A neuropsychological assessment of phobias in patients with stiff person syndrome

Abstract—A neuropsychological assessment was performed in 10 patients with stiff person syndrome (SPS) to determine whether their anxiety and phobic symptoms precede stiffness and spasms or represent a reaction to disability. No neurocognitive dysfunction was noted. Patients perceived fears and anxiety as realistic and caused by SPS rather than due to an inherent phobic neurosis.

NEUROLOGY 2005;64:1961–1963

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Stiff person syndrome (SPS) is an immune-mediated CNS disorder characterized by rigidity of the axial and proximal limb muscles, intermittent superimposed spasms, and heightened sensitivity to external stimuli or emotional upset.[1,2] It affects GABAergic neurotransmission, presumably due to anti-glutamic acid decarboxylase (anti-GAD) antibodies, resulting in reduced γ-aminobutyric acid (GABA) level in the brain and CSF.[1,2] Anticipatory anxiety is common in SPS patients, occurring in situations perceived as physically unsafe, such as crossing a busy street or walking unaided in open spaces, and precipitates attacks of increasing stiffness or spasms that result in falls. A startle response to unexpected stimuli is also common and bears similarities to phobic disorders,[3] leading often to the erroneous diagnosis of a psychiatric disease. Whether these phobias are primary, inherently associated with the disease and the low GABA level, or secondary, due to the physical condition, is unclear. We report on the personality profile, neurocognitive function, and origin of these patients' phobias by examining if anxiety antedates the physical signs of the disease or represents a reaction to disability.

Methods. We studied 10 patients (7 women, 3 men), ages 35 to 60 (mean age 52), with typical SPS and high anti-GAD antibodies,[1,2] under institutional review board-approved protocols. Disease duration ranged from 5 to 30 years (mean 11 years). At time of psychiatric evaluation, all patients were symptomatic, despite receiving therapy with diazepam, clonazepam, or baclofen for a mean period of 13.8 years (range 8 to 15 years). One patient was receiving IV immunoglobulin (IVIg) but was still symptomatic. Anxiety was reported by six and depressed mood by five; four patients had seizures controlled with phenytoin, carbamazepine, or lamotrigine.

The validated Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) Axis I (SCID-I/P)[4] was employed under informed consent to determine the frequency of current and lifetime co-morbid Axis I psychiatric diagnoses as well as Axis V (Global Assessment of Functioning [GAF]). The Inventory of Depressive Symptomatology–Clinician Version[5] and the Hamilton Anxiety Scale[6] were utilized to assess current severity of depression and anxiety. A measure of normal personality functioning, the NEO Five-Factor Inventory-Revised (NEO FFI),[7] was also administered to assess personality characteristics.

Cognitive functioning was assessed by the following: Wechsler Abbreviated Scales of Intelligence Matrix Reasoning[8]; declarative memory (Hopkins Verbal Learning Test-Revised [HVLT-R])[9]; working memory (Cambridge Neuropsychological Test Automated Battery [CANTAB], Spatial Working Memory)[10]; attention (CANTAB Rapid Visual Information Processing); and executive functioning (Intradimensional-Extradimension Shift).[10]. CANTAB and HVLT tests[4] are routinely used to detect neurocognitive deficit in other neurologic disorders such as Alzheimer disease, Parkinson disease, Huntington disease, and HIV dementia.

Results. Nine of 10 subjects underwent psychiatric assessment (table 1) Four patients met criteria for DSM-IV diagnoses; one met the criteria for current (and lifetime) depression and another for lifetime depression; a third patient met criteria for lifetime alcohol dependence and polysubstance abuse (in remission); the fourth met criteria for current (and lifetime) social phobia and dysthymia and lifetime criteria for posttraumatic stress disorder, cannabis use, and stimulant (crystal meth) dependence (in remission). The GAF ratings (mean = 42.8, on a 1-to-100 scale [1 most severe]) indicated functional impairments; the depression and anxiety severity ratings ranged from normal to mild. One patient with marital distress reported clinically significant levels of current depression and anxiety.

