# Stiff-Man Syndrome

## *Results of Interviews and Psychologic Testing*

JOHN L. BLACK, M.D., F.A.P.M., ELAINE M. BARTH, M.D.
DONALD E. WILLIAMS, PH.D., JOYCE A. TINSLEY, M.D.

*Thirteen patients with stiff-man syndrome (SMS) were studied with the Minnesota Multiphasic Personality Inventory (MMPI), the Self-Administered Alcoholism Screening Test (SAAST), the State-Trait Anxiety Inventory (STAI) profiles, and by telephone interviews. The mean MMPI, SAAST, and STAI were within normal limits; however, several patients had abnormal profiles. The results of telephone interviews revealed that 8 patients (62%) had been given at least 1 psychiatric diagnosis and 4 (31%) abused alcohol or were dependent on it. Two patients had a psychiatric diagnosis that preceded the onset of symptoms of SMS. The authors hypothesize that SMS patients have a γ-aminobutyric acid deficiency or GABAergic neuron dysfunction that leads to psychiatric symptoms, including depression and chemical abuse. Clinicians treating patients with SMS must be alert to the possible presence of comorbid psychiatric illnesses in this patient population.* (Psychosomatics 1998; 39:38–44)

Stiff-man syndrome (SMS) is a rare autoimmune neurologic disorder characterized by 1) a prodrome of stiffness and rigidity in axial muscles; 2) slow progression of stiffness to include proximal limb muscles, making volitional movements and ambulation difficult; 3) a fixed deformity of the spine, usually pronounced lordosis; 4) the presence of superimposed episodic spasms precipitated by sudden movement, jarring, noise, or emotional upset; 5) normal findings on motor and sensory nerve examinations; 6) normal intellect; 7) electromyographic findings typical of continuous motor activity abolished by intravenous administration of diazepam or a positive response to a therapeutic trial of orally administered diazepam;[1] and, 8) usually, positive serologic results for antiglutamic acid decarboxylase (anti-GAD65) autoantibodies.[2] It is common for type I diabetes mellitus to coexist with SMS; anti-GAD65 autoantibodies are characteristic of both disorders.[3]

Solimena et al.[4] first described anti-GAD antibodies in the serum and cerebrospinal fluid of a patient with epilepsy, type I diabetes mellitus, and SMS. Pancreatic islet beta cells, which also contain glutamic acid decarboxylase, are a useful substrate to test serum for anti-GAD65 antibodies (also called "islet cell cytoplasmic antibodies") in patients with suspected SMS.[5,6]

Anti-GAD65 antibodies have not been demonstrated to have a pathogenic role in SMS. However, the GAD enzyme is involved in the production of γ-aminobutyric acid (GABA), and it has been hypothesized that SMS patients

Received November 14, 1996; revised February 26, 1997; accepted April 7, 1997. From the Department of Psychiatry and Psychology, Mayo Clinic and Mayo Foundation, and the Zumbro Valley Mental Health Center, Rochester, Minnesota. Address reprint requests to Dr. Black, Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905.

are GABA-deficient because of anti-GAD antibodies or because of GABAergic neuron dysfunction. GAD has 65,000 molecular-weight (GAD65) and 67,000 molecular-weight (GAD67) isoforms. GAD65 is associated with the membrane of synaptic vesicles in brain and pancreatic islet cells,[7] and may serve as the antigenic stimulus involved in the pathogenesis of SMS, because it may be transiently accessible to the immune system during exocytosis. Sera from patients with SMS who have anti-GAD antibodies bind to and inactivate the GAD65 isoform.[8] Alternatively, GAD65 may be exposed to a patient's immune system upon destruction of GABA secreting (GABAergic) cells by another, as yet, undiscovered process. The observation that the use of GABA agonists (e.g., diazepam) in high doses greatly alleviates symptoms of SMS supports the hypothesis that GABA activity in the central nervous system is reduced in SMS patients.

The role of GABA in psychopathology has been reviewed by Zorumski and Isenberg.[9] The GABA receptor complex is implicated as the site of action of several psychoactive agents, including benzodiazepines, barbiturates, and alcohol. Because of the relationship between SMS and GABA and the putative relationship between GABA and various mental illnesses, we believed that it would be useful to assess psychopathology in patients with SMS. We report on the results of telephone interviews and limited psychologic testing of 13 patients with SMS. We conducted our study 1991–1996.

