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CASE REPORT

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Stiff person syndrome in a Nepalese man with uncontrolled diabetes mellitus and ketonuria: A rare case report

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Abstract

Stiff Person Syndrome (SPS), a progressive Central Nervous System disorder is accompanied by progressive muscle rigidity, hyperreflexia, and spasms mainly in truncal and proximal leg muscles mainly associated with autoimmune disorders. Here, we report a rare case of SPS in a middle-aged Nepalese man with uncontrolled diabetes mellitus and ketonuria.

KEYWORDS

diazepam, glutamic acid decarboxylase, stiff-person syndrome, uncontrolled diabetes mellitus

1 | INTRODUCTION

Stiff-person syndrome (SPS) is a progressive central nervous system disorder in which muscle rigidity progresses proximally to distally and is accompanied by recurrent falls, muscle spasms, and chronic muscle pain.[1] One or two persons in a million can present with this disorder which has female predominance (2–3 times).[1]

Though the pathogenesis of SPS is still unclear, the likely etiology is an autoimmune insult. It demonstrates the formation of antibodies against glutamic acid decarboxylase (GAD) and antibodies against gephyrin, the glycine-alpha1 receptor, or gamma-aminobutyric acid (GABA) receptor-associated protein. More than 70% of cases of SPS have autoantibodies against glutamic acid decarboxylase (GAD-Abs). Autoimmune disorders like Type 1 diabetes and Hashimoto's thyroiditis are associated with SPS while paraneoplastic SPS, linked with anti-amphiphysin antibodies, is associated with malignant tumors of the lung, thymus, breast, and lymphoma.[2,3]

Here, we report a rare case of SPS in a middle-aged Nepalese man with uncontrolled diabetes mellitus and ketonuria.

2 | CASE PRESENTATION

A 43-year-old married male farmer, with a known case of diabetes, presented to our emergency department with a 1-year history of pain over bilateral lower limbs, hip, and low back with muscle spasms and startling type of movement of bilateral lower limbs for the last 4 days. He initially noted difficulties with walking, and standing and could not bear weight. He had also experienced on-and-off

neck tightness and jerky limb movements for the same duration. There were worsening jerks with touch and movement, but not with auditory stimulus. There was no history of fever, headache, vomiting, trauma, loss of consciousness, trouble swallowing, weakness, or difficulty in balance, speech, or vision. The patient denied any loss of sensation, autonomic dysfunction, or changes in bowel or bladder habits. He did not give a history of surgery, medicine, vaccination, or exposure to toxins and heavy metals. The patient consumes a non-veg diet and does not smoke or consume alcohol. There is no family history of similar complaints or any known neurological disease.

On admission, his general condition was fair and his Glasgow Coma Score (GCS) was 15/15. He was well-oriented to time, place, and person; vital signs were stable and within normal limits. There was no pallor, icterus, lymphadenopathy, edema, cyanosis, or clubbing. On neurological examination, his higher mental functions, cranial nerves, sensation, and coordination were normal. There were no meningeal signs elicited. Motor examination showed normal muscle bulk, reflexes, and power (5/5) in both upper and lower limbs while the tone was increased in bilateral upper and lower limbs. The patient had muscle jerks involving all the limbs, predominantly the lower limbs. These symptoms were repetitive, with a frequency of one episode in 2–3 s. The spasms were painful, and the patient scored nine out of 10 in the visual analog score. The rest of the systemic examination findings were normal.

His hematological profile showed a total count of 7700/mm^3, hemoglobin of 11.9 gm/dL, and platelets of 160,000/mm^3. His serum urea and creatinine levels were 9.5 mmol/L and 89 mmol/L, respectively, sodium was 139 mEq/L, and potassium was 4.3 mEq/L. His thyroid function test was normal; Triiodothyronine (T3) level was 3.06 ng/dL, Thyroxine (T4) level 1.84 ng/dL, and Thyroxine Stimulating Hormone (TSH) level 1.93 mU/L. The serological studies for Anti-Nuclear Antibodies (ANA) and Human Leukocyte Antigen (HLA-B27) were negative.

