Psychological factors in the diagnosis and pathogenesis of stiff-man syndrome

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Article abstract—Retrospective psychological evaluation of nine patients with stiff-man syndrome (SMS), seven of whom evidenced autoimmune disease, revealed a characteristic set of psychological symptoms or features: Major stressful life events preceded the development of permanent symptoms by 6 months or less (seven patients); transient motor symptoms occurred in emotionally distressing situations months or even years before the onset of a permanent motor deficit (five patients); after onset, similar situations specifically precipitated or augmented stiffness and spasms (five patients). We also found task-specific fear resembling agoraphobia (six patients) and loss or invalidation of one or both parents, or loss of home, in childhood (seven patients). Eight patients were initially misdiagnosed as having psychogenic movement disorder. We conclude that the common misdiagnosis of SMS as a psychogenic movement disorder is due to the compelling association of a set of salient psychological features, bizarre and fluctuating motor symptoms, and lack of approved neurologic signs.

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Stiff-man syndrome (SMS), a rare neurologic disorder, is characterized by fluctuating symmetric rigidity of the trunk and proximal limb muscles superimposed by painful muscle spasms. In most cases, there is a lack of physical signs usually present in neurologic disease.[1-3] In some cases, minor and often transient neurologic signs, such as eye movement disturbances, may occur; such cases are referred to here as progressive encephalomyelopathy with rigidity and myoclonus (PERM).[3] The etiology and pathogenesis of SMS are unknown, and prior hypotheses included psychogenesis.[4,5] However, the high frequency of autoantibodies against glutamic acid decarboxylase (GAD), the GABA synthesizing enzyme, in most patients with SMS, but not in other neurologic diseases,[6] strongly suggests an autoimmune component in the pathogenesis of SMS.

In clinical practice, psychogenic movement disorder is the most frequent initial diagnosis in patients later diagnosed as having SMS.[3] Obviously, absence of neurologic signs in a bizarre movement disturbance contributes to such misdiagnosis. In many patients with SMS, however, the history suggests contribution of psychological factors to the disease.[1-3] To identify such factors, we added a psychological evaluation to the neurologic workup of patients with SMS.

Methods. *Subjects.* Nine SMS patients were asked on the occasion of their attendance at the Department of Neurology and agreed to take part in an individual interview; four of them had additional family interviews together with their spouses. Patients were selected solely on the basis of availability in the study period.

Neurologic assessment. A survey of the patients' neurologic data is given in table 1. Patients 1 to 6 had "typical" SMS, i.e., intense rigidity of the trunk and arms (patients 1 and 5) or legs (patients 2, 3, 4, 6) superimposed by painful spasms, and no additional neurologic symptoms or signs except for hyperactive deep tendon reflexes. In particular, none of the patients had clinical or electrophysiologic evidence for involvement of pyramidal tracts, dorsal columns, anterior visual pathways, motor neurons, or peripheral nerves. Patient 9 had atypical SMS with stiffness and spasms of her trunk and only one leg. Patients 7 and 8 had transient ocular motor disturbances, including transient severe bilateral lid drop in patient 7, before stiffness and spasms of the trunk and legs developed; these patients were diagnosed as having the encephalomyelopathic variant of SMS, PERM.[3] For brevity, PERM will hereafter be referred to as SMS as well. Patients 1, 2, 3, and 5 have been reported previously.[2,7-9]

Autoantibodies against GAD were identified in both serum and CSF in five patients (nos. 2, 3, 6, 8, 9) with techniques described earlier.[6] Among the patients tested negative for GAD autoantibodies, one (patient 5) had breast cancer and cancer-associated autoantibodies against amphiphysin, a synaptic vesicle protein,[7] and another (patient 1) had persistent intrathecal production of immunoglobulin G (IgG) and oligoclonal banding without pleocytosis.[2] So far, none of the patients has type I diabetes mellitus, a condition frequently associated with the presence of GAD autoantibodies,[6] or other immune-mediated diseases. MRI of the brain and spinal cord yielded normal results in all but patient 1, who showed multiple small-diameter lesions located mainly in the subcortical white matter.[9]

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Table 1 Survey of patients

Patients*	Age at onset	Age at evaluation	GAD-AB	Comments
1 F	37	68	–	Increased IgG in CSF; case 1 in refs. 3, 8, 12
2 F	48	58	+	Case 7 in refs. 3, 12
3 M	27	33	+	Case 4 in refs. 3, 12
4 M	25	35	–	
5 F	58	60	–	Amphiphysin autoantibodies positive; patient had breast cancer; case 4 in ref. 7
6 F	57	63	+	
7 F	48	51	–	
8 F	59	66	+	
9 F	52	55	+	

* All patients had stiff-man syndrome except for patients 7 and 8 who had progressive encephalomyelopathy with rigidity and myoclonus (PERM).

