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Stiff-Person Syndrome: A Rarity

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A B S T R A C T

1. **Aim:** To report a case of stiff-person syndrome presented with paraparesis, musclespasm and newly diagnosed case of Diabetes Mellitus.

2. **Methods and result:** A 27 years old female presented to us with complaints of progressive difficulty in walking with intermittent muscle spasm. It was in the form of extensor posturing. Patient also had past history of Diabetes Mellitus. On evaluation patient found to have Stiff-Person Syndrome on the basis of clinical examination, electrophysiology and positive anti GAD-65 antibody. Our patient responded well to IvIG and Inj. Methylprednisolone with symptomatic therapy with diazepam and baclofen.

3. **Conclusion:** Here we reviewed the case presentation, diagnostic and therapeutic options for this severe disabling disease. Our case shows treatment strategies for Stiff Person Syndrome on the basis of evidence based studies. As large evidence based studies for treatment of SPS is still lacking, So further observation and large case series will be of use in future.

Key words :stiff-person syndrome; anti-glutamic acid decarboxylase antibodies; Intravenous Immunoglobulin

INTRODUCTION

Stiff Person Syndrome (SPS) is a rare immune mediated disorder of the central nervous system characterized by progressive stiffness and stimulus triggered painful muscle spasms of predominantly axial and proximal limb muscles associated lumbar hyper lordosis. Most common antibody implicated in this disease till now is anti-glutamic acid decarboxylase-65. The current clinical classification of SPS includes [1]

1. Classic SPS which is characterized by generalized body stiffness which is gradually worsen over time and co-exist with some other associated autoimmune disorders like Diabetes Mellitus type-1, autoimmune thyroid disease, pernicious anaemia, celiac disease, vitiligo[2].

2. Partial SPS variants which is characterized by focal body involvement including single limb known as stiff limb syndrome, cerebellar variant, and SPS with epilepsy. The paraneoplastic variant is associated with breast, colon, thyroid, lung malignancies, Hodgkin and non-Hodgkin lymphomas and tends to clinically manifest before cancer itself [2].

3. Progressive encephalomyelitis with rigidity and myoclonus (PERM) which is characterized by axial and limb muscle rigidity, diffuse myoclonus of with dysautonomia[2].
Identification of associated antibodies and common comorbidities with other autoimmune diseases and malignancies has been important for a better understanding of disease mechanisms and approaches to treatment. Here we described a patient presented with classic SPS variant.

