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Anti-glutamic acid decarboxylase 65: Related stiff person syndrome – A report of two cases and literature review

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Abstract

Stiff person syndrome is a rare neurological disorder characterized by muscular rigidity, painful spasms, and gait abnormalities. The diagnosis is primarily clinical and often requires a high index of suspicion. While the pathophysiology is not fully understood, stiff person syndrome is frequently associated with anti-glutamic acid decarboxylase 65 antibodies, and in some cases, paraneoplastic syndromes. We present two cases of anti-glutamic acid decarboxylase 65positive stiff person syndrome in the Philippines: a 53-year-old diabetic woman presenting with a classical stiff person syndrome case that responded well to symptomatic treatment, and a 62-year-old woman with a history of thyroiditis presenting with paraneoplastic stiff person syndrome that showed significant improvement on follow up after plasmapheresis and tumor excision. These cases are particularly valuable due to their rare local presentation, contributing to the limited data on stiff person syndrome in our region. This article also includes a review of the existing literature on stiff person syndrome, highlighting key diagnostic and therapeutic approaches. The findings emphasize the importance of early diagnosis and intervention, as well as expanding clinical awareness of this condition in regions where it is not widely recognized.

Keywords

stiff person syndrome, anti-GAD 65, anti-glutamic acid decarboxylase, paraneoplastic

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Introduction

Stiff person syndrome (SPS) is an extremely rare neurological disease characterized by progressive muscular rigidity, stiffness, and painful paroxysmal spasms causing significant functional disability.[1] Due to its varying clinical presentation, which evolves over time, diagnosis can be quite challenging. The exact prevalence is unknown, but it is estimated to be one to two per million, with an incidence of one per million per year.[2] In South Asia, with a population of nearly two billion, only 14 cases had been reported as of 2016.[3] Most cases present between the ages of 20–50

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and preferentially affect women two to three times more often than men.[4] In the Philippines, only one case has been published, though it was noted to be negative for anti-glutamic acid decarboxylase (anti-GAD) antibodies.[5]

The pathogenesis of this disease is incompletely understood; however, it is usually associated with anti-GAD65 antibodies which target GABAergic neurons responsible for central nervous system (CNS) inhibition, ultimately leading to excess motor unit firing.[6] In 5%–8% of cases, SPS can also present as a paraneoplastic condition, associated with malignant tumors such as thymoma.[7] Although there is no established treatment, prompt initiation of therapy is crucial, as patients often develop early disability and may become more refractory as disease progresses.[2] This article presents two cases of SPS with positive anti-GAD65 antibodies, along with a review of related literature.

Case presentation

Case 1

A 53-year-old Filipino female from Leyte, with a history of diabetes, consulted due to progressive stiffness causing difficulty in ambulation. She initially complained of intermittent back pain 7 years ago. Two years later, the symptoms progressed, now accompanied by paroxysmal arching of the trunk and marked stiffness of the bilateral lower extremities, triggered mostly by sudden movement and cold ambient temperature. Ambulation was difficult, and the patient was no longer able to work. Notable findings on examination included a board-like abdomen and stiff paraspinal muscles, which did not improve with lying down, with no upper motor neuron signs. Standing up or sitting down caused notable painful extension spasms of the trunk and the lower extremities, lasting for 1–2 min. She had an unsteady and cautious gait with notable exaggerated lumbar lordosis.

Initial work-up included a metabolic evaluation, cranial computed tomography (CT) scan, magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine, electromyography (EMG) and nerve conduction study – all of which yielded inconclusive results. She was eventually referred to a Movement Disorder specialist, and SPS was considered based on the clinical features. Testing for anti-GAD65 antibodies turned out positive (Table 1), and she was started on oral diazepam (7.5 mg/day) and baclofen (15 mg/day). On follow-up after 1 week, the patient showed near-complete resolution of her symptoms, making it possible for her to work again.

Case 2

A 62-year-old Filipino women from Manila, with a history of thyroiditis, was referred to the Adult Neurology Department for a 3-month history of progressive rigidity and intermittent painful tonic spasms of the bilateral lower extremities, eventually involving the upper extremities, usually exacerbated by sudden auditory and tactile stimuli. As the disease progressed, she eventually lost the ability to walk and became bedbound. On systemic physical examination, the patient also had hypopigmented patches all over her body, and neurologic examination revealed rigid and extended bilateral lower extremities in an equinovarus position with associated hyperreflexia.