His HbA1c level was raised to 11.4%. His urine was positive for acetone. A needle Electromyogram (EMG) revealed spontaneous persistent motor discharges in the right tibialis anterior and soleus muscles. After ruling out the differentials, we suspected a possible common link between insulin-dependent diabetes mellitus and neurological disease, possibly SPS. A test of GAD-65 (Glutamic Acid Decarboxylase-65) Immunoglobulin G via serum enzyme immunoassay showed GAD autoantibodies to be high in our patient with the value of more than 2000 IU/mL (Reference: <10 IU/mL).

Hence, the presence of muscle spasms and limb pain, positive GAD autoantibodies, positive therapeutic response to oral diazepam, and findings of EMG while simultaneously ruling out other differentials pointed toward the diagnosis of SPS with uncontrolled diabetes mellitus.

During the hospital stay, the patient was treated with Diazepam, Metformin, Teneligliptin, Diltiazem, and Lantus insulin. The patient showed signs of improvement in his reduction of jerk episodes and stiffness. The symptoms responded very well to 10 mg of diazepam given twice a day and were comfortable with minimal stiffness and occasional jerks on the fifth day of admission. His fasting and postprandial sugar levels were improved on the seventh day of admission. The patient was discharged on the seventh day on 5 mg of diazepam twice a day with advice to follow-up and to continue supportive care and physiotherapy. On his follow-up at 3 months, the patient was asymptomatic and the dose of diazepam was reduced to 2.5 mg twice a day and antidiabetic medications were continued as previous.

3 | DISCUSSION

Focal or segmental SPS, Jerky SPS, Progressive encephalomyelitis with rigidity, and Myoclonus and paraneoplastic-related SPS are the variants of SPS. These variants are collectively called "stiff-person plus syndromes".[1] SPS presents with muscle spasms and stiffness in the thoracolumbar, paraspinal, and abdominal muscles. This causes difficulty in turning and bending, progressive muscle rigidity, hyperreflexia, and spasms mainly in truncal and proximal leg muscles.[4] Patients describe they walk like "tin-man" and have severe truncal stiffness resembling a "statue" like appearance. Patients may have severe anxiety and the symptoms can be precipitated by stimuli like a phone ringing, sudden touches, or emotional upset.[5] Our patient had a muscle spasm in the low back and bilateral lower limb but with no precipitating factor.

The revised diagnostic criteria in 2009 for SPS consists of (a) stiffness of the axial muscles, particularly the abdominal and thoracolumbar paraspinal, leading to hyperlordosis; (b) superimposed painful spasms triggered by unexpected tactile or auditory stimuli; (c) severe anxiety with task-specific phobias especially in anticipation of physically challenging tasks; (d) EMG evidence of continuous motor unit activity of agonist and antagonist muscles; (e) absence of other neurological findings that may suggest an alternative diagnosis; and (f) highly positive GAD-antibody titers by immunocytochemistry, Western blot, Enzyme-Linked Immunosorbent Assay (ELISA), or radioimmunoassay.[6] As in our case, most of the points of the criteria are fulfilled.

Other differentials for this case were tetanus, neuromyotonia, and rabies. The patient did not give any

history of facial spasm or trismus; there is no history of trauma, wound, needle prick, or animal bite and the patient responded very well to low-dose diazepam. Rabies usually manifests with encephalitic or paralytic features along with agitation, hydrophobia, hypersalivation, and seizures, none of which were seen in this patient. Neuromyotonia usually has muscle cramps, and confusion, associated with paraneoplastic antibodies such as Contactin-associated Protein-like 2 (caspr2) and the patient usually responds with plasma exchange or intravenous immunoglobulin treatment. Clinical manifestations along with the high level of anti-GAD antibody, persistent motor discharges on EMG, and significant clinical improvement with benzodiazepine treatment were supportive of SPS.[7] Ankylosing spondylitis, Parkinson's disease, axial dystonia, and focal spinal cord lesions can also be other mimickers of SPS.[8] These mimickers did not meet our patient history and lab investigations, so were ruled out.

