

Stiff-Man Syndrome and Variants

Clinical Course, Treatments, and Outcomes

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Background: Little information is available about the incidence of stiff-man syndrome (SMS) (the classic form or its variants) or about long-term treatment responses and outcomes.

Objective: To comprehensively describe the characteristics of a cohort of patients with SMS.

Design: Observational study.

Setting: Mayo Clinic, Rochester, Minnesota.

Patients: Ninety-nine patients with classic SMS vs variants of the disorder, both glutamic acid decarboxylase 65 kD isoform (GAD65) antibody seropositive and seronegative.

Main Outcome Measures: Neurological, autoimmune, serological, and oncological findings; treatments; and outcomes between January 1984 and December 2008.

Results: The median follow-up duration was 5 years (range, 0-23 years). Seventy-nine patients (59 having classic SMS, 19 having partial SMS, and 1 having progressive encephalomyelitis with rigidity and myoclonus [PERM]) were GAD65 antibody seropositive. Sixty-seven percent (53 of 79) of them had at least 1 coexisting autoimmune disease, and 4% (3 of 79) had cancer. GAD65 antibody

values at initial evaluation were significantly higher among patients with classic SMS (median value, 623 nmol/L) than among patients with partial SMS (median value, 163 nmol/L) ($P < .001$). The initial GAD65 antibody value was positively correlated with the last follow-up Rankin score ($P = .03$). Among 20 patients who were GAD65 antibody seronegative (6 with classic SMS, 12 with partial SMS, and 2 with PERM), 15% (3 of 20) had at least 1 coexisting autoimmune disease, and 25% (5 of 20) had cancer (3 with amphiphysin autoimmunity and breast carcinoma and 2 with Hodgkin lymphoma). Excluding patients with PERM, all patients but 1 had sustained improvements with at least 1 γ -aminobutyric acid agent, usually diazepam; the median dosage for patients with classic SMS was 40.0 mg/d. Additional improvements occurred among 14 of 34 patients (41%) who received immunotherapy (intravenous immune globulin, azathioprine, prednisone, mycophenolate mofetil, or cyclophosphamide). Sixteen of 25 patients (64%) with extended follow-up duration remained ambulatory.

Conclusions: Recognition of classic SMS vs variants is important because appropriate therapy improves symptoms in most patients. Classification by anatomical extent and by GAD65 antibody serostatus gives important diagnostic and prognostic information.

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IN 1956, MOERSCH AND WOLTMAN¹ described 14 patients who were seen at the Mayo Clinic, Rochester, Minnesota, with chronic fluctuating truncal and limb muscle rigidity and spasms. The authors named the disorder stiff-man syndrome (SMS), noting that muscle involvement was “fairly symmetrical,” the lower extremities were affected more commonly than the upper extremities, and proximal limb segments were affected more severely. In 12 patients, back and abdominal muscles were involved (“hard,” “firm,” and “board-like”), but 2 patients lacked truncal symptoms. Frequently,

there was significant disability from painful spasms and falls, and many patients had fixed spinal deformities from long-standing rigidity. Chest wall spasms caused respiratory impairment in some patients. Distinctive neurophysiological findings reflect hyperexcitability of spinal motor neurons.²⁻⁵ Continuing the Mayo Clinic integrated practice of neurology, Howard⁶ and Olafson et al⁷ reported the therapeutic benefit of diazepam for this disorder, which was so impressive that it was included in diagnostic criteria.⁸ In 1988, Solimena et al⁹ recognized that SMS was an organ-specific autoimmune disorder. Clues include female sex predominance, the co-

existence of other autoimmune disorders, seropositivity of most patients for a neuroendocrine autoantibody specific for glutamic acid decarboxylase 65 kD isoform (GAD65) (in orders of magnitude higher than that in patients with type 1 diabetes mellitus alone), and clinical improvements occurring with immunotherapy.¹⁰⁻¹⁶

Since the original description, more limited forms of SMS (sometimes paraneoplastic), including “stiff limb” and “stiff trunk,” have been reported (often in patients who are GAD65 antibody seronegative).^{14,17-29} Furthermore, some patients with high GAD65 antibody values have other neurological disorders coexisting with SMS, including epilepsy^{1,9} and cerebellar ataxia, brainstem disorders, and myelopathies.³⁰ Also, a rapidly progressive form with diffuse central nervous system findings, known as progressive encephalomyelitis with rigidity and myoclonus (PERM), has been described.³¹ There is little information about the incidence of SMS (the classic form or its variants) or about long-term treatment responses and outcomes.

