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Single Case – General Neurology

Recurrent Acute on Chronic Respiratory Failure in Stiff Person Syndrome

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Abstract
Stiff person syndrome (SPS) is an extremely rare disease that presents with episodic painful muscle spasms and progressive muscle rigidity. Recent evidence suggests that SPS can rarely manifest with life-threatening respiratory complications. However, the pathophysiology behind respiratory failure in SPS is still not clearly understood. Here, we explored an extremely rare case of a 36-year-old African-American female with SPS presenting with multiple episodes of respiratory failure events for the past 9 years. She had an in-situ tracheostomy and was admitted to the hospital for tracheostomy evaluation and decannulation. 11 years ago she initially presented with gait abnormalities, stiffness, and spastic episodes. She was diagnosed 1 year later with SPS after detecting elevated anti-glutamic acid decarboxylase antibody levels in her blood. Through this report, we were able to follow a very rare case of SPS that presented with multiple episodes of respiratory failure. We pointed out the importance of early start and regular administration of diazepam, baclofen, and IVIg in not only controlling the symptoms and progression of the disease but also in preventing further respiratory failure and possible sudden death.

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Introduction

Stiff person syndrome (SPS) is a rare disorder of the central nervous system characterized by rigidity and stimulus triggered painful muscle spasms of predominantly axial and proximal limb muscles. It was first described in 1956 by Frederick Moersch and Henry Woltman based on a case series of 14 patients with progressive fluctuating tightness of the spinal, abdominal, and thigh muscles. This condition was formerly named stiff-man syndrome and is also known as Moersch-Woltman syndrome [1].

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The disease affects women two to three times more than men with a prevalence of one to 2 patients per million. SPS presents with muscle rigidity, which starts in the proximal muscles and progresses distally. Patients have recurrent falls, muscle spasms, and chronic muscle pain [2].

The etiology of SPS has an apparent autoimmune root, but its pathogenesis is not completely clear. It is generally associated with antibodies against glutamic acid decarboxylase (GAD) and antibodies against gephyrin, the glycine-alpha1 receptor, or gamma-aminobutyric acid (GABA), receptor-associated protein [3]. The diagnosis is often delayed due to the rarity of the disease and the lack of knowledge of this condition by clinicians [2].

Acute respiratory failure manifesting with apneic episodes is an extremely rare life-threatening and unpredictable complication of SPS, let alone multiple episodes occurring in a patient over time. Its pathophysiology is not well known. The two suggested mechanisms are as follows: (1) apnea due to muscle rigidity and paroxysmal muscle spasms and (2) paroxysmal autonomic hyperactivity [2]. In severe cases of SPS, apnea, and sudden death have been described [3–5]. In this paper, we present a patient diagnosed with SPS who developed recurrent acute on chronic respiratory failure episodes, currently on ventilator support with intravenous immunoglobulin (IVIG) therapy and GABA-ergic drugs. The report also highlights that physicians should be extremely vigilant in the treatment of SPS patients with a history of respiratory distress.

Case Report

A 36-year-old African-American female with previously diagnosed stiff person syndrome, with an in-situ tracheostomy was admitted to the hospital for tracheostomy evaluation and decannulation. She was unable to tolerate Passy-Muir valve trials and was temporarily placed under observation on oxygen via nasal cannula and capping of the tracheostomy cannula. But during this period, she developed rapid changes in her mental status. She became unresponsive and developed tachycardia and hypotension. She was transferred to ICU on assist control mode ventilator support. Her blood cultures showed methicillin-sensitive Staph aureus (MSSA) bacteremia and chest X-ray suggestive of right lobar pneumonia. Her first presentation of SPS was in 2010 when she presented with complaints of multiple fall episodes. During the episodes of muscle spasm, she was not able to move her body voluntarily. She had no issues with breathing, swallowing, voiding, or defecation. She initially presumed her fatigue, cramps, and stiffness to be related to her work but presented to the hospital when it started affecting her daily routine. The patient had no history of other autoimmune diseases like type 1 diabetes, pernicious anemia, vitiligo, or carcinoma. Her symptoms continued to worsen over the next year. Psychological and physical stress were the triggering factors for the spastic episodes. Clinical examination during these episodes showed arterial hypertension, profuse sweating, agitation, and increased tone of affected limbs. Mental status was normal between hypertonic crises and there was no neck stiffness, myoclonus, or ataxia. Cardiovascular and respiratory examinations were unremarkable. She underwent various investigations including blood tests, cerebrospinal fluid studies, imaging studies of the brain and spinal cord, and an electroencephalogram. They all were unremarkable, suggesting the need for an alternate diagnosis. She was eventually diagnosed with stiff person syndrome in 2013, after an electromyographic study revealed continuous motor-unit activity and a high titer of circulating anti-GAD antibodies (>1200 U/mL, *N* <1 U/mL).

