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Stiff-Person Syndrome: A Rare Neurological Disorder

Amit Mandal*

Department of General Medicine, Christian Medical College, Vellore, India

Corresponding author: Amit Mandal, Department of General Medicine, Christian Medical College, Vellore, India, E-mail: amit.mandal78@yahoo.co.in

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Abstract

The Stiff-person syndrome 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 years old gentleman with recent onset of progressive asymmetric spastic ataxia, subsequently diagnosed with Stiff-person syndrome.

Keywords: Stiff-person syndrome; Anti-Glutamic Acid Decarboxylase (GAD) antibodies; Type 1 diabetes mellitus

Introduction

The Stiff-Person Syndrome (SPS) is a rare disorder, characterized by progressive fluctuating muscular rigidity and spasms. It is triggered by increased muscle activity due to reduced inhibition by the central nervous system resulting from the blockade of Glutamic Acid Decarboxylase (GAD), an enzyme crucial for maintaining inhibitory pathways. Stiff-person syndrome is often associated with Type 1 Diabetes Mellitus (T1DM), as well as other autoimmune disorders. It may also occur as a paraneoplastic disorder.

Case Presentation

A 49 years 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 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 of 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 and sensory symptoms.

On examination, his blood pressure was 130/80 mmHg in the right upper limb. His pulse rate was 88 beats/minute respiratory rates were 18 breaths/minute and arterial oxygen saturation on room air was 98%. The central nervous system examination revealed facial hypomimia, fine, gaze evoked multi-directional 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.

Investigations

His routine blood investigations revealed the following **(Table 1)**.

Table 1: Lab investigations.

Investigations	Results	Normal values
Haemoglobin (g/L)	13.3	14-17
Total count (×109/L)	7300	4.5-11.0
Differential count (%)	NE: 70, LY: 20, MO: 8, EO: 2, BA: 0	
Platelet count (×109/L)	309000	150-350

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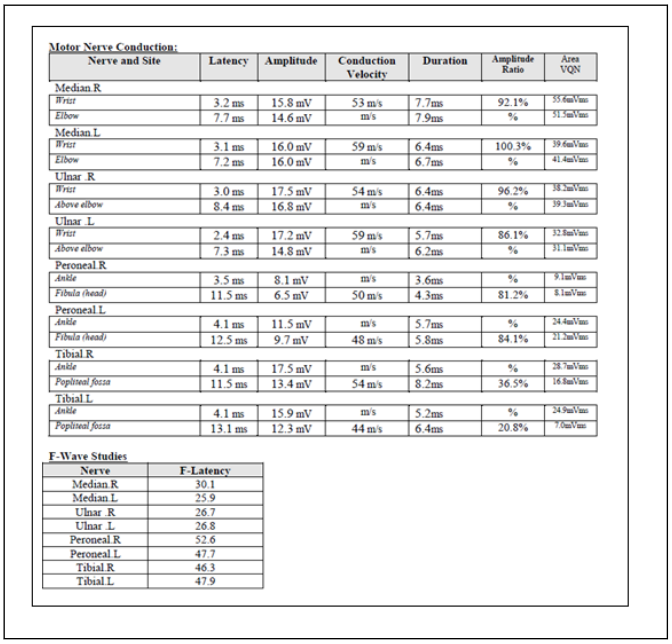
HIV, HBV, HCV serology	Negative	
Thyroid Stimulating Hormone(TSH) (mIU/L)	1.592	0.4-4.2
Serum sodium (mmol/L)	140	135-145
Serum potassium (mmol/L)	3.6	3.5-5
Serum creatinine (µmol/L)	68.97	38-106
Total and direct bilirubin (µmol/L)	0.56/0.24	5-21/1.7-5.1
Serum total protein/albumin (g/L)	68/40	60-80/35-50
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	2.5-4.6
ANTI-PR3 and ANTI-MPO RU/mL	5/<2	<20,<20
Vitamin B_{12} and Folic acid pgm/ml/ngm/ml	541/10.3	200-950
Copper ug%	130	70-170
CPK (CK) 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 protein	CSF Glucose 59 CSF, protein 45	
Cell counts CSF	T.WBC 2/CUMM (Normal)	
PCR for multiple viruses CSF,HSV,CMV, EBV,VZV and Adenovirus PCR	Negative	
ESR	28	
HbA1c (Glycosylated Hb)	9.7	<5.7
ANTI Tissue Transglutaminase Antibody-ANTI-TTG	Negative	
ANTI-neuronal/onconeural antibody profile	GAD65-Positive^{++}	

