CASE REPORTS

A Child Presenting with Recurrent Corneal Ulcers: Hereditary Sensory and Autonomic Neuropathy IV (HSAN IV)

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ABSTRACT

Hereditary Sensory and Autonomic Neuropathy IV (HSAN IV) or Congenital Insensitivity to pain and Anhidrosis is an autosomal recessive condition. It is characterized by absence of reaction to painful stimuli, anhidrosis, self-mutilating behaviour and episodic fever. We report a child with HSAN IV who presented primarily with recurrent corneal ulcers and the classical history helped us clinch the diagnosis. Molecular testing revealed a homozygous pathogenic frameshift mutation in *NTRK1* c.717delG, p.(Met239fs). Molecular testing is confirmatory and this will help the family in future prenatal diagnosis.

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Introduction

Corneal ulcers that develop due to decrease or absence of corneal sensation are called neurotrophic corneal ulcers. These ulcers can be due to systemic illness, ocular disease, congenital or iatrogenic diseases that lead to damage to the fifth cranial nerve, which is responsible for corneal innervation.¹ Among the congenital causes, hereditary sensory and autonomic neuropathies (HSAN) forms an important group which should be considered especially when the patient presents with recurrent corneal ulcers and systemic manifestations.

HSAN are a group of inherited peripheral neuropathies primarily affecting the peripheral sensory and autonomic neurons. Sensory neuropathy leads to chronic ulcers of hands and feet, corneal ulcers and arthropathy. Autonomic dysfunction leads to manifestations like anhidrosis and fever.^{1,2} Here we present a child with HSAN IV with corneal ulcers and subsequently confirmed by molecular testing.

Case history

TM is the second child of a nonconsanguineous couple. He was brought to us at 10 months for evaluation of suspected ectodermal dysplasia. TM was a healthy boy born at term by LSCS with a birth weight of 3 kg

with a good birth cry. On day three of life neonate had refusal of feeds, high temperature and lethargy. He was treated for fever and discharged on day nine of life. Subsequently his milestones and development were age appropriate. Child has recurrent respiratory infections, recurrent corneal ulcers and several febrile episodes. He was also noted to have decreased sweating and skin biopsy from scalp was done elsewhere which revealed small adnexal glands and absence of sebaceous glands. Hair follicles contained small hair shafts. Hence the diagnosis of anhidrotic ectodermal dysplasia was reported.

At evaluation the child was 10 months and he weighed 7 kg (just below the third centile). Length was 70 cm (third centile) and he could stand with support and say a few bisyllable words. Development was appropriate for age. He was irritable with definite signs of pain insensitivity and self-mutilation in the form of healing ulcers on the dorsum of index finger and corneal ulceration (Figure 1 and 2).

There was anhidrosis and serum uric acid levels were normal (2.7 mg/dl range 1.4–6.7), ruling out Lesch Nyhan syndrome. His nerve conduction studies revealed that the sensory responses were smaller in amplitude but otherwise normal. Hence the provisional diagnosis

Table 1. Salient features of various HSAN. ^{5,6,7}

	HSAN 1	HSAN2	HSAN3	HSAN4	HSAN5
Inheritance	Autosomal Dominant	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Age of onset	Second decade	Infancy	Birth	Birth	Birth
Insensitivity to pain	++	++	+	++	+
Sweating	Normal	Normal	Decreased	Decreased (widespread)	Normal
Ophthalmic manifestation	Not reported	Slow blink reflex	Alacrima and corneal anaesthesia	Corneal anaesthesia	Corneal anaesthesia
Mental retardation	-	-/+	+	++	±
Muscle hypotonia	Absent	Absent	+	Absent	Absent
Biopsy	Loss of UF > MF	Absent MF	Reduced UF	Absent UF	Absent/small MF
Genes	<i>SPTLC1</i> , <i>SPTLC2</i> , <i>ALT1</i> , <i>DNMT1</i>	<i>WNK1</i> , <i>RETREG1</i>	<i>IKBKAP</i>	<i>NTRK1</i> , <i>PRDM12</i> ⁶	<i>NGF B</i> , <i>NTRK1</i>

Notes. UF – Unmyelinated fibres, MF – Myelinated fibres, AR – Autosomal recessive, AD – Autosomal Dominant

