

## Rhabdomyolysis and autoimmune variant stiff-person syndrome

Shreyas Gangadhara,<sup>1</sup>  
 Suhas Gangadhara,<sup>1</sup> Chetan Gandhi,<sup>1,2</sup>  
 Derrick Robertson<sup>1</sup>

<sup>1</sup>Division of Vascular Neurology, Department of Neurology, University of South Florida, Morsani College of Medicine, Tampa, FL; <sup>2</sup>Department of Neurology, James A Haley Veterans Hospital, Tampa, FL, USA

### Abstract

Stiff-person syndrome (SPS) is a rare neurologic disorder characterized by waxing and waning muscular rigidity, stiffness and spasms. Three subtypes have been described: paraneoplastic, autoimmune and idiopathic. Rhabdomyolysis has been described in the paraneoplastic variant, but to our knowledge no case has been reported involving the autoimmune variant. We report a case report of a 50-year-old man with history of SPS who presented with recurrent episodes of severe limb and back spasms. He was hospitalized on two separate occasions for uncontrollable spasms associated with renal failure and creatinine phosphokinase elevations of 55,000 and 22,000 U/L respectively. Laboratory tests were otherwise unremarkable. The acute renal failure resolved during both admissions with supportive management. Rhabdomyolysis has the potential to be fatal and early diagnosis is essential. It should be considered in patients who have SPS and are experiencing an exacerbation of their neurologic condition.

### Introduction

Stiff-person syndrome (SPS) is a rare neurologic disorder first reported by Moersch and Woltman in 1956 characterized by progressive fluctuating muscular rigidity, stiffness and spasms.<sup>1</sup> Its prevalence is estimated to be around 1-2 cases per million and incidence is estimated to be around 1 case per million per year.<sup>2</sup> There are mainly three types of SPS: autoimmune, paraneoplastic and idiopathic. Approximately 60-80% of patients with SPS have antibodies to glutamic acid decarboxylase (GAD) and 10% of patients develop SPS as a paraneoplastic neurologic disorder most commonly associated with antibodies to amphiphysin.<sup>2,3</sup> The

paraneoplastic variant has a well described association with adenocarcinoma of the breast in women.<sup>2</sup> The muscle spasms initially start insidiously but gradually worsen in severity and can be severe enough to generate sufficient force to break bones and also cause rhabdomyolysis from muscle breakdown.<sup>4</sup> Rhabdomyolysis has been described in paraneoplastic variant but to our knowledge, no case has been reported in autoimmune variant.<sup>5</sup>

### Case Report

A 50-year-old man with recurrent episodes of painful back spasms was diagnosed with SPS by positive serum test for GAD antibodies. He had no additional past medical history. Of note, the patient underwent a malignancy work-up including CT scanning of his chest, abdomen, and pelvis along with age appropriate cancer screenings. All malignancy work-up was negative. Subsequently, he was hospitalized on two separate occasions for uncontrollable painful spasms. He experienced 3-5 episodes per day, with the spasms predominantly involving his paraspinal muscles, and each episode lasting approximately 2-5 minutes. During the first admission, his laboratory workup showed creatinine phosphokinase (CPK) elevated up to 55,559 U/L, creatinine elevation up to 4.5 mg/dL denoting acute kidney injury, and a marked leukocytosis to  $19.36 \times 10^3/\mu\text{L}$ . Infectious work-up was nonrevealing. Six months later during his second admission, again his laboratory workup showed CPK elevated up to 22,400 U/L, creatinine elevation up to 2.5 mg/dL, and a leukocytosis up to  $22.93 \times 10^3/\mu\text{L}$ . Infectious work-up was again investigated and nonrevealing. During both admissions, the acute renal failure and leukocytosis resolved after rehydration with intravenous fluids along with the patient receiving courses of intravenous immunoglobulin and a moderate increase in his antispasmodic medications.

