

Hereditary Sensory and Autonomic Neuropathy Type IV- A Case Report

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Abstract

Hereditary sensory and autonomic neuropathy type IV or Congenital insensitivity to pain with anhidrosis is a rare disorder. It is an autosomal recessive disorder characterized by absence of small myelinated and unmyelinated sympathetic nerves resulting in pain and temperature insensitivity. There is also anhidrosis due to lack of innervations of sweat glands resulting in recurrent episodes of hyperpyrexia. Two cousins with history of insensitivity to pain and temperature with signs of self mutilation, recurrent episodes of febrile seizures, and corneal anaesthesia are reported.

Key words: Congenital pain insensitivity, Hereditary sensory autonomic neuropathy.

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Introduction

Hereditary sensory autonomic neuropathy type IV or Congenital insensitivity to pain with anhidrosis is an autosomal recessive disorder characterized by recurrent episodes of unexplained fever, failure to thrive, anhidrosis, insensitivity to pain, self mutilation and commonly associated with mental retardation. It is primarily due to lack of maturation of small myelinated and unmyelinated fibres of peripheral nerves which convey sensation of pain and temperature. So far only sixty cases have been documented in medical literature with very few cases reported in the India [1]. Two cousins born to second degree consanguineous parents with this syndrome are reported.

Case report

Case 1

One year old male child born to second degree consanguineous parents with history of no pain sensation to intramuscular injections. There were ulcerations of the finger tips as a result of the repeated episodes of finger chewing by the child and there were thermal injuries in the lower limbs. There is also a history of recurrent episodes of hyperpyrexia with seizures and anhidrosis. The child's development was normal for age. On examining the child there were signs of self mutilation in the form of ulcerations of the lower lip, tongue and oral mucosa and auto amputations of the finger tips and toes. (Fig-1A, B). On neurological examination, child was conscious with no cranial nerve deficit, with normal tone, power and reflexes and the fundus examination was normal. On sensory system examination there was absence of corneal reflex, the response to pinprick was severely limited and there was no response to temperature sensation. There were neither hypopigmented patches nor any thickened palpable nerves. Nerve conduction study was normal. Sympathetic skin testing response was absent. The crude bedside sweat test showed total absence of sweating and there was no postural hypotension. Skin biopsy showed normal sweat glands. The sural nerve biopsy suggested absence of small sympathetic myelinated and unmyelinated sympathetic nerve fibres consistent with the findings of hereditary sensory autonomic neuropathy of type IV. CT scan was done to rule out intracranial bleed and was normal. The haematological profile and serum uric acid level were normal.

Case 2

The second case was a two year old female child born to second degree consanguineous parents and cousin of the first case presented to our hospital with history of recurrent episodes of hyperpyrexia with seizures, insensitive to painful stimulation and absence of sweating. There were signs of self mutilation in the form of ulceration of oral mucosa and of finger tips. There was also ulceration of the knee, scar marks over the hand and auto amputation of the thumb (Fig 2 A, B). There was no family history of seizure disorder and the developmental milestones were normal for age. On physical examination child was conscious, normotensive with stable vitals with mild pallor. On neurological examination, the tone and reflexes were normal. The sensory system examination showed absence of response to painful stimulus and temperature. There was corneal anaesthesia without any ulceration. The nerve conduction velocity was normal. The crude



1A



2A



1B



2B

Figure 1: Clinical photograph showing ulceration of thumb (A) and autoamputation of toe (B) in case 1

Figure 2: Clinical photograph showing auto amputation of thumb (A) and ulceration over knee (B) in case 2

Sweat test showed the absence of sweating and the sympathetic skin stimulation test was negative. Skin biopsy showed normal sweat glands. Sural nerve biopsy showed absence of small myelinated and unmyelinated sympathetic nerve fibres, which is consistent with hereditary sensory neuropathy type IV.

Discussion

Since the two children had insensitivity to pain and temperature with anhidrosis and recurrent episodes of febrile seizures the diagnosis of hereditary sensory and autonomic neuropathy type IV was made. It has been suggested that the clinical signs of this disorder are related to peripheral sensory nerves. The syndrome was classified by Dyck and Ohta [2]. Hereditary sensory and autonomic neuropathies (HSAN) are characterized by congenital insensitivity to pain, temperature changes and autonomic nerve formation disorders and are of five types: Sensory radicular neuropathy (HSAN type 1), Congenital sensory neuropathy (HSAN type II), Familial dysautonomia or Riley Day syndrome (HSAN III), Congenital insensitivity with pain and anhidrosis (HSAN IV) and Congenital insensitivity to pain (HSAN V).

Congenital insensitivity with pain and anhidrosis (HSAN IV) was first reported by Nishida et al in 1951 [3]. It is caused by mutation in the neurotrophic tyrosine kinase receptor type 1, NTRK1 and TRKA gene. Mutations in the TRKA gene correlate with the signs and symptoms in these patients. This gene is located on the Chromosome 1q and contains 17 exons and 16 introns [4].

It has been considered to be a developmental disorder where the peripheral sensory nerve fibres concerned with pain and temperature are not formed. Rafael et al [5] reported a case of a nine year old girl with pain insensitivity and the

nerve biopsy suggested complete absence of small myelinated and unmyelinated nerve fibres. They suggested that the disorder is not hereditary sensory neuropathy, but rather a developmental defect. Ishii et al [6] described a Japanese girl with pain insensitivity, high fever and anhidrosis who died at the age of twenty one months. Courtney and Freenberg [7] described a patient to have Hereditary sensory and autonomic neuropathy type 4 but did not have developmental delay. Yagev et al [8] studied fifteen Bedouin children with congenital pain insensitivity syndrome with anhidrosis and found all of them to have lack of corneal sensation and out of which ten of them developed corneal opacities. Bonowsky et al [9] studied a one year old male with congenital pain insensitivity with anhidrosis whose diagnosis was confirmed by molecular analysis. The clinical features included an abnormally high pain threshold, normal nerve conduction and the absence of epidermal and sweat gland innervations in skin biopsy.

We report two cousins presenting with history of pain insensitivity, corneal anaesthesia, febrile seizures and signs of self mutilation. Both the cases showed absence of sweating which was perhaps accounting for the recurrent episodes of hyperpyrexia. We did crude sweat test which showed absence of sweating and the sympathetic skin test was negative. Serum uric acid and liver function tests were normal. Sural nerve biopsy demonstrated uniform loss of small sympathetic myelinated and unmyelinated nerve fibres which is consistent with hereditary sensory autonomic neuropathy type IV.

Navajo community in United States have also reported cases with pain insensitivity with self mutilation with corneal anaesthesia similar to our case but most of their cases on follow up developed severe hepatopathy [10]. Though no disorder exactly mimics hereditary sensory autonomic neuropathy, impairment of pain sensation and oral mutilation have been reported in some syndromes such as Lesch Nyan syndrome, Tourette syndrome and de Lange syndrome. In our patients, even though there were signs of self mutilation the other features associated with these syndromes were absent. Absence of nail and hair abnormalities and presence of normal sweat glands on skin biopsy exclude the diagnosis of anhidrotic ectodermal dysplasia.

Hereditary Sensory and autonomic neuropathy type IV is a rare developmental disorder due to lack of sensory nerve fibres responsible for the sensation of pain and temperature. An early diagnosis is of paramount importance in order to prevent severe life threatening injuries.

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