Case Report

Stiff-Person syndrome: A rare neurological disorder

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ABSTRACT

The Stiff-person syndrome (SPS) is an uncommon disorder characterized by progressive rigidity, muscle stiffness, and spasm involving the axial muscles, resulting in severe impairment of ambulation. We present the case of a 49-year-old gentleman with recent onset of progressive asymmetric spastic ataxia, subsequently diagnosed with SPS.

Key words: Muscles, Nervous system, Rigidity, Stiff person syndrome

The Stiff-person syndrome (SPS) is a rare disorder, characterized by progressive fluctuating muscular rigidity and spasms [1]. It is triggered by increased muscle activity due to reduced inhibition by the central nervous system (CNS), resulting from the blockade of glutamic acid decarboxylase (GAD), an enzyme crucial for maintaining inhibitory pathways [2]. SPS is often associated with type 1 diabetes mellitus (T1DM), as well as other autoimmune disorders. It may also occur as a paraneoplastic disorder [1,3]. SPS is a rare and rather unique disease as it lacks significant similarity to any other neurological disorder and does not have any satisfactory treatment [4].

There has been limited research due to the low occurrence of the syndrome. Hence, we present the case of a 49-year-old gentleman with recent onset of progressive asymmetric spastic ataxia who was diagnosed with SPS and treatment options in the context of a severe disabling disease presentation.

CASE PRESENTATION

A 49-year-old married gentleman, a teacher by profession, presented with pain and stiffness of the right lower limb and progressive reduction in velocity while walking short steps for a month with slurring of speech for a week. The patient was apparently functioning well before a month, following which, he presented with symptoms characterized by a feeling of giddiness and a sense of being pushed while walking. On consultation, he was found to have high blood glucose and was initiated on oral therapy. A week later, he developed pain in the right hip accompanied by tightness in the right leg. His right leg could straighten with great difficulty in walking, and he was unable to walk or stand without support. He had noticed some difficulty with brushing teeth, tightening of the right arm, and more recent, slurring of speech with effortfulness and normal comprehension. There was no history of cranial nerve symptoms, bladder, or sensory symptoms.

On examination, his blood pressure was 130/80 mmHg in the right upper limb. His pulse rate was 88 beats/min, respiratory rate was 18 breaths/min, and arterial oxygen saturation on room air was 98%. The CNS examination revealed facial hypomimia, fine, and gaze-evoked multidirectional nystagmus. He had spasticity of both upper and lower limbs (lower limb>upper limb) (right>left). His sensory system examination revealed no abnormality and deep tendon reflexes were normal. He had incoordination in both upper limbs, grossly abnormal finger nose testing, with terminal intentional tremors and dysmetria. He could stand with support, and the gait was spastic and ataxic.

His routine blood investigations revealed the following (Table 1): both serum and CSF GAD antibody titers were elevated. Routine nerve conduction velocity studies and electromyography (EMG) were normal (Fig. 1). Paraspinal EMG showed continuous motor unit activity suppression with diazepam confirming the central origin of stiffness. Exteroceptive impulse testing neurophysiologically revealed the involvement of other muscle groups on the stimulation of the median nerve suggestive of central hyperexcitability. Magnetic resonance imaging (MRI) of the brain did not reveal any vascular lesions. MRI of the cervical spine was normal. A whole-body fluorodeoxyglucose-positron emission tomography scan was done to look for paraneoplastic etiology and was negative.

This gentleman presented with a recent onset progressive asymmetric spastic ataxic syndrome, clinically localizing to the

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Table 1: Laboratory investigations of the patient

Investigations	Results	Normal values
Hemoglobin (g/L)	13.3	14–17
Total count ($\times 10^9$/L)	7300	4.5–11.0
Differential count (%)	NE: 70, LY: 20, MO: 8, EO: 2, BA: 0	
Platelet count ($\times 10^9$/L)	309000	150–350
HIV, HBV, HCV serology	Negative	
Thyroid stimulating hormone (mIU/L)	1.592	0.4–4.2
Serum sodium (mmol/L)	140	135–145
Serum potassium (mmol/L)	3.6	3.5–5
Serum creatinine (µmol/L)	68.97	38–106
Total and direct bilirubin (µmol/L)	0.56/0.24	5–21/1.7–5.1
Serum total protein/albumin (g/L)	68/40	60–80/35–50
Serum aspartate aminotransferase (U/L)	24	10–35
Serum alanine aminotransferase (U/L)	30	10–40
Serum alkaline phosphatase (U/L)	87	30–120
Prothrombin time	18.6	11.7–16.1
INR	1.35	
APTT	34.9	27.8–40.4
Calcium (mg%)	10.45	8.3–10.4
Phosphorous (mg%)	3.0	2.5–4.6
ANTI - PR3 and ANTI - MPO RU/mL	5/<2	<20, <20
Vitamin B12 and folic acid pgm/mL/ngm/mL	541 10.3	200–950
Copper (ug%)	130	70–170
Creatine phosphokinase u/L	105	45-195
Vitamin D (25 OH) ng/mL	11.9	>30
Glutamic acid decarboxylase autoantibody (U/ml)	>2000	Negative <5.0; Positive >5.0
CSF glucose (GRBS=88 mg/dL)	CSF glucose 59	
CSF protein	CSF protein 45	
Cell counts CSF	T.WBC 2/CUMM (NORMAL)	
Polymerase chain reaction for multiple viruses (csf) HSV, CMV, EBV, VZV, adenovirus PCR	Negative	
ESR	28	
HBA1 C (Glycosylated Hb)	9.7	<5.7
Anti-tissue transglutaminase antibody - anti-TTG	Negative	
Anti-neuronal/onconeural antibody profile	GAD65 - Positive ++	