Herein, we review 25 years of continuing clinical experience with SMS and its variants in patients seen by an integrated practice of neurology and immunology specialists at the Mayo Clinic. We report the following: (1) clinical and electrophysiological findings, (2) frequency and spectrum of coexisting autoimmune disorders and autoantibodies, (3) usefulness of antibody markers of type 1 diabetes mellitus in addition to GAD65 antibody for predicting which patients with SMS might develop diabetes, (4) cancer frequency, (5) optimum treatments, (6) long-term outcomes, and (7) clinical relevance of GAD65 antibody values.

METHODS

This study was approved by the Mayo Clinic institutional review board (approval 08-807). We searched the Mayo Clinic’s computerized diagnostic index for patients (January 1984 to December 2008) with the following diagnoses: *stiff-man syndrome*, *stiff-limb syndrome*, *stiff-person syndrome*, and *progressive encephalomyelitis, rigidity, myoclonus*. We reviewed 242 medical records, eliminating 143 patients without these diagnoses. We included patients with the final diagnosis of SMS, a partial form of the disorder, or PERM. The 99 patients included were determined to have classic SMS if at least lower extremity and lumbar stiffness and spasms were present and partial SMS if only one axial lower extremity symptom or upper body symptom was present. Patients were classified as having PERM if a rapidly progressive encephalomyelopathy accompanied whole-body stiffness and spasms.

For all patients, we documented a detailed history, examination findings, and serological and electrophysiological data at the time of initial evaluation. A level of disability diagnosis was assigned using the modified³² Rankin score as follows: 0 (no symptoms), 1 (symptoms but no disability), 2 (slight disability but able to look after own affairs), 3 (moderate disability with a need for help but able to walk without assistance), 4 (unable to walk without assistance), 5 (bedridden), or 6 (dead). Using medical record review and telephone interview, we documented extended follow-up data where available.

Serum samples from all 99 patients were evaluated in the Mayo Clinic neuroimmunology laboratory using radioimmuno-precipitation assays for GAD65 antibody³³ and other autoantibody markers of type 1 diabetes mellitus (insulin and

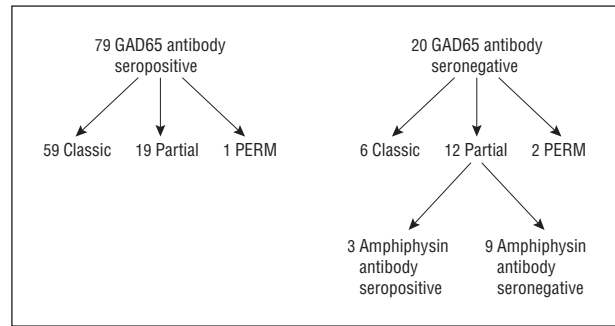


Figure 1. Classification of 99 patients with classic stiff-man syndrome and variants. PERM indicates progressive encephalomyelitis with rigidity and myoclonus; GAD65, glutamic acid decarboxylase 65 kD isoform.

IA2 antibodies).^{34,35} We also tested for paraneoplastic autoantibodies.^{36,37}

Electrophysiological studies consisted of multichannel surface electromyographic recording over the right orbicularis oculi, sternocleidomastoid, biceps, abductor pollicis brevis, thoracic paraspinals, lumboparaspinals, anterotibialis, gastrocnemius, and soleus muscles. Auditory startle reflexes (pattern and habituation of motor responses) were evaluated using binaural 105-dB intensity stimuli, 1 minute apart, for 3 to 5 trials.⁴ Exteroceptive responses were determined by electrically stimulating the medioplatar nerve.³⁸ Concentric-needle studies were performed on the lumboparaspinal muscles.

Using Wilcoxon rank sum test, GAD65 antibody values were compared in patients with classic vs partial SMS. The relationship between initial GAD65 antibody values and last follow-up Rankin scores was evaluated using Kruskal-Wallis test. Patients with classic SMS who were ambulatory after 5 years of follow-up duration were compared with nonambulatory patients using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. All statistical analyses were performed using commercially available software (JMP 8.0; SAS Institute, Inc).

RESULTS

DEMOGRAPHICS

Of 99 patients, 67 were female, and 89 were of white race/ethnicity. The median age at symptom onset was 40 years (age range, 5-70 years). Five patients had symptom onset before age 18 years. The median follow-up duration from symptom onset to the last follow-up visit was 5 years (range, 0-23 years).

CLASSIFICATION AND NEUROLOGICAL FINDINGS

Classification and neurological findings are summarized in **Figure 1**, **Table 1**, and **Table 2**. Eight of 99 patients received a psychogenic diagnosis initially.