Both serum and CSF GAD antibody titres were elevated. Routine Nerve Conduction Velocity Studies (NCV) and Electromyography (EMG) were normal **(Figure 1)** paraspinal EMG showed Continuous Motor Unit Activity (CMUA) suppression with diazepam confirming the central origin of stiffness. Exteroceptive impulse testing neuro-physiologically revealed involvement of other muscle groups on stimulation of the median nerve suggestive of central hyper excitability. An MRI of the brain did not reveal any vascular lesions. MRI of the cervical spine was normal. A whole body FDG PET scan was done to look for paraneoplastic aetiology and was negative.

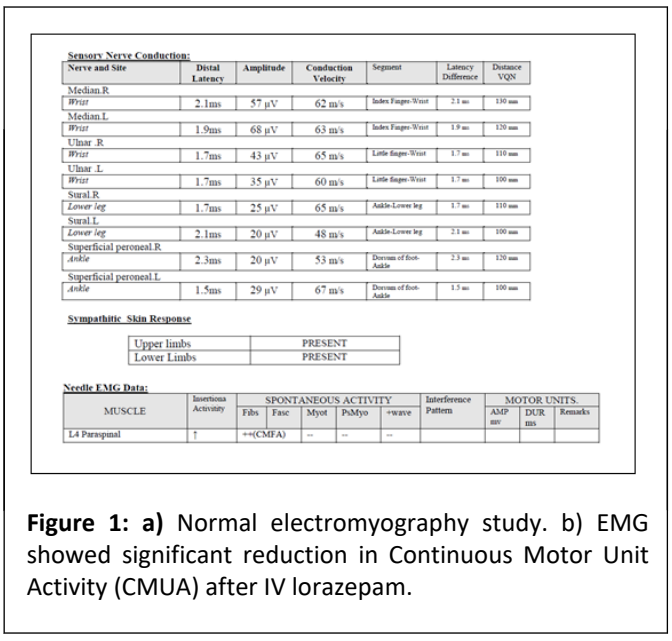


Motor Nerve Conduction:

Nerve and Site	Latency	Amplitude	Conduction Velocity	Duration	Amplitude Ratio	Area VQN
Median R						
Wrist	3.2 ms	15.8 mV	53 m/s	7.7ms	92.1%	55.6mVms
Elbow	7.7 ms	14.6 mV	m/s	7.9ms	%	51.5mVms
Median L						
Wrist	3.1 ms	16.0 mV	59 m/s	6.4ms	100.3%	39.6mVms
Elbow	7.2 ms	16.0 mV	m/s	6.7ms	%	41.4mVms
Ulnar R						
Wrist	3.0 ms	17.5 mV	54 m/s	6.4ms	96.2%	38.2mVms
Above elbow	8.4 ms	16.8 mV	m/s	6.4ms	%	39.3mVms
Ulnar L						
Wrist	2.4 ms	17.2 mV	59 m/s	5.7ms	86.1%	32.8mVms
Above elbow	7.3 ms	14.8 mV	m/s	6.2ms	%	31.1mVms
Peroneal R						
Ankle	3.5 ms	8.1 mV	m/s	3.6ms	%	9.1mVms
Fibula (head)	11.5 ms	6.5 mV	50 m/s	4.3ms	81.2%	8.1mVms
Peroneal L						
Ankle	4.1 ms	11.5 mV	m/s	5.7ms	%	24.4mVms
Fibula (head)	12.5 ms	9.7 mV	48 m/s	5.8ms	84.1%	21.2mVms
Tibial R						
Ankle	4.1 ms	17.5 mV	m/s	5.6ms	%	28.7mVms
Popliteal fossa	11.5 ms	13.4 mV	54 m/s	8.2ms	36.5%	16.8mVms
Tibial L						
Ankle	4.1 ms	15.9 mV	m/s	5.2ms	%	24.9mVms
Popliteal fossa	13.1 ms	12.3 mV	44 m/s	6.4ms	20.8%	7.6mVms