The NEO FFI was administered to seven patients (table 2). One of the five factors (neuroticism, extraversion, openness, agreeableness, and conscientiousness) was elevated. The mean score on this scale was in the high range with a small standard deviation, indicating a uniform trend within the study patients.

Neurocognitive performance, administered to eight patients, compared the performance of each patient with published normative data for each test (table 3). An a priori t score of ≤ 35 and z score of -1.5 or lower were indicators of neuropsychometric impairment. None of the mean scores (excluding Patient 7; see below) fell below the a priori impairment level. The mean HVLT-R percentage retention, a measure of verbal delayed memory, was in the borderline impairment range (z score between 1 and 1.5), although unduly influenced by Patient 4 (see table 3). The mean estimated IQ (Matrix Reasoning) was in the high-average range. Individuals with high-average IQs typically perform similarly on other cognitive measures; therefore, the discrepancy between high IQ and average to low-average performance on the remaining tests is unexpected and suggests possible mild cognitive decline.

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Received October 29, 2004. Accepted in final form March 1, 2005.

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Table 1 *Diagnosis and clinical ratings of patients with SPS*

Patient no.	Years with SPS	GAD Ab (nl 0.00–0.02 nmol L)	Current SCID diagnosis	Lifetime SCID diagnosis	GAF		IDS-C*	HAM-A†
1	16	206	Depression	Depression	40	Marked	21	20
2	8	2,499	None	Depression	40	Marked	12	12
3	12	72	None	None	60	Moderate	2	3
4	31	427	None	Alcohol dep, poly-substance abuse	35	Marked	4	6
5	11	1,246	None	None	55	Moderate	8	10
			Social phobia					
6	6	197	Dysthymia	PTSD; cannabis dep; stimulant (crystal meth) dep	50	Moderate	6	8
7	8	254	None	None	35	Marked	13	14
8	3	141	None	None	35	Marked	3	2
10	6	1,205	None	None	35	Marked	6	12
Mean	11.2	694			42.8		8.3	9.7
SD	8.3	811			9.7		6.1	5.7

* IDS-C (depression rating): normal 0–13; mild 14–22; moderate 23–30; severe 31–38; very severe 39+.
† HAM-A (anxiety rating): normal 0–5; mild 5–14; moderate to severe 14+.

SPS = stiff person syndrome; GAD Ab = glutamic acid decarboxylase antibody; nl = normal; SCID = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV; GAF = Global Assessment of Functioning; IDS = Inventory of Depressive Symptomatology; HAM-A = Hamilton Anxiety Scale; dep = dependence; PTSD = posttraumatic stress disorder.

Discussion. We found current DSM-IV diagnoses in 2 of 10 SPS patients and a mixture of nonspecific lifetime DSM diagnoses in 4. The diagnosis of social phobia was made in only one. A high score on agreeableness, which refers to individuals who report themselves as trusting, straightforward, altruistic, compliant, modest, and tender-minded, was noted in the patients' personality testing. We did not observe a significantly high score on neuroticism or introversion, which are commonly associated with psychopathology.[7] Collectively, the results do not support neurocognitive impairment in SPS patients, although a slight decline in cognitive functioning from premorbid levels is suggested.

No consistent pattern of simple phobia emerged from the SCID interviews. A DSM-IV diagnosis of simple phobia requires an acknowledgment by the patient that his or her fears are unreasonable.[4] Although our patients had many avoidance behaviors to a variety of circumstances, similar to those reported in the literature,[3] they did not endorse that their fears were unrealistic. To the contrary, they believed that anyone confronted with such unpredictable episodes of stiffness with potential harmful consequences as they had could develop similar fears. Some patients, however, were puzzled by certain physiologic reactions such as profuse sweating and excessive startle or freezing response to innocuous situations (i.e., light touch) and considered these reactions as irrational, but they did not endorse an internal experience of "fear" to these situations. In contrast to a recent study in which SPS patients

