Stiff Person-Like Syndrome: An Unusual Presentation of Pituitary Macroadenoma with Panhypopituitarism

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Abstract
Pituitary adenoma can manifest as pituitary hypofunction, which can cause symptoms of panhypopituitarism. Commonly, symptoms of hormonal deficiencies such as lethargy, weight change, cold intolerance, and sexual dysfunction are reported. Optic chiasmal compression leads to visual field changes and the discovery of the pituitary lesion. However, limb stiffness is a rare presentation of hypopituitarism, especially hypocortisolism. We report a 68-year-old man who presented with progressive lower limb stiffness associated with truncal instability mimicking a stiff person syndrome (SPS). Hypoglycaemia and hyponatraemia prompted the discovery of pituitary macroadenoma with panhypopituitarism. Investigation showed pituitary macroadenoma on magnetic resonance imaging with hypocortisolism, hypothyroidism, and hypogonadotropic hypogonadism. After initiating hydrocortisone replacement, the patient had complete resolution of lower limb stiffness with no permanent neurological sequelae. It is postulated that hypocortisolism and hyponatraemia disrupt the metabolic function of muscle leading to stiffness. As a result, lower limb rigidity, flexion deformities, and pain are more common. Differentiating adrenal insufficiency associated with rigidity and SPS is important as the response to treatment for both conditions differs. Prompt treatment leads to fast resolution and prevents contractures in adrenal insufficiency-associated rigidity. Thus, recognizing limb rigidity as the first presentation of hypopituitarism is important to avoid long-term complications.
Introduction

Stiff-person syndrome (SPS) is an uncommon disorder characterized by progressive stiffness, rigidity, and painful spasm affecting axial muscle. It can lead to significant debilitation and affects ambulation. Usually, it is associated with autoimmunity as it has a significant overlap with autoantibody in type 1 diabetes. Hypopituitarism, especially hypocortisolism, can lead to axial muscle stiffness and rigidity, similar to an SPS. This case highlights a patient with pituitary adenoma and panhypopituitarism with a stiff person-like syndrome as the initial presentation.

Case Report/Case Presentation

We report the case of a 68-year-old man who presented with progressive stiffness of lower limbs associated with falls. He first noticed an unsteady gait and difficulty in initiating strides together with truncal instability. Symptoms progressively worsened over 2 weeks. He was unable to weight bear, needed assistance to transfer, and became bedbound. No symptoms of resting tremor or bradykinesia were reported. He complained of lethargy, poor appetite, and back pain attributed to frequent falls. He denied any lower limb numbness or incontinence. There was no headache, visual disturbance, or problem with swallowing and speech. There was no excessive thirst, polyuria, cold intolerance, or weight gain. He denied prior head trauma or family history of inheritable neurological diseases. He was a teetotaller. At presentation, he had possible symptoms of hypoglycaemia with the lowest blood sugar of 3.8 mmol/L but was normotensive.

There was no postural hypotension. Muscle wasting or fasciculations were absent. There was no resting tremor or cogwheel rigidity. Hip and knee joints were held in flexion deformity. Lower limbs were hypertonic but with no clonus. The power of extensor/flexors was 4 over 5. Sensory examination was normal. Knee jerk reflex was present but ankle jerk was absent. Plantar reflexes were down-going. Upper limb neurological examination was entirely normal and there were no cerebellar signs. Cranial nerves were normal with no evidence of ophthalmoplegia, mask-like facies, or speech slowness. Gait could not be assessed.

Blood investigations showed hyponatraemia (sodium 122 mmol/L) and normokalaemia (potassium 4.6 mmol/L). The thyroid function test was suggestive of either central hypothyroidism or non-thyroidal illness with TSH 0.75 mU/L (normal range: 0.34–5.60 mU/L) and free T4 5.5 pmol/L (normal range: 7.9–14.4 pmol/L) (using Beckman Coulter UniCel DxI). Morning cortisol was low (24 nmol/L), and subsequently a full anterior pituitary function test was performed. Short Synacthen® test (tetracosactide 250μg injection followed with serum cortisol sampling at 30 and 60 min) showed peak serum cortisol of 71 nmol/L, which was an inadequate response, and ACTH was low at less than 1.1 pmol/L. Full blood count showed normochromic normocytic anaemia (haemoglobin 9.7 g/dL, MCV 88.3 fL, MCH 30.7 pg, and MCHC 34.8 g/dL). FSH and LH were low (0.2 mU/mL and 0.8 mU/mL, respectively), and serum testosterone was below the detection limit (less than 0.35 nmol/L). Prolactin was 546 µU/mL, which was mildly elevated. Magnetic resonance imaging pituitary showed multilobulated sellar lesion measuring 1.4 cm × 1.0 cm × 1.7 cm with a small area of hyperintensity signal on T1/T2 sequence measures 0.9 cm × 1.0 cm × 0.9 cm (shown in Figs. 1, 2). Magnetic resonance imaging of whole spine otherwise demonstrated mild spinal canal narrowing with no abnormal signal intensity or enhancement of cord.

