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Case Report

Paediatrics Section

Hereditary Sensory and Autonomic Neuropathy V: A Case Report

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ABSTRACT

Hereditary Sensory and Autonomic Neuropathy (HSAN) are a group of rare inherited disorders that comprises a varied set of disorders which mainly present with sensory dysfunction and deficits in autonomic functions, along with other associated manifestations. This case report describes the case of a four-year-old male child, who was referred to the department of Paediatric Neurology and Pedodontics due to loss of multiple teeth and drooling of saliva, coupled with multiple oral ulcers that worsened over time. During the assessment, sensory and autonomic abnormalities were observed, while the remaining systems were normal. Following a strong clinical suspicion and the involvement of a geneticist, a genetic analysis yielded the diagnosis of HSAN V. Given its rarity and varied presentation, reporting this case would help to open discussions on diagnostic and therapeutic dilemmas involved in treating these children, which usually comprises a multidisciplinary team, consisting mainly of dental and neurology departments.

Keywords: Corneal transplantation, Hypohidrosis, Self-mutilation, Sensory dysfunction

CASE REPORT

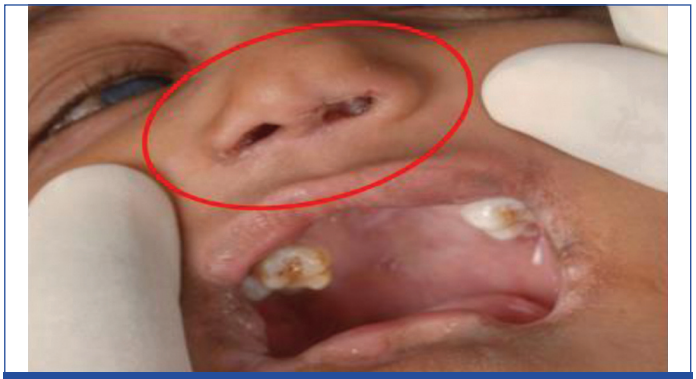
A four-year-old male child presented to the department of Paediatric Neurology and Pedodontics with a history of loss of multiple teeth, drooling of saliva, and multiple oral ulcers that had been present for 11 months. The oral ulcers appeared gradually and were spread throughout the oral cavity, including lesions on the tongue and lips. The loss of teeth also occurred gradually during the same time as the ulcers. The patient was the first and only child of a non-consanguineous Indian couple and was born after an uneventful pregnancy. The parents reported no family history of neurological problems. The child was apparently normal until he was 15 months old. By the age of two years and six months, the whole set of deciduous teeth had emerged regularly. He had recurring and inexplicable episodes of fever up to 39 degrees Celsius at the age of two. He had developed a deformed oral configuration by the age of three as a result of tooth plucking and constant teeth-biting. His parents also reported a history of self-mutilation in which he would bite his fingers, resulting in painful abrasions.

On general examination, the overall condition of the patient was poor. Normal reactions to fine and crude touch, pressure, and thermal stimuli were present. Normal deep tendon reflexes were noted. Corneal clouding was observed in both eyes, associated with poor vision [Table/Fig-1]. Traumatic swelling on the left frontal bone and self-inflicted injury to the left thumb, which had reduced the nail to half its size and increased wrinkles on the hand, were observed. Self-induced injury to the nostrils was also noted, along with scar tissue under the lower left eyelid [Table/Fig-2]. Swelling at the angle of the lower jaw was noted, along with bony crepitus, suggestive of mandibular trauma [Table/Fig-3] which was managed conservatively with closed reduction and immobilisation [Table/Fig-4].

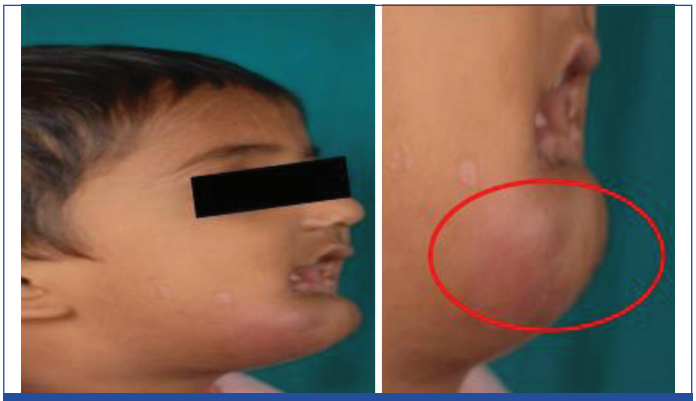
On oral examination, severe scar tissue at the commissures of the lower lip was observed. An important feature observed was ulceration of the buccal mucosa and tongue, associated with constant drooling from the angle of the mouth due to incompetence of the lips. Also, a high arched palate was present, along with angular cheilitis. The absence of all eight incisors and six premolar teeth were noted, which reduced the vertical height of occlusion [Table/Fig-5].

Basic blood tests, metabolic panels, and organ function tests were normal. Given the above symptoms and with the opinion

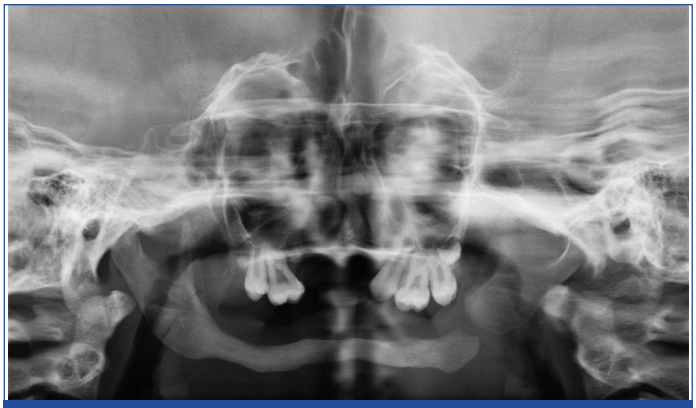
[Table/Fig-1]: Corneal clouding and scarring.