EMG showed continuous motor unit activity in the tibialis anterior and gastrocnemius muscles. Thoracolumbar MRI also revealed lumbar spondylosis and an incidental finding of an enlarged thymus, for which she was admitted for elective thoracotomy (Figure 1). The patient also tested positive for anti-GAD65 autoantibodies (Table 1). The patient was then managed as a case of SPS, initially started on oral levetiracetam (1 g/day), baclofen (40 mg/day), clonazepam (6 mg/day), and prednisone (30 mg/day) with minimal relief. The patient then underwent thoracotomy and excision of the tumor, which showed thymoma type B2, and five sessions of plasmapheresis. On follow-up after a month, the patient showed significant improvement in the rigidity of both lower extremities and a reduction in the frequency of painful spasms, which allowed the patient to sit and ambulate over short distances.

Discussion

SPS is a rare disease, affecting approximately one in a million people, with women being more affected in 70% of the cases, ranging from 20 to 50 years.[4] Patients typically present with fluctuating and progressive rigidity and painful muscle spasms of the trunk and extremities, all of which were seen in both of our patients. The episodic nature of the spasms can eventually lead to gait difficulties, falls, and a characteristic "wooden man" appearance.[8] The spasms are often triggered by stress or unexpected stimuli, such as startling or sudden movements.[9] The stiffness develops from the trunk and then spreads to the proximal and distal extremities. This leads to slow voluntary movements, muscle hypertrophy, abnormal posturing, and the characteristic lumbar hyperlordosis.[8]

SPS is subtyped into four categories based on the presence and absence of antibodies and other diseases.[10] (1) Classic SPS is the most common subtype seen in 70%–80% of patients, characterized by truncal stiffness, generalized rigidity, and frequent muscle spasms leading to a wide-based gait. It is classically associated with anti-GAD65 antibodies. (2) Partial SPS or stiff limb syndrome is seen in 10%–20% of cases, affecting only one limb, usually the leg, leading to marked difficulty in ambulation. It is typically anti-GAD65 negative. (3) Paraneoplastic SPS is a rare subtype seen in 5% of cases and is clinically indistinguishable from classic SPS cases. It can also be anti-GAD65 negative but may test

Table 1. Summary of available diagnostic work-up.

Case 1	Case 2
Cranial CT scan • Atherosclerotic internal carotid and vertebrobasilar arteries • Unremarkable plain cranial study Cervical MRI • Cervical and thoracic spondylosis • Multiple posterior disk bulges at C3–7 • No evident myelopathy Thoracolumbar MRI • Disk desiccation at L5–S1 • Central disk protrusion with ventral dural sac indentation and mild central canal stenosis • Posterior disk bulge with ventral dural sac indentation and central annular tear at L5–S1 • Intramuscular edema of dorsal thoracolumbar region Lumbosacral MRI • Posterior disk bulge with central disk annular fissure at L5–S1 • Mild posterior disk bulge at L1–2 and L4–5 • Sacral root cyst at S2 level Spinal survey MRI • Apparent posterior convexity with ventral dural sac indentation at C5–7 • Disk desiccation at C2–7 • Straightening of the cervical and lordosis likely due to muscle spasm EMG-nerve conduction studies • Electrophysiologic evidence of chronic lumbosacral radiculopathy involving the L4–5 to L5–S1 on both right and left sides of mild to moderate severity. Chronic denervation was observed in the paraspinal muscles, with signs of partial denervation in the muscles innervated by the affected roots • Co-existing bilateral focal median neuropathy at the level of the wrist of moderate severity. This is consistent with carpal tunnel syndrome if symptomatic • No evidence of diffuse large or small fiber neuropathy • No evidence of myopathic process Immunology and serology tests • FT4 – 18.79 pmol/L (12–22) • TSH – 2.77 µIU/mL (0.27–4.20) • T3 – 1.18 nmol/L (1.3–3.1) • ANA titer <80 • Rheumatoid factor – nonreactive • Anti-JO-1 – 0.7 (<15) • Anti-cyclic citrullinated peptide antibodies (anti-CCP) – 0.9 U/mL (<5) • Vitamin B12 >1476 pmol/L (145–569) • Anti-GAD65 MAGLUMI-CLIA – 53 UI/mL (<17) (Eurofins Biomnis®, Lyon, France)	Cranial MRI with contrast • No evidence of an acute infarct, mass, or hemorrhage • Few nonspecific punctate signal abnormalities involving the bilateral cerebral white matter, commonly seen in association with chronic migraine headaches and chronic small vessel ischemic changes Thoracolumbar MRI (Figure 1) • Thoracic spondylosis • No abnormal cord signals, distinct disk herniations, canal, or neuroforaminal stenosis • Probable intraosseous hemangiomas, T2 vertebral body • Incidental note of a suggestive right anterior mediastinal mass, dilated ascending aorta, cardiomegaly, small right pleural effusion, and bilateral renal cysts Lumbosacral MRI (Figure 1) • Mild lumbar spondylosis • L4–5: posterior disk bulge, flaval hypertrophy, and mild bilateral facet arthropathy, causing thecal sac indentation and mild bilateral neuroforaminal stenoses with bilateral exiting L4 nerve root contact • L5–S1: posterior disk bulge, left flaval hypertrophy, and moderates bilateral facet arthropathy, causing moderate bilateral neuroforaminal stenoses with bilateral exiting L5 nerve root contact • Dorsal lumbar subcutaneous edema • Large uterine leiomyoma • Small bilateral renal cysts Chest CT scan with contrast • Anterior mediastinal mass to consider thymoma • Histopathology done on the thymus revealed a thymoma type B2 EMG-nerve conduction study • Normal insertional activities in all muscles. No spontaneous potentials were observed on the vastus lateralis • Continuous motor unit activities in tibialis anterior and gastrocnemius with normal looking MUAP • Normal MUAP amplitude, duration, and phases in all muscles tested • Preserved recruitment in all muscles tested 3-Hz repetitive nerve stimulation and single fiber EMG • Normal. No significant decremental response Immunology and serology tests • FT4 – 12.9 pmol/L (12–22) • TSH – 2.4214 µIU/mL (0.27–4.20) • FT3 – 4.11 pmol/L (2–7) • Glutamic acid decarboxylase AB: 175.258 U/mL (<5)