Hydrocortisone (intravenous 50 mg 3 times a day for 24 h and then oral 20 mg 3 times a day) was initiated, and the response was monitored as an inpatient over 1 week. Levothyroxine was added 4 weeks later (25 and 50 µg/day). He was referred to a physiotherapist.
for lower limb mobility exercises. Hydrocortisone dose was tapered to 15 mg/day after 2 weeks, and he was started on testosterone replacement (testosterone enanthate 250 mg injection thrice weekly) for hypogonadism. Lower limb stiffness and truncal instability improved after 1 week of hydrocortisone replacement, and he was able to ambulate without aid with no further falls. Repeated examination showed normal tone in both lower limbs, and power recovered to full strength in both extensors and flexors. Reflexes were normal. Hypoglycaemia symptoms resolved. He was ambulant at 3 and 6 months, with no further complaints. Rigidity resolved, and neurological examination of lower limbs remained normal. Haemoglobin normalized to 13.5 g/dL and thyroid function was in euthyroid range (free T4 12.1 pmol/L).

Fig. 1. T1-weighted sagittal (a) and coronal section (b) of MRI brain showing multilobulated sellar lesion giving rise to 'snowman appearance' (yellow arrow) and largest diameter of 1.7 cm. This features suggestive of pituitary macroadenoma. MRI, magnetic resonance imaging.

Fig. 2. T2-weighted sagittal (a) and coronal section (b) of MRI brain. There is a small area of hyperintensity in anterior pituitary (yellow arrow). The largest diameter is 1.0 cm. MRI, magnetic resonance imaging.
Discussion/Conclusion

The above case illustrates hypopituitarism manifesting as neuromuscular symptoms. SPS is a rare condition defined as progressive rigidity of axial muscles that result in severe impairment of ambulation [1]. The causes include autoimmunity and paraneoplastic syndrome. There is an association between glutamic acid decarboxylase (GAD) autoantibodies in serum and cerebral spinal fluid with SPS [1]. GAD antibodies are used as markers for GABAergic neurons and their terminals since the antibodies appear localized in the nerve terminal. The presence of anti-GAD antibodies reduced GABA production in crude rat cerebellar extracts. Loss of GABA results in reduced neural inhibition, thus leading to muscle rigidity. Other autoimmune diseases often coexist in SPS, such as type 1 diabetes, Hashimoto’s thyroiditis, Grave’s disease, vitiligo, and adrenal insufficiency [2].

On the contrary, panhypopituitarism, specifically hypocortisolism, can manifest as a neuromuscular illness like SPS. There is predilection for lower limb rigidity, causing flexion deformity and pain. Occasionally, it involves abdominal muscles and upper limbs [3]. Chroni et al. [4] reported a case of occult pituitary deficiency due to postpartum haemorrhage presenting with painful muscle stiffness and spasm that responded to glucocorticoid replacement. Similarly, a Japanese patient with progressive stiffness for 3 years after postpartum haemorrhage was found to have hypopituitarism [5]. Therefore, it was postulated that the cause of muscle stiffness is hyponatraemia and hypocortisolism, unlike in typical SPS [3]. The pathophysiology revolves around glucocorticoid deficiency, which reduces membrane Na-K-ATPase activity and eliminates beta-adrenergic stimulation of the Na-K pump. Glucocorticoids are necessary for maintenance of muscles’ metabolic function and energy metabolism. In addition, it has immunosuppressive effects on the muscles [3].

It is important to differentiate adrenal insufficiency-associated rigidity from SPS. In SPS, rigidity involves both flexion and extension, and limbs are held in extension. Adrenal insufficiency-associated rigidity predominantly causes flexion deformities. There are no specific biochemical test and radiological and neurophysiological study such as electromyography to confirm the condition. Cerebrospinal fluid and muscle biopsy are non-specific. In adrenal insufficiency-associated rigidity, the response is poor to muscle relaxants, whereas a typical SPS shows general improvements. Most cases improve after starting corticosteroid replacement, and symptoms may resolve over time [4, 5]. Cortisol replacement is postulated to act via hormonal correction rather than immunomodulation effects as the replacement dose was low [4]. Although central hypothyroidism does coexist in panhypopituitarism, and there were reports of muscle stiffness with hypothyroidism [6], this patient’s stiffness resolved with hydrocortisone therapy alone.

Treatment delay often leads to slower recovery. Typically, muscle spasm resolution is within days, but recovery can be protracted. Due to late diagnosis, contracture takes a longer time to resolve [3, 5–7]. In addition, contracture can relapse with corticosteroid withdrawal [8]. In the case illustrated above, panhypopituitarism was diagnosed due to a myriad of symptoms and signs of adrenal insufficiency and hydrocortisone were replaced early. Hence, recovery occurred within the first week of treatment with no neurological sequelae detected during the follow-up. Adrenal insufficiency and hypothyroidism resolved after hormonal replacement. Therefore, it is imperative to recognize adrenal insufficiency-associated rigidity and initiate hormonal replacement early to increase recovery and prevent long-term neurological sequelae.

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Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance to local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.G. is the primary physician of the patient and wrote the first draft. A.H.K.Y.K. contributed to part of the manuscript. A.N. edited and approved the final draft and supervised the overall management of the case.

Data Availability Statement

No datasets were generated or analysed during the current study. All information is provided within the manuscript.

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