Symptom onset was acute or subacute in all patients. The classic SMS phenotype was noted in 65 patients (59 were GAD65 antibody seropositive). In 30 patients, stiffness and spasms were anatomically limited initially (to the lower back in 17 and to the lower extremities in 13), with unilateral onset in 6 and cervical muscle onset in 1, but ultimately progressed to the classic SMS phenotype. Simultaneous-onset lumbar and lower extremity

Table 1. Phenotypic Features Among Patients With Stiff-Man Syndrome (SMS)

Type	No. of Patients With Feature								
	Low Back Stiffness and Spasms	Exaggerated Lumbar Lordosis	Lower Extremity Stiffness and Spasms	Neck Symptom Stiffness and Spasms	Upper Extremity Stiffness and Spasms	Abdominal Wall Stiffness and Spasms	Respiratory Symptoms With Spasms	Falls	Exacerbating Factors
GAD65 Antibody Seropositive									
Classic SMS (n=59)	59	52	59	10	4	26	6	30	Emotional stress (n=19), ^a startle (n=31), cold (n=4), movement (n=5)
Partial SMS (n=19)	2	2	17 ^b	4	7	2	3	4	Emotional stress (n=1), startle (n=4), movement (n=4), cold (n=2)
PERM (n=1)	1	0	1	1	1	0	0	1	None
GAD65 Antibody Seronegative									
Classic SMS (n=6)	6	6	6	0	0	3	1	1	Startle (n=2)
Partial SMS (n=12)	4	4	7 ^c	1	2	1	0	2	Startle (n=4), movement (n=2)
PERM (n=2)	2	0	2	2	2	1	0	0	Movement (n=1)

Abbreviations: GAD65, glutamic acid decarboxylase 65 kd isoform; PERM, progressive encephalomyelitis with rigidity and myoclonus.

^aThree patients had social phobia or agoraphobia.

^bFour patients had unilateral lower extremity involvement.

^cOne patient had unilateral lower extremity involvement.

Table 2. Comorbid Neurological and Psychiatric Findings Among Patients With Stiff-Man Syndrome (SMS)

Type	GAD65 Antibody Seropositive, No. of Patients			GAD65 Antibody Seronegative, No. of Patients		
	Classic SMS (n=59)	Partial SMS (n=19)	PERM (n=1)	Classic SMS (n=6)	Partial SMS (n=12)	PERM (n=2)
Cognitive disorder	1	1	1	0	1	2
Myoclonus	0	0	1	0	0	2
Seizure disorder	6	0	0	0	1	0
Cerebellar ataxia	2	2	0	0	0	0
Parkinsonism	1	0	0	0	0	0
Eye movement disorder	2	1	0	0	0	0
Myelopathy	Brisk DTRs (n=41), extensor plantars (n=7)	Brisk DTRs (n=7), extensor plantars (n=2)	Brisk DTRs (n=1), extensor plantars (n=1)	Brisk DTRs (n=3)	Brisk DTRs (n=4), extensor plantars (n=1)	Brisk DTRs (n=2), extensor plantars (n=2)
Peripheral neuropathy	1 ^a	1 ^a	1	0	4	2
Comorbid anxiety disorder	9	2	0	1	0	0
Comorbid depression	12	4	0	2	1	0
Reported that SMS symptoms improved with alcohol consumption	9	1	0	1	1	0
Reported alcohol dependence	3	1	0	1	1	0

Abbreviations: DTRs, deep tendon reflexes; GAD65, glutamic acid decarboxylase 65 kD isoform; PERM, progressive encephalomyelitis with rigidity and myoclonus.

^aCoexisting type 1 diabetes mellitus.

symptoms were reported in 7 patients. Stiffness and spasms fluctuated and were predominant in the lower back and proximal lower extremities but were not exclusive to these regions (Table 1) and included abdominal spasms and respiratory difficulties. Falls were common and were frequently precipitated by emotional stimuli or startle. Examinations revealed stiff-legged gait, hyperlordotic

spine with limited flexibility, and usually incomplete resolution of lordosis when lying supine or bending forward from the waist.

