

Stiff Person Syndrome: A Tough and Rigid Case

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Stiff person syndrome (SPS) is an uncommon disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, which leads to severely impaired ambulation [1]. SPS is subdivided into three variants – autoimmune, paraneoplastic and idiopathic. The autoimmune variant, which accounts for 60% of cases, is associated with other autoimmune diseases such as thyroiditis, pernicious anemia, vitiligo, and particularly type 1 diabetes mellitus. The most prominent clinical symptom of SPS is extreme muscle stiffness and rigidity. These symptoms are usually persistent and may lead to pronounced lumbar or cervical lordosis. The onset of stiffness and rigidity is insidious and generally progresses slowly over time to involve proximal limb muscles. Episodic muscle spasms may be precipitated by sudden movement, noise or emotional upset; these features are characteristic and rather specific of SPS. Spasms usually begin in the axial muscles and may spread to the extremities. They are painful and can generate sufficient force to induce bone fractures [1]. Paroxysmal autonomic dysfunctions, characterized by transient hyperpyrexia, diaphoresis, tachycardia, pupillary dilatation and arterial hypertension, have been described and may result in sudden death [1,2]. SPS is rare and not easily recognized and a high level of suspicion should be exercised to avoid misdiagnosing these patients [1,2].

We present a patient with SPS in association with Hashimoto's thyroiditis and review the autoimmune mechanisms and therapeutic approach to this unusual syndrome.

PATIENT DESCRIPTION

A 56 year old Jewish woman of Yemenite descent was evaluated for significant pelvic and shoulder girdle muscular pain. In addition, a few weeks before her examination she adopted a hyperextended stiff gait. The patient's chief complaint was spinal muscle pain which gradually spread to her proximal limbs. She described severe pelvic and shoulder stiffness. Her gait and mobility were significantly impaired. She had been physically active until shortly before, but the pain and stiffness caused her to cease most of her activities. Self-treatment with non-steroidal anti-inflammatory drugs for pain relief was not beneficial.

Her medical history included bilateral anterior ischemic optic neuropathy (AION) 7 years earlier which resolved successfully with corticosteroid therapy. During that time she was diagnosed with hypothyroidism and began taking l-thyroxine hormonal replacement. The patient often uses omeprazole for dyspepsia. She has 10 siblings of whom 3 died in infancy but the etiology was not known.

On examination, the patient's temperature was 37.6°C, her pulse was regular at 100 beats/minute and blood pressure was 116/72 mmHg. She felt neck sensitivity upon movement and had no evidence of synovitis. Neurologically, bilateral 4/5 quadriceps weakness was evident. There was no sensory impairment and no pyramidal signs. Cardiac, respiratory and abdominal examinations were normal.

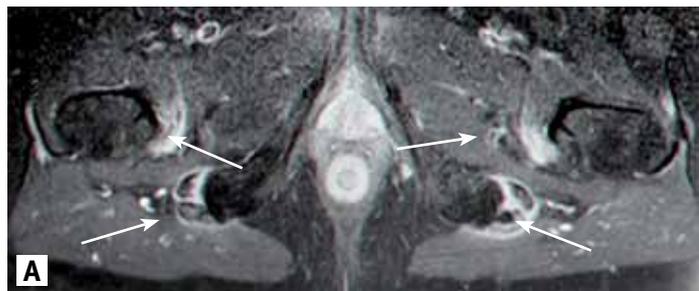
Laboratory results showed anemia (hemoglobin 10.1 g/dl, mean corpuscular volume 78 fl), erythrocyte sedimentation rate (ESR) 81 mm/hr (normal < 30) and C-reactive protein (CRP) 10.5 mg/dl (normal 0–0.5 mg/dl). The results for electrolytes and for kidney and liver function tests were normal. C3 level was elevated at 190 mg/dl (normal 90–180 mg/dl) and C4 level was low at 63 mg/dl (normal 90–180). Antithyroglobulin antibodies were highly positive (1580 IU/ml, normal < 20), as were antithyroid peroxidase antibodies (592 IU/ml, normal < 35). Results for various autoantibody tests such as rheumatoid factor, antinuclear antibody, anti-Jo1, SCL-70, anticentromer, myeloperoxidase, RNP and others were all negative.

The nature of the patient's pain, the anemia and the low grade fever raised a reasonable suspicion of polymyalgia rheumatica. Treatment with prednisolone at an initial dose of 20 mg/day resulted in partial improvement. However, after 2 weeks of therapy, her ESR and CRP levels remained extremely high at 118 mm/hr and 10.8 mg/dl, respectively.