Case report

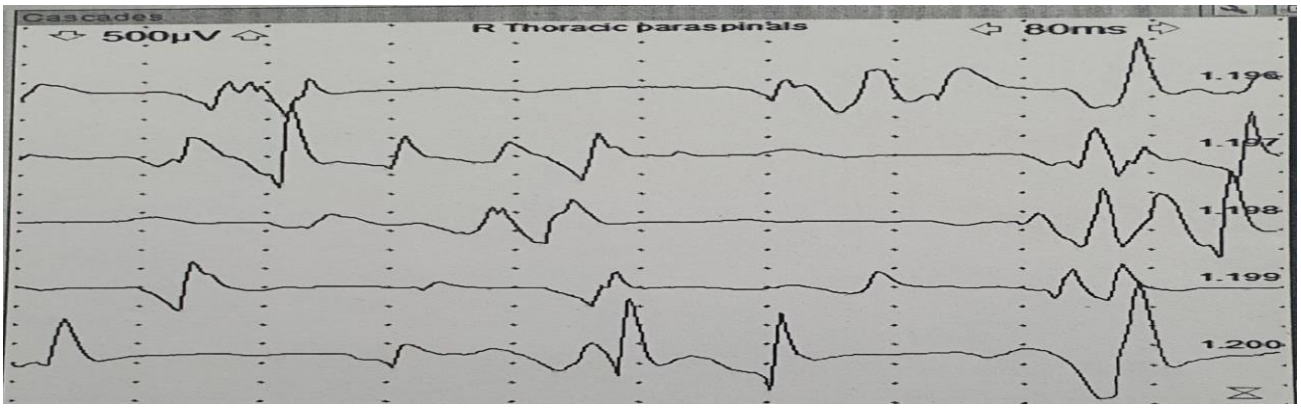
Presentation

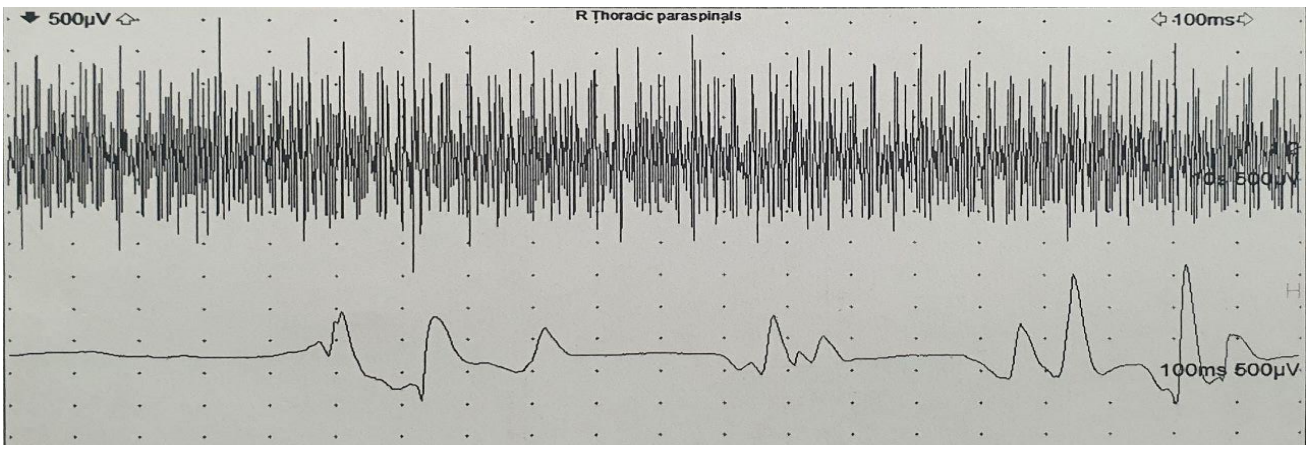
A 27 years old female, right handed, married housewife, tobacco chewer, resident of village Babri, district Jodhpur, presented with complaints of lower limb weakness with difficulty in walking in the form of stiffness of both lower limb

and associated with frequent falls for last one and half months with painful spasms of trunk, upper and lower limbs causing intermittent extensor posturing. Weakness was insidious in onset, progressive in the form of difficulty in wearing slippers and getting up from sitting position from ground. Gradually patient had stiffness of both lower limbs causing repeated falls while walking and gradually patient needed 1 person support to walk. Patient also complained of intermittent painful muscular spasms of lower limbs, hip and trunk causing extensor posturing of body noticed by family members, which remained for 10-15 secs. Gradually patient became bed bound due to fear of injury and fall and worsening of her symptoms.However there was No history of vision loss, bladder and bowel symptoms seizure, loss of consciousness, head injury. In past history patient recently diagnosed with Diabetes Mellitus and on treatment with insulin therapy with no other significant past history. The family history was unremarkable.

On admission examination patient`s vitals were stable and patient was afebrile. Patient was awake, alert, and oriented to time,place and person with normal speech. Cardiovascular, abdominal and respiratory examination were normal. On motor examination bulk was normal bilaterally, tone was significantly increased in all 4 limbs (lower limbs >upper limbs) with trunk. Power examination in lower limbs was insufficient proximally on admission due to painful spasms and decreased range of motion due to pain and MRC grading 5/5 distally. Power in upper limbs was 5/5 proximally and distally. Patient was not able to turn on her side to assess the spine and even patient was not to sit. There was associated abnormal movements of trunk and limbs in the form of extensor posturing of trunk and extension of limbs at all joints. Other neurological examination of cognition, cranial nerves, sensory and cerebellum were unremarkable. Planter reflex were flexor and deep tendon reflexes were +2 all bilaterally along with hung up reflex.