Stiffness and spasms remained anatomically limited in 31 patients with partial SMS (19 of whom were GAD65 antibody seropositive), most of whom had a disorder confined to one or both lower extremities. Of these, 3 pa-

Table 3. Autoimmune Diseases and Autoantibody Findings Among Patients With Stiff-Man Syndrome (SMS)

Variable	GAD65 Antibody Seropositive, No. of Patients			GAD65 Antibody Seronegative, No. of Patients		
	Classic SMS (n=59)	Partial SMS (n=19)	PERM (n=1)	Classic SMS (n=6)	Partial SMS (n=12)	PERM (n=2)
≥1 Coexisting autoimmune disease	40	12	1	1	1	1
Type 1 diabetes mellitus	28 ^a	6 ^b	0	0	1	1
Thyroid disease	21	7	0	0	0	0
Pernicious anemia	5	1	1	0	0	0
Vitiligo	5	2	0	0	0	0
Other	5 ^c	1 ^d	0	1	0	0
Other antibody detected	32	9	0	1	2	0
Amphiphysin antibody	0	0	0	0	2	0
Thyroid antibody	22	6	0	1	0	0
TPO antibody	19	6	0	1	0	0
Thyroglobulin antibody	9	4	0	0	0	0
Insulin antibody	8	0	0	0	0	0
IA2 antibody	2	1	0	0	0	0
Gastric parietal cell antibody	10	2	0	0	0	0
α-3 Ganglionic AChR antibody	1	1	0	0	0	0
Striational antibody	1	0	0	0	0	0
Voltage-gated potassium channel complex antibody	0	1	0	0	0	0

Abbreviations: AChR, acetylcholine receptor; GAD65, glutamic acid decarboxylase 65 kD isoform; PERM, progressive encephalomyelitis with rigidity and myoclonus; TPO, thyroid peroxidase.

^aNineteen patients had diabetes before the onset of SMS.

^bThree patients had diabetes before the onset of SMS.

^cOne patient each had premature ovarian failure, Addison disease, Sjögren syndrome, systemic lupus erythematosus, and celiac disease.

^dOne patient had rheumatoid arthritis.

tients had amphiphysin antibody seropositivity and breast carcinoma diagnosed after the onset of partial SMS. All had stiffness and spasms isolated to the lower extremities, and 2 had a monomelic distribution. All had coexisting clinical and electromyographic evidence of a lower motor neuron disorder. A focal jerking limb was noted in 3 patients with partial SMS; 2 were GAD65 antibody seropositive.

A rapidly progressive and widespread disorder of stiffness and spasms associated with PERM was seen in 3 patients (1 was GAD65 antibody seropositive). All had abnormal lower motor neuron findings (peripheral neuropathy or an anterior horn cell disorder) clinically or electrophysiologically.

At initial evaluation, myelopathic findings (usually isolated brisk deep tendon reflexes) were documented in 58 patients (Table 2). Additional neurological findings were documented in 16 patients, 11 of whom (69%) had classic SMS and were GAD65 antibody seropositive.

COEXISTING AUTOIMMUNITY

Type 1 diabetes mellitus (in 43% [34 of 79]) and autoimmune thyroid disease (in 35% [28 of 79]) were common among GAD65 antibody-seropositive patients (Table 3). The onset of diabetes predated SMS diagnosis in 22 patients by a median of 5.0 years (range, 1-33 years). The onset of diabetes postdated SMS diagnosis in 12 patients by a median of 4.5 years (range, 2-12 years). Seropositivity for other autoantibodies associated with diabetes was detected in 9 patients (insulin antibody in 8 and IA2 antibody in 3); all but one had type 1 diabetes

mellitus before SMS diagnosis (median latency, 4 years; range, 1-33 years). One or more autoantibodies other than GAD65 were detected among 52% (41 of 79) of GAD65 antibody-seropositive patients and among 15% (3 of 20) of GAD65-seronegative patients (all 3 had amphiphysin antibody positivity).

COEXISTING CANCER

Among 79 GAD65 antibody-seropositive patients, 3 (4%) had carcinoma (thyroid, renal cell, and colon); all had classic SMS (cancer was found in 2 of them after onset of neurological symptoms). Among 20 GAD65 antibody-seronegative patients, 5 (25%) had cancer. Three of these patients had amphiphysin antibody positivity and breast carcinoma, and 2 (1 with classic SMS and 1 with partial SMS) had non-Hodgkin lymphoma.

NEUROPHYSIOLOGICAL FINDINGS

Neurophysiological assessment for spinal hyperexcitability was performed in 40 patients. This was documented in 19 of 31 patients (61%) with classic SMS (15 were GAD65 antibody seropositive) and in 9 of 20 patients (45%) with partial SMS (4 were GAD65 antibody seropositive) (Table 4). Among patients without detected neurophysiological abnormalities, 7 were being treated with benzodiazepines or baclofen (masking the findings) at the time of evaluation. Among 3 GAD65 antibody-seronegative patients with partial SMS who had normal electrophysiological findings, the diagnosis of SMS was made by the treating neurologist on clinical grounds;

Table 4. Electrophysiological Findings Among 51 Patients With Stiff-Man Syndrome (SMS) Who Were Tested

SMS Type	No. (%)			
	Abnormal Test Result	Exaggerated and Poorly Habituating Acoustic Startle Reflex	Exaggerated Exteroceptive Reflex	Continuous Paraspinal Motor Unit Activity
GAD65 Antibody Seropositive				
Classic (n=26)	15 (58)	13 (50)	8 (38)	10 (37)
Partial (n=13)	4 (31)	4 (30)	1 (8)	2 (15)
GAD65 Antibody Seronegative				
Classic (n=5)	4 (80)	4 (80)	1 (20)	2 (100)
Partial (n=7)	5 (71)	2 (29)	4 (57)	2 (29)

Abbreviation: GAD65, glutamic acid decarboxylase 65 kd isoform.

