

# Panhypopituitarism and hereditary sensory autonomic neuropathy

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## Abstract

A 20 year old gentleman manifested with poor perception of pain since infancy, recurrent painless poorly healing trophic ulcers of finger and toes, reduced sweating and mild distal motor weakness. Electrophysiological studies revealed evidence of sensori-motor axonal neuropathy and absent sympathetic skin response. Nerve biopsy showed uniform loss of myelinated fibers. These are consistent with the diagnosis of hereditary sensory autonomic neuropathy (HSAN). The patient also had short stature and features of hypogonadism. Hormonal assay confirmed panhypopituitarism. The association of HSAN and panhypopituitarism has not been previously reported.

## INTRODUCTION

Degeneration predominantly affecting the peripheral sensory and autonomic neurons is well recognized and has been classified as the hereditary sensory autonomic neuropathies (HSAN).<sup>1</sup> This clinically and genetically heterogeneous group of neuropathies is uncommon in clinical practice and its manifestations are usually confined to the nervous system. Significant mortality and morbidity associated with impaired regulation of body temperature, and abnormal function of the endocrine system in HSAN type IV patients have been reported.<sup>2</sup> We report a patient with a rare association of HSAN and panhypopituitarism.

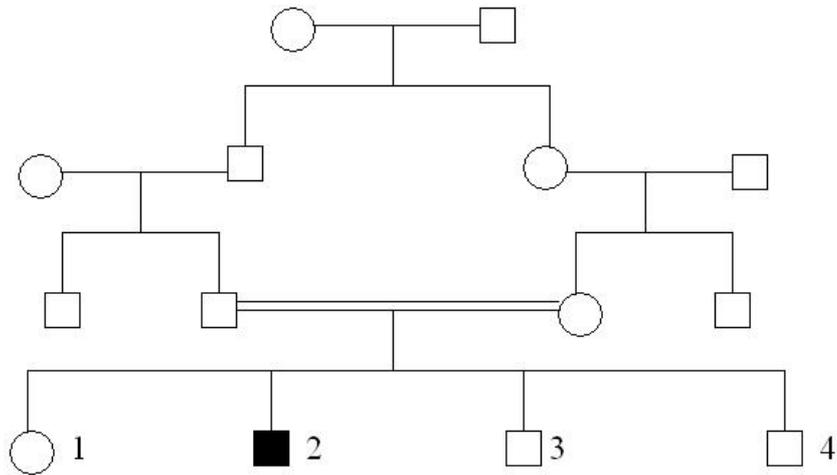
## CASE REPORT

A 20-year-old gentleman, born of third degree consanguineous parentage, presented with reduced pain sensation since infancy. From 10 years of age, he developed recurrent, painless and slowly healing ulcers over the soles and toes and later involving the fingertips. During the preceding 6 years, he had noticed auto-amputation of the toe digits. He also reported reduced sweating and frequent drying of the nasal cavity. His initial physical growth was normal, but there was no growth spurt during adolescence. He had poor development of secondary sexual features and libido. He was second of the four siblings. There was no history of similar illness in the family (Figure 1).

On examination, his anthropometrical measures were as follows: height - 137 cm, upper to lower body segment ratio - 1.1: 1, arm span - 129 cm, head circumference - 52 cm. Axillary, pubic and facial hairs were sparse, voice was high pitched and penis was infantile. He had multiple ulcerations over the dorsum and sole of the feet, and most of the digits of the hands and feet showed resorption with superadded infection (figure 2a). The skin was dry and cracked. No sweating was observed. There was no hyper or hypothermia, orthostatic hypotension, optic atrophy, retinal degeneration or deafness. He had hypotonia of all four limbs and mild weakness of the intrinsic muscles of hands. Both ankle jerks were absent while other tendon reflexes were normal. Plantar response was flexor bilaterally. He had graded and symmetrical sensory loss to pain, touch, vibration and proprioceptive sensations in the limbs, below the elbow and knee. Tests for autonomic dysfunction such as blood pressure at 60° tilt and cardiovascular responses to isometric exercise, respiration, cold pressor and mental arithmetic were normal. Quantitative sudomotor axon reflex test (QSART) was not carried out.

