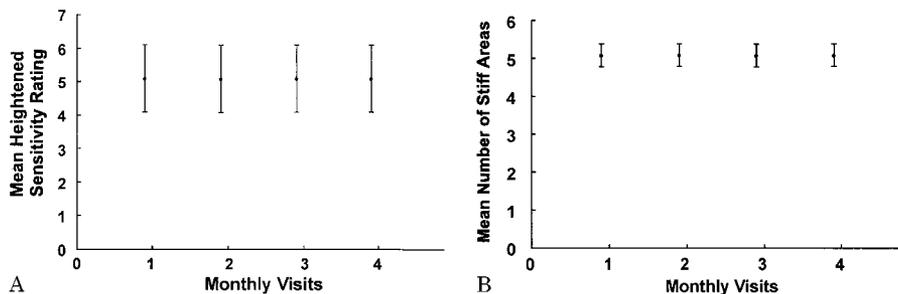


Figure 2. Mean number of heightened sensitivity rating (A) and stiff areas (B) for five patients with stiff-person syndrome evaluated monthly for 4 consecutive months. The scores of heightened sensitivity and stiff areas remain constant (5 ± 0.49 and 5.4 ± 0.25 , respectively).

because the frequency of DR β 1 alleles in normal people of this race is not known, the frequency of DR β 1 0301 allele among all white patients with SPS was 70.5%, compared to 13% in the controls.

Discussion. Based on observations in 20 bona-fide patients with SPS selected because of high titer anti-GAD-65 antibodies, several overlooked points have emerged regarding the clinical picture of SPS, its association with other disorders, and objective means of assessing stiffness and spasms.

SPS affects women more often than men (70% in our series); hence the preference for the more appropriate term “stiff-person syndrome.” Although a hallmark diagnostic sign remains the presence of hyperlordosis and co-contractions of the abdominal and thoracic paraspinal muscles, asymmetric presentation with predominance of stiffness in one leg was very common. Whether “stiff-limb” syndrome is a separate subset of SPS, as proposed,^{8,9} is unclear because all our patients who started asymmetrically progressed to generalized symptomatology. A previ-

ously unrecognized sign is the stiffness in the facial muscles that was present in 70% of the patients. Due to reduced facial expression, one of the patients was initially diagnosed and treated for Parkinson disease.

SPS remains not only a clinical diagnosis but also a diagnosis of exclusion; hence the delay in reaching early diagnosis by as many as 18 years (mean 6.2 years). A primary diagnosis of anxiety and phobias was common. In five SPS patients, task-specific phobias were prominent, resulting in the initial diagnosis of “phobic neurosis”; in some of them, only in retrospect was the proper diagnosis made when benzodiazepines, prescribed for the phobias, improved gait and mobility. Two patients were misdiagnosed with multiple sclerosis (spinal MS) supported by the presence of oligoclonal bands in the CSF, which are frequently found in SPS patients (unpublished observations).

SPS can be serious or disabling. As shown in table 1, some patients sustain frequent falls and injuries, others use walkers or wheelchairs, and still others are bedridden due to severe stiffness, necessitating vigilance in early diagnosis and initiation of therapy. Sudden death and paroxysmal autonomic dysfunction have also been reported.¹⁵

Although the cause of the disease is unknown and the role of autoantibodies debated,¹⁶ a series of observations strengthens the autoimmune hypothesis.^{10-13,17-19} Various nonspecific autoantibodies and an association with autoimmune diseases such as thyroid, IDDM, and gastrointestinal autoimmune conditions were noted in our series. Elevation of CK, initially attributed to stiffness, was also observed in 5 of 20 patients but muscle biopsy in two of them showed mild endomysial inflammation with immunopathologic findings identical to polymyositis (unpublished observations). A very strong association with alleles in the DR and DQ phenotypes, which are often associated with IDDM, myasthenia gravis, inflammatory bowel disease, autoimmune hepatitis, systemic lupus erythematosus, and inclusion body myositis,²⁰⁻²³ was also observed. A common immunogenetic background has been noted for both IDDM and SPS due to overlapping alleles in the HLADR β 1 and DQ β 1 loci in more than 75% of patients with IDDM and SPS, which coincides with the presence of anti-GAD antibodies in both conditions.^{10-12,17-19} There are distinct differences, however, in the anti-GAD antibody titers and the recognition of immunoreactive epitopes in the GAD antigen between SPS and IDDM that explain

Table 2 Immunogenetic studies and allele association in patients with stiff-person syndrome

Patients	DR β 1	DQ β 1
1	07, 13	02, 06
2	15, 16	05, 06
3	0101, 0301	0201, 0501
4	13,	06
5	0301, 0403	0201, 0302
6	0301, 0403	0201, 0301
7	04, 14	03, 05
8	03, 16	02, 05
9	0301, 0403	0201, 0302
10	03, 13	02, 06
11	0301, 0401	0201, 0302
12	0301, 0701	0201
13	0301, 0701	02
14	14, 1501	0503, 06
15	07, 16	02, 05
16	0103, 0301	02, 0501
17	0701, 13	02, 0603
18	13, 15	06 06

why the incidence of SPS in IDDM is low (about 1:10,000).^{17,18} The observation that GAD activity and synthesis of GABA are directly inhibited in vitro by the anti-GAD-specific IgG from SPS patients but not by the IgG from GAD-negative SPS patients^{24,25} has strengthened the immunopathogenic role of these antibodies. The occurrence of seizures, noted in four of our patients, is also consistent with the reduced brain GABA, presumably due to anti-GAD antibodies,²⁶ that we have found in the brains of patients with SPS. A reduction of GABA in the brain and CSF has been associated with increased incidence of seizures or poor seizure control in epileptic patients.²⁷ The seizures in our patients were well controlled with anticonvulsants that enhance GABA, such as gabapentin, which also help the symptomatology of SPS.

Based on reduced GABA due to anti-GAD antibodies, two types of therapies had been used by our patients; one with agents that potentiate the action of GABA, and the other with immunotherapies. Diazepam, which increases the frequency of opening of the GABA_A receptor and leads to hyperpolarization, was the most effective drug used by 14 of 20 patients. Baclofen was used by six patients and gabapentin by two. Clonazepam, dantrium, and vigabatrin had been tried each by two patients with mild benefit. Plasma exchange or IVIg have been reported to benefit patients with SPS,^{12,28-30} but they had not been used in any of our patients at the time of initial assessment. A number of our patients, however, have participated in a controlled study using high-dose IVIg. The study is now completed and the results analyzed.

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