F = female; M = male; – = negative; + = positive; CSF = cerebrospinal fluid; GAD-AB = autoantibodies against glutamic acid decarboxylase; IgG = immunoglobulin G.

Psychological assessment. The interviewers were not blinded as to the diagnosis of the patients. They were asked to take the diagnostic attitude appropriate for suspected psychogenic disorder,[10] i.e., to look for evidence or risk factors in the patient's life circumstances and biography commonly associated with the development of psychogenic disease such as a history of psychiatric disease, loss of parental figures, sexual/physical abuse in childhood, or loss or significant change in currently relevant personal or professional relationships.

The interviews[11] were semi-structured and included a systematic inquiry about the patient's biography, previous psychiatric diagnoses and treatment, relevant life events prior to onset of the illness (as in axis IV of DSM-IV;[12] only life events less than 6 months prior to onset of disease were taken into account), situational variability of symptoms and patterns of family interactions influencing symptoms, and psychiatric symptoms after onset of SMS. In two patients (nos. 2 and 5), additional information was obtained from the clinical notes on their psychiatric inpatient treatment for suspected psychogenic movement disorder. Self-report or other questionnaires were not added as they are not part of the usual clinical workup when diagnosing such patients. Because of the small number of cases, we did not attempt to rank the severity of stressful life events; we preferred to give a brief description for each case instead, illustrating the patient's and interviewer's ascription of the life event as a profound and lasting change of the patient's personal or professional situation.

Results. *Psychiatric comorbidity.* Before onset of motor symptoms. No patient ever had contact with a psychiatrist or had suffered from manifest psychiatric disease before onset of SMS. In particular, there was no history of psychogenic neurologic signs or of multiple somatizations. Two patients (nos. 7 and 8) reported mild claustrophobia since youth when being in an elevator or in an unfamiliar darkened room, e.g., a cinema. Four patients (nos. 1, 2, 8, 9) reported symptoms resembling agoraphobia (see below), which occurred transiently 6 to 9 months before the onset of unexpected falls and before they became aware of a permanent gait disorder; they were suddenly unable to cross a street without help or to complete a staircase because of intense attacks of fear.

After onset of motor symptoms. An initial misdiagnosis of psychogenic or hysteric movement disorder was made in all patients except one (patient 4) after onset of motor symptoms. In most patients (nos. 1-3, 5-7, 9), this false diagnosis was made by neurologists—in 3 of these patients (nos. 1, 2, 7) after hospitalization in one or two neurologic units. Two patients were treated as psychiatric inpatients under this diagnosis—patient 2 for 2 months and patient 5 for 3 months; a combination of psychotherapy, psychopharmacotherapy, and physiotherapy was used without success in both cases.

Six patients (nos. 1, 2, 6-9) developed attacks of intense fear regularly understood by physicians as agoraphobia as the attacks appeared when the patients attempted to cross a square, a street or even a corridor. However, this fear differed from common agoraphobia as it was specifically confined to situations in which patients had to stand or walk without sufficient support or were forced to walk in a hurry. Fear disappeared instantaneously if sufficient support was given to the patients.

One patient (no. 4) developed subacute depression 6 years after onset of his disease immediately after completion of a series of successful plasmaphereses.

Manifestation of precedential motor symptoms. Five patients reported transient and occasionally recurrent motor symptoms that preceded the onset of a permanent motor deficit by weeks or even years. In all of these patients, they occurred in a specific emotionally distressing situation:

- attack of stiffness in right arm when attempting to stop her 3-year-old child from running into the street (patient 1) months before onset of permanent shoulder stiffness
- painless sudden falls while bowling or playing football in professional competitions $3\frac{1}{2}$ years before stiffness and spasms became manifest (patient 4)
- stiffness of right leg for about 1 minute during burial of

sister, completely free of symptoms for the following 3 years (patient 6)
- first attack of leg stiffness on last day of work before retirement, weeks before the onset of permanent SMS (patient 8)
- first fall when she saw her little grandson in a crowd of people and feared him to be hurt; 3 months later, permanent leg stiffness gradually developed (patient 9)

In two patients (nos. 2 and 7), the very first manifestation of SMS happened in an insignificant situation at work; in another two (nos. 3 and 5), this situation was not remembered.