On initial laboratory evaluation, complete blood counts normal Hb, no leucocytosis, ESR (08mm in 1st hour), CRP(2mg %), liver function test, renal function test (S.creatinine 1.5mg%), were normal. Her fasting and postprandial sugar level were high and HbA1C was 11.05% showing poor sugar control or poor drug compliance. Serum electrolytes were normal. ECG, Chest x-ray and ultrasonography abdomen were unremarkable. Serum thyroid function test and vitamin B12 were normal. CSF examination were normal. Serum ANA by immunofluorescence assay and CPK-NAC levels was normal. MRI brain and whole spine with contrast was normal with no signs of inflammation or mass in paraspinal muscles. As disease is associated with some malignancies we planned for contrast enhanced CT thorax and abdomen and pelvis to rule out any malignancies which reported uterine fibroid and right ovarian cyst. On further evaluation we did electromyography and we found spontaneous discharges (myotonic discharges) in paraspinal muscles with normal MUAPs and recruitment. We planned for immunological testing and foundanti GAD-65 antibodies positive.





We treated the patient initially with injection methylprednisolone pulse therapy (1gm for 5days) followed by oral prednisolone 20mg/day. We gave the symptomatic treatment with diazepam 5mg thrice a day with baclofen 10mg thrice days with pregabalin 75mg along with physiotherapy. Patient was partially improved symptomatically over 5 days so we planned further treatment with IvIG 2gms/kg over 5 days. We managed patient sugar levels with insulin therapy. During hospitalization for 13 days patient improved in her stiffness and patient could turn into bed without support and could stand walk with 1 person support.

We discharged the patient in stable condition with partial symptoms. On discharge we adviced the patient diazepam 2.5mg thrice a day, baclofen 10mg thrice a day, prednisolone 10mg once a day, along with insulin therapy. We planned on follow ups to taper off prednisolone, and monthly IvIG and for rituximab of patient worsen in her sympotms.

On next follow up after 15 days patient improved significantly in her symptoms and patient was able to stand walk unassisted. We tapered off steroids and planned to wait for maintenance IvIG therapy. At present she is on prednisolone 1.25mg once a day, diazepam and baclofen. She is doing well in her activities of daily livings.

Discussion

Stiff person syndrome (SPS) is a rare immune mediated disorder of the central nervous system characterized by progressive stiffness and stimulus triggered painful muscle spasms of predominantly axial and proximal limb muscles with estimated prevalence of 1-2 cases per million[3]. 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.The condition has an insidious onset with gradual worsening over time and, if left untreated, can lead to permanent disability and mortality. There is underlying etiology associated with high titers of autoantibodies to various components of inhibitory synapses and some paraneoplastic syndromes in 5-10% patients with underlying malignancies most common of which is breast adenocarcinoma followed by adenocarcinoma of the colon, small-cell lung carcinoma, malignancies of thymus and thyroid gland, and Hodgkin's lymphoma[2], which leads to their impaired functioning through a low level of gamma-aminobutyric acid (GABA) on pre-synaptic or post-synaptic neuronal junctions. Production of autoantibodies against antigens involved in GABA synthesis and release within the central nervous system results in a dysfunction of major inhibitory pathways leading to impaired truncal and axial muscles impaired relaxation due to hyperexcitability the motor cortex. Glutamic acid decarboxylase (GAD) is an intracellular enzyme that transforms glutamate into GABA and is a primary target and the most common antigen identified in classic SPS[4].Primarily, the production of anti-GAD65 antibodies is a hallmark of a pathological process in classic SPS and is found in 70-80% of cases which is associated with other neurological disorders e.g.limbic encephalitis, autoimmune epilepsy, cerebellar ataxia, myoclonus, and nystagmus. It is also associated with diabetes Mellitus, vitiligo, pernicious anemia. Other antibodies associated are anti-amphiphysin antibodies found in adenocarcinoma breast and GABA(A) receptor-associated protein (GABARAP), dipeptidyl-peptidase-like protein-6 (DPPX) as well as glycine receptor (GlyR), which is associated with PERM[5].SPS is notoriously difficult to diagnose as it is rare, uncommonly considered, and symptoms evolve over time.Diagnostic criteria for SPS evolved over the years and usually made clinically by thorough neurological examination with the support of electrodiagnostic and laboratory findings, and at present most accepted are criteria revised by Dalakas in 2009[6].The current diagnostic criteria for classic SPS include:

