# Hypopituitarism presenting with features of stiff person syndrome

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## Introduction

- Stiff person syndrome[1] (SPS) is a progressive neurological disorder characterised by fluctuating stiffness, rigidity and spasms in both axial and limb muscles along with a heightened sensitivity to stimuli 1. Stiff Leg Syndrome, an SPS variant mainly affecting limb muscles, is emerging as a distinct identity.
- SPS is associated with type 1 diabetes mellitus, thyroiditis, vitiligo, pernicious anaemia, myasthenia gravis, malignancy, epilepsy and cerebellar ataxia. There are a few reported cases of hypopituitarism presenting with features suggestive of SPS. [2-4]

## Case

- A 66-year-old woman presented to the neurologists with a 12-month history of lower back pain & progressive stiffness, spasms and painful cramps involving the lower limbs.
- Sudden worsening of symptoms led to admission as she was barely able to walk. She had been experiencing migrainous headaches. Cranial nerve and upper limb examination were normal. Lower limb examination showed resistance to passive movements, power was normal but limited by pain, reflexes were brisk and planters were equivocal. Continuous muscle activity was noted over the medial thighs bilaterally.
- A diagnosis of possible SPS was made and regular benzodiazepines were commenced. Extensive investigation ruled out other neurological disease and conditions associated with SPS (table 1).
- Endocrine assessment showed TSH and gonadotrophin deficiency (table 2) along with minimal pituitary enlargement on MRI.
- EMG was normal and anti-GAD antibodies were negative (Table 3).
- Her symptoms improved significantly and she was walking almost independently. Benzodiazepines were stopped pending the EMG and she became unwell with nausea and recurrence of cramps. These persisted despite re-introduction of benzodiazepines.
- She became hyponatraemic, hypoglycaemic and mildly hypotensive. IV fluids and hydrocortisone were commenced with a dramatic clinical improvement.
- A short synacthen test (SST) was normal and urinary sodium low, consistent with salt and water deficiency. Hydrocortisone was therefore stopped.
- After 2 weeks of hospitalization and improved mobility on benzodiazepines she was discharged. Thyroxine was commenced and endocrine review arranged.
- A random cortisol in clinic 8 weeks later was low at 74nmol/l. Hydrocortisone was recommenced and a repeat SST followed by a Glucagon Stimulation Test showed a sub-optimal response suggestive of partial ACTH deficiency (Table 2).

- Regular hydrocortisone was weaned down and stopped, with advice to take steroids during intercurrent illness. Within 4 days of stopping treatment her symptoms recurred and mobility worsened. There was no response to baclofen and increased benzodiazepines.
- Recommencement of hydrocortisone replacement resulted in a dramatic resolution of symptoms. Three months later she remains in remission with normal mobility.

## Investigations

**Table 1 – Blood and CSF results**

| Test | | Result |
|---|---|---|
| Haematology | Full Blood Count | Normal |
| | ESR | 60 |
| Biochemistry | U & E 's | Normal except Na (132/117/121/134/139) |
| | LFT/Bone Profile/CK | Normal |
| Connective Tissue and Auto- Antibodies Screen | ANA, ANCA, RA, Complement | Normal |
| | ACE | 101 |
| | Anti-GAD Antibodies | Normal (< 5 ) |
| | Paraneoplastic Antibodies- Hu, Yo, R, Ma2, CV2, Amphiphysin | Negative |
| | Potassium Channel Ab | Negative |
| Immunoglobulins and Serum Paraprotein | IgG, IgA, IgM | Normal |
| | Paraprotein | Weak Monoclonal IgG kappa |
| CSF Analysis | • Routine – NAD and no malignant cells<br>• Pattern 2 Oligoclonal IgG band in CSF & Polyclonal IgG in serum | |