A complete hemogram and serum biochemical parameters including fasting blood glucose, hepatic and renal function tests, and serum electrolytes were normal. X-rays of the feet and hands showed resorption of phalanges, evidence of chronic osteomyelitis and osteoporosis (Figure 2c). X-rays of the elbow and wrist suggested a

Figure 1: Family pedigree of the patient



- 1: 22 years
- 2: 20 years, Index case
- 3: 18 years
- 4: 17 years

Figures 2a: Multiple ulcerations over the dorsum and sole of the feet and the digits with resorption of most of the digits of the hands and feet. 2b: X-ray hand showing delayed epiphyses around the elbow. 2c: X-ray foot showing eroded phalanges, chronic osteomyelitis and osteoporosis.



**Table 1. Hormonal assays**

| Hormone  | Patient's value | Normal range        |
|--|-----------------|---------------------|
| Growth hormone<br>(60 minutes after clonidine) | 4.9 ng/mL       | >10 ng/mL           |
| Cortisol<br>(60 minutes post ACTH)             | 18.6 mcg/dL     | >20 mcg/dL          |
| Follicle-stimulating hormone                   | 6.4 mIU/mL      | 1.4-18.1 mIU/mL     |
| Luteinizing hormone                            | 2.9 mIU/mL      | 1.5-9.3 mIU/mL      |
| Prolactin                                      | 2.8 ng/mL       | 2.1-17.7 ng/mL      |
| Testosterone                                   | 118 ng/dL       | 241-827 ng/dL       |
| Free Thyroxine (FT <sub>4</sub> )              | 0.9 ng/dL       | 0.89-1.76 ng/dL     |
| Total thyroxine (T <sub>4</sub> )              | 8.40 mcg/dL     | 4.5-10.9 mcg/dL     |
| Thyroid-stimulating hormone                    | 2.07 microIU/mL | 0.35-5.5 microIU/mL |

**Table 2: Nerve conduction parameters**

| Nerve  | Parameters | Control    | Right side        |
|--------|------------|------------|-------------------|
| Median | DL (ms)    | 2.6 ± 0.5  | 2.8               |
|        | CMAP (mV)  | 14.5 ± 3.4 | D - 7.8, P - 7.5  |
|        | CV (m/s)   | 58.7 ± 3.8 | 53.0              |
| Ulnar  | DL (ms)    | 2.0 ± 0.5  | 2.5               |
|        | CMAP (mV)  | 10.9 ± 2.6 | D - 10.6, P - 9.8 |
|        | CV (m/s)   | 59.9 ± 4.8 | 50.0              |
| CP*    | DL (ms)    | 3.6 ± 0.5  | 1.8               |
|        | CMAP (mV)  | 8.0 ± 2.9  | D - 3.3, P - 3.1  |
|        | CV (m/s)   | 51.2 ± 3.1 | -                 |
| Median | SNAP (uV)  | 29.8 ± 8.1 | Not Recordable    |
|        | CV (m/s)   | 59.4 ± 4.2 |                   |
| Ulnar  | SNAP (uV)  | 22.5 ± 6.7 | Not Recordable    |
|        | CV (m/s)   | 56.2 ± 4.1 |                   |
| Sural  | SNAP (uV)  | 21.5 ± 8.5 | Not Recordable    |
|        | CV (m/s)   | 48.8 ± 4.7 |                   |

D - distal, P - proximal, DL – distal latency, CMAP – compound muscle action potential, CV – conduction velocity, SNAP– sensory nerve action potential, ‘\*’– recorded over tibialis anterior.

bone age of 12 - 14 years, as the pisiform had appeared while epiphyses of lower end of humerus and upper ends of radius and ulna were unfused (Figure 2b). Endocrine evaluation revealed evidence for secondary adrenal insufficiency, secondary hypothyroidism, hypogonadotropic hypogonadism, growth hormone and prolactin deficiency (Table 1). MR imaging of the sellar

region was normal. There was no evidence of other systemic illnesses, and a metabolic screening was negative.