Table 5. Mobility Outcomes Among 20 GAD65 Antibody–Seropositive Patients With Stiff-Man Syndrome (SMS) Having a Rankin Score of 4 or Higher at Baseline and Having at Least 1 Year of Follow-up Duration

Patient No.	SMS Type	Rankin Score		Treatments Reported to Have Improved Symptoms	Follow-up, y
		Initial Disability	Final Disability		
1	Classic	4, Needs cane	4, Needs cane	Oral baclofen, clonazepam	7
12	Classic	4, Needs walker	4, Needs walker	Oral baclofen, clonazepam, plasma exchange	12
13	Classic	4, Needs wheelchair	4, Needs wheelchair	Diazepam	8
17	Classic	4, Needs wheelchair	4, Needs cane	Baclofen pump	12
20	Classic	4, Needs wheelchair	4, Needs wheelchair	Clonazepam	2
21	Classic	4, Needs wheelchair	0	Clonazepam, dantrolene, mycophenolate mofetil	12
27	Classic	4, Needs cane	5	Diazepam, amitriptyline	11
32	Classic	4, Needs walker	0	Clonazepam, lorazepam	8
40	Classic	4, Needs cane	4, Needs cane	Clonazepam, oral baclofen, azathioprine, intravenous immune globulin	6
49	Partial	4, Needs cane	4, Needs cane	Intravenous immune globulin, oral baclofen, gabapentin	5
69	Partial	4, Needs cane	4, Needs cane	Nothing helpful	11
72	Classic	5	4, Needs cane	Diazepam, oral baclofen	9
73	Classic	5	2	Prednisone, azathioprine	23
76	Classic	4, Needs cane	3	Clonazepam, oral baclofen, intravenous immune globulin	16
78	Classic	5	1	Diazepam	17
82	Classic	4, Needs cane	4, Needs cane	Prednisone, clonazepam	3
83	Classic	5	6	Diazepam	6
86	Classic	4, Needs wheelchair	4, Needs cane	Baclofen pump, diazepam	12
87	Classic	4, Needs wheelchair	4, Needs wheelchair	Clonazepam, valproic acid	10
96	Classic	4, Needs cane	4, Needs cane	Diazepam	12

1 was amphiphysin antibody seropositive, and 2 improved remarkably with symptomatic treatment.

TREATMENTS AND LONGITUDINAL OUTCOMES

GAD65 Antibody–Seropositive Patients With Classic SMS

Table 5 and **Figure 2** summarize the treatments and longitudinal outcomes in GAD65 antibody–seropositive patients with classic SMS. All of these patients were treated with a benzodiazepine (usually diazepam) initially and at the last point of follow-up care. Improvements in stiffness and spasms were noted in all. The median dosage required (in milligram equivalents of diazepam) was 40.0 mg/d (range, 5–360 mg/d). Oral

baclofen was used as an adjunct in 23 patients (18 reported improvement); the median dosage was 60.0 mg/d (range, 7.5–160 mg/d). Three other patients received intrathecal baclofen; all had improved symptom control. Symptoms were also ameliorated by gabapentin (in 2 of 5 treated) and by dantrolene sodium (in 1 of 2 treated).

Among 18 patients treated with immunotherapy, 7 (39%) found this sufficiently beneficial to warrant continuation a median of 8 years after initial review. Improved symptoms were reported with the use of intravenous immune globulin pentetate alone in 3 patients, with azathioprine alone in 2 patients, with azathioprine and immune globulin intravenous in 1 patient, and with mycophenolate mofetil alone in 1 patient. **Although improvements in stiffness and spasms were noted with immunotherapy, mobility status changes were infrequent.**

