

## Case Report

# Stiff person syndrome: A rare pediatric case in Southern Brazil

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**Abstract**

**Introduction:** Here we report a rare pediatric case of stiff person syndrome (SPS), an uncommon neurological disorder characterized by persistent muscular rigidity and spasm affecting primarily axial muscles.

**Patient description:** An 11 year-old boy presented with a 1-year history of axial muscle pain associated with sternocleidomastoid muscle contractions that progressed to bilateral arm muscle contractions. His medical history included febrile seizures and a learning disability. Physical examination revealed generalized bilateral rigidity of the arms and lateral neck. Laboratory test results were normal. Electroneuromyography showed unremitting paravertebral muscular contraction. Clonazepam treatment improved the patient's functional status and diminished his pain.

**Conclusion:** Although SPS is rare, pediatricians should be aware of its diagnostic criteria and the potential to treat juvenile SPS with benzodiazepines.

**ABBREVIATIONS**

SPS: Stiff Person Syndrome; GAD: Glutamic Acid Decarboxylase

**INTRODUCTION**

Stiff person syndrome (SPS; formerly stiff-man syndrome) is an uncommon neurological disorder characterized by insidious and persistent muscular stiffness, rigidity, and spasm. Classically, SPS affects primarily the axial muscles, though limb involvement occurs in some cases [1-3]. Typically, SPS onset occurs in the fourth to sixth decades of life (average, ~40 years) [4]. The syndrome is extremely rare in childhood [5]. The rarity of SPS, particularly in childhood [5-8], makes SPS diagnosis challenging in the pediatric population. Indeed, in a recent review of eight pediatric SPS cases at the Mayo Clinic over a period of 29 years, Clardy and colleagues reported that three of the cases were not diagnosed until adulthood [9].

Intermittent muscular spasms in SPS-which can be triggered by external stimuli, such as tactile or auditory stimulation, sudden movements, and emotional stress-can be painful and may be strong enough to induce bone fractures [1,2]. Co-activation of the opposing paraspinal and abdominal muscle groups disrupts postural stability and can lead to lumbar or cervical hyperlordosis [1]. Patients with SPS may also experience symptoms of

autonomic dysfunction, such as hyperpyrexia, diaphoresis, tachycardia, pupillary dilatation, and arterial hypertension [2].

In most SPS cases, patients exhibit signs of autoimmunity and the syndrome may be comorbid with another autoimmune diseases, such as thyroiditis, vitiligo, or type 1 diabetes mellitus [2]. Common comorbidities of SPS include psychiatric disorders (depression and generalized anxiety disorder), malignancy (of the breast, colon, lung, thymus, or lymph tissues), cerebellar ataxia, and limb encephalitis [1,10]. Some 60–80% of patients with SPS are seropositive for antibodies against the 65-kDa isoform of glutamic acid decarboxylase (GAD) [1,2,11,12]. Thus, while anti-GAD antibody detection is diagnostically important, some 20% of patients with SPS are anti-GAD antibody negative [13]. Patients with SPS have also been found to have autoantibodies against various other proteins involved in GABAergic transmission, including: amphiphysin, which is involved in synaptic vesicle endocytosis and membrane recycling following GABA exocytosis; gephyrin, which has been implicated in postsynaptic membrane clustering of GABA; and GABA<sub>A</sub> receptor-associated protein [14]. The presence of GABAergic system component autoimmunity suggests SPS pathogenesis may be related to dysfunction of inhibitory GABAergic pathways, which would be expected to lead to hyperactive motor neurons and, ultimately, the spasms and stiffness that are characteristic of SPS [1,2].

The aim of this report was to describe an extraordinarily rare pediatric case of SPS. We present the clinical, laboratory, and electrophysiological findings of the case together with the case management strategy and outcome.

## CASE PRESENTATION

A white, right-handed 11-year-old boy born to non consanguineous parents following a non complicated pregnancy presented at our children's hospital with a 1-year history of chest, spine, and cervical muscle pain associated with sternocleidomastoid muscle contractions that had progressed to bilateral superior limb contractions. He had normal neuropsychomotor development. The only remarkable features of his medical history were febrile seizures and a learning disability. There was no family history of neuromuscular disease. The patient's characteristics and laboratory test results are summarized in Table (1). Notably, anti-GAD autoantibody was not detected serologically.