## MATERIALS AND METHODS

Thirty-nine patients with the diagnosis of SMS were identified either by direct referral (2 patients) or through computer search of the Mayo Clinic record-keeping system (37 patients). Of these 39 patients, 14 had died, leaving 25 potential participants. The study was approved by the Institutional Review Board of the Mayo Foundation, and consent for patient participation was obtained first from the patient's physician and then from the patient. Two patients were not included because of lack of physician approval, four patients indicated they did not wish to participate, and two consent forms were returned unsigned. Originally, a total of 17 patients were in the study pool sample.

The medical records of the participating patients were reviewed, and the patients were classified as either "definite" or "not definite" SMS, depending on the certainty of the diagnosis indicated in the medical record, whether patients met the strict criteria outlined in the introduction of this article, and whether the patient's serum contained anti-GAD65 antibodies. Only "definite" patients were included in this study ($N = 13$). Those patients not previously tested for islet cell antibodies were asked to send a blood sample for testing. Testing was performed by indirect immunoperoxidase staining of immunoglobulin G binding to baboon pancreas islet cells (results of 1:120 dilutions or greater were considered significant)[6] or radioimmunoprecipitation assay using recombinant (Iodine)$^{125}$I-labeled GAD65 (results greater than 0.02 nm/L of serum were considered significant).[10]

The patients were asked to complete and return three self-report questionnaires: the Minnesota Multiphasic Personality Inventory (MMPI),[11,12] the Self-Administered Alcoholism Screening Test (SAAST),[13] and the State-Trait Anxiety Inventory (Form X) (STAI).[14] The MMPI was chosen for its usefulness in identifying a wide range of psychopathology, particularly on Axis I, and to allow for possible comparisons of the profile with medical and psychiatric populations. The SAAST was selected to address the apparently high prevalence of alcohol abuse or dependence noted in the records of the patients at the time of their clinical evaluation at the Mayo Clinic. The STAI was selected to measure anxiety levels in the patients at the time of the study and to allow for comparisons of these scores with STAI normative data.[13]

Mean and standard deviations were calculated for the *T*-scores obtained from the MMPI and STAI as well as for the raw and weighted scores of the SAAST. The mean and standard

deviations were then compared with their respective normative samples.[11–14]

All 17 patients participated in a telephone interview, but 4 were not included in this report because they did not meet the criteria for definite SMS. The interview was standardized and semistructured and was done by a single interviewer. The questions were designed to determine the chronology and treatment of SMS and psychiatric diagnosis and symptoms as remembered by the patient. Medication and alcohol use were also assessed. Alcohol abuse or dependence was assessed by using the criteria from DSM-III-R[15] but no attempt was made to diagnose other psychiatric illnesses by DSM-III-R criteria. Rather, we recorded the predominant symptoms that lead to psychiatric consultation. Some interviewed patients did not complete the MMPI, STAI, or SAAST. Of the 13 SMS patients, 10 completed the SAAST, 11 completed the MMPI, and 11 completed the STAI.

## RESULTS

Thirteen patients (8 women, 5 men) were studied. Their mean ± standard deviation (SD) was 47.2 ± 9.1 years (range: 35–68 years) at the time of the study. All were seropositive for anti-GAD65 autoantibodies. Figure 1 shows the average *T*-scores of the 2 subscales of the STAI. These results do not differ from those of normal samples. Figure 2 shows the mean MMPI profile for the patients, which were also within normal limits for a medically ill population of patients.[16] However, 6 patients (Patients 1, 7, 8, 10, 12, and 13) had clinically significant elevations of at least 1 scale ($T \geq 70$th percentile). Typically, the scales measuring somatic preoccupation, depression, emotionality, or anxiety (Scales 1, 2, 3, or 7) were elevated. No "typical" SMS MMPI profile score came from these results. Figure 3 shows the average raw and weighted scores from the SAAST, which were also within normal limits. However, the SAAST showed much variability because of the four alcohol abusers, resulting in high SDs. The alcohol abusers had elevated SAAST scores consistent with the diagnosis of alcohol abuse or dependence.

Table 1 gives the results of the telephone interviews. The mean time from the onset of symptoms to the time of diagnosis of SMS was 2.9 ± 3.2 years (range: 4 months–11 years). Two patients had psychiatric symptoms before the onset of SMS. Strikingly, six patients had psychiatric symptoms after the onset of the symptoms and before the diagnosis of SMS. Four patients had no psychiatric history at the time of the interview. Five patients reported that they had the diagnosis of depression, and four reported a diagnosis of either alcohol abuse or dependence. We confirmed alcohol dependence in two patients and alcohol abuse in two at the interview. Of all the study subjects, 10 took diazepam (53.5–34.2 mg) to control SMS symptoms, and 2 took clonazepam (6 ± 5.7 mg). Other drugs used at the time of interview are listed in Table 1.