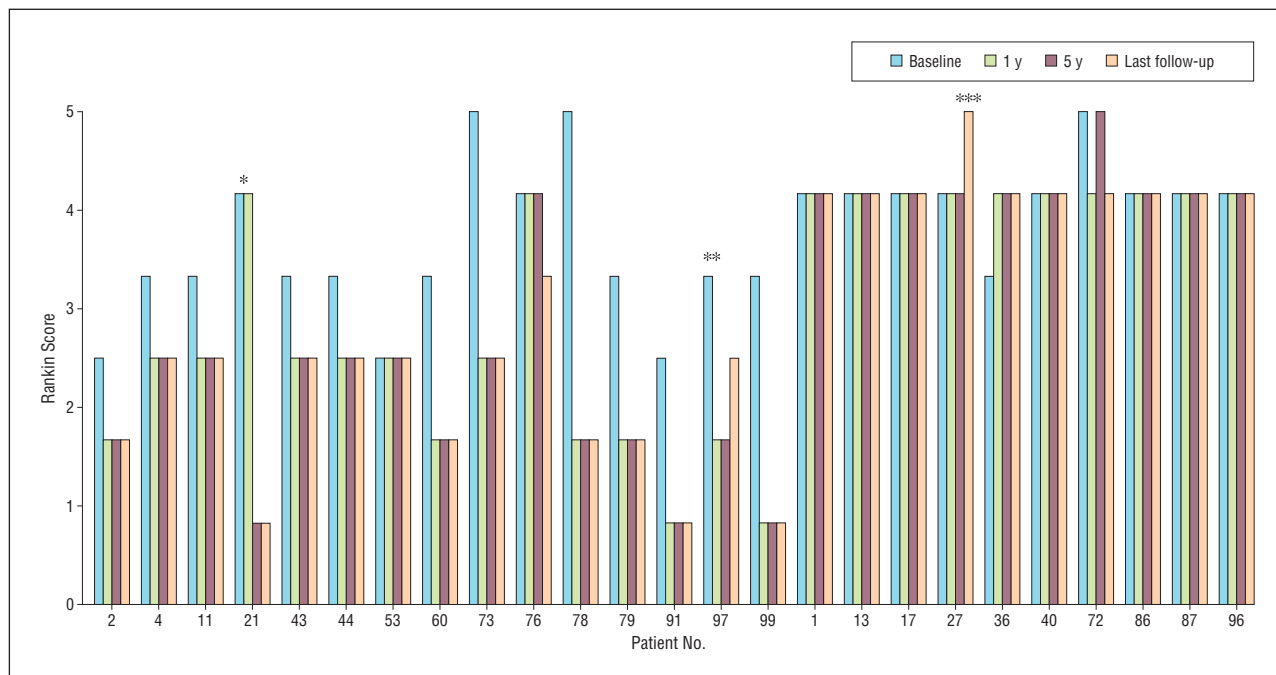


Figure 2. Outcomes of 25 patients with classic stiff-man syndrome who were followed up for at least 5 years. *Patient 21 had improvement in Rankin score after treatment with mycophenolate mofetil, which was initiated after 4 years of symptoms. **Patient 97 initially improved with azathioprine but deteriorated after discontinuing the drug. ***Patient 27 eventually became bed-bound because of progressive cerebellar ataxia.

Rankin scores were not significantly different in those treated with immunotherapy vs those not treated at baseline ($P=.87$) or at the last follow-up visit ($P=.79$).

Outcomes showed that, among 35 patients with follow-up duration of at least 5 years, the median Rankin score was 3 (range, 0-5) initially and 2 (range, 0-6) at the last follow-up visit. Employment status at follow-up visits was available for 28 patients: 12 were permanently disabled because of SMS symptoms, 10 had retired (5 because of SMS), and 4 were unemployed before SMS onset and at the follow-up visits. Two were still working.

Among 25 patients for whom 4 follow-up time points were available (Figure 2), any improvements that occurred were almost always in the first year. Progressive disease (occurring in 2 patients, 1 of whom had progressive cerebellar ataxia) was rare. Fifteen patients with independent ambulation at the 5-year time point were not significantly different from 10 patients with dependent ambulation for sex, age at symptom onset, history of autoimmune disease, presence of a coexisting neurological disorder or cancer, occurrence of falls, immunotherapy treatment, or diazepam dosage ($P>.05$ for all).

GAD65 Antibody–Seropositive Patients With Partial SMS

Symptomatic benefits were reported in all 16 patients treated with benzodiazepines (median milligram equivalents of diazepam, 17.5 mg/d; range, 2-90 mg/d) and in all 7 patients treated with adjunctive oral baclofen (median dosage, 60.0 mg/d; range, 30-90 mg/d). Among 8 patients treated with immunotherapy, 3 found it beneficial and continued it for the long term (1 with intravenous immune globulin alone, 1 with intravenous immune globulin and mycophenolate, and 1 with intra-

venous immune globulin and azathioprine). One patient initially had no response to intravenous immune globulin alone but improved considerably after 6 months of treatment with a combination of intravenous immune globulin and intravenous methylprednisolone infusions.