Table 2 *Neo-FFI t scores of patients with stiff person syndrome*

Patient no.	N	E	O	A	C
2	61	41	55	57	29
4	68	55	75	62	25
5	51	41	25	56	60
6	62	25	57	53	53
7	55	51	43	57	36
8	36	57	70	72	62
10	43	50	47	57	45
Average	53.714	45.714	53.143	59.14	44.286
SD	11.28	11.056	16.896	6.256	14.784
Norms	50 ± 10	50 ± 10	50 ± 10	50 ± 10	50 ± 10

NEO FFI = NEO Five-Factor Inventory; N = neuroticism; E = extraversion; O = openness; A = agreeableness; C = conscientiousness.

Table 3 *Neuropsychological performance of patients with stiff person syndrome*

	WASI	HVLT-R			IDED		SWM			RVIP		
Patient no.	Matrix Reasoning	Trial 1–3	% retention	Recognition	Pre-ED	EDS errors	Between errors	Within errors	Strategy	A′	B″	Latency
2	59	−2.6	0.6	−0.2	−1.1	−0.1	0.3	−0.5	0.1	−1.3	−0.7	1.4
3	61	−0.4	−0.9	−2.0	0.2	−1.6	1.0	0.7	−0.4	−1.6	0.1	0.5
4	56	−1.8	−7.2	−1.1	0.7	0.4	−0.4	−0.5	0.1	−1.4	0.2	−1.1
5	61	−1.8	−1.4	−0.2	−1.1	0.5	1.0	0.7	0.1	0.3	0.1	0.3
6	61	0.3	−0.2	−1.1	0.0	−3.4	0.1	0.5	−1.1	−0.1	0.4	−0.1
7	36	−2.8	−6.0	−6.4	0.0	−0.3	−2.0	−0.5	−1.2	−0.2	0.6	1.3
8	63	0.3	0.6	−0.2	0.0	0.4	−1.8	−4.5	−0.4	−1.7	0.4	1.1
9	52	0.8	0.6	0.7	0.3	0.6	−0.5	−0.3	−0.7	1.0	0.0	0.7
Mean*	59.0	−0.7	−1.1	−0.6	−0.2	−0.5	−0.1	−0.6	−0.3	−0.7	0.1	0.4
SD	3.8	1.3	2.8	0.9	0.7	1.5	1.0	1.8	0.5	1.1	0.4	0.8
Norms†	50 ± 10	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1

WASI = Wechsler Abbreviated Scales of Intelligence; HVLT-R = Hopkins Verbal Learning Test–Revised; IDED = intradimensional–Extradimensional Shift Test; SWM = Spatial Working Memory Test; RVIP = Rapid Visual Information Processing; EDS = extradimensional stage.

* Mean and SD scores were calculated excluding Subject 7, who had a substantially lower estimated IQ (Matrix Reasoning = 36).
† t scores or *z* scores derived from each test's normative sample.

believed that their fears were unrealistic,[3] our patients reported that their fears and avoidance behavior were realistic and developed after the onset of SPS symptoms.

Clinical experience in making DSM diagnoses cautions us in diagnosing anxiety disorders in SPS patients, given the reality of their physical disability and the unpredictable nature of their "freezing" and falling episodes. Although at the time of examinations, all patients were symptomatic, in spite of receiving treatment for their motor symptoms, the possibility that muscle relaxants or antianxiety agents had masked some of their fears and confounded the proper assessment of an anxiety disorder or neurocognitive dysfunction cannot be excluded. The absence of premorbid phobias, however, and the realization that the fear of falling is realistic strongly suggest that the anxiety in SPS patients is secondary to the primary neurologic disorder rather than due to a primary inherent phobia, as justified by the reduced GABA level. This conclusion is also supported by our clinical trial with IVIg, which demonstrated that when the physical signs of stiffness improved, so did the anxiety.[2] Considering that reduced GABA is connected to anxiety disorders, it remains a possibility that the reduction of GABA, as observed in SPS patients, may predispose them to an exaggerated anxiety response triggered by the primary motor deficit.

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