Nerve conduction study showed symmetric reduction of the amplitude of compound muscle action potentials (CMAPs), absent sensory nerve action potentials (SNAPs) and absent sympathetic skin response (SSR) from the palm and sole,

Figure 3: Sural nerve biopsy showing several fascicles with extensive and uniform nerve fiber loss, Masson's trichrome stain. Inset: Nerve fascicle with a lone surviving myelinated fiber (arrow)



suggestive of sensorimotor axonal neuropathy with sympathetic dysfunction. (Table 2) Nerve conduction studies were normal in the sibling. Biopsy of the left dorsal cutaneous branch of radial nerve showed extensive and uniform fiber loss in all the fascicles without evidence of active degeneration. There was no onion bulb formation. K-Pal staining showed extensive and uniform loss of both small and large myelinated fibres (Figure 3). Clinical, electrophysiological and histopathological features were suggestive of a sensory autonomic neuropathy and the age of onset and absence of other illnesses suggested the diagnosis of HSAN. Genetic analysis was not carried out.

The diagnosis of autosomal recessive HSAN (type 2) with panhypopituitarism was made. He was counseled about the illness and received extensive skin grafts for facilitating ulcer healing and was advised proper podiatric care. He was started on thyroxine supplements, prednisolone and testosterone. During his last follow up after 2 years, the ulcers had healed, but he had developed a chronic abscess of right foot.

## DISCUSSION

HSAN are phenotypically and genetically heterogeneous group of neuropathies. It has been classified, based on age of onset, natural history, and electrophysiological and histopathological observations.<sup>1</sup> Our patient had clinical features of sensory autonomic neuropathy manifesting as reduced pain appreciation from infancy, distal sensory loss, recurrent, painless poorly healing trophic ulcers of the distal extremities, chronic osteomyelitis and reduced sweating distally. Electrophysiological evaluation confirmed the presence of predominantly severe sensory-autonomic neuropathy and histopathology revealed uniform loss of myelinated fibers. Additional striking clinical and laboratory features were short stature and hypogonadism and panhypopituitarism. The clinical, electrophysiological and pathological features were consistent with HSAN II. HSAN I has an autosomal dominant inheritance, onset in 2<sup>nd</sup> or 3<sup>rd</sup> decade, and hence was not considered. HSAN III was excluded in view of autonomic

symptoms as its phenotype. HSAN IV was less likely due to absent SNAPS on nerve conduction studies, loss of large myelinated fibers on nerve biopsy, lack of febrile episodes and mental retardation. HSAN V was not considered because the patient has loss of large myelinated fibers and there was no insensitivity to pain.<sup>3</sup>

Patients with HSAN may have other associated nervous system manifestations like sensorineural deafness, spasticity and retinitis pigmentosa.<sup>1,2,4</sup> Association between pituitary failure and peripheral neuropathy has been described<sup>5</sup>, one syndrome being the Oliver Macfarlane syndrome, consisting of pigmentary retinal degeneration, trichomegaly, prenatal onset growth failure, anterior pituitary deficiencies and peripheral neuropathy.<sup>6</sup> However, HSAN associated with pituitary failure has not been described. A search of published literature did not find any report of an association between HSAN and panhypopituitarism.

HSAN type IV (HSAN IV) is caused by mutations in the Tyrosin kinase-A (TrkA) gene, encoding for the receptor of nerve growth factor (NGF), which is expressed in many endocrine glands. Loewenthal *et al* studied the basal endocrine system status of 31 patients of HSAN type IV. There were high rates of mortality (22%) and morbidity (30%) in patients with HSAN type IV. Their patients had hypothermia (40%), unexplained fever (56%), hypoadrenalism (30%) and lower plasma norepinephrine levels (30%). They emphasized the importance of NGF-TrkA pathway in the physiology of the neuroendocrine system and its response to stress. Inadequate response to stress might contribute to the observed significant mortality, morbidity, and temperature instability in HSAN IV patients.<sup>2</sup>

Growth hormone therapy has been shown to improve the height in a group of patients of familial dysautonomia, although these patients did not have growth hormone deficiency.<sup>7</sup> By identifying associated endocrinopathy in patients with HSAN, replacement therapy can be initiated and may have a trophic effect, in addition to improving physiological, psychological and sexual functions. The pathogenesis of HSAN is uncertain. It is postulated that in HSAN type 2, myelinated fibers are selectively affected and either do not develop or they prematurely degenerate.<sup>1</sup> However, panhypopituitarism as in our patient, may be a chance association rather than part of the underlying disease process.

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