### Discussion and Conclusions

The pathophysiology of autoimmune-SPS is thought to be due to dysfunction of inhibitory neurotransmitters in the central nervous system (CNS).<sup>2</sup> Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the CNS and GAD is the rate-limiting step in the synthesis of GABA.<sup>2</sup> There are two isoforms of GAD: GAD 65 and 67; however it is GAD 65 that is commonly associated with SPS.<sup>2</sup> The exact mechanism of inhibition of GAD is debated<sup>2</sup>, however inhi-

Correspondence: Derrick Robertson, 12901 Bruce B Downs Blvd, MDC 55, Tampa, FL 33612, USA. Tel.: +1.813.974.8859 - Fax: +1.813.905.9838. E-mail: droberts@health.usf.edu

Key words: Stiff-person syndrome; rhabdomyolysis; spasms.

Contributions: SG1, SG2, CG, drafting of the manuscript; DR, critical revisions of the manuscript.

Conflict of interests: S. Gangadhara and S. Gangadhara report no disclosures. C. Gandhi has served as a consultant for Genzyme, Teva Neuroscience; is on the speakers' bureaus of EMD Serono and Genzyme. D. Robertson has served as a consultant for Biogen, Genzyme, Teva Neuroscience and Pfizer; is on the speakers' bureaus of Biogen, EMD Serono, Genzyme, Teva Neuroscience, Mallinckrodt and Acorda; and has received grant support from Biogen, Genzyme, Novartis, Sun Pharma, MedImmune, Actelion, Mallinckrodt, EMD Serono and Genentech.

Received for publication: 23 August 2016.

Revision received: 13 October 2016.

Accepted for publication: 17 November 2016.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright S. Gangadhara et al., 2016  
 Licensee PAGEPress, Italy  
 Clinics and Practice 2016; 6:885  
 doi:10.4081/cp.2016.885

bition of GAD results in functional inhibition of GABA which in turn causes simultaneous contraction of agonist and antagonists muscles of a part or full body.<sup>2</sup> Electrophysiological evidence shows continuous involuntary firing of the motor nerves.<sup>6</sup> GAD antibodies are found in serum and cerebrospinal fluid but their titer level do not seem to correlate with symptom severity.<sup>6</sup> GAD antibody is not specific to SPS as it can also be seen in type 1 diabetes mellitus, cerebellar ataxia, myoclonus, epilepsy and other neurologic disorders.<sup>6</sup> Another antibody implicated in SPS is gephyrin; a postsynaptic cellular protein responsible for GABA and glycine transmission in brain and spinal cord, respectively.<sup>6</sup> In the paraneoplastic variant, antibodies against amphiphysin have been most commonly reported however it is unclear precisely how these antibodies inhibit GABA activity.<sup>2</sup> Treatment of SPS mainly involves muscle relaxants such as baclofen, tizanidine and benzodiazepines.<sup>6</sup> Immunomodulation therapies such as intravenous immunoglobulin, plasma exchange and rituximab have also been used.<sup>6</sup>

While SPS is an autoimmune condition long thought to be limited to isolated spastic-

ity and pain, our case demonstrates that this condition has broad implications in the overall health of these patients. Our case shows that rhabdomyolysis with extremely elevated CPK can be seen in SPS, which can lead to medical complications such as renal failure, leukocytosis, and pulmonary edema. Early diagnosis and management of this potentially life-threatening event is of utmost importance and should be considered in a patient experiencing a SPS exacerbation.

## References

1. 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;31:421-7.
2. Baizabal-Carvallo JF, Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. *J Neurol Neurosurg Psychiatry* 2015;86:840-8.
3. Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. *Curr Treat Options Neurol* 2009;11:102-10.
4. Helfgott, SM. Stiff-person syndrome. In: *UpToDate*, Targoff IN, Shefner JM, Romain PL (Eds), *UpToDate*, Waltham, MA. Accessed: April 16, 2016.
5. Petzold GC, Marcucci M, Butler MH, et al. Rhabdomyolysis and paraneoplastic stiff-man syndrome with amphiphysin autoimmunity. *Ann Neurol* 2004;55:286-90.
6. Hadavi S, Noyce AJ, Leslie RD, Giovannoni G. Stiff person syndrome. *Pract Neurol* 2011;11:272-82.