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Rare case of Stiff person syndrome with negative GAD Antibodies - case report and literature review

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Abstract

Introduction: Stiff person syndrome (SPS) is an uncommon and debilitating condition marked by increasing muscle stiffness, spasm, and rigidity. It classically presents with truncal and appendicular muscle spasms associated with lumbar hyper lordosis. It may be caused by autoimmune mechanisms, paraneoplastic factors, or have an unknown origin. This condition can occur alongside other autoimmune diseases, including type 1 diabetes mellitus, pernicious anemia, vitiligo, and Hashimoto's thyroiditis.

Up to 80% of patients have positive anti glutamic acid decarboxylase (GAD) antibody. Few individuals are GAD negative.

Case report: We present a 32-year-old male who presented with intermittent tonic spasm and was misdiagnosed as seizures and was treated for the same. He was seen in our hospital during one of the episodes and was suspected of having stiff person syndrome (SPS). His anti-GAD antibody and paraneoplastic workup were negative. His electromyogram (EMG) showed continuous spontaneous activity in both agonist and antagonist muscles, confirming the diagnosis of possible SPS - seronegative. He was started on intravenous immunoglobulin and benzodiazepines and showed significant improvement.

Conclusion: Stiff Person Syndrome remains a rare and frequently under-recognized neurological disorder, particularly in seronegative cases where the absence of characteristic autoantibodies complicates the diagnosis. This case highlights the importance of maintaining a high index of suspicion for SPS in patients presenting with recurrent episodes of generalized stiffness and normal EEG findings.

Keywords: Stiff person syndrome, anti glutamic acid decarboxylase antibody, GAD antibody, intravenous immunoglobulin, case report

Introduction

Stiff person syndrome (SPS) is an uncommon and debilitating condition marked by increasing muscle stiffness, spasm, and rigidity. It classically presents with truncal and appendicular muscle spasms associated with lumbar hyperlordosis [1]. It may be caused by autoimmune mechanisms, paraneoplastic factors, or have an unknown origin. This condition can occur alongside other autoimmune diseases, including type 1 diabetes mellitus, pernicious anemia, vitiligo, and Hashimoto's thyroiditis [2].

Up to 80% of patients have positive anti glutamic acid decarboxylase (GAD) antibody. Few individuals are GAD negative.

Here we present 32-year-old male diagnosed with stiff person syndrome with negative GAD antibody. After treatment with immunoglobulin patient improved significantly.

Case report

This 32-year-old patient presented to our hospital with an episode of acute spasms involving all 4 limbs and lasting for less than 5 minutes with evidence of tongue bite aborted with injection diazepam. He had similar presentation and was shown to other facilities where he was initially diagnosed as generalized tonic-clonic seizures and started on levetiracetam 500 mg two times per Day. Despite good compliance, patient was having recurrent episodes of these spasms. On examination, patient was conscious but had generalized stiffness of the limbs, jaw and blepharospasms. Moreover, patient was unable to eat, talk, open his eyes fully or walk independently.

Patient had Electroencephalogram (EEG) done previously during one of those episodes and showed no definite epileptiform discharges.

Magnetic resonance imaging (MRI) showed multiple bilateral frontoparietal subcortical and periventricular small foci of altered signal (along watershed zones) likely representing small lacunar infarcts. His basic blood reports were normal.

Given the above clinical features, stiff person syndrome was suspected in this patient, and we proceeded with electromyography and antibody to GAD.

Electromyography (EMG) done in gastrocnemius, extensor indicis, flexor carpi radialis, peroneus muscles showed continuous spontaneous motor unit activity in both agonist and antagonist group of muscles confirming the diagnosis of stiff person syndrome (fig 1,2). His blood sample was negative for GAD antibodies. Since GAD antibodies were negative, we worked up for paraneoplastic etiology. His paraneoplastic antibody profile came negative, Computed tomography (CT) chest and abdomen were unremarkable with no evidence of primary malignancy or metastatic disease.

He was started on intravenous immunoglobulins 400 mg/kilogram and patient significantly improved. Patient was discharged on oral diazepam. He was reviewed after one month and showed significant improvement.

