Sisters with No Pain, No Tears: A Report of a New Variant of Hereditary Sensory and Autonomic Neuropathy (Type IX) Caused by a Novel SCN11A Mutation

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Abstract
Lack of pain sensation in children involves a rare group of heritable disorders; hereditary sensory and autonomic neuropathy (HSAN). Till date, eight types of HSAN have been described depending on the clinical phenotype and the underlying gene mutation. We report a new variant of HSAN (Type IX) in two siblings (of Indian origin) with a novel mutation of SCN11A gene and a distinct clinical phenotype.

Key Words: Anhidrosis, hereditary sensory and autonomic neuropathy Type IX, insensitivity to pain, SCN11A gene

Introduction
Hereditary sensory and autonomic neuropathy (HSAN) is a genetic disorder of sensory and autonomic dysfunction. Till date, eight types of HSAN have been described depending on the clinical phenotype and the underlying gene mutation.[1,2] We report a new variant of HSAN in two siblings (of Indian origin) with a novel mutation of SCN11A gene and a distinct clinical phenotype.

Case Report
Two sisters (aged 6 and 3 years) born of a nonconsanguineous marriage presented with absence of pain sensation and sweating since birth along with redness over the body on heat exposure, recurrent febrile episodes, dry mouth, and decreased tears. The elder child complained of recurrent episodes of mild abdominal pain. History of celiac disease and hypothyroidism was present in the paternal cousin sister. There was no evidence of mental retardation, self-mutilating behavior, developmental delay, or history of recurrent infections. Superficial and deep pain sensations were absent over the entire body, while touch, temperature, pressure, and vibration sensations were normal. Tendon reflexes and muscle power in both the upper and lower limbs were normal. Erythema was present on the bilateral malar areas in both children [Figure 1a]. On oral examination, overcrowded, dysplastic teeth, and malocclusion with dental caries were present [Figure 1b]. Xerophthalmia was evident with positive Schirmer's test. Electromyography (EMG) and nerve conduction velocity (NCV) studies of both sisters showed impaired sympathetic skin responses from both the hands and feet, suggestive of small fiber neuropathy or autonomic dysfunction. Biopsies from the palms of both sisters showed sweat ducts but mostly absent secretory portion of eccrine glands. Intelligence quotient of both girls was normal. Anti-Ro and anti-La antibodies and transglutaminase antibodies were negative.

Based on the clinical features and preliminary investigations, the diagnosis of HSAN with idiopathic non-Sjögren Sicca Syndrome-like symptoms was considered. Targeted gene sequencing in elder sister
detected a heterozygous missense variation (c.4064G>T [p.Cys1355Phe]) in exon 25 of SCN11A (chromosome 3:38892235; C>C/A; Depth: 41x) with autosomal dominant inheritance, resulting in substitution of phenylalanine for cysteine at codon 1355 (p.Cys1355Phe; ENST00000302328). Younger sibling and father also showed the same heterozygous missense variation in exon 25 of SCN11A. However, the father was asymptomatic with normal EMG and NCV studies. Genetic analysis of mother was normal. Parents were counseled to prevent both sisters from high-impact activities and extreme temperatures. Soft-sole footwear for the prevention of trophic changes, lubricant eye drops, and professional dental care were advised.

Discussion

In 1993, Dyck provided a detailed classification of HSAN based on the clinical features. The classification has been modified subsequently based on causative genes and identification of new types. The types of HSAN with their clinical features, genetic defect, and mode of inheritance are listed in Table 1. This heterogeneous group of disorders can arise through (i) congenital absence or a progressive degeneration of sensory and/or autonomic neurons (neuropathy) or (ii) altered function of voltage-gated sodium channels (Na\(_{1.7}\) and Na\(_{1.9}\)) within normal sensory neurons (channelopathy).

The neuropathies are caused by a variety of genes affecting neurotrophic functions (neurotrophic receptor tyrosine kinase-1 and nerve growth factor), sphingolipid metabolism (SPTLC1 and SPTLC2), structural integrity of the endoplasmic reticulum (ATL1) and Golgi apparatus (FAM134B), vesicular trafficking (KIF1A), and epigenetic regulator expressed in nociceptors (PRDM12).

Voltage-gated sodium channels in cell membranes are essential for initiation and propagation of action potentials in neurons. Ten such channels (Na\(_{1.1-1.9}\) and Na\(_{2.1-2.4}\)) which are encoded by genes SCN1A-SCN5A and SCN7A-SCN11A have been discovered till date. Defects in Na\(_{1.7}\), Na\(_{1.8}\), and Na\(_{1.9}\) encoded by SCN9A, SCN10A, and SCN11A, respectively, have been reported to cause pain disorders.