**Table 2 - Endocrine assessment**

| Pituitary Profile | | | | | | | |
|---|---|---|---|---|---|---|---|
| TFT's | TSH (0.35-5.00miu/L) | 3.86 | | | | | 3.11 |
| | fT4 (11-23 pmol/L) | 5.8 | | | | | 6.9 |
| Prolactin (<496 mU/L) | | 512 | | | | | 408 |
| FSH (IU/L) | | 3.5 | | | | | 3.2 |
| LH (IU/L) | | 0.8 | | | | | 0.8 |
| IGF-1 (6-22) nmol/L | | 6 | | | | | 9 |
| Urine Analysis | Osmolality (mmol/kg) | 170 | | | | | |
| | Sodium (mmol/L) | 14 | | | | | |
| Random Cortisol (nmol/L) | | 241 | | | | | 74 |
| Short Synacthen Test (SST) - Cortisol (nmol/L) | Time | 0' | | 30' | | | 60' |
| | In-Patient | 435 | | 735 | | | 863 |
| | Out-Patient | 188 | | 431 | | | |
| Glucagon Stimulation Test | Time | 0' | 60' | 120' | 150' | 180' | 210' | 240' |
| | Cortisol (nmol/L) | 293 | 302 | 285 | 278 | 267 | 303 | 426 |
| | GH (ug/L) | - | 0.14 | 014 | 0.15 | 0.21 | 0.40 | 0.23 |

**Table 3 - Radiological investigations and neurophysiology**

| | |
|---|---|
| MRI Brain | • Minimal pituitary enlargement without any focal abnormality<br>• No structural brain abnormality |
| MRI Spine | • No spinal cord compression<br>• Central disc portions - D4/5, D5/6<br>• No intrinsic cord abnormality |
| CT – Thorax/Abdomen/Pelvis | • No evidence of malignancy |
| PETCT (18FDG ) SCAN | • No evidence of malignancy<br>• Increased uptake in the right tonsil |
| Electromyography (EMG) | • No characteristic abnormalities seen.<br>• Not possible to sample adductor muscles as patient was unable to lie on her back with legs extended |
| Nerve Conduction Study (NCS) | • Incidental asymptomatic generalised sensory neuropathy<br>• Mild to moderate Carpal Tunnel Syndrome |

## Discussion

- The diagnosis of SPS is based on characteristic clinical features, supported by the presence of anti-GAD antibodies and continuous motor-unit activity on EMG.[5]
- Our patient's history, examination findings and response to benzodiazepines were suggestive of SPS even though the stiffness was confined to the legs & anti-GAD antibodies were negative[6] (can be absent in 40% of cases). Although EMG was negative the muscles of interest (adductors) could not be assessed.
- Complete resolution of neuromuscular symptoms with hydrocortisone in our case, as well as in a few previously reported cases,[2-4] has led to the suggestion that presentation of hypopituitarism with a syndrome like SPS is a rare but recognised entity.
- The pathogenesis of SPS is unclear, although an autoimmune aetiology is suspected.[6]
- The role of cortisol deficiency in the pathophysiology needs to be elucidated further. Glucocorticoids have a role in maintaining metabolic function within muscles. The features of SPS in our patient could simply represent the musculoskeletal manifestations of cortisol deficiency.[7]
- Thus, we describe a case of hypopituitarism (GH, gonadotrophin, TSH and partial ACTH deficiency) presenting in a patient with clinical features suggestive of SPS. Despite a favourable initial response to GABA-enhancing drugs, a lasting clinical remission was only achieved with hydrocortisone replacement therapy.
- Appropriate endocrine evaluation and pituitary hormone replacement may alleviate the significant morbidity associated with this condition

**References:**

1. Moersh FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome): report of a case and some observations in 13 other cases. Mayo Clin Proc. 1956; 31:421-7.
2. Lee MT, Lee TI, Won JG, Chau WK, Yang HJ, Li JC, Lin HD, Tang KT. Primary hypothalamic lymphoma with panhypopituitarism presenting as stiff-man syndrome. Am J Med Sci. 2004 Aug; 328(2):124-8.
3. George TM, Burke JM, Sobotka PA, Greenberg HS, Vinik AI. Resolution of stiff-man syndrome with cortisol replacement in a patient with deficiencies of ACTH, growth hormone, and prolactin. N Engl J Med. 1984 Jun 7; 310(23):1511-3.
4. Chroni E, Papadimitriou A, Avramidis T, Terentiou AE, Tzioras C, Divari R. Stiff-person like syndrome in a patient with multiple pituitary hormone deficiencies. Acta Neurol Scand. 2000 Dec;102(6):403-5.
5. Lorish TR, Thorsteinsson G, Howard FM Jr. Stiff-man syndrome updated. Mayo Clin Proc. 1989; 64:629-36.
6. Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, Vicari AM.Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med. 1988 Apr 21;318(16):1012-20.
7. Odagaki T, Noguchi Y, Fukui T, 2003 Flexion contractures of the legs as the initial manifestation of adrenocortical insufficiency. Intern Med 42: 710-713.

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