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Stiff-Person Syndrome and Graves' Disease: A Pediatric Case Report

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Abstract

A 9-year-old female child presented with a history of falls, weight loss, diffuse leg pain, and progressive gait disorder, following 1 previous event described as a tonic–clonic seizure. She had increased thyroid volume, brisk symmetric reflexes, abnormal gait, and painful spasms of the paraspinal musculature. Thyroid function tests indicated biochemical hyperthyroidism, and thyrotropin receptor antibodies were positive. Her electromyography showed continuous activation of normal motor units of the paraspinal and proximal lower extremity muscles. The patient had a diagnosis of Graves' disease with associated stiff-person syndrome, with elevated anti–glutamic acid decarboxylase antibody levels. After intravenous immunoglobulin therapy, her ambulation was substantially improved and the symptoms of stiff-person syndrome decreased dramatically.

Keywords

stiff-person syndrome, anti-GAD, graves' disease, autoimmune, spasticity

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A 9-year-old right-handed white female child, born to nonconsanguineous parents, presented to the emergency department with a history of falls, weight loss, diffuse leg pain, and progressive gait disorder. The review of systems revealed frequent leg muscle aches and stiffness in the back and legs; she was bedridden for 1 week. Her medical history did not disclose any early disease, except for 1 event described as a tonic–clonic seizure 1 month before admission. On physical examination, the patient's weight was 34 kg, height was 158 cm, and her pulse was 100 beats/minute. She looked malnourished, with legs bent in the bed. She had increased thyroid volume without palpable nodules, brisk symmetric reflexes, no weakness, spastic gait, and obvious painful spasm of the paraspinal musculature. The rest of her examination was unremarkable. Initial thyroid function tests indicated biochemical hyperthyroidism, and thyrotropin receptor antibodies were positive (Table 1). Thyroid ultrasound images revealed markedly increased vascularity throughout the thyroid gland (referred to as ''thyroid storm''). The treatment consisted of oral propranolol (40 mg, 3 times daily) and antithyroid drugs. She had an extensive evaluation, including magnetic resonance imaging of the brain and spine, which showed typical normal findings. The erythrocyte sedimentation rate (Westergren), C-reactive protein, serum protein electrophoresis, and rheumatoid factor were all within normal limits. She had normal chest X-ray findings. Her electromyography showed continuous activation of normal motor units of the paraspinal and proximal lower extremity muscles.

The patient had a diagnosis of Graves' disease with associated stiff-person syndrome, considering the elevated anti–glutamic acid decarboxylase antibody level (200 IU/mL; normal, $\leq$10 IU/mL). As stiff-person syndrome is an autoimmune disorder, steroids and intravenous immunoglobulin, either alone or in combination, is the first-line immunotherapy. She was treated with oral baclofen (40 mg/d) and clobazam (30 mg/d) to reduce the muscle spasms. She also received a 5-day intravenous course of methylprednisolone at 1 g/d, but

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Table 1. Results of Thyroid Function Tests.

Date	T3	FT4	TSH	TRAb
At admission	536 ng/dL	23.4 ng/dL	0.01 μIU/mL	33.3 IU/mL
After 1 week of treatment	265 ng/dL	22.6 ng/dL	0.01 μIU/mL	
Reference value	80-200 ng/dL	0.93-1.7 ng/dL	0.27-4.2 μIU/mL	<1.22 IU/mL

Abbreviations: T3, triiodothyronine; T4, thyroxine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibodies.

she had little clinical improvement in her neurological condition. The patient received a course of intravenous immunoglobulin therapy (400 mg/kg daily), which yielded improvement in her painful spasms and gait, and she had no further falls. Her ambulation was substantially improved (as shown on Video 1). At follow-up, her tonic–clonic seizures were well controlled with antiepileptic drugs. Currently, the patient is treated with intravenous immunoglobulin therapy monthly and remains clinically euthyroid. The results of follow-up thyroid function tests were notably improved, with dramatically decreased symptoms of stiff-person syndrome.

Discussion

Stiff-person syndrome is an uncommon autoimmune neurological disorder, mostly reported in women. The syndrome is characterized by the presence of progressive painful spasms with stiffness and rigidity of the axial and proximal leg muscles. There are many variants of stiff-person syndrome; these include classical stiff-person syndrome, stiff-leg syndrome, paraneoplastic variant, and gait ataxia, associated with dysarthria and abnormal eye movements. Electromyography reveals characteristic changes, and positive anti–glutamic acid decarboxylase antibody serology occurs in about 60% of cases.[1-3] Stiff-person syndrome is thought to be attributable to an autoimmune process because of the positive GAD antibodies. Moreover, about 5% to 10% of patients with stiff-person syndrome have associated autoimmune thyroid disease.[4] Despite that, the association of stiff-person syndrome with hyperthyroidism is extremely rare. The pathological mechanism of autoantibodies in stiff-person syndrome remains unclear, but there is evidence that points to blockade of γ-aminobutyric acid (GABA) production.[3] Glutamic acid decarboxylase is the rate-limiting enzyme that catalyzes the conversion of glutamic acid into the inhibitory neurotransmitter GABA. The loss of GABAergic input to motor neurons is thought to result in tonic firing at rest and excessive excitation in response to sensory stimuli.[5] Glutamic acid decarboxylase autoantibody titer in serum or cerebrospinal fluid does not correlate with symptom severity. Therefore, titer monitoring is unnecessary.[7] The authors report a case of stiff-person syndrome associated with symptomatic thyrotropin receptor antibody–positive Graves' disease at diagnosis in a child. The incidence of stiff-person syndrome is very low, and the prevalence of the disease is 1 in a million.[8] Most children with stiff-person syndrome also have negative anti–glutamic acid decarboxylase and exhibit acute onset and a short benign course. No prospective clinical study has been carried out to outline specific modalities for use in pediatric patients.[9] It is a rare but treatable disorder with few case reports in children. Treatment of worsening stiff-person syndrome with intravenous immunoglobulin substantially diminished the neurologic symptoms of our patient. The immunopathology of Graves' disease is complicated, and this case adds to the information base that will allow us to understand the pathogenesis of Graves' disease and other autoimmune diseases, including stiff-person syndrome.

The treatment of stiff-person syndrome should reduce symptoms and improve the quality of life by the use of GABAergic agonists, such as baclofen, gabapentin, levetiracetam, diazepam, or other benzodiazepines, and appropriate immunotherapy that includes the usage of steroids, plasmapheresis, intravenous immunoglobulin, and rituximab.[6] There is no clinical consensus for the duration of immunotherapy. A therapeutic approach combining standard drugs, treatment of associated diseases, and cognitive behavioral therapy seems to be promising.[8]

In conclusion, this case highlights that an acute gait disturbance syndrome in children with Graves' disease should raise clinical suspicion of autoimmune diseases and stiff-person syndrome. Immunotherapy can alleviate symptoms of Graves' disease and improve neurological function in these patients.

Author Contributions

LMM, TCM and MSGR contributed to patient diagnosis and neurologic follow-up. LMM contributed to writing draft. TCM and MSGR also contributed to article review and draft edit. VCS and AELP contributed to patient care.

Declaration of Conflicting Interests

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Ethical Approval

Participation was voluntary for parents. They signed a term of agreement authorizing this report. It has been approved by the Research and Ethical Committee at the Hospital Santa Marcelina.

Supplemental Material

The online supplemental video is available at http://journals.sagepub.com/doi/suppl/10.1177/2329048X16684397.

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