APTT: Activated partial thromboplastin clotting time, INR: International normalized ratio, ESR: Erythrocyte sedimentation rate, CSF: Cerebrospinal fluid, GAD: Glutamic acid decarboxylase

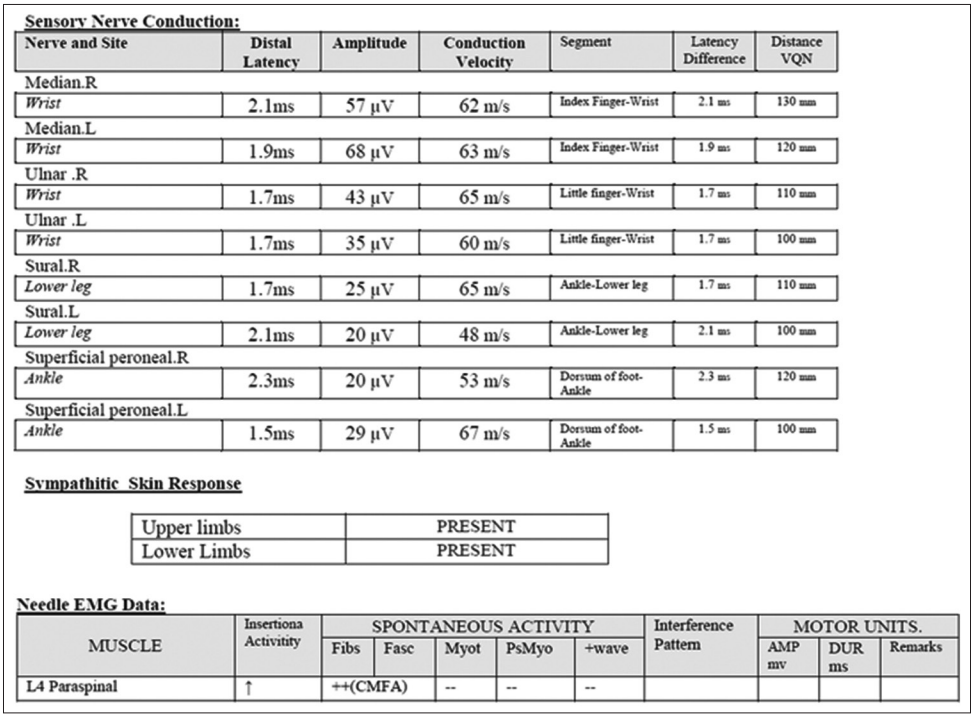
cerebellum/tracts along with corticospinal tracts. The etiology considered was inflammatory (white matter disease/autoimmune disease/SPS/paraneoplastic origin) versus infection of CNS.

In view of clinical presentation, we suspected the stiff-person spectrum with both serum and CSF GAD antibody titers being positive he was diagnosed as SPS. He satisfied the criteria of SPS. He was started on symptomatic management with central sympatholytic agents and diazepam. A total of five cycles of plasmapheresis and 1gm methylprednisolone for 5 days was given. Home-based physiotherapy was advised. Rituximab 600 mg was given as a second-line immunosuppressive agent. Injection rituximab 600 mg once a week for a total of 4 weeks was planned. Injection of methylprednisolone for 500 mg once a week for 6 weeks and 250 mg once a week for 4 weeks was planned. At the end of 6 weeks, there was a significant improvement in spasticity and ataxia and he could walk without support.

DISCUSSION

SPS is an uncommon disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, which results in severely impaired ambulation [1].

