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CASE REPORT

Stiff-Person Syndrome: Case Series

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ABSTRACT

Stiff-person syndrome (SPS) is a rare disorder, characterized by progressive fluctuating muscular rigidity and spasms. Glutamic acid decarboxylase (GAD) antibody is primarily involved in the pathogenesis of SPS and SPS is strongly associated with other autoimmune disease. Here we report three cases of patients with classical SPS finally confirmed by high serum level of GAD antibodies. All of our patients respond favorably to gamma amino butyric acid-enhancing drugs and immunotherapies.

Key Words Stiff-person syndrome; Glutamic acid decarboxylase antibody; Autoimmune disease.

Stiff-person syndrome (SPS) is a rare disorder, characterized by progressive fluctuating muscular rigidity and spasms. Most patients with classical SPS have antibodies against glutamic acid decarboxylase (GAD), but there are also paraneoplastic variants, commonly secondary to breast cancer or small cell lung cancer. Both classical and paraneoplastic SPS have an autoimmune basis and are strongly associated with other autoimmune diseases.[1-5] The symptoms of SPS range from mild to severe and can develop into a significant disability.[1,2] Here, we report three cases of patients with classical SPS who had favorable outcomes.

CASE

Case 1

A 55-year-old previously healthy woman presented with a year-long history of progressive rigidity of the lower limb muscles. She had experienced constant thigh pain on both sides and difficulty in walking. She occasionally fell to the ground because of a sudden spasm precipitated by startle. Therefore, she was required the use of a walker. Physical examination revealed a generalized rigidity and hyperreflexia in both the upper and lower extremities. Examination of the cranial nerve, motor and sensory functions were intact. Findings from magnetic resonance imaging (MRI) of the brain and cervical/thoracic spine were normal. Laboratory analyses, including thyroid function tests and vitamin B_{12} and folate levels, were unremarkable. However, anti-GAD antibody was elevated at 93.57 U/mL. Electromyography showed continuous motor unit activity in agonist and antagonist muscle. She responded favorably to diazepam. By taking diazepam up to 30 mg per day, the rigidity and spasm were improved.

Case 2

A 58-year-old woman presented with a 15-year history of rigidity in muscles of the lower extremities and abdomen. Startle-induced spasm and pain were shown in the lower extremities, but the symptoms were alleviated while she was sleeping. There was no evidence of peripheral nerve abnormalities on nerve conduction studies, spine MRI or cerebrospinal fluid abnormalities. Antibody against human T-lymphotropic virus 1 and a panel of paraneoplastic antibodies, including Hu, Ri and Yo, were negative. Investigations revealed elevated level of anti-GAD antibodies (86.17 U/mL). She was a vegetarian and had a history of pernicious anemia. She had routinely received a vitamin B_{12} injection, and laboratory tests showed mild anemia, with hemoglobin at 11.8 g/dL, and a mean corpuscular volume of 89.6. Additionally, her serum vitamin B_{12} level was 1551 pg/mL. She was diagnosed with diabetes mellitus (DM) 7 years previously and treated with insulin. She often suffered from hypoglycemia characterized by a loss of consciousness, and her glycemic control was poor: high fasting plasma glucose (225 mg/dL) with increased glycosylated hemoglobin level (HbA1c,

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7.6%). Serum C-peptide was 0.2 ng/mL, and total serum insulin was 27.8 μU/mL. She was highly suggestive of insulin-dependent diabetes because of impaired insulin secretion and positive anti-GAD antibodies in serum. She showed gradual improvement in functional status and diminished pain by treatment with diazepam and baclofen.

Case 3

A 49-year-old previously healthy woman visited our hospital with a 10-month history of tightness in the epigastric area and progressive stiffness of the left leg. Neurologic examination revealed bilateral lower limb hyperreflexia. There was no weakness or sensory changes. Because of repetitive 'shock-like' movements in the left leg, we performed video electroencephalography (EEG) monitoring. EEG showed intermittent epileptiform discharges in the right temporal area when her left arm and leg were sequentially flexed, though MRI and fluorine 18-fluorodeoxyglucose positron emission tomography scanning of the brain were unremarkable. We diagnosed her with temporal lobe epilepsy (TLE) and prescribed trileptal. Ten days later, her EEG normalized, and the patient remained seizure free. Her anti-GAD level was elevated at 32420 U/mL. Electromyography showed continuous motor unit activity at rest in spite of voluntary relaxation. We performed treatment with diazepam and several steroid pulse therapies. Baclofen and lorazepam were sequentially added, after which, the stiffness improved.