## DISCUSSION

SMS is a rare autoimmune disorder associated with anti GAD65 antibodies. We hypothesize that patients with anti-GAD antibodies have decreased neuronal GAD activity or decreased GABA production in the central nervous system. This explanation seems plausible because SMS symptoms respond to GABA agonists. However, we cannot explain why antibody production is triggered by this vesicle membrane-associated enzyme. It is possible that anti-GAD antibodies are an epiphenomenon of some process destructive to cells containing GAD or that vesicle membrane-associated GAD65 is transiently exposed to the immune system during exocytosis and functions as the antigenic trigger or that viral antigens closely resembling GAD65 trigger the immune response. The latter is suggested by the finding that there is antibody cross-reactivity induced by homologous regions in GAD65 and the 2C protein of Cox sackie virus B4.[17] The proposed decrease in GAD activity and the proposed GABA deficiency led us to study our group of patients. On the basis of the hypothesis that perturbation of GABA metabolism is involved in the generation of various forms of psychopathology, as suggested by Zo-

**FIGURE 1. State-Trait Anxiety Inventory. Normal *T*-score, 50 ± 20. $P \geq 0.05$ for both scales**

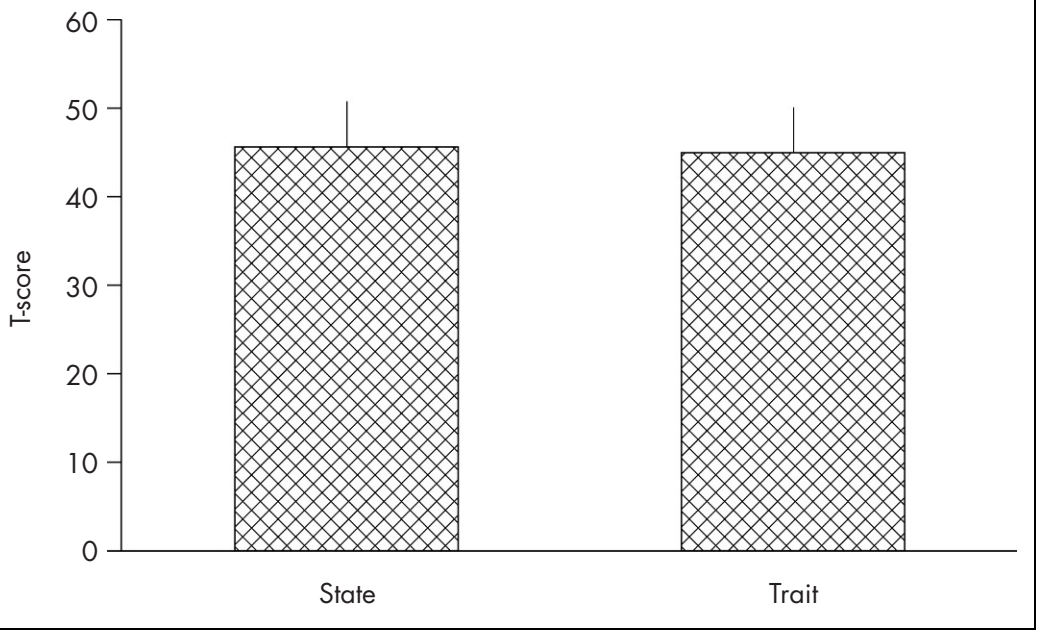
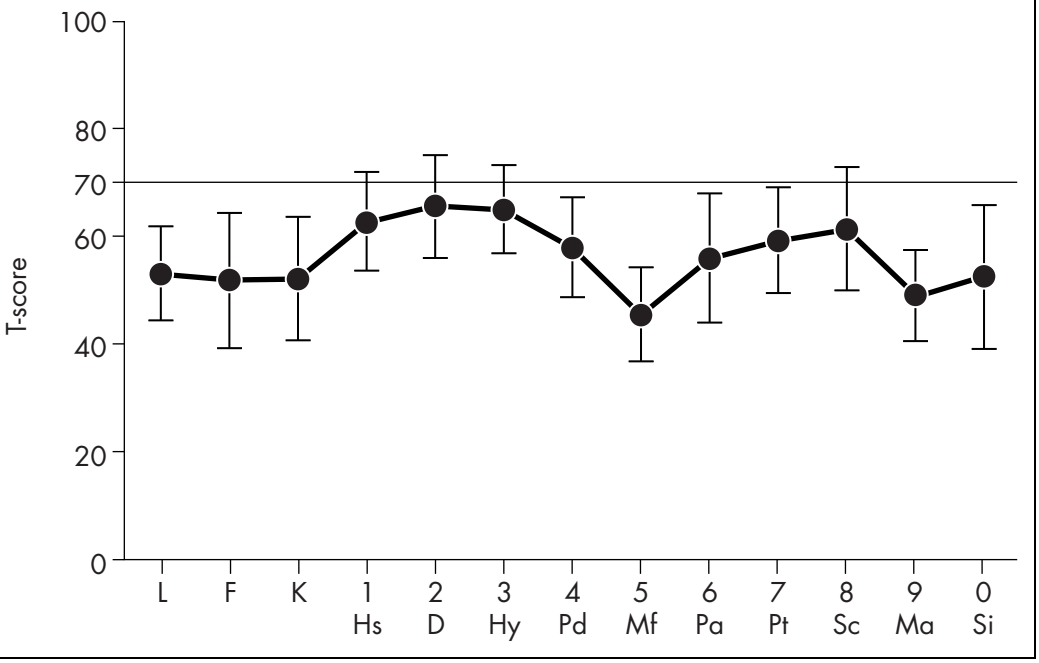