Figure 1. Bilateral corneal opacities. **Figure 2.** Healing ulcers on the dorsal aspect of index finger.

was HSAN IV or Congenital Insensitivity to Pain and Anhidrosis. In view of recurrent corneal ulcers he underwent a detailed ophthalmological evaluation and was noted to have neurotrophic keratitis with decreased corneal sensation. He was treated with 0.3% Tobramycin eye drops 3 hourly, atropine eye drops and carboxymethyl cellulose eye drops 0.5%w/v for a week and the ulcers healed with a resultant corneal opacity. Subsequently the child presented with recurrence of corneal ulcers and underwent bilateral lateral tarsorrhaphy which had reduced the frequency of his corneal ulcers.

Molecular testing revealed that the child was homozygous for pathogenic frameshift mutation *NTRK1* c.717delG, p. (Met239fs) and the parents

are heterozygous for the same mutation, thereby confirming the diagnosis of **HSAN IV**.

Discussion

Hereditary sensory and autonomic neuropathy type IV (HSAN IV), also called as congenital insensitivity to pain with anhidrosis (CIPA) or Nishida syndrome, is an autosomal recessive disorder characterized by recurrent episodic fevers, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behaviour and mental retardation. HSAN IV is due to the absence of afferent neurons, which are activated by tissue-damaging stimuli. Nerve growth factor (NGF) supports the survival of nociceptive sensory and autonomic sympathetic neurons as well as cholinergic neurons of the basal forebrain. Defects in NGF signal transduction at its receptor leads to failure of neuronal survival. ²⁻⁴

The human Neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) gene located on chromosome 1 (1q21-q22) encodes a receptor tyrosine kinase (RTK) which is autophosphorylated in response to NGF. *TRKA* mutations are distributed in extracellular domain and intracellular signal-transduction domain. ⁵

The HSANs were classified into five types by PJ Dyck based on age of onset, mode of inheritance, clinical features, electrophysiological findings and pathology (Table 1).

HSAN 4 is the second most common HSAN. Characteristic features of HSAN 4 are repeated episodes of pyrexia due to anhidrosis, severe mutilation, non-healing ulcers and mental retardation. ^{2,7} Our

child presented with recurrent corneal ulcers. Because of the characteristic pain insensitivity and anhidrosis we were able to narrow down on the diagnosis based on clinical features. According to a study by Jarade et al. among 52 patients with HSAN 4, only 14 had corneal involvement.⁸

Absence of pain perception leads to self-mutilating behaviour especially involving the finger tips, tongue and corneal ulcers. Sural nerve biopsies from HSAN4 patients reveal that unmyelinated fibres are absent. These fibres characteristically transmit pain. Skin biopsy from these patients reveals deficient C and A δ fibres in the epidermis and hypoplastic dermal sweat glands without innervation.⁹ This accounts for the severe anhidrosis. Hypotonia and delayed development have been reported in literature but our patient had normal tone and appropriate development for age. The patient reported by Prasanth et al. also had normal development.¹⁰

Ophthalmic findings in HSAN 4 include superficial punctate keratopathy, corneal ulcers and corneal opacity. Tear break up time was also noted to be lower. Hence these children will benefit by care for dry eyes, prevention of corneal infection and daily observation of the ocular surface to maintain good visual function.^{11,12}

Most treatment options for HSAN 4 aim at treating the associated comorbidities. However Naloxone has been shown to reverse analgesia in some patients. Naloxone is an opioid receptor antagonist and has been shown to lower the thermal and mechanical nociceptive threshold.¹³ Though Naloxone has been reported to be of benefit in HSAN4, as the exact dose and details were not available, we have not started it in our patient. In order to prevent self-mutilation full mouth teeth extraction can be tried or alternately customised bite guards can be provided.¹⁴

Thus HSAN 4 should be one of the differential diagnosis in patients who present with insensitivity to pain, hyperpyrexia or recurrent corneal ulcers. Sometimes there may be suspicion of ectodermal dysplasia in young children due to presence of widespread anhidrosis and it is important to look for self-mutilation, pain insensitivity and corneal ulcers to clinch the diagnosis of HSAN IV. Though other types of HSAN may have overlapping features, the clinical diagnosis is based on the fact that HSAN 4 is the only HSAN that is associated with widespread anhidrosis.

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