F-Wave Studies

Nerve	F-Latency
Median R	30.1
Median L	25.9
Ulnar R	26.7
Ulnar L	26.8
Peroneal R	52.6
Peroneal L	47.7
Tibial R	46.3
Tibial L	47.9



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

Figure 1: a) Normal electromyography study. b) EMG showed significant reduction in Continuous Motor Unit Activity (CMUA) after IV lorazepam.

Differential diagnosis

This gentleman presented with a recent onset progressive asymmetric spastic ataxic syndrome, clinically localizing to the cerebellum/tracts along with corticospinal tracts. The aetiology considered were inflammatory [white matter disease/ autoimmune-disease/stiff-person syndrome/paraneoplastic orig -in] versus infection of central nervous system.

Treatment

In view of clinical presentation we suspected the stiff person spectrum with both serum and CSF GAD antibody titres being positive he was diagnosed as stiff person syndrome. He satisfied the criteria stiff person syndrome. He was started on symptomatic management with central sympatholytic agents and diazepam.

A total 5 cycles of plasmapheresis and 1 gm methyl-prednisolone for 5 days was given. Home based physiotherapy was advised. Rituximab 600 mg was given as second line immunosuppressive agent.

Outcome and follow-up

Injection rituximab 600 mg once a week for total four weeks was planned. Injection methylprednisolone for 500 mg once a week for six weeks and 250 mg once a week for four weeks was planned.

At the end of six weeks there was significant improvement in spasticity and ataxia and he could walk without support.

Results and Discussion

Stiff-person syndrome 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 stiff-person syndrome including an association with type 1 diabetes mellitus and other autoimmune disorders has been suggested. Glutamic acid decarboxylase is the rate-limiting enzyme for Gamma Amino Butyric Acid (GABA) synthesis.

As GABA is the major inhibitory neurotransmitter in the central nervous system, the dysfunction of GABAergic pathways due to presence of autoantibodies is believed to be involved in the pathogenesis of SPS [2-4]. There is an association between anti-Glutamic Acid Decarboxylase (GAD) antibodies and stiff person syndrome. These antibodies target GABAergic neurons and their nerve terminals [5,6]. In patients positive for anti-GAD antibodies, there is a strong association with other autoimmune diseases, like 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 [7].

There are three subtypes of stiff person syndrome.

- Classic SPS, being the most common where patients present with truncal stiffness, generalized rigidity and frequent muscle spasms.
- Partial SPS, in which there is involvement of one limb, or a localized group of muscle.
- Paraneoplastic SPS variant, which is extreme rare form and these patients, are usually Glutamic Acid Decarboxylase (GAD)

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antibody-negative. Most common malignancies include breast and lung cancer and Hodgkin lymphoma [8].

To diagnose a patient with stiff person syndrome requires a high index of suspicion. Diagnosis of stiff person syndrome is generally based on following criteria's [8,9].

- Stiffness in the axial and limb muscles causing ambulatory impairment.
- 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 Electromyography (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 antibody in blood and CSF, electromyography, imaging of neuro-axis 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 like glucocorticoids, IVIG, anti-CD20 (rituximab), plasma exchange [10-13].

We treated our patient using both categories of agents and ultimately our patients showed favorable outcome.

Conclusion

SPS is a rare disorder and high index of suspicion is required for diagnosing a case with SPS. Presence of Anti-GAD antibody 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 anaemia in addition to insulin dependent DM should be considered. Early diagnosis and appropriate treatment improves prognosis.

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