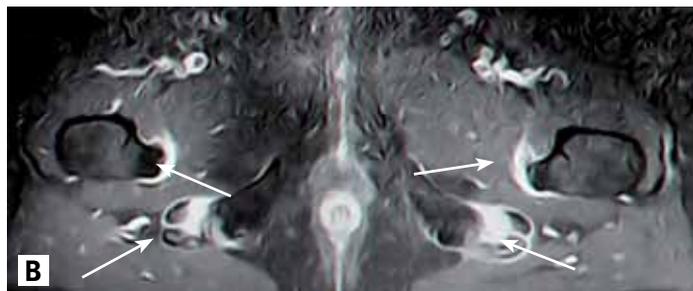
A pelvic X-ray showed signs suggestive of sacroiliitis, and subsequent magnetic resonance imaging showed further supportive signs, with marked enthesopathy [Figure 1]. Various anti-tumor necrosis factor-alpha (TNF α) agents were tried (etanercept, adalimumab and infliximab), but did not confer any benefit.

Seeking a second opinion yielded a diagnosis of "refractory polymyalgia." She started taking prednisolone at a higher dose, 30 mg/day, and her symptoms abated. At that stage, an anti-GAD (glutamic acid decarboxylase) blood test that had been sent several months earlier came back showing a high antibody titer, which established the diagnosis of stiff person syndrome.

Figure 1. [A] Axial T2-weighted fat-suppressed image showing edematous changes at the origin of the iliopsoas and hamstring tendons (arrows)



[B] Axial T1-weighted fat-suppressed (post-contrast) image demonstrating typical marked contrast enhancement of the involved tendons (arrows)



COMMENT

Circulating anti-GAD antibodies are present in approximately 60% of SPS patients [1-3]. GAD is the presynaptic enzyme that catalyzes the decarboxylation of glutamate to γ -aminobutyric acid (GABA). GABA serves as one of the main inhibitory neurotransmitters in the central nervous system. Impairment of the GABA-ergic pathways by reduction of brain GABA leads to excessive spinal motor neuron excitatory activity, resulting in stiffness and spasms that are identified with SPS.

The relevance of anti-GAD antibodies to the pathogenesis of SPS is supported by several observations. Firstly, sera and cerebrospinal fluid from a patient with SPS, epilepsy, and type 1 diabetes were incubated with formaldehyde-fixed cat brain, which was subsequently stained using anti-human immunoglobulin (Ig) G antibodies. The areas of brain that stained corresponded to the distribution of GABA-ergic terminals [1-3]. Another observation demonstrated the effect of anti-GAD antibodies on GAD enzymatic activity in vitro: the incubation of crude rat cerebellar extracts with the sera from 21 of 25 SPS patients with anti-GAD antibodies reduced GABA production from these brain cells [3].

Besides recognizing GAD, anti-GAD antibodies also recognize a 64 kilodalton islet cell protein, which is present in the sera of approximately 80% of new-onset

insulin-dependent diabetes mellitus (IDDM) patients even long before the onset of clinical disease [1-4]. Despite this frequent occurrence, SPS is an extremely rare condition in these patients. One explanation for this phenomenon is that the titer of anti-GAD antibodies in SPS patients is much higher than that observed in IDDM patients, occasionally differing 100 to 500-fold [4]. Another possible explanation could be related to the integrity of the blood-brain barrier, which if opened by an additional insult may result in the passage of anti-GAD antibodies from the peripheral blood to the cerebrospinal fluid.

The correlation between SPS and other autoimmune diseases is well established. In a review by Blum and Jankovic [5], 15 of 84 SPS patients (18%) had clinical evidence of one or more autoimmune diseases, which is significantly higher than in the normal population. The history of Hashimoto's thyroiditis and AION underline this concept.

Benzodiazepines are generally considered the optimal initial therapy for SPS patients [1-4]. Benzodiazepines are thought to enhance the GABA effect at the GABAA receptor. Baclofen (GABAB receptor agonist) may also be an initial therapeutic option and can be administered orally or intrathecally. Immunosuppressive therapy should be considered in severe cases that do not respond to benzodiazepines or baclofen. Glucocorticoids given

orally or intravenously have been effective in many cases [1-4]. The initial dosage of prednisone is 60 mg/day and is usually tapered according to the patient's clinical response. Azathioprine has been used as a steroid-sparing agent in some cases; non-responsive patients can be treated with plasmapheresis and intravenous immune globulin (IVIG).

In conclusion, stiff person syndrome is a rare disorder. A high index of suspicion is required to avoid missed or delayed diagnosis of these patients.

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“I think we have all experienced passion that is not in any sense reasonable”

Stephen Fry (born 1957), English comedian, actor, writer, presenter and activist