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STIFF PERSON SYNDROME-MANAGING A RARE AUTOIMMUNE DISORDER IN A LOW RESOURCE SETTING: A CASE REPORT

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ABSTRACT

Stiff Person Syndrome (SPS) is a rare neurological disorder characterized by muscle stiffness and painful muscle spasms. The symptoms often progress slowly and can cause disability. Auto-antibodies to glutamic acid decarboxylase (anti-GAD) have been reported in up to 80% of the classic type of SPS. Delayed diagnosis may occur especially in low-resource settings if a high index of suspicion is not applied when individuals manifest characteristic symptoms. We report a case of a 63-year-old Nigerian female who presented with progressive onset low back pain, lower body rigidity and painful muscle spasm with subsequent loss of ambulation and development of depression. Serologic tests detected high-titer anti-GAD, confirming the diagnosis of SPS. Due to limited availability and the financial implications of out-of-pocket treatment, escalation therapy to immune-based therapy for this neurological disorder was hindered in our case.

INTRODUCTION

Stiff person syndrome (SPS) is an uncommon neuroimmunological condition characterized by a variety of symptoms with differing degrees of disability among affected individuals. Due to the great variability of SPS, a wide range of clinical manifestations are included in the classification of SPS spectrum disorders (SPSD).[1] There are several SPSD phenotypes, each of which could have a distinct immunological basis and in most cases this results in individuals with SPS being misdiagnosed early in their disease course and may even be undiagnosed in some cases especially in low resource setting where investigative modalities are limited with high cost implications where available.[2]

It typically presents with rigidity and painful, stimulus-triggered muscle spasms, primarily in the proximal and axial limb muscles[3] Frederick Moersch and Henry Woltman initially reported it in 1956, drawing on a case series of 14 patients with gradually increasing and fluctuating tightness in their thigh, abdominal, and spinal muscles. Most cases associated with antibodies against the glycine-α1 receptor and GABA(A) receptor-associated protein are recognized. The clinical progression of the illness is one of slow progression at first, then gets worse over time, and frequently results in lifelong disability and, in extreme circumstances, death.[5] Other autoimmune conditions like type 1 diabetes, thyroid issues, pernicious anemia, and, less frequently, vitiligo are frequently linked to SPS.[1]

We describe a patient who presented with complaints of low back pain, muscles spasms and difficulty with ambulation that was subsequently found to have SPS.

CASE PRESENTATION

A 63-year-old teacher presented to the Emergency Department with low back pain of 5 years duration and difficulty to ambulate of two years duration.

The low back pain was felt as muscle cramps and progressively worsened over the years despite several analgesics. The pain radiated to the proximal thighs with accompanying intermittent spasms and difficulty bending her hips. Subsequently, she noticed difficulty climbing stairs with associated clumsiness and was struggling to walk with occasional falls. She became bedbound about a year later as the symptoms progressed and occasionally she experienced painful and sustained contractions and assumption of a fixed posture. Additionally, she developed myoclonic jerks that were triggered by startling sounds, loud noises, and with mood change. She preferred lying prone because she believed that the supine position exacerbated the jerks. Her symptoms more prominently involved her lower limbs and trunk with relative sparing of her upper limbs.

She reported no sphincteric disturbance, cognitive decline, dysphagia or speech changes and visual disturbances.

She became socially embarrassed, depressed and withdrew from all social activities. This affected her activities of daily living, and she required assistance to tend to her needs.

Except for systemic hypertension for which she was taking PO Co-diovan 160/12.5mg daily, she did not have any other relevant medical, medication and /or alcohol history.

She did not report any family history of neurological conditions

On examination, she was fully oriented, however she had a low mood which was congruent with her affect.

No obvious cranial nerve abnormality. She had episodes of painful spasms which were triggered by touch. Mild disuse atrophy of the lower limbs was noted, and the lower limb muscles were tense, and rigid.

Assessment of other aspects of the neurologic exam proved difficult due to the heightened sensitivity.

Below is a link to a clinical video of the patient demonstrating an episode of painful spasm
https://click.email.vimeo.com/?qs=44fdecf50ad5797 7ef58474b337c7d04da50314127bd1d2640f052c7792ab79e63435 405eb0e35094773c19d393393e243470714ffe899edbe9a3d8743684290

A working diagnosis of hyperkinetic movement disorder was entertained with serotonin syndrome, neuroleptic malignant syndrome, myelopathy and possible stiff person syndrome considered as differentials.

Her investigations are listed in Table 1 below.

Except for electromyographic evidence of continuous motor unit activity in agonist and antagonist muscles which was not available as an investigative modality in our setting, our patient fulfilled the Dakala's criteria: (a) stiffness of the axial muscles, particularly in the abdomen and thoracolumbar paraspinal;, (b) superimposed painful spasms triggered by tactile or auditory stimuli; (c) absence of other neurological findings that may suggest an alternative diagnosis; and (d) positive serology of anti GAD 65 antibody [2] leading to a final diagnosis of stiff person syndrome (SPS).

She was treated with diazepam 5mg TDS dose and was subsequently placed on tabs baclofen 10mg TDS. We administered opiate based and simple analgesic when in painful spasms. Intrathecal Baclofen was another option, but was not readily available. She could not afford plasmapheresis or immunoglobulin due to financial constraint.