Discussions

Stiff person syndrome (SPS) is an uncommon and debilitating condition marked by increasing muscle stiffness, spasm and rigidity. It classically presents with truncal and appendicular muscle spasms associated with lumbar hyper lordosis [1]. It may be caused by autoimmune mechanisms, paraneoplastic factors, or have an unknown origin. This condition can occur alongside other autoimmune diseases, including type 1 diabetes mellitus, pernicious anemia, vitiligo, and Hashimoto's thyroiditis [2].

Estimated prevalence of SPS was 1-2 cases per million people. Population based retrospective analysis done by Crane *et al* estimated 1.36 cases per 1000000 people [3].

Diagnosis of SPS is based on clinical presentation of generalized muscle stiffness, antibody testing and electrophysiological evidence. 80% of patients have GAD antibody positive. Rarely can other antibodies be directed like glycine receptor alpha 1 subunit (glyR-IgG), Amphiphysin and gamma aminobutyric acid A(GABA A) receptor antibody. Few patients are seronegative for any known antibodies [4, 5].

Study of 22 patients conducted by Khan *et al* showed 27% of the patients were negative and another 13 % antibody status were unknown. They were diagnosed only by the electrophysiological criteria [6].

Electromyography (EMG) provides clues to the diagnosis of SPS by demonstrating continuous motor unit activity in both agonist and antagonist muscles. These activities can be triggered by certain stimuli and improve with diazepam [7].

Chia *et al* proposed diagnostic criteria for stiff person syndrome (tab1). As per this criteria patient is diagnosed as definitive SPS if they fulfill all 5 categories.

They are diagnosed as probable seropositive if they fulfill the clinical criteria with positive antibody titers with the exclusion of other causes.

Patient is diagnosed as probable seronegative if other criteria are met, with negative antibody titers [4].

According to them, misdiagnosis of SPS is common. They attribute misdiagnosis related to misinterpretation of antibody results, clinical signs and symptoms or lack of electrophysiological assessment. GAD antibodies are present in 80% of SPS patients this is also found in other patients like type 1 diabetes mellitus, thyroid gastric autoimmunity and sometimes even in normal individuals.

Treatment of SPS focuses on symptomatic treatment and immunomodulation. Benzodiazepines like diazepam or clonazepam in divided doses or oral baclofen are considered for the initial symptomatic therapy for patients with SPS [4].

Squintani G *et al* used pregabalin for symptomatic relief in their patient after the patient developed excessive sedation with diazepam. He noticed that rigidity and painful spasm improved dramatically and she could walk without assistance. The clinical benefit persisted for 3 months and, he noticed there was complete disappearance of electromyogram activity at rest [8]. Abatemarco *et al* -in their retrospective case series, which included 9 patients among which 7 received chronic intrathecal baclofen infusion. He concluded that intrathecal baclofen is ineffective therapy for medical intractable spasticity due to SPS [9].

Dalakas *et al* in his case series of 16 patients with an anti-GAD antibody paucity used high dose intravenous immunoglobulin which resulted in significant improvement and was well tolerated [10]. Baker *et al* and Antonia *et al* in their article have shown that treatment with rituximab induced a good clinical remission especially in refractory cases [11, 12]. Kumawat *et al* in their study of five patients, treated them with therapeutic plasma exchange along with immunotherapy and concluded that TPE is helpful as an adjuvant therapy [13]. Vaiyapuri *et al* demonstrated that physical therapy interventions like range of motion exercises, stretching, hydro and heat therapy significantly reduced spasm and stiffness [14].

There were multiple case reports which demonstrated the usefulness of autologous hematopotic stem cells transplantation, intravenous ketamine infusion, botulinum toxin for long term disease control [15, 16, 17]

Our patient presented with generalized spasm and rigidity with intermittent tonic spasm was initially misdiagnosed as convulsion and was started on antiepileptics without much improvement.