Based on several observations, the role of an autoimmune component in the pathogenesis of SPS including an association with T1DM and other autoimmune disorders has been suggested. GAD is the rate-limiting enzyme for gamma amino butyric acid (GABA) synthesis. As GABA is the major inhibitory neurotransmitter in the CNS, the dysfunction of GABAergic



Sensory Nerve Conduction:

Nerve and Site	Distal Latency	Amplitude	Conduction Velocity	Segment	Latency Difference	Distance VQN
Median.R						
Wrist	2.1ms	57 µV	62 m/s	Index Finger-Wrist	2.1 ms	130 mm
Median.L						
Wrist	1.9ms	68 µV	63 m/s	Index Finger-Wrist	1.9 ms	120 mm
Ulnar .R						
Wrist	1.7ms	43 µV	65 m/s	Little finger-Wrist	1.7 ms	110 mm
Ulnar .L						
Wrist	1.7ms	35 µV	60 m/s	Little finger-Wrist	1.7 ms	100 mm
Sural.R						
Lower leg	1.7ms	25 µV	65 m/s	Ankle-Lower leg	1.7 ms	110 mm
Sural.L						
Lower leg	2.1ms	20 µV	48 m/s	Ankle-Lower leg	2.1 ms	100 mm
Superficial peroneal.R						
Ankle	2.3ms	20 µV	53 m/s	Dorsum of foot-Ankle	2.3 ms	120 mm
Superficial peroneal.L						
Ankle	1.5ms	29 µV	67 m/s	Dorsum of foot-Ankle	1.5 ms	100 mm

Sympathitic Skin Response

Upper limbs	PRESENT
Lower Limbs	PRESENT

Needle EMG Data:

MUSCLE	Insertiona Activitity	SPONTANEOUS ACTIVITY					Interference Pattern	MOTOR UNITS.		
		Fibs	Fasc	Myot	PsMyo	+wave		AMP mv	DUR ms	Remarks
L4 Paraspinal	↑	++(CMFA)		--	--	--				

Figure 1: Normal electromyography study. Electromyography showed significant reduction in continuous motor unit activity after IV lorazepam

pathways due to the presence of autoantibodies is believed to be involved in the pathogenesis of SPS [5-7]. There is an association between anti-GAD antibodies and SPS. These antibodies target GABAergic neurons and their nerve terminals [8,9]. In patients positive for anti-GAD antibodies, there is a strong association with other autoimmune diseases such as insulin-dependent DM, hypothyroidism, Grave's disease, and pernicious anemia. It is currently believed that one-third to two-thirds of patients with SPS are accompanied by DM [10].

There are three subtypes of SPS: classic SPS, being the most common where patients present with truncal stiffness, generalized rigidity, and frequent muscle spasms. Partial SPS, in which there is the involvement of one limb or a localized group of muscles. Paraneoplastic SPS variant, which is an extreme rare form, and these patients are usually GAD antibody negative. Most common malignancies include breast and lung cancer and Hodgkin's lymphoma [2].

Yadav *et al*. reported a case of SPS with balance and gait abnormalities [11], whereas, Smith and Storey reported a case of SPS with acute onset vertical diplopia with subacute lower limb spasticity [12]. Dumitrascu *et al*. [13] and Barker *et al*. [14] reported some SPS patients presenting with urinary retention. Some reports have described myositis in patients with SPS [15,16] as well. Mitsumoto *et al*. have reported sudden death in two patients with SPS due to severe paroxysmal autonomic dysfunction causing muscle spasms [17].

Diagnosis of SPS patient requires a high index of suspicion and is based on the following criteria [2,18]: stiffness in the axial and limb muscles causing ambulatory impairment, the presence of episodic spasms which are precipitated by sudden movement, noise, or emotional upset, a positive therapeutic response to oral diazepam or findings of continuous motor-unit activity on EMG which are abolished by intravenous diazepam, absence of other neurologic disorders explaining the clinical scenario. Investigations for SPS include basic laboratory studies including CBC, testing for anti-GAD antibodies in blood and CSF, EMG, and imaging of neuroaxis to rule out degenerative, infectious, malignant, or inflammatory diseases.

Treatment strategies for SPS are broadly divided into two categories: the first category includes GABA-enhancing drugs, and the second category includes immunomodulatory agents such as glucocorticoids, IVIG, anti-CD20 (rituximab), and plasma exchange [19-22]. We treated our patient's using both categories of agents, and ultimately our patients showed favorable outcomes.

CONCLUSION

SPS is a rare disorder with a high index of suspicion. The presence of anti-GAD antibodies provides an important clue for diagnosing SPS. In patients diagnosed with SPS, screening for other autoimmune diseases such as hypothyroidism, Grave's disease, and pernicious anemia in addition to insulin-dependent DM should be considered. Early diagnosis and appropriate treatment improve prognosis.

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