Table 1: Showing outcome of available investigations

Investigations	Results
Urea and Electrolytes	Normal
Complete blood count, blood glucose and HbA1c	Normal
ESR, CRP and CK	Normal
EMG and NCS	Not done
Serum Glutamate Decarboxylase 65 Ab (GAD)	**Positive (136.6 U/mL). Ref Range: < 17U/mL**
Serum Amphiphysin Antibody	Negative (Ref Range 1: <10 titer)
MRI Spine	Normal

In the course of her management, the mental health team was invited to review to exclude neuropsychiatric complications such as anxiety and depression. Despite management, our patient symptoms progressed with associated disability and need for wheelchair for mobility

DISCUSSION

SPS is an autoimmune mediated central nervous system disorder that manifests in adults.[5] SPS has a prevalence of 1-2 per million and an incidence of 1 per million per year. Most patients present between the ages of 20 and 50 and women are affected more often than men as seen in this case study.[6]

In SPS, sudden stimuli can cause episodic spasms which lead to progressive muscle stiffness in the trunk and limbs and impair mobility. In the early phase of the illness, lumbar lordosis and falls due to spasms can frequently result in social anxiety and phobia[7] Individuals may experience myoclonus which can occur with the spasms and usually resolve gradually. Patients with SPS often have neuropsychiatry abnormalities such as depression, anxiety, and alcohol abuse.[8] In one study, agoraphobia and other situation-specific phobias were reported in 44 percent of the 43 SPS patients.[9] These characteristic clinical features were all present in our patient and have been linked to dysfunction of inhibitory mechanisms within the central nervous system. This is thought to have an autoimmune background with the responsible anti-antibodies directed against GAD, the rate-limiting enzyme in the decarboxylation of L-glutamate to γ-aminobutyric acid (GABA).[10, 11] Patients with high serum and CSF levels of these antibodies are more likely to develop a severe form of this disease.[12] Furthermore, constant firing of motor neurons, which involves both agonist and antagonist muscles, results in muscle stiffness in SPS patients despite attempts at relaxation. This is demonstrable in EMG studies which show continuous

motor unit activity. Patients with SPS exhibit both vibration-induced inhibition of H-reflex and enhanced H-reflex recovery. These effects are thought to be mediated by GABAergic interneurons that produce presynaptic inhibition of stretch reflex afferents and are seen in neurophysiological studies.[13] In our context, it is quite challenging to get such electrophysiological studies and when available they cost quite a lot. Additional neurological symptoms include paroxysmal dysautonomia, nystagmus, gaze palsy, and increased reflexes.[14]

The GABAergic system with glycinergic neurons has also been implicated in SPS. Ten to fifteen percent of SPS cases also show antibodies against the α-1 subunit of the glycine receptor[15] Less than 10% of patients with SPS have paraneoplastic variants. Antibodies against amphiphysin are mostly attributed to this variant and frequently observed in breast cancer patients. Unlike the classical SPS, the stiffness is typically present in a rostro caudal manner involving the neck and the upper limb.[16]

Histological examinations of individuals suffering from SPS have revealed chromatolysis and vacuolization of anterior horn cells, typically in the caudal region of the spinal cord, as well as a gliosis and loss of α-motor, γ-motor, and spinal interneurons[17]

SPS is diagnosed by recognizing cardinal symptoms and using EMG, antibody testing, and response to benzodiazepine as supporting evidence. [18] SPS has a wide range of differential diagnoses, including tetanus, myelopathies, serotonin syndrome, neuroleptic malignant syndrome, parkinsonian syndromes, dystonia, hereditary spastic paraparesis, motor neuron disease, myelopathies, neuromyotonia (Morvan's and Isaac's syndrome), and psychogenic disorders. A search for a coexisting autoimmune aetiology and malignancy is highly advocated for.

Treatment is aimed at relieving symptoms and modulation of the autoimmune response. GABA agonists such as diazepam (type-A receptors) and oral baclofen (type-B receptors) alone or in combination are usually effective for rigidity and muscle spasms with intrathecal baclofen serving as a rescue therapy; however, this is not readily available in our setting with additional cost implication.[21] We gave our patient, when in extreme painful crises, parental opiates which can be used in this context spinal cord stimulation may also help with excruciating muscle spasms when available, while botulinum toxin may be helpful for extreme rigidity.[22] In a randomized control study, intravenous immunoglobulin (IVIg) demonstrated significant improvement as compared to placebo as shown by a marked improvement in muscle spasms, mobility, frequency of falls, and activities of daily living, as well as a decrease in anti-GAD titres.[23] Other immunomodulating options include rituximab and plasmapheresis have demonstrated variable efficacy in patients with SPS.[24] These therapies were not administered to our patient because of significant financial implications for her. The effectiveness of corticosteroids in treating SPS is debatable and now mostly avoided because of adverse effects associated with prolonged use of the high doses needed to control symptoms.[23] Appropriate treatment of neuropsychiatry comorbidity, especially depression in a multidisciplinary team approach remains key to the management of this disorder.

Immunotherapies for immune-related neurological disorders have shown promise in improving outcomes. Accordingly, this paper advocates for policies including government subsidies, the integration of immunotherapies into national healthcare plans, and strategic collaborations with pharmaceutical companies to reduce costs and enhance access to these treatment modalities

PROGNOSIS

The prognosis can vary and often depends on the initial clinical presentation. Regretfully, even after receiving numerous symptomatic and immunological treatments, many patients still have progressive symptoms and disability. Patients with SPS experience significant reductions in quality of life, with depression playing a major influence on disability adjusted life years (DALYs).[25]

CONCLUSION

SPS is a multifaceted and clinically diverse autoimmune disease. Diagnosis of this condition is made based on symptom recognition, response to benzodiazepine, and results of antibody testing and EMG studies, thus identification of the cardinal clinical manifestation especially in resource constrained setting and confirmation through more focused investigation greatly aid in prognostic counselling for patients and directs treatment planning within the framework of available therapy in these settings.

Conflict of Interest Statement

The authors affirm that they have no conflict of interests to declare.

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