His routine investigations were normal including electroencephalogram (EEG) and magnetic resonance imaging (MRI). After the suspicion of SPS, we did anti-GAD antibody which was also negative. EMG demonstrated continuous motor activity in both agonist and antagonist muscles. Paraneoplastic work up was negative for the patient. He was diagnosed as probable SPS – seronegative according to the criteria (4, table 1)

He was started on benzodiazepines along with intravenous immunoglobulin (IVIG) and showed significant improvement.

This case underscores the importance of considering SPS in patients presenting with recurrent episodes of stiffness and unremarkable EEG findings, as well as the effectiveness of IVIG in managing refractory symptoms. Further awareness of this rare condition is essential to reduce diagnostic delays and optimize patient outcomes.

Conclusion

Stiff Person Syndrome remains a rare and frequently under-recognized neurological disorder, particularly in seronegative cases where the absence of characteristic autoantibodies complicates the diagnosis. This case highlights the importance of maintaining a high index of suspicion for SPS in patients presenting with recurrent episodes of generalized stiffness and normal EEG findings, especially when initial treatment for presumed epilepsy fails to provide sustained improvement. Electromyography played a crucial role in confirming the diagnosis, underscoring its value in evaluating unexplained muscle rigidity.

The patient’s marked clinical response to intravenous immunoglobulin reinforces the role of immunotherapy as an effective treatment modality, particularly in refractory or seronegative presentations. Early identification and timely initiation of appropriate therapy are essential to prevent progression, reduce morbidity, and improve quality of life. Increased clinical awareness and understanding of SPS can help reduce diagnostic delays and ensure better outcomes for affected individuals.

In this case, the patient had been previously treated for epilepsy despite normal EEG findings, highlighting the diagnostic challenges associated with SPS.

Statements

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Author contributions

1. Dr. Anandi Damodaran- Designed the case study, conceptual development and editing
2. Dr. Usman othi- Designed the case study, conceptual development and editing
3. Dr. Saima Majid - Data acquisition and analysis
4. Dr Devdutt Nayak Kotekar- Conceptual development
5. Sara Mohammed - Data acquisition and analysis

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Data availability statement

Data is not available online due to legal and ethical issues.

Patient's consent

Patient written informed consent has been taken to use his images and relevant information for publication.