**Table 1:** Patient characteristics and laboratory results.

| Variable   | Patient   |
|--|---|
| Age onset/diagnosis, y                             | 10/11   |
| Demographics, race sex                             | White male  |
| SMS phenotype                                      | Classic   |
| <i>Symptom/sign by location</i>                    |   |
| Upper limbs  | +   |
| Lower limbs  | -   |
| Trunk  | +   |
| Head/neck  | +   |
| Respiratory muscles                                | -   |
| Deep tendon reflexes                               | Normal  |
| Autoimmunity, auto-antibodies                      | Negative, none detected                                     |
| Family history                                     | Negative  |
| Electrophysiology                                  | Unremitting paravertebral muscles contraction, even at rest |
| Treatment  | Clonazepam  |
| Follow-up  | 2 years without recurrence                                  |
| <i>Laboratory results</i>                          |   |
| Creatine phosphokinase                             | 136 U/L   |
| Lactic acid dehydrogenase                          | 651 U/L <sup>a</sup>  |
| Hemosedimentation velocity                         | 20  |
| Aldolase   | 5.1 U/L   |
| Complement component 3                             | 86 mg/dL <sup>b</sup>                                       |
| Complement component 4                             | 26 mg/dL  |
| Total hemolytic complement                         | 92.4 hemolytic U <sup>c</sup>                               |
| Reticulocytes                                      | 0.6%  |
| Thyroid stimulating hormone                        | 1.96 mU/L   |
| Free T4  | 0.98 ng/dL  |
| Venereal Disease Research Laboratory syphilis test | Negative  |

<sup>a</sup>Normal upper limit, 280 U/L. <sup>b</sup>Normal lower limit 88 mg/dL. <sup>c</sup>Normal upper limit, 90 hemolytic U.

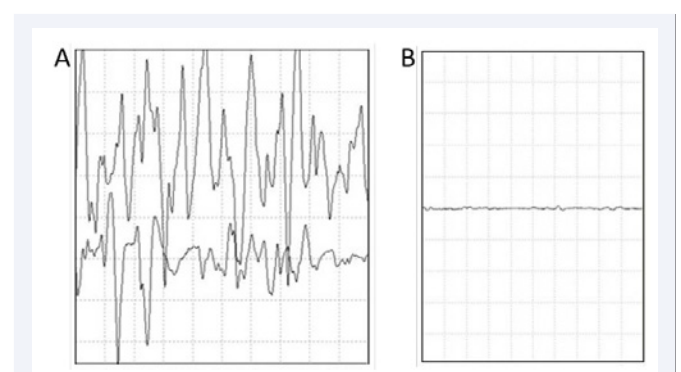
Physical examination revealed generalized rigidity of the upper extremities and sternocleidomastoid muscles, with intact motor, sensory, and cranial nerve functions. He had a normal gait and normal reflexes with a negative Babinski sign. Kidney function, liver function, and electrolyte test results were normal. Brain and spinal cord magnetic resonance imaging scans were also normal. Electroneuromyography showed normal motor and sensory nerve conduction, but unremitting paravertebral muscular contraction even at rest, and responsive to intravenous benzodiazepine administration (Figure 1). Electromyography showed continuous motor unit activity in all tested muscles at rest.

The patient was treated with benzodiazepines. First, he was given 5mg of midazolam intra-venously upon hospital admission, which provided immediate relief of his symptoms. For maintenance care, the patient was prescribed clonazepam (*per os*, 0.9 mg three times/day). He has responded well to the maintenance treatment, showing an improved functional status and reporting pain diminution. Eventually, some spasms affecting his right arm returned without any other symptoms. He has been stable for 2 years as of the time of writing this report.

## DISCUSSION

Here, we reported the case of a child who presented with the classic features of SPS. A diagnosis of SPS was made based principally on electroneuromyography findings. The patient's condition was improved with benzodiazepine therapy, the long-term maintenance of which has been associated with non-recurrence for 2 years.

Diagnosis of SPS is based on clinical observations, electromyography, and serology (most commonly anti-GAD) and should involve a multidisciplinary team, including a neurologist, physiotherapist, psychologist, and psychiatrist. The prognosis for patients with SPS is variable. In a recent review of 72 cases, Sarva and colleagues divided SPS-spectrum cases into three etiological classifications: autoimmune (definitive anti-GAD seropositivity without neoplasticity), paraneoplastic (definitive neoplastic comorbidity with or without anti-GAD positivity), and cryptogenic (no causative factor identified) [15]. According to this scheme, the present case, in which the patient was anti-GAD seronegative and had no signs of neoplastic disease, would be classified as cryptogenic. This classification, consistent with the present case, was described as involving mostly male patients



**Figure 1** Electroneuromyography of the patient's paravertebral muscles. A. Permanent muscular contraction at rest. B. Positive sharp waves.

and having a likely good prognosis [15].

There is a well-established association between autoimmune and neoplastic diseases [2]. We ruled out major autoimmune diseases, including hypothyroidism, Grave's disease, pernicious anemia, and diabetes mellitus. Although the patient had abnormal complement component 3 and total hemolytic complement levels, we were unable to identify any clinical significance of these findings, which is not uncommon [2]. In our neoplasm screening, which was negative, particular attention was paid to cancers with a relatively high prevalence in children, namely lymphoma and thymus neoplasia.