**FIGURE 2. Minnesota Multiphasic Personality Inventory. Normal *T*-score, 50 ± 20. $P > 0.05$ for all scales**

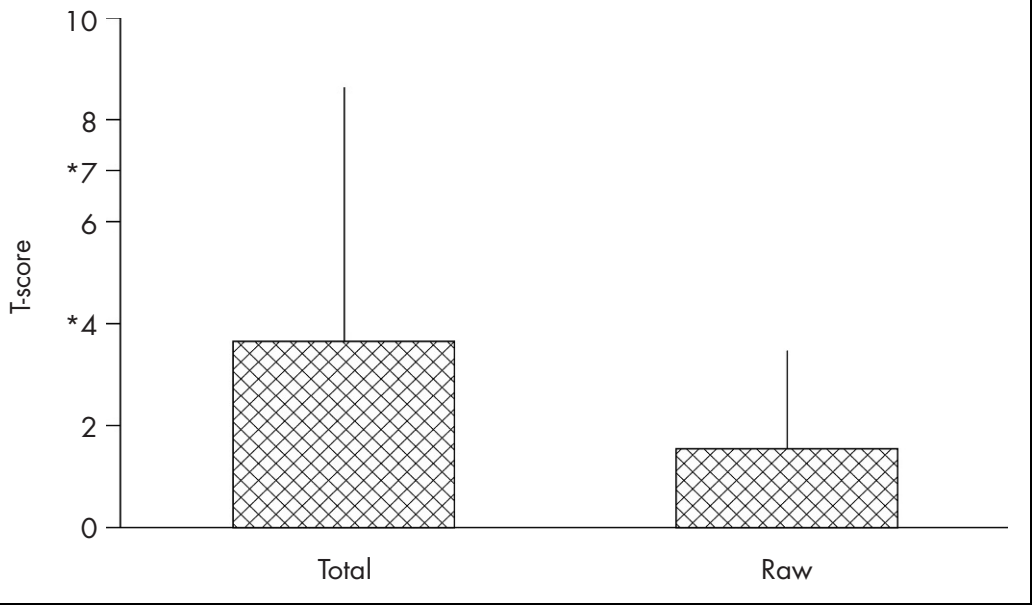


rumski and Isenberg,[9] we hypothesized that SMS patients would have a high incidence of psychiatric difficulties because of their putative decrease in central nervous system GABA.

According to the results of our patient interviews, a disproportionate number of those with SMS have experienced significant psychiatric symptoms (62%), and the incidence of alcohol abuse and dependence in the patients we studied (31%) was greater, compared with that of the Epidemiologic Catchment Area Study, in which 13.6% of the general population had alcohol abuse or dependence.[18]

However, the STAI results show no difference compared with those of normative samples. A possible explanation for this unexpected result is that most of the patients were taking benzodiazepines and some used alcohol and, consequently, did not report symptoms of anxiety. The effect of these substances on the STAI is unknown. Although the average MMPI profile of these patients did not differ from that of populations with known medical illnesses,[16] the profile shown in Figure 2 would be interpreted as showing evidence of mild-to-moderate depression, increased emotionality, increased concern of bodily function and health issues, and mild-to-moderate anxiety. Patients with this profile would also see themselves as different from others and feel isolated. Such a profile is often seen in patients with chronic medical illnesses. It is informative that even though Patients 12 and 13 did not report a previous psychiatric diagnosis, their MMPI scores were in the abnormal range, which suggests that had a psychiatrist seen these patients, a psychiatric diagnosis may have been made. Thus, our interview results may actually underestimate the prevalence of psychopathology in this sample. Again, the effect of alcohol and medications on a patient's symptoms may have also affected the MMPI results. SAAST scores were not elevated compared with normal populations, but the standard deviation was large, reflecting variability caused by the two alcohol-dependent and two substance-abusing patients in the study.