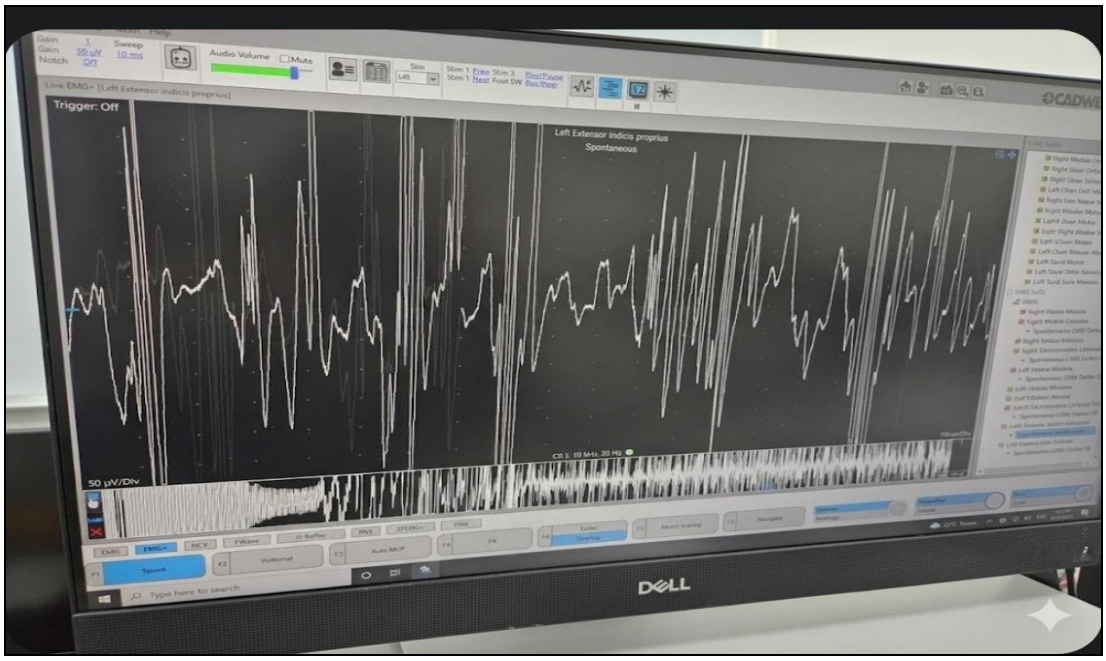

Fig 1: EMG of extensor indices showing continuous spontaneous motor activity

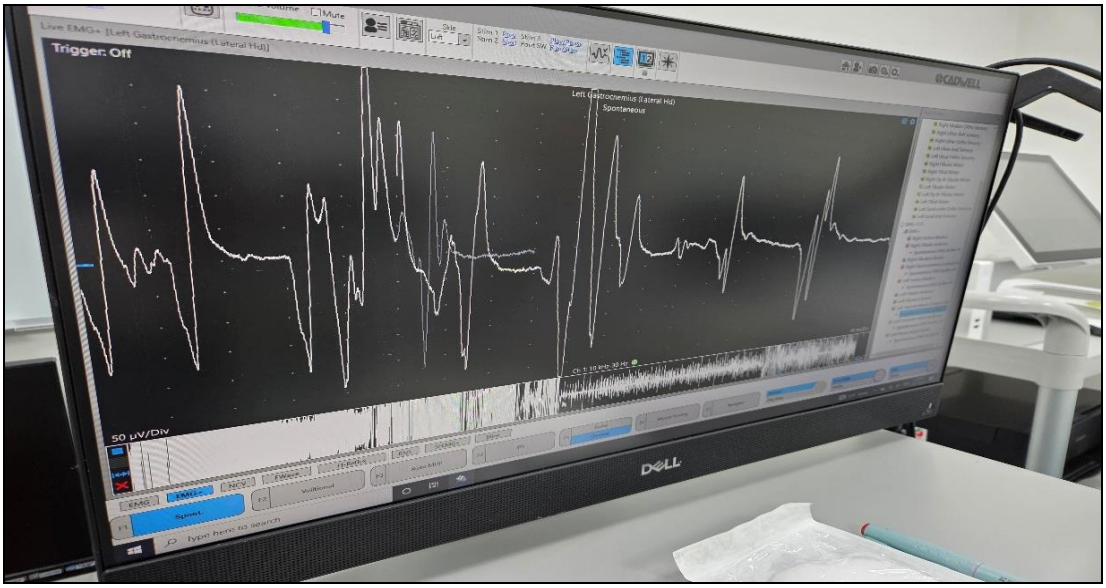

Fig 2: EMG of gastrocnemius showing continuous spontaneous motor activity

Table 1: Proposed diagnostic criteria for stiff person syndrome

Proposed diagnostic criteria for stiff person syndrome.
1. Clinical—Symptoms (1 of 2)
a. Stiffness (axial regions, limbs, or both)
b. Episodic spasms (axial regions, limbs, or both) triggered by noises, tactile stimuli, emotional stress
2. Clinical—Signs during symptomatic phase of illness (1 of 3)
a. Increased muscle tone (axial or limb)
b. Exaggerated lumbar lordosis
c. Concurrent stiffness of lumbar paraspinal and abdominal muscles
3.Serological findings (1 of 3)
a. High-titer GAD65-IgG in the serum (≥20 nmol/L by radioimmunoprecipitation assay or 10,000 IU/mL by ELISA) or any positive titer in CSF
b. Glycine-R-IgG in serum and/or CSF by live cell binding assay
c. Amphiphysin-IgG in serum and/or CSF by immunohistochemistry and antigen-specific assay as confirmation
4.Electrophysiological studies (1 of 3)
a. Inability to relax paraspinal muscles in needle EMG
b. Exaggerated acoustic or exteroceptive responses by surface EMG
c. Co-contraction of agonist/antagonist muscles by EMG
5.Exclusion of alternative diagnosis
Definite: All (1–5). Probable: At least one of #1 or #2 AND #3 AND
#5 (seropositive). OR #1, #2, #4 and #5 (seronegative).

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