Life events prior to onset of permanent motor symptoms. The onset of permanent motor symptoms was preceded in seven patients by a variety of life events that strongly affected their personal and professional relationships. Life events happened during the preceding 6 months, and in five patients during the preceding 2 months, before onset of a permanent motor impediment. Life events comprised the following:

- confirmation of husband's infidelity (patient 2)
- accident while diving, his favorite sport, leading to mild tetraparesis for 3 weeks (patient 3)
- separation from fiancée and marriage to another woman he knew for 2 weeks (patient 4)
- dissolution of her bookstore department because of low profits (patient 5)
- death of her son in a traffic accident (patient 6)
- retirement (patient 8)
- death of mother followed by her starting to work again (patient 9)

In two patients (nos. 1 and 7), no significant life events occurred within the time span of 6 months before onset of permanent motor symptoms.

Characteristic situations precipitating motor symptoms. In addition to physical triggers such as sudden unexpected noise (the telephone bell or a clapping door), stumbling on uneven ground, or being jolted, nonspecific emotional upset in all patients led to increased stiffness and spasms often associated with inability to stand or walk. In five patients (nos. 1, 2, 3, 6, 8), mental anticipation of an additional effort required in a specific situation, real or imagined, carried a high risk of increasing motor symptoms, sometimes associated with attacks of fear (see above):

- having the intention of crossing a street or using stairs without a railing
- withdrawal of support, e.g., when losing the grip on a door handle, or when discharge from the hospital was planned
- being challenged to do something, e.g., by relatives, colleagues, or doctors
- imagining an obstacle, a situation, or a motor task difficult to meet

Traumatic life events in childhood. Exploration of the biographical background revealed early traumatic life events in seven patients:

- loss of one or both parents before age 7 (patients 2, 4, 7, 8) or at age 9 (patient 1)
- experiencing father as severely handicapped with traumatic blindness from age 6 (patient 9)
- being exiled from northeastern Europe at age 5 (patient 5)

Two patients did not report traumatic events in childhood (patients 3 and 6).

Discussion. In our series of nine patients with SMS, seven with evidence for autoimmune disease, there were features in the patients' histories that usually are considered suggestive of a psychogenic causation of symptoms: major life events 6 months or less prior to onset of disease, occurrence of first transient motor symptoms during acute emotional distress, characteristic situational triggers of both stiffness and spasms, apparently phobic symptoms after onset of motor symptoms, and loss of significant others in childhood. All patients showed at least two of these features (table 2). Thus, the common misdiagnosis of a psychogenic disorder relies on a compelling association of findings: bizarre and fluctuating movement disturbance, lack of approved neurologic signs, and a set of salient psychological features. In some of the patients with SMS, the temporal association of disease onset with significant life events lends itself readily to a symbolic interpretation of the occurrence of symptoms (e.g., patients 2, 4, 6). In these and in other cases,[4,5] such an interpretation of symptoms as conversion reaction was one of the main reasons to suggest a psychogenic etiology of SMS.

Six patients (nos. 1, 2, 4, 6, 8, 9) had transient physical or psychological symptoms, or both, up to $3\frac{1}{2}$ years before the onset of a permanent motor disturbance, suggesting that the CNS disorder related to clinical SMS might have begun long before patients became aware of their disease. In all of these patients, transient symptoms occurred acutely and in immediate association to emotional distress. Four of these patients reported acute, task-specific phobia months before the onset of motor symptoms, particularly before falls. We feel that this peculiar sequence was reported correctly and was not biased by the many uncertainties of a retrospective exploration. Paroxysmal task-specific fear prior to motor symptoms would further substantiate the hypothesis that this type of fear is a symptom in its own right in SMS and is not simply the consequence of gait instability and repeated falls.[3]

The proportion of patients experiencing severe life events in the 6 months prior to onset of permanent disease (7/9) is difficult to compare with figures obtained in other settings. Nevertheless, in a large German epidemiologic study,[13] 65 of 152 subjects (43%) judged to be cases of psychogenic disease reported significant life events in the last 6 months before interview (as compared with 95 of 436 (22%) in non-cases). In a study of subjects with abdominal pain,[14] those finally diagnosed with functional disease showed a rate of severe life events in the last 38 weeks before onset of disease of 67% (53/79), and those with a physiologic cause showed a rate of 23% (13/56), similar to the rate of healthy controls (31/135).