Outcomes showed that, among 8 patients with follow-up duration of at least 5 years, the median Rankin score at initial evaluation was 3 (range, 1-4) and at the last point of follow-up care was 2 (range, 0-4). Rankin score changed by no more than 1 point in all 8. Seven patients were receiving disability benefits or had retired because of SMS.

GAD65 Antibody–Seronegative Patients

At least 5 years of follow-up data were available for 10 GAD65 antibody–seronegative patients (all had partial SMS); 9 improved with treatments to address symptoms. Benefits from immunotherapy were reported for 4 of 8 treated patients (50%), 2 with immune globulin intravenous, 1 with methylprednisolone, and 1 with cyclophosphamide (after mastectomy in the setting of amphiphysin antibody seropositivity and breast adenocarcinoma). The latter patient initially had severe lower extremity spasms and was dependent on a wheelchair for ambulation; after 1 year, she had resolution of spasms and improved to using a walker. Another patient became symptom free after treatment for Hodgkin lymphoma. Among the patients, the median Rankin score was 3 at the initial evaluation and at the last point of follow-up care (median, 7 years; range, 1-12 years).

Follow-up data were available for 1 of 3 patients with PERM. The disease course was rapidly progressive and treatment refractory, and the patient died 14 months after symptom onset.

INITIAL AND LONGITUDINAL GAD65 ANTIBODY VALUES

GAD65 antibody values at initial evaluation were significantly higher among patients with classic SMS (median value, 623 nmol/L; range, 0.24-8620 nmol/L) than among patients with partial SMS (median value, 163 nmol/L; range, 0.08-1550 nmol/L) ($P < .001$, Wilcoxon rank sum test). The initial GAD65 antibody value was positively correlated with the last follow-up Rankin score ($P = .03$, Kruskal-Wallis test). Additional serum samples were obtained at the last point of follow-up care from 26 GAD65 antibody-seropositive patients (20 with classic SMS and 6 with partial SMS); the median follow-up duration was 10 years (range, 1-22 years). At the last point of follow-up care, antibody values had decreased in 18 patients and had increased in 8 patients.

COMMENT

During 25 years of surveillance, approximately 4 patients with classic SMS or a variant were identified annually at the Mayo Clinic (two-thirds were women), making this a rare disorder. Most were GAD65 antibody seropositive, with high serum levels (usually > 100 nmol/L). GAD65 antibody-seronegative patients accounted for fewer cases, and the GAD65 antibody-seronegative form of classic SMS and PERM cases were very rare. Although fewer patients had partial SMS, symptoms restricted to one anatomical region were similar initially to those in patients with classic SMS. As at the time of initial description of the syndrome by Moersch and Woltman,¹ SMS among the patients described herein was often mistaken for a psychogenic disorder. Electrophysiological findings consistent with brainstem and spinal hyperexcitability^{2-5,39} helped confirm the clinical suspicion in many cases. Because most patients had neurological findings other than stiffness (most commonly brisk deep tendon reflexes), previously described strict diagnostic criteria⁸ were not too helpful in clinical practice. Recognition of classic SMS vs variants was important because treatments were beneficial in almost all patients described herein and had oncological significance in some. Because these disorders are rare, large prospective studies are difficult to perform. Therefore, limitations of our study include the retrospective classification of disorders and assessment of disability. Most patients were evaluated by 1 or more of us. The approach to evaluation and treatment was fairly similar across patients.

GAD65 antibody-seropositive patients with SMS were often had classic SMS, usually had coexisting autoimmune diseases, and rarely had cancer. GAD65 antibody-seronegative patients with SMS usually had partial SMS, rarely had other autoimmune diseases, but frequently had cancer (in 25% [5 of 20]). Barker et al¹⁷ reported similar findings in classifying their patients with SMS. They reported 2 cases of PERM, usually a rapidly fatal condition, which was similarly rare in our experience. GAD65 antibody-seronegative SMS is very rare, and therapeutic experience is limited. Seventeen patients in the present series were seronegative for both GAD65 and am-

phiphysin autoantibodies. Therefore, we were uncertain about an autoimmune basis for their disorder. Nonetheless, 2 patients had significant improvements with intravenous immune globulin, and another 2 patients had coexisting Hodgkin lymphoma and improved following oncological therapy or corticosteroid use. Cyclophosphamide seems to be beneficial in patients with paraneoplastic neurological disorders,⁴⁰ as was the case in an amphiphysin antibody-seropositive patient with breast carcinoma in our series. Antibody-targeting the glycine receptor $\alpha 1$ subunit has been reported in 5 patients with GAD65 antibody-seronegative "SMS-like" disorders, including 2 patients with PERM. This autoantibody holds promise as an additional biomarker for variants of SMS.^{41,42}