Na\(_{1.9}\) is expressed in peripheral sensory, trigeminal and dorsal root ganglia, and enteric plexus. The main function of Na\(_{1.9}\) is to transmit pain signals from the periphery to the central nervous system. It consists of a 260-kDa \(\alpha\)-subunit and an auxiliary \(\beta\)-subunit. Each \(\alpha\)-subunit consists of six \(\alpha\)-helical transmembrane-spanning segments (S1–S6). S1–S4 segments form the voltage-sensing domain that controls voltage-dependent gating while S5–S6 segments form the pore domain which conducts selective sodium filtering.

SCN11A gene (chromosome 3), which encodes Na\(_{1.9}\), has 26 exons that annotate 31 domains. Gain-of-function mutations in SCN11A have been reported to cause loss of pain sensation (HSAN VII) as well as the severe paroxysmal pain disorder (familial episodic pain syndrome 3). These seemingly contradictory consequences of similar mutations are explained by the impact on resting membrane potential (RMP), wherein large depolarizations of RMP caused by some mutations are associated with hypoexcitability (insensitivity to pain, HSAN VII), whereas lesser degrees of membrane depolarization caused by other Na\(_{1.9}\) mutations are associated with hyperexcitability (familial episodic pain disorder).

Till date, HSAN VII has been reported to be caused by two heterozygous missense mutations in SCN11A; (1) c.2432T>C (p.Leu811Pro) in exon 15 and (2) c.3904C>T (p.Leu1302Phe) in exon 23. These gain-of-function mutations result in excess sodium influx, and subsequent cell depolarization at rest may cause progressive conduction block in other ion channels. Insufficient activation of calcium ion channels results in impaired neurotransmitter release at presynaptic nerve terminals resulting in nontransmission of pain signals to the spinal cord.

Apart from congenital sensitivity to pain, Type VII HSAN clinical phenotype comprises severe self-mutilation, multiple painful fractures, delayed motor development, and hyperhidrosis. None of these were present in the present cases. Possibly, the novel mutation in SCN11A might have caused a different structural alteration in the Na\(_{1.9}\) channel resulting in hypohidrosis, alacrimia, lack of salivary secretion, a much lesser severity of sensory dysfunction, and lack of any developmental delay. Thus, we propose this hitherto undescribed phenotype of HSAN with non-Sjögren sicca syndrome-like symptoms (alacrimia and dry mouth) and a novel mutation (p. Cys1355Phe) of SCN11A to be a new type of HSAN, i.e., HSAN Type IX. Another notable feature in this family is the incomplete penetrance of the mutation with the father having virtually no symptoms despite carrying the same mutation.

This case report highlights the variability of phenotypes and penetrance in HSAN, variability of phenotype in...
### Table 1: Classification of HSAN based on age of onset, mode of inheritance, clinical presentation and their genetic background