1. Stiffness in the limb and axial muscles, prominent in the abdomen and thoracolumbar region
2. Painful spasms precipitated by unexpected tactile and auditory stimuli
3. Evidence of the continuous motor unit activity in agonist and antagonist muscles demonstrated by EMG
4. Absence of other neurological impairments that could support an alternative diagnosis
5. Positive serology for anti-GAD65 or anti-amphiphysin autoantibodies
6. Clinical response to therapy with benzodiazepines.

Our patient also presented with a history of insidious onset, gradually progressive lower extremity weakness and gait disturbance with stiffness with grossly normal neurological examination except increased tone. It raise diagnostic considerations including apossible psychogenic component to the patient's stiffness and inability to move. Other diseases under consideration were non compressive myelopathy based on her presentingsymptoms of painful spastic quadriparesis without sensory lossin a middle age woman, HIV myelopathy,young onset Parkinsonism and neurosarcoid.

Treatment options for SPS can be divided into two main categories: symptomatic and disease-modifying or immunotherapy[2].Symptomatic management is a standard initial therapy and focuses on decreasing stiffness, rigidity, and painful muscle spasms and achieved by using medications that promote GABA effects, such as benzodiazepines, baclofen, gabapentin, and vigabatrin. Disease-modifying therapy is a specific immune-modulating treatment that aims at reducing or removing autoantibodies. Intravenous immunoglobulin (IVIG) and corticosteroids is proven to be the effective immunotherapy in SPS initially and for refractory cases rituximab is better option which efficacy is variable. Other immunomodulators like mycophenolatemofetil, azathioprine, cyclophosphamide use of which is controversial and still uder trials.

Patient need maintainenceIvIG therapy for 3-5 months and may present with worsening of symptoms if IvIG stop in between. So patient need long term follow up and may need extended IvIG therapy or some other available immunomodulator therapy. There is limited trial for use of IvIG in SPS demonstrating that monthly maintenance IVIg therapy offers long-term benefits in about 67% of patients for a median 3.3-year period[7].

Our patient responded well to initial symptomatic and immunosuppressive therapy and she is in regular follow up every month. She is doing well in her activities of daily livings and has no fresh complaints so we withdrew our plan for further IvIG and other immunosuppressive therapy.

The prognosis for patients with SPS is multifactorial and depends on clinical presentation, the longitude of symptoms, co-existing neoplastic process, and a response to therapy. It is crucial to timely initiate therapy to prevent or lessen progression and avoid long-term complications.Most of the patients improve with medications, however fluctuatiating course precipitated by physical and emotional stressors still occur and leads topermanent orthopedic abnormalities, inability to walk, and disability. In one longitudinal study, only 19% of patients could work after 4 years of follow up[7].

Long term complications associated with SPS are at higher risk of developing orthopedic problems such as lumbar hyperlordosis, joint deformities, and muscle atrophies, leading to abnormal posturing and gait abnormalities with increased fall risk and dysautonomia with tachycardia, hypertension, and hyperthermia triggered by tactile and auditory stimuli[3,9].

Conclusion

SPS is a rare disease and remains an important consideration in the differentialdiagnosis in patients presented with muscle stiffness as timely diagnosis and treatmentcan arrest the course of the disease and even reverse some of thedisabilities. So a strong clinical suspicion is of immense importance for outcome a treatable diease upto an extent. It is crucial to monitor patients who receive immunotherapy for possible side effects. Our case also highlights the hungup reflex[10] in Stiff Person Syndrome. Further studies and case series will be helpful.

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