Typically, SPS is treated with immunomodulatory therapy combined with pharmacotherapy aimed at alleviating symptoms [1,5]. Benzodiazepine therapy is an interesting treatment strategy for SPS because it enhances GABA receptor activity directly [6]. Other options for symptom control include the muscle relaxant baclofen (in teens and adults), antiepileptic drugs, and intramuscular botulinum toxin. In severe cases, immunomodulatory agents, such as intravenous immunoglobulin, plasmapheresis, mycophenolate, cyclophosphamide, rituximab, or prednisone can be used [1,5].

## CONCLUSIONS

First-line use of the benzodiazepine clonazepam yielded a great response in our pediatric patient with cryptogenic SPS. Benzodiazepines may represent an optimal initial therapy for SPS owing to their direct enhancing action on GABA receptors. Given the well-established association between autoimmune and neoplastic diseases, it is important that patients with an SPS-spectrum diagnosis be screened for these conditions.

## DECLARATIONS

### Ethical approval

This study was approved by our institutional ethics committee (registration #CAAE 71705517.7.0000.0097). All procedures were performed in accordance with the ethical standards of our institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments.

### Consent

Written informed consent was obtained from the parents of the patient for publication of this case report and the accompanying diagnostic images.

### Availability of data and materials

Data and other materials will be available upon written request to Dr. Matos (email:marilia.bm@hotmail.com)

### Author's contributions

MBM, TBS and MLC wrote the case report. ABO supervised

the therapy. MBM and ALN conducted clinical evaluations, physical examinations, and treatment administration. All authors read and approved the final manuscript.

## REFERENCES

1. Liran O, Kots E, Amital H. Stiff person syndrome: a tough and rigid case. *Isr Med Assoc J*. 2015; 17: 261-262.
2. Buechner S, Florio I, Capone L. Stiff Person Syndrome: A Rare Neurological Disorder, Heterogeneous in Clinical Presentation and Not Easy to Treat. *Case Rep Neurol Med*. 2015; 2015: 278065.
3. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome); report of a case and some observations in 13 other cases. *Proc Staff Meet Mayo Clin*. 1956; 31: 421-427.
4. Dalakas MC, Fujii M, Li M, McElroy B. The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. *Neurology*. 2000; 55: 1531-1535.
5. Fekete R, Jankovic J. Childhood stiff-person syndrome improved with rituximab. *Case Rep Neurol*. 2012; 4: 92-96.
6. Bhatti AB, Gazali ZA. Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients. *Cureus*. 2015; 7: 427.
7. Jun HO, Yum MS, Kim EH, Lee YJ, Seo JJ, Ko TS. A Rare Case of Childhood Stiff Person Syndrome Associated With Pleuropulmonary Blastoma. *Pediatr Neurol*. 2015; 53: 448-451.
8. Medeiros LM, Morais TC, Primo AEL, Speltri VC, Rocha MSG. Stiff-Person Syndrome and Graves' Disease. *Child Neurol Open*. 2016; 3: 2329048X1668439.
9. Clardy SL, Lennon VA, Dalmau J, Pittock SJ, Jones HR, Renaud DL, et al. Childhood onset of stiff-man syndrome. *JAMA Neurol*. 2013; 70: 1531-1536.
10. Cerqueira ACR de, Bezerra JMF, Rozenthal M, Nardi AE. Stiff-Person syndrome and generalized anxiety disorder. *Arq Neuropsiquiatr*. 2010; 68: 659-661.
11. Manto M, Honnorat J, Hampe CS, Guerra-Narbona R, López-Ramos JC, Delgado-García JM, et al. Disease-specific monoclonal antibodies targeting glutamate decarboxylase impair GABAergic neurotransmission and affect motor learning and behavioral functions. *Front Behav Neurosci*. 2015; 9: 78.
12. Solimena M, Folli F, Denis-Donini S, Comi G, Pozza G, De Camilli P, et al. Autoantibodies to Glutamic Acid Decarboxylase in a Patient with Stiff-Man Syndrome, Epilepsy, and Type I Diabetes Mellitus. *N Engl J Med*. 1988; 318: 1012-1020.
13. Jung YJ, Jeong HG, Kim R, Kim HJ, Jeon BS. Stiff-person syndrome: case series. *J Mov Disord*. 2014; 7: 19-21.
14. Buddhala C, Hsu CC, Wu JY. A novel mechanism for GABA synthesis and packaging into synaptic vesicles. *Neurochem Int*. 2009; 55: 9-12.
15. Sarva H, Deik A, Ullah A, Severt WL. Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports. *Tremor Other Hyperkinet Mov*. 2016; 6: 340.

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