Amphiphysin autoimmunity, associated with breast or small cell carcinoma in particular, should be considered in patients with stiffness and spasms confined to the extremities.²⁵ Amphiphysin antibody-seropositive patients may have additional neurological findings, including neuropathy, encephalopathy, myelopathy, and cerebellar ataxia.²⁶ More than 80% of amphiphysin antibody-seropositive patients with small cell carcinoma have coexisting autoantibodies predictive of that cancer type, while patients with breast carcinoma are generally seropositive for amphiphysin antibody alone.⁴³ Cancer has been reported rarely among GAD65 antibody-seropositive patients with SMS (renal,⁴⁴ breast,⁴⁵ and neuroendocrine⁴⁶ carcinomas and thymoma²⁹) and among patients with SMS who are seronegative for both GAD65 and amphiphysin antibodies (Hodgkin lymphoma^{21,47} and breast carcinoma²⁷).

Coexisting autoimmunity, particularly diabetes mellitus and thyroid disease, was common among GAD65 antibody-seropositive patients (in 66%) but was uncommon among seronegative patients. Autoantibody markers of type 1 diabetes mellitus targeting other islet autoantigens (IA2 and insulin) were found only in GAD65 antibody-seropositive patients who had evidence of diabetes before the onset of SMS symptoms. Those with the strongest genetic predisposition to develop type 1 diabetes mellitus early in life usually have multiple islet cell autoantibodies.³⁴ Our retrospectively obtained data suggest that GAD65 antibody values may have additional diagnostic and prognostic significance; this finding would be difficult to apply to an individual patient in clinical practice. Patients with partial SMS had lower GAD65 antibody values than those with the classic form, and patients with classic SMS having worse disability at follow-up visits had higher GAD65 antibody values. All GAD65 antibody-seropositive patients for whom we received follow-up serum samples remained GAD65 antibody seropositive. The trend for GAD65 antibody values to decline over time likely reflects the effects of immunotherapy.

All GAD65 antibody-seropositive patients with classic or partial SMS had chronic symptoms that required long-term symptomatic therapies, regardless of concomitant immunotherapy. These treatments included benzodiazepines (often at high dosages)⁶ and baclofen (including intrathecal therapy).^{48,49} Higher median dosages of benzodiazepines were reported in patients with classic SMS (40.0 mg/d) than in patients with partial SMS (17.5 mg/d). Nevertheless, individual improvements varied, and

symptomatic treatments in practice should be titrated according to individual patient symptoms. Levetiracetam,^{50,51} valproic acid,⁵² vigabatrin,⁵³ propofol,⁵⁴ and gabapentin⁵⁵ should have been reported to reduce stiffness and spasms in patients with SMS.

Consistent with previous investigations, patients receiving immunotherapy frequently reported reduction in stiffness and spasms. Improvements in major disability (change in Rankin score) were less common. In a randomized controlled trial with crossover design among patients with classic SMS,¹¹ intravenous immune globulin was efficacious in reducing spasms and in improving social and occupational function and activities of daily living and is a recommended therapy.⁵⁶ Findings from case reports and small uncontrolled series suggest that corticosteroids, azathioprine, and rituximab are also beneficial.^{14,57-59} Rituximab was recently evaluated in a randomized controlled trial and was found to be of no significant benefit compared with placebo, although one-third of patients in the rituximab arm improved.⁶⁰ Evaluating immunotherapy responses in patients with SMS retrospectively or prospectively is difficult because most clinically important measures of disability are chronic, fluctuating, and subjective. Only gross measures of disability, such as the Rankin score, were used in our retrospective study.

The immunotherapeutic and symptomatic treatments used among patients herein varied. Most patients had at least mild to moderate subjective improvements in stiffness and spasms over time and remained independent in ambulation but also sufficiently disabled to require assistance, and few returned to employment. It is unclear why some patients' mobility improved with treatment and showed mild disability, while others were poorly responsive to therapy and required assistance with ambulation. In patients who are unresponsive to standard immunotherapies, we speculate that major histocompatibility complex class I-restricted GAD65 peptide-specific cytotoxic CD8⁺ T lymphocytes might cause early irreversible neuronal damage. In patients responsive to antibody-depleting therapies, the pathogenic effector might be antibodies targeting a synaptic cell surface antigen, such as the glycine receptor, or an antigen as yet uncharacterized.

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