Following the diagnosis, symptomatic treatment was initiated with diazepam 10 mg q8h and baclofen 10 mg q8h with IVIg therapy every 6 weeks. Whenever she missed a few doses of IVIg, she started having repeated episodes of stiffness and rigidity with

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gradual progressive breathing difficulty. In late 2013, she was admitted in the ICU for respiratory failure and was on mechanical ventilation via tracheostomy and feeding tube for nutrition. She was sent for respiratory rehabilitation after decannulation and sent home with her maintenance medications. For the next 3 years, she was able to perform all the activities of daily life independently and her symptoms were well maintained on pharmacological therapy. In 2016, she again developed shortness of breath and was admitted to the hospital for a month with respiratory failure after missing her medications. She was transferred to various hospitals with respiratory failure with minimal improvement and was discharged on diazepam 10 mg q8h and baclofen 10 mg q8h. In 2020, the treating physician at a hospital felt the need to adjust her diazepam dose (10 mg Q8H) as it was not alleviating her respiratory problems and changed it to a dose of 30 mg once daily, but it caused worsening of the respiratory symptoms forcing the doctor to go back to her regular dose of 10 mg Q8H. She had multiple relapses of respiratory failure warranting short hospital admissions over the past few years. With baclofen, diazepam, and IVIG, she reported improvement in her motor symptoms. She could walk on her own with support. Currently, she is responding well with antibiotics for her bacteremia and pneumonia. She is still on ventilatory support via tracheostomy and continues to have spasms on prompt stimulus.

Discussion

Acute respiratory failure manifesting with apneic episodes is a life-threatening and unpredictable complication of SPS. It is thought that impairment of GABAergic pathways by autoantibodies and a reduction of brain GABA result in clinical manifestations of stiffness, spasms, and phobias. Thus, respiratory difficulties may be caused by spasms of the diaphragm, impaired respiratory function, and sudden tonic rigidity involving the respiratory muscles [4]. The lack of GABA-ergic inhibition in the intermediolateral cell column, however, may lead to sympathetic overactivity. This autonomic hyperactivity can lead to paroxysmal attacks of transient arterial hypertension, hyperpyrexia, tachycardia, pupillary dilatation, agitation, and diaphoresis during painful muscle spasms. In our case, mechanical ventilation by itself did not alleviate respiratory symptoms; and only neuromuscular-blocking agents allowed correct ventilation parameters. Sudden and unexpected deaths have been reported in SPS, and all described cases have been associated with apnea [3–5]. Thus, we believe that the onset of apnea during SPS, regardless of the underlying mechanism, should be considered as a criterion of high severity and should lead to ICU admission for continuous monitoring until the effect of immunotherapy. In patients with life-threatening complications, early immunotherapy by IVIG should be considered [6]. Multiple discrete episodes of respiratory failures in this patient may have been triggered due to interruptions in the treatment. History elicited from this patient suggests that some episodes were triggered by missing medications. In the most recent episode of respiratory failure needing ventilator support, the patient also had pneumonia with MSSA sepsis which exacerbated the episode or possibly triggered it. So, adherence to regular medications should be a priority while treating a person with SPS. We should anticipate respiratory distress in patients with SPS and should monitor and tailor-make appropriate therapy including early immunotherapy, especially in patients with a previous history of respiratory distress. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material1 (for all online suppl. material, see https://doi.org/10.1159/000532093).

Conclusion

Progression to respiratory failure in stiff person syndrome is a fatal deteriorating complication leading to prolonged ICU stay for continuous monitoring. Many described cases of sudden and unexpected deaths being reported in SPS have been strongly associated with apnea and respiratory failure. We strongly believe in the need to know more about the pathophysiology behind the respiratory failure events in this patient as it has a pernicious effect on her mental and physical health. We also were able to point out the efficacy of early start and regular administration of diazepam, baclofen, and IVIg in controlling symptoms and progression of the disease to an extent. Physicians should anticipate respiratory distress in SPS, especially in patients with a prior history of respiratory distress. Clinicians should be vigilant of further episodes and must ensure adherence to medical therapy at all possible situations to prevent respiratory failure events and possible sudden death.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Bhumika Bheemavarapu: gathering data, drafting, and reviewing. Arkaja Singh: gathering data, drafting, and reviewing. Nived Jayaraj Ranjini: gathering data, drafting, and reviewing. Venkata Sai Abhilash Meda: drafting and reviewing. Dhrumil Patil: drafting and reviewing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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