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Hereditary Sensory and Autonomic Neuropathy Type VIII

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ABSTRACT

Hereditary sensory and autonomic neuropathy type VIII (HSAN 8 or HSAN VIII) is a rare genetic disorder that usually begins in infancy and is characterized by an inability to feel pain and inability to sweat (anhidrosis). The sensory loss in individuals with HSAN VIII is due to abnormal functioning of the sensory nerves that control responses to pain and temperature. Anhidrosis can cause recurrent episodes of fever and high body temperature. An inability to feel pain can lead to unintentional self-mutilation, repeated fractures, and joint damage. Affected individuals and especially children or infants may be unaware of injury delaying treatment. HSAN VIII is caused by mutations in the PRDM12 gene which is essential for human pain perception.

Key words: *Hereditary Sensory and autonomic neuropathy; PRDM 12 Gene; Pain; Sensation*

The hereditary sensory and autonomic neuropathy type 8 is caused by homogenous mutation in PRDM 12 gene on chromosome 9q34 [1]. It is an autosomal recessive neurological disorder characterized by congenital insensitivity to pain resulting in ulceration in fingers, lips, tongue and other body parts. Affected individual also have decreased sweating and tear production. The hereditary sensory and autonomic neuropathies (HSAN), also known as the hereditary sensory neuropathies, include at least six similar, but distinct inherited degenerative disorders of the nervous system (neurodegenerative) that frequently progress to loss of feeling, especially in the hands and feet. Some of these disorders have several subtypes based upon the specific associated genes. Some types of HSAN are related to or identical with some forms of Charcot-Marie-Tooth disease, and others are related to or identical with familial dysautonomia (Riley-Day syndrome). Furthermore, HSANs are classified more broadly as peripheral neuropathies or disorders of the peripheral nervous system, which encompasses all of the nerves outside of the central nervous system (i.e. brain and spinal cord). Here we report a child that was diagnosed to have congenital insensitivity to pain with anhidrosis due to mutation in the PRDM 12 gene.

CASE REPORT

A 3 year old male child brought with complaints of repeated episodes of high grade fever with recurrent infections. He was born to third degree consanguineous marriage, and was 4th in birth order. Child was apparently normal at birth and was on exclusive breast feeding till 6 months of age. Child achieved neck holding at 6 months of age, was able to sit with support at 1 year and walk independently at 2 years. He achieved social and language mile stones as per age. Mother first noticed whitish discoloration of both corneas at 6 months of age, which gradually progressed over the age. Child underwent a tarrsoraphy procedure for corneal ulcer at the age of 18 months of age.

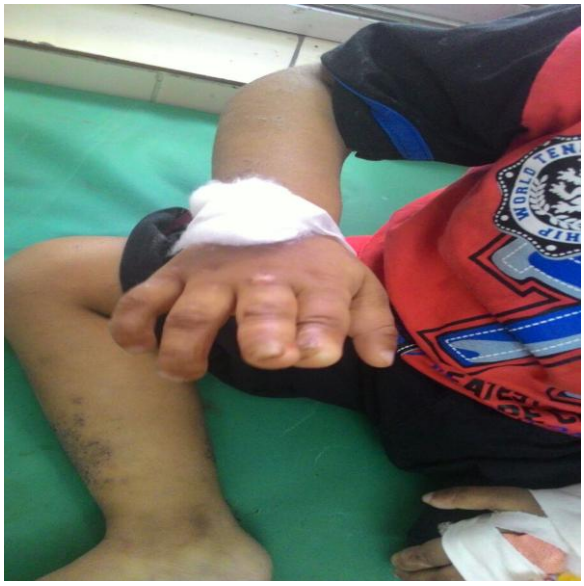

Figure 1: Mutilation of the distal phalanx

Mother also observed child never cried during his vaccination visits. Child also expressed self mutilation behavior where he deliberately bit his lips, tongue, fingers etc and sustained bleeding injuries. There were several instances where child burnt his fingers over a burning gas stove without a wince. Also mother noticed child had repeated episodes of fever, especially during the months of summer, which was relieved by cold water bath. He also had dry and rough skin with increased pigmentation over friction areas. Child had remarkably reduced ability to sweat. In the family, similar complaint was found in another sibling who was expired at 2 yrs of age due to unknown cause. Child has two normal siblings.

Nerve conduction studies (motor and sensory) were normal. A sweat test using pilocarpine showed total absence of sweating. Skin biopsy showed normal sweat gland. Sural nerve biopsy showed reduced numbers of myelinated and unmyelinated small-diameter fibers with normal numbers of large-diameter fibers. Next generation gene sequencing showed homozygous missense-mutation in PRDM12 gene

DISCUSSION

The HSAN is classified on their inheritance pattern, clinical features, and pattern of the central nervous system involvement. They have been categorized into five types based on inheritance pattern, time of presentation, clinical and electrophysiological features [1]. Their patterns of presentation are different and it differs from types and individual cases also. Some cases are present with the common systems with the mental retardation and some cases are in the same group present without mental retardation. These five types are 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 [2].