ANA: Antinuclear antibody; EMG: electromyography; GAD65: glutamic acid decarboxylase 65; MUAP: motor unit action potential.

positive for other antibodies against Amphiphysin and Gephyrin. It is usually associated with mediastinal tumors like thymoma, or other malignancies such as breast, renal, lung, colon carcinoma, and lymphoma. In some cases, it can coexist with other autoimmune disorders such as vitiligo and thyroiditis, as seen in our second patient.[8] (4) Lastly, Progressive Encephalomyelitis with Rigidity and Myoclonus is an extremely rare subtype seen in 0.1% of cases, generally more severe in presentation, and is associated with anti-glycine alpha-1 receptor antibodies.[2,9,11]

Recent studies have also examined the increased prevalence of diabetes in patients with SPS, such as in Case 1. Approximately 60% of anti-GAD65-positive individuals develop insulin-dependent diabetes mellitus, which may be related to the underlying autoimmune process of the disease.[12]

The pathophysiology is incompletely understood, but high titers of anti-GAD65 antibodies strongly associate with SPS. GAD is said to catalyze the rate-limiting step responsible for gamma-aminobutyric acid (GABA) synthesis, which is the major inhibitory neurotransmitter of the CNS. Hence, autoantibodies against GAD can decrease the GABAergic inhibitory neurotransmission, ultimately leading to cortical hyperexcitability. This will then impair the ability of the antagonizing skeletal muscles to relax when contralateral muscles contract, manifesting as the characteristic rigidity and spasms on patients with SPS.[2] The diagnosis of SPS is primarily clinical, based on the Dalakas criteria, which were mostly fulfilled by the two cases discussed (Table 2). These criteria include: (1) stiffness of axial muscles (abdomen and thoracolumbar paraspinals), which may lead to hyperlordosis; (2) painful spasms triggered by unexpected stimuli (auditory or tactile); (3) continuous motor unit firing in both agonist and antagonist muscles, as observed in EMG; (4) positive serology for GAD/amphiphysin autoantibodies; and (5) absence of other neurological impairments that might suggest an alternative diagnosis.[8,13]

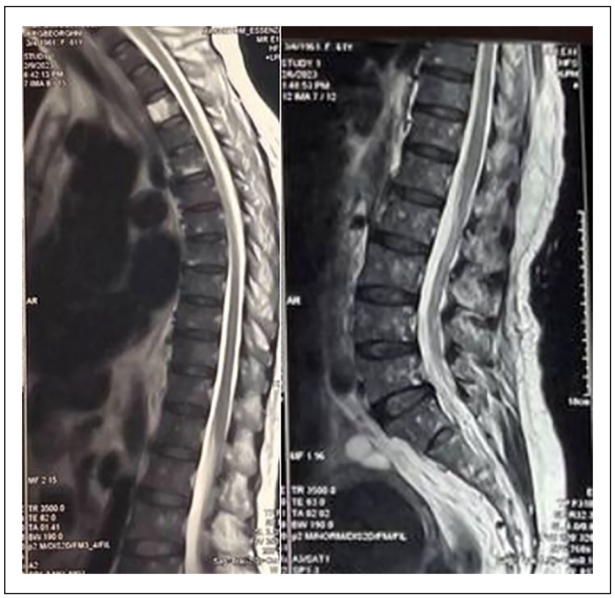

Figure 1. Thoracolumbar and lumbosacral MRI representative cuts of Case 2 showing mild thoracic and lumbar spondylosis, with L4–S1 mild posterior disk bulges. No other noted abnormal cord signals, distinct disk herniations, canal, or neuroforaminal stenosis.