**FIGURE 3. Self-Administered Alcoholism Screening Test. Raw≥7 or weighted≥4 indicates suspected or probable alcoholism.**



Previous authors have suggested that SMS symptoms may be preceded by psychopathologic symptoms,[19] and our results support this possibility in that two patients were symptomatic for psychopathology before the onset of SMS. Six other patients had psychiatric symptoms that began after the onset of SMS but before a diagnosis of SMS was made, raising the possibility that psychopathology was misdiagnosed because of the unusual nature of the patients' symptoms, although the patients did describe symptoms consistent with the diagnoses listed in Table 1. Depression was the most commonly reported diagnosis, followed by alcohol abuse/dependence. It was significant that two patients explained that they began to abuse alcohol in an attempt to self-medicate their SMS symptoms. Specifically, these patients reported that when they drank, their symptoms were less severe. One patient described using five shots of liquor before golfing to successfully reduce the stiffness that he experienced. These findings are consistent with the hypothesis that GABA or GABA-receptor abnormalities may be involved in the onset of depression and alcoholism.

The shortcomings of the methods used in this descriptive study include difficulties encountered in collecting retrospective data from the patients. The self-report instruments were administered in an unsupervised setting. Also, the telephone interview did not permit visual contact with the patient, which could lead to difficulty in assessing and validating the accuracy of reported psychiatric symptoms. It also is possible that our patients did not recall their psychiatric histories accurately. Our small sample sizes contributed to difficulties in finding significant differences between the samples; however, the rarity of this condition makes it impossible to find large numbers of patients to study. Finally, the study permitted patient self-selection, which may induce bias. Nonetheless, in our sample, the prevalence of a psychiatric diagnosis was 62%, and the rate of alcohol abuse or de-

**TABLE 1. Clinical and psychiatric data for 13 patients with Stiff-Man Syndrome (SMS)[a]**

| Patient | Year Symptoms Began (Year Diagnosis Made) | Medicines Used to Treat SMS When Interviewed | Psychiatric Diagnosis, (Year of Diagnosis), Past Treatment |
|---|---|---|---|
| 1 | 1985 (1986) | Diazepam, 50 mg/d<br>Prednisone, 15 mg qod | Depression/(1985)/Psychotherapy, antidepressant |
| 2 | 1979 (1990) | Prednisone, 16 mg qod<br>Clonazepam, 10 mg/d | Depression, conversion disorder, alcohol abuse/(1988)/Antidepressant |
| 3 | 1988 (1989) | Diazepam, 80 mg/d<br>Cyclobenzaprine, ? dose<br>Prednisone, 25 mg qod | Depression/(1988)/Antidepressant |
| 4 | 1981 (1982) | Diazepam, 110 mg/d | Alcohol abuse/(1989)/Hypnosis |
| 5 | est 1975 (1981) | Diazepam, 25 mg/d | Depression, alcohol abuse/(1977)/ Psychotherapy |
| 6 | 1987 (1989) | Diazepam, 20 mg/d | None |
| 7 | 1982 (19909) | Clonazepam, 2 mg/d<br>Indomethacin, 100 mg/d | Adjustment disorder/(1976)/Psychotherapy |
| 8 | 1980 (1984) | Diazepam, 70 mg/d | Depression, alcoholism, anxiety/(1960)/ Antidepressant, counseling |
| 9 | 1982 (1982) | Diazepam, 30 mg/d<br>Carbamazepine, 600 mg/d | None |
| 10 | 1985 (1985) | Diazepam, 100 mg/d | ? Conversion disorder/(1985)/Psychotherapy |
| 11 | 1981–1982 (1981–1982) | Diazepam, 30 mg/d | None |
| 12 | 1972 (1988) | None | None |
| 13 | 1982 (1982) | Diazepam, 20 mg/d | None |

*Note:* est = estimated; qod = every other day.
[a]Data obtained at time of interview with patients.

pendence was 31%. We believe that this finding supports our hypothesis that patients with anti-GAD65 antibodies have psychopathology induced by decreased neuronal GAD activity and decreased GABA production. On the basis of our results, we conclude that clinicians treating SMS patients must be alert to the potential presence of the comorbid psychiatric illnesses of depression and alcoholism.

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