DISCUSSION

In our series of cases, we diagnosed three patients with classical SPS. We used the Dalakas[2] for the diagnosis, and the diagnosis was finally confirmed by a high serum level of anti-GAD antibodies.

Glutamic acid decarboxylase is the rate-limiting enzyme for gamma amino butyric acid (GABA) synthesis. Because GABA is the major inhibitory neurotransmitter in the central nervous system, it has been believed that the dysfunction of GABAergic pathways is involved in the pathogenesis of SPS.[1-5] A proposed mechanism for the development of stiffness is that the loss of GABAergic input into motor neurons produces tonic firing at rest and leads to excessive excitation in response to sensory stimulation.[4] This theory was supported by the presence of high-titer anti-GAD antibodies in more than 85% of patients[6] and the reduction in brain GABA.[7]

Stiff-person syndrome is an autoimmune disease, and the anti-GAD antibody is primarily involved in the pathogenesis of SPS.[1-5] In this report, the three patients are all women. In line with other adult-onset autoimmune diseases, SPS affects twice as many women as it does men.[5] In patients positive for anti-GAD antibodies, there was a strong association with other organ-specific autoimmune diseases, such as insulin-dependent DM, hypothyroidism, Grave's disease and pernicious anemia.[8] It is currently accepted that DM is accompanied in one-third to two-thirds of patients with SPS.[9] One of the cases in this report had insulin-dependent DM, which might be associated with autoantibodies against GAD and an enzyme found in both the central nervous system and the pancreatic islets of Langerhans. It is hypothesized that an immune response directed against pancreatic islet cells is triggered by an exogenous agent, causing diabetes in genetically predisposed individuals.[9] It is also known that approximately ten percent of GAD antibody-positive SPS patients have epilepsy[4] and, conversely, that the presence of anti-GAD antibodies in epilepsy, especially TLE, is not a rare condition.[10,11] In GAD antibody-positive patients with epilepsy, there is a significant increase in the frequency of inhibitory postsynaptic potentials in hippocampal neurons,[12] which may suggest that anti-GAD antibodies specifically interfere with the GABAergic synapses of the hippocampus, a critical site in the pathogenesis of TLE.[12,13]

Stiff-person syndrome is usually cryptogenic but can also be paraneoplastic, commonly secondary to breast cancer or small cell lung cancer.[2,4] We previously reported a case of a 54-year-old woman with recurrent breast cancer who showed progressive stiffness of the neck and arms and horizontal gaze palsies. She also had breathing difficulty due to stiffness of the thoracic muscle. In this case, anti-Ri antibody was positive, but anti-GAD antibody was negative. Electromyography showed continuous motor unit activity in all tested muscles at rest. This patient was diagnosed as having paraneoplastic SPS, which is considered an SPS variant.[14] Paraneoplastic SPS is usually not associated with anti-GAD antibodies but with anti-amphiphysin or -gephyrin antibodies.[15,16] In a recent study, the injection of the IgG fraction, including antibodies to amphiphysin, into rats

resulted in a dose-dependent stiffness resembling human SPS. This experiment supports the hypothesis that paraneoplastic SPS is also an antibody-mediated autoimmune disorder.[17]

Current therapeutic strategies for SPS are divided into two categories: the first category includes GABA-enhancing drugs known to interact with pharmacologic mechanisms underlying the production of muscular rigidity, and the second category includes immunomodulatory agents.[1,2,4] We performed treatment using both categories of agents, and ultimately all of our three patients showed favorable outcomes.

In conclusion, we present a series of SPS patients confirmed by anti-GAD antibodies. The diagnosis of SPS is often questionable, but the presence of anti-GAD antibody is an important clue. Anti-GAD antibody is primarily involved in the pathogenesis of SPS, and several autoimmune diseases can be associated with SPS.[1-5] Clinical suspicion and the measurement of anti-GAD antibody are essential for this diagnosis, and early diagnosis and appropriate treatment are important to improve the prognosis of SPS. Furthermore, a screening for other autoimmune diseases such as hypothyroidism, Grave's disease and pernicious anemia in addition to insulin-dependent DM should be considered in patients diagnosed with SPS.

Conflicts of Interest

The authors have no financial conflicts of interest.

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