Basic laboratory tests such as Complete blood count, metabolic panel, and imaging techniques. Along with Anti-GAD Ab, a confirmatory test positive in 60% of patients is performed for SPS patients.[9] Though these antibodies are also found in type 1 diabetes (80%), SPS patients possess a far higher anti-GAD Ab titers (differing up to 100-folds–500-folds).[10] Another important diagnostic tool is EMG which shows continuous spontaneous motor unit activity in both agonist and antagonist muscles.[11] Our patient also had a high degree of anti-GAD Ab titers and persistent EMG discharges. A post-diagnostic evaluation is also necessary for SPS patients to know the association with other autoimmune diseases as most SPS patients with positive anti-GAD Ab will develop type 1 Diabetes.[9,10] Similar was our case, the SPS patient was worked up for autoimmune disease and found to have uncontrolled diabetes with ketonuria.

Patients of uncontrolled Diabetes Mellitus with ketonuria should be treated as per the principles of acute management of metabolic decompensation. Oral antidiabetic medications are needed while insulin replacement therapy is administered in an insulin-deficient state and hyperglycemia crisis. Lifestyle modifications, optimal diet, weight loss, and exercise are also components of the treatment regimen.[12] For the treatment of spasms and muscle pain in SPS, benzodiazepines such as diazepam or clonazepam are preferred. Currently, a 60 mg daily dose of diazepam although intolerably high is used for patients with classic or partial SPS and GAD-65-positive antibody.[13]

But our patient responded well to 10 mg of diazepam twice a day and slowly tapered thereafter.

Glutamic acid decarboxylase enzyme is necessary for the formation of the neurotransmitter GABA which helps in the control of muscle movements. The attack of antibodies on GAD decreases the levels of Gamma-Aminobutyric Acid (GABA).[14] Benzodiazepines (such as diazepam and clonazepam) enhance the GABA neurotransmitter's effect on the GABA receptor. The possibility of withdrawal from benzodiazepines' long-term, high-dose use is a concern. This has resulted in the use of alternative treatments such as tizanidine, an N-methyl-D-aspartate receptor (NMDAR) blocker. Sedation and somnolence are the main issues with using diazepam as a therapy. As an alpha 2 inhibitor that also inhibits glutamate release, tizanidine protects SMS patients from glutamatergic hyperactivity, which can induce convulsions.[15]

Studies have suggested the addition of levetiracetam or pregabalin if symptoms persist after the initial treatment of benzodiazepines. Oral baclofen over rituximab and tacrolimus is also recommended as second-line therapy because of fewer side effects. Similarly, rituximab is recommended over tacrolimus because of its better safety and the requirement of an intermittent intravenous dose. While for refractory symptoms, intrathecal baclofen, Intravenous Immunoglobulin (IVIG), or plasmapheresis are used.[16] Our patient was on oral anti-diabetic medication, long-acting insulin, and comparatively low dose of diazepam; and was symptom-free on follow-up.

4 | CONCLUSIONS

SPS is a rare, debilitating treatable disorder mainly associated with diabetes mellitus and anti-GAD antibodies. SPS requires a high degree of clinical suspicion differentiating it from other causes of muscle spasms and also its association with autoimmune disease and malignancy. Early diagnosis is needed for better management and appropriate treatment of SPS.

AUTHOR CONTRIBUTIONS

Rajeev Ojha conceptualized the study, reviewed, and edited the manuscript and was in charge of the case; Sanjeev Kharel, Siddhartha Bhandari, and Amit Sharma wrote the original; Naresh Parajuli, Bikram Prasad Gajurel, Ragesh Karn, Reema Rajbhandari, Niraj Gautam, and Ashish Shrestha were in charge of case and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Ethical approval was not required for this study in accordance with local/national guide-lines.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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