Table 2 Psychological data in nine patients with stiff-man syndrome

Feature	Patients								
	1	2	3	4	5	6	7	8	9
Autoimmune evidence	+	+	+	–	+	+	–	+	+
Before onset of permanent disturbance									
Trauma in childhood	+	+	–	+	+	–	+	+	+
Early psychiatric symptoms	–	–	–	–	–	–	+*	+*	–
Transient symptoms in acute distress	+	–	–	+	–	+	–	+	+
Task-specific fear	+	+	–	–	–	–	–	+	+
Major life events <6 months	–	+	+	+	+	+	–	+	+
After onset of permanent disturbance									
Situation-specific increase of symptoms	+	+	+	–	–	+	–	+	–
Task-specific fear	+	+	–	–	–	+	+	+	+
Emotional upset triggers symptoms	+	+	+	+	+	+	+	+	+
Late psychiatric symptoms	–	–	–	+	–	–	–	–	–
Considered hysteric	+	+	+	–	+	+	+	+	+

* Mild claustrophobia.

How is one to reconcile the obvious physiologic clinical, immunologic,[8] and neurophysiologic[12] alterations with the set of salient psychological features in the history of patients with SMS? Methodologic problems such as the small number of cases and the retrospective, uncontrolled nature of data collection do not allow us to draw any far reaching conclusion from our series. However, considering the autoimmune hypothesis of SMS, three speculations might explain some of our observations:

(a) Psychosocial stressors could activate an underlying immune process. Such interactions of behavior and nervous and immune systems have been established experimentally[15] and exist in other neurologic diseases with suspected autoimmune pathogenesis, e.g., multiple sclerosis.[16,17] By psychosocial stressors, the hitherto subclinical state of SMS might become clinically manifest.

(b) Phobic attacks prior to or after onset of motor symptoms may have a reverse, immunopsychological background: by acting on GABAergic neurotransmission, e.g., in mesiotemporal/limbic areas, autoantibodies against GAD could lower the threshold for experiencing this type of fear. Nevertheless, the fact that insufficient support in specific situations constitutes an essential prerequisite for this psychiatric symptom points to a combined psychoreactive-physiologic causation.[18]

(c) The high proportion of patients who have lost one or both parents early in life hints at the possibility that developmental trauma may lead to vulnerability not only on the psychological level (where early loss of parents is an established risk factor for adult psychiatric/psychogenic disease[18,19]), but also on the immunologic level. Psychoneuroimmunologic evidence in animals confirms the negative influence of early separation from the mothers on the function of the immune system in adult animals.[20,21] Patients with immune-mediated bowel diseases show exacerbations of systems after the disruption of personal relationships and the divorce or death of parents in childhood has been suspected to "condition" them to subsequent losses.[22]

We conclude that psychological factors may not only bias the diagnosis, but may also play a prominent role in the pathogenesis of SMS, an undoubtedly neurologic motor disorder. Psychological factors may exert their influence in three ways: (1) immediate elicitation of new symptoms, or augmentation of preexisting ones; (2) activation of the autoimmunologic process suspected to be relevant in this disease; and (3) induction of a long-term vulnerability of the immune system to specific psychological stressors. Some psychological features of the disease, on the other hand, may be mediated by autoimmune mechanisms targeted to, for example, limbic neurons. We feel that SMS represents a type of disorder that might easily escape a categorical classification to either a physiologic or a psychogenic origin such as is required in ICD 10[23] or DSM-IV. This diagnostic dichotomy, helpful as it is in most cases, might even contribute to the high rate of misdiagnoses as psychogenic movement disorder in patients with SMS. A set of salient psychological features, either primary or secondary to the motor disturbance, should be regarded as a characteristic part of this neuropsychiatric syndrome.

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