Therapeutic intervention for SPS mainly involves symptomatic treatment, immunosuppression, and tumor management for paraneoplastic SPS. Symptomatic therapy is based on increasing GABAergic inhibitory neurotransmission and is given to provide immediate relief. This may include GABA-A agonists such as benzodiazepines like Diazepam or Clonazepam, GABA-B agonists such as Baclofen, and other anti-epileptics such as Gabapentin, which functions by inhibiting GABA degradation. The first patient showed a good response with symptomatic treatment only using Diazepam and Baclofen.

If symptomatic agents did not provide adequate benefit for the patient, immunomodulators may also be considered. Intravenous immunoglobulin (IVIg) is usually the first-line therapy, using a dose of 2 g/kg divided in 2–5 days. The duration of IVIg efficacy can last between 6 weeks and 1 year after therapy.[2,9]

Some patients presenting with more aggressive symptoms can also benefit from high-dose steroids (oral prednisone, 60 mg/day or IV methyprednisolone, 1000 mg/day for 5 days) or plasmapheresis.[2] Though evidence supporting plasmapheresis is not yet well established, some reports have reported improvement in symptoms and

Table 2. Dalakas criteria.

Criteria	Case 1	Case 2
1) Axial muscles (abdomen and thoracolumbar paraspinals) stiffness which may lead to hyperlordosis	Fulfilled	Fulfilled
2) Painful spasms triggered by unexpected stimuli (auditory or tactile)	Fulfilled	Fulfilled
3) Continuous motor unit firing of both agonist and antagonist muscles as seen in electromyography	Not fulfilled	Fulfilled
4) Positive serology for GAD/amphiphysin autoantibodies	Fulfilled	Fulfilled
5) Absence of any other neurologic impairments which may suggest other diagnosis	Fulfilled	Fulfilled

GAD: glutamic acid decarboxylase.

serologic markers in patients who did not benefit from first-line treatment.[14] Monitoring of antibodies is usually not recommended, given level of titers does not usually correlate with treatment response or severity.[10] The second patient had no response to oral symptomatic treatment but showed marked improvement after tumor excision and plasmapheresis. Other second-line immunotherapies such as Cyclophosphamide, Mycophenolate Mofetil, Azathioprine, or Rituximab can also be given for refractory cases.

In general, early initiation of treatment is essential. As the disease progresses, patient may become more refractory to management and are at higher risk of developing permanent disabilities.[2] While some may respond to treatment and maintain a reasonable level of activity, no proven therapy leads to spontaneous remission and a progressive decline in functional status and quality of life is still generally observed.[15] Paroxysmal autonomic dysfunction from repeated spasms or sudden death can also occur in 10% of the SPS patients.[2] Although rare, SPS is considered as severely disabling, and hence, a better understanding of its natural history, pathophysiology, and management options is necessary.

Conclusion

In conclusion, this study highlights two rare cases of SPS in the Philippines, emphasizing the clinical challenges in diagnosis and management. Both cases were anti-GAD65 positive, with one presenting as a classic SPS case that showed a good clinical response to symptomatic treatment, and the other, a paraneoplastic type, which improved following plasmapheresis. These cases are particularly significant given the rarity of SPS in the local population, contributing to the limited data available in the region. This report underscores the importance of maintaining a high index of suspicion, early diagnosis, and appropriate management. Given the autoimmune nature of SPS, further exploration of novel therapeutic approaches may help slow disease progression and improve patients' quality of life.

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Ethical considerations

Our institution does not require ethical approval for reporting individual cases or case series.

Consent to participate

Informed consent was obtained from both patients, and they consented to participate in this study in which the publication of case report was permitted.

Consent for publication

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Author contributions

Ena Elizabeth L. Naoe: conceptualization, data collection, manuscript writing, editing of final manuscript. Redentor R. Durano II: conceptualization, data collection, manuscript writing, editing of final manuscript. Ranhel C. De Roxas-Bernardino: conceptualization, editing, review, and critique of manuscript. Gerard Saranza: conceptualization, editing, review, and critique of manuscript.

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Data availability Statement

The datasets generated and/or analyzed during the current study are available in the manuscript. Additional data related to this study are available from the corresponding author upon reasonable request.

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