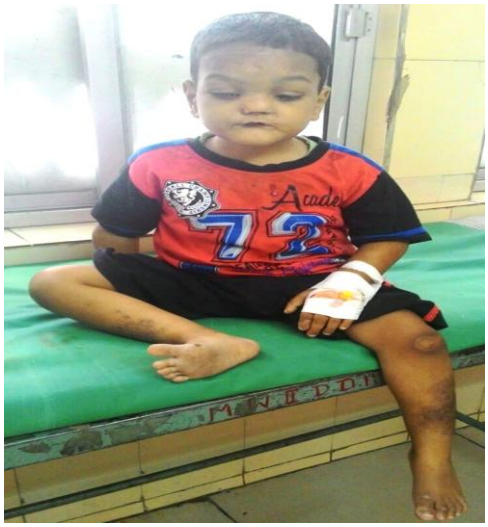

Figure 2: Multiple painless ulcers on left leg

HSAN 1 usually presents with loss of pain and temperature but there is preservation of the tactile sensation. HSAN type 1 is autosomal dominant and usually present in second to third decade. Type 1 is associated with minor autonomic involvement that is limited to urinary dysfunction and decreased sweating in the feet. Peripheral nerve examination reveals loss of all diameters of axons, mostly involving the C and A-δ fibers. The dorsal root ganglia and dorsal columns also show degeneration.

HSAN 2 is an autosomal recessive disorder with onset in infancy. There is generalized pansensory loss usually affecting the limbs more than the trunk or face [3-4]. Autonomic disturbances included bladder dysfunction, impotence and distal anhidrosis. Motor function is preserved but tendon reflexes are lost. There is loss of myelinated fibers in the sural nerve biopsy. HSAN types 3,

4 and 5 are autosomal recessive. Usually type 3 presents with autonomic involvement and type 5 usually presents with acropathy and bilateral neurotrophic keratitis. Motor functions and tendon reflexes are normal [5-6].

Our case typically presented with severe anhidrosis, absence of pain sensation, and self-mutilating behavior, starting in infancy. The investigations and common symptoms are suggestive of HSAN type 4 with normal intellectual. It seems that there are similar findings between the type 4 and type 8. As reported the cases of PRDM 12 gene involved are having normal intelligence.

With the evolution of molecular genetics, seven gene loci and six disease causing genes for autosomal dominant and recessive HSAN have been recognized. These genes play an essential role in the metabolism of lipids and regulation of intracellular vesicular transport, as a nerve growth factor and presumptive transcriptional regulator. In our patient, the next generation gene sequencing showed homozygous missense mutation in PRDM 12 gene. This PRDM 12 mutation causes an autosomal recessive type of HSAN 8 which has been recently described [4]. The patient having PRDM 12 gene involvement does not seem to have an intellectual disability in contrast to the NTRK1 patients. The mutation is very rare and found in Pakistani families as studied by Chen YC [5]. The mutation affects highly conserved amino acid in a zinc finger motif of the protein and other missense-mutations in the PRDM12 zinc fingers.

Identification of this and other such cases of HSAN VIII can help us better understand this rare disease and perform further research on its genetics, which can help us to develop treatment options for it. Understanding the mechanisms involved in the degeneration of pain receptors or nerve fibers in HSAN VIII can also help in developing novel treatment options for patients suffering from intractable pain.

CONCLUSION

Hereditary Sensory and Autonomic Neuropathy VIII (HSAN-VIII) is a very rare especially in an Indian family. Genetic analysis is essential to identify this rare disease.

REFERENCES

1. Nagasako EM, Oaklander AL, Dworkin RH. Congenital insensitivity to pain: an update. Pain. 2003;101(3): 213–9.
2. Nishida G. Congenital Anhidrosis, Saishin Igaku (Japan) 1951; 6:1100-1104.
3. DonaghyM. Hereditary sensory and autonomic neuropathy. In: Walton J; eds. Brains diseases of nervous system 10th edition. Oxford. Oxford univerity press; 1993:592.
4. OMIM Entry - # 616488 - Neuropathy, Hereditary Sensory And Autonomic, Type VIII; HSAN8. Available at - http://omim.org/entry/616488. [Last accessed on 10/06/2016].
5. Chen YC, Auer-Grumbach M, Matsukawa S, Zitzelsberger, M, Themistocleous AC, Strom TM, et al. Transcriptional regulator PRDM12 is essential for human pain perception. Nature Genet. 47: 803-808, 2015.
6. Axelrod FB, Pearson J. Congenital sensory neuropathies: Diagnostic distinction from familial dysautonomia. Am J Dis Child 1984;138:947-54.

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