| Types of HSAN | Gene/locus and mode of Inheritance | Pathogenic defect | Onset | Impairment of sensation | Sweating | Clinical characteristics |
|---------------|-----------------------------------|-------------------|-------|-------------------------|----------|--------------------------|
| I-A           | AD SPTLC1/9q22.31                 | Serine C-palmitoyl transferase deficiency; formation of atypical and neurotoxic sphingolipid metabolites | Adolescence to adulthood | Loss of pain and temperature sensation, lancinating pain | Normal | Hearing loss, loss of distal reflexes/distal muscle weakness, (no autonomic dysfunction) |
| I-B           | AD SPTLC1/3p24-p22               | Serine C-palmitoyl transferase deficiency; formation of atypical and neurotoxic sphingolipid metabolites | Adulthood | Sensory loss, lancinating pain | Normal to mild distal hypohidrosis | Chronic cough, gastropharyngeal reflux, hearing loss, alacrima, impotence |
| I-C           | AD SPTLC2/14q24.3                | Serine C-palmitoyl transferase deficiency; formation of atypical and neurotoxic sphingolipid metabolites | Adulthood | Loss of pain, lancinating pain, loss of temperature sensation in parts of the body, sensory loss in the upper and lower limbs | Normal | Ulcerative mutilations, variable distal motor involvement, distal muscle weakness, osteomyelitis |
| I-D           | AD ATL1/14q22.1                  | Atlastin-1 Endoplasmic reticulum | Adulthood | Distal sensory loss of the lower limbs | Normal | Ulcerative mutilations, trophic skin and nail changes, distal amyotrophy in the lower limbs |
| I-E           | AD DNMT1/19p13.2                 | DNA methyltransferase 1 | Adulthood | Loss of all somatosensory modalities, lancinating pain | Normal | Ulcerative mutilations, hearing loss, dementia |
| I-F           | AD ATL3/11q13.1                  | Atlastin3:Endoplasmic reticulum structure altered | Adulthood | Distal sensory loss of the lower limbs | Normal | No autonomic involvement, diminished tendon reflexes, painless ulceration of the feet |
| II-A          | AR WNK1/12p13.33                 | WNK (With No lysine (K)) protein; Transmembrane ionic transport, vesicles of trans – golgi network | Childhood | Loss of pain, temperature and touch sensation, no autonomic dysfunction | Normal | Self-mutilation behavior resulting in extensive orofacial injuries, weakness, acropathy |
| II-B          | AR FAM134B/5p15.1                | Located in dorsal root ganglia, Golgi apparatus | Childhood | Impaired pain sensation | Hyperhidrosis | Ulcerative mutilation of hands, feet, and orofacial structures, osteomyelitis, urge incontinence |
| II-C          | AR KIF1A/2937.3                  | KIF1A (kinesin family) reduction in synaptic vesicles in nerve terminals | Childhood to adolescence | Impaired position and vibration senses | N/A | Ulcerative mutilation and orofacial injuries, absent deep tendon reflexes, minor distal weakness, distal numbness of the hands and feet |
| II-D          | AR SCN9A/2q24.3                  | Nav1.7 Reduced action potential firing in nociceptor neurons in DRG neurons | Infancy or adolescence | Loss of pain and temperature sensation, hypogeusia | Hypohidrosis | Autonomic nervous dysfunction, hearing loss, hyposmia, bone dysplasia, orofacial self-mutilation injuries |

Contd...
SCN11A mutations, and also the importance of the genetic mutation in designating appropriate classification of HSAN.

### Table 1: Classification of HSAN based on age of onset, mode of inheritance, clinical presentation and their genetic background

| Types of HSAN | Gene/locus and mode of Inheritance | Pathogenic defect | Onset | Impairment of sensation | Sweating | Clinical characteristics |
|---------------|-----------------------------------|------------------|-------|-------------------------|---------|--------------------------|
| III           | AR IKBKAP/9q31.3                   | (I-κ-B kinase complex associated protein); affects neuronal polarity, differentiation and survival. | At birth/Infancy | Loss of pain and temperature sensation | Hyperhidrosis | Profound autonomic dysfunction, vasomotor instability, absence of deep tendon reflexes, alacrima, impaired blood pressure regulation, failure to thrive, orofacial self-mutilation, absent fungiform papillae on the tongue, increased salivation, low caries index |
| IV            | AR NTRK1/1q23.1                   | Tyrosine kinase receptor I; affects signal transduction | At birth/Infancy | Loss of pain and temperature sensation | Hypohidrosis to anhidrosis | Self-mutilation with orofacial injuries, deep tendon reflexes usually intact, recurrent fever, corneal lesions, mental retardation, recurrent infections, skin hyperkeratosis and fissuring, generalized tonic-clonic seizures, emotional lability |
| V             | AR NGFB/1p13.2                    | Nerve growth factor beta (NGFB):Affects regeneration of damaged axons, sympathetic axon growth | At birth/Infancy | Loss of pain and reduced thermal sensation, loss of deep pain perception | Normal to hypohidrosis | Similar to HSAN IV but normal intelligence |
| VI            | AR DST/6p12.1                     | Dystonin: Cytoskeletal formation and vesicle transportation affected | At birth/Infancy | Loss of pain and temperature sensation | N/A | Lack of psychomotor development, autonomic abnormalities, absence of deep tendon reflexes, feeding and respiratory difficulties, neonatal hypotonia, alacrima, blotching |
| VII           | AD SCN11A/3p22.2                  | Nav1.9, impaired action potential generation | At birth/Infancy | Loss of pain sensation | Hyperhidrosis | Self-mutilation, painless fractures, delayed motor development, gastrointestinal dysfunction |
| VIII          | AR PRDM12/9q34.12                 | PR domain-containing protein 12; loss of the small myelinated Aδ fibers, alteration of unmyelinated C fibers | Onset in infancy | Reduced pain and temperature sensation | Hypohidrosis | Self-mutilation behavior with orofacial injuries, painless fractures, skin and bone infections, corneal injuries, no mental retardation |
| HSN with spastic paraplegia | AR CTT5/5p15.2                   | Actin and tubulin folding | Early childhood | Loss of all somatosensory modalities | Normal | Mutilation, acropathy, septic paraplegia |

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the
patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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