

STIFF-MAN SYNDROME

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Stiff-man syndrome (SMS) is a rare disorder of the central nervous system characterized by progressive rigidity and painful intermittent spasms.^{1,2} The muscle stiffness starts insidiously in the axial and proximal musculature, with a steady, slow progression over months or years. Muscle spasms are early complaints and may dominate the clinical presentation. These are often precipitated by tactile or emotional stimuli, volitional movements and startling noises. Neurologic examination usually reveals no abnormalities other than rigidity and spasms in the affected muscles. The etiology of the disease is unknown, although the association of SMS with diseases such as diabetes, vitiligo and hypothyroidism, and the detection of auto-antibodies against (γ -aminobutyric acid) GABA-ergic neurons in serum and cerebrospinal fluid (CSF) suggest that the disease has an autoimmune nature.³⁻⁵ This is a report of a patient with stiff-man syndrome with unusual presentation, high titers of anti-GAD (glutamate acid decarboxylase) antibodies in serum and CSF, other organ-specific auto-antibodies and a favorable response to vigabatrin.

Case Report

A 66-year-old man presented with a two-year history of progressive stiffness and painful intermittent spasms of his right lower limb that started distally, and gradually involved the proximal muscles and the lumbosacral paraspinal muscles one year later. His stiffness continued without daily fluctuation and the painful spasms were mainly precipitated by volitional movements and tactile stimuli of his right leg. This gradually affected his gait and he became unable to walk without assistance. His left lower limb was not affected. He had had insulin-dependent diabetes mellitus for the previous nine years.

Clinical examination revealed prominent stiffness of all muscles of the right leg and the lumbosacral paraspinal muscles. The left leg tone was normal. Tendon reflexes

vibration sense at ankle bilaterally. He could walk with some assistance, but his movements were interrupted by painful spasms in the affected muscles. His higher mental functions, cranial nerves and upper limbs were entirely normal on examination.

MRI of the head and spinal cord were unremarkable. Oligoclonal IgG bands were detected in serum and CSF. An assay based on immunoprecipitation of ¹²⁵I-recombinant GAD was used to measure anti-GAD antibodies.¹⁰ High titers of anti-GAD antibodies were detected in the serum and CSF (Figure 1). In addition, the patient had positive pancreatic islet cell and gastric parietal cell antibodies. EMG showed continuous motor unit activity that reduced markedly when the patient fell asleep during the test. The patient was put on 15 mg of diazepam and 60 mg of baclofen daily, resulting in an improvement in the spasms and, to a lesser extent, in the rigidity, but the patient was still unable to walk unassisted. However, the main improvement was achieved after vigabatrin 2000 mg daily was added to the above medication. Eight months after initiation of vigabatrin, the patient is relatively well and is able to walk independently.

Discussion

The clinical presentation of this patient was unusual for SMS, as the stiffness started in his right lower limb distally and remained confined to the leg for one year before involving the back, but spared the left lower limb. In SMS, rigidity is usually proximal and symmetrical. The involvement of the lumbosacral axial region is usually early in this disease and makes some authors doubt the diagnosis of SMS without hyperlordosis.¹

The EMG findings of continuous motor unit activity that disappeared during sleep in this patient are also characteristic of this disease. The disappearance of rigidity, spasms and continuous motor unit activity during sleep, and after peripheral nerve block, spinal or general anesthesia, favor a central origin of the disease.^{2,5} The current hypothesis regarding the pathogenesis of SMS is that there is an imbalance between the catecholaminergic and GABA-ergic pathways controlling motor unit activity, probably due to impaired GABA-ergic pathways.^{1,2,4} The discovery of autoantibodies against glutamic acid decarboxylase (GAD) in patients with SMS provided conclusive evidence of the autoimmune nature of SMS.^{3,4} GAD catalyses the

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Accepted for publication 7 December 1997. Received 28 May 1997. were normal and plantar responses were on a downward trend. No sensory deficit was detected apart from loss of

conversion of glutamate to GABA and thus anti-GAD antibodies are responsible for the reduction of GABA-ergic activity. GAD is concentrated in GABA-ergic nerve terminals and outside the nervous system in pancreatic beta cells. The fact that anti-GAD autoantibodies are detected in 60% of patients with SMS indicates that this antibody response may identify at least a subgroup of patients with the syndrome.⁴ The GABA-ergic autoantigen heterogeneity and the assay method may be reasons for seronegativity.¹

Serum only anti-GAD antibodies are found in the majority of patients with SMS. Anti-GAD autoantibodies may also be found in the CSF of these patients. The presence of anti-GAD antibodies in CSF may indicate a higher risk for seizures.⁹ Epileptic seizures occur approximately in 12% of SMS patients, mainly in the positive autoantibody group, and in the majority of those with positive anti-GAD antibodies in CSF.⁴ Our patient did not have seizures and his EEG was normal, despite high titers of anti-GAD antibodies in serum and CSF.

The association of SMS with other autoimmune diseases such as IDDM, hypothyroidism, vitiligo and pernicious anemia and the detection of organ-specific antibodies is well documented. IDDM is the most common, being present in one- to two-thirds of patients. Our patient had evidence of autoimmunity manifested with late onset IDDM and positive pancreatic islet cell and gastric parietal cell antibodies. In addition, he had oligoclonal IgG bands in blood and CSF which were previously reported.^{1,2} The concept that SMS may be caused by an autoimmune mechanism prompted the use of immunotherapy such as steroids, plasmapheresis and intravenous immunoglobulin, with varying results and improvement in stiffness and spasms.^{5-7,9} Symptoms of SMS are improved by drugs that enhance neurotransmission mediated by GABA, such as diazepam, baclofen and sodium valproate, but the course of the disease is not altered. The remarkable improvement in the condition of our patient on vigabatrin was previously reported in another two patients.^{8,11} Vigabatrin enhances GABA transmission by preventing its breakdown through a selective and irreversible inhibition of GABA transaminase, which is the enzyme converting GABA to glutamate and succinic semialdehyde.



FIGURE 1. Titration of the stiff-man syndrome patient serum and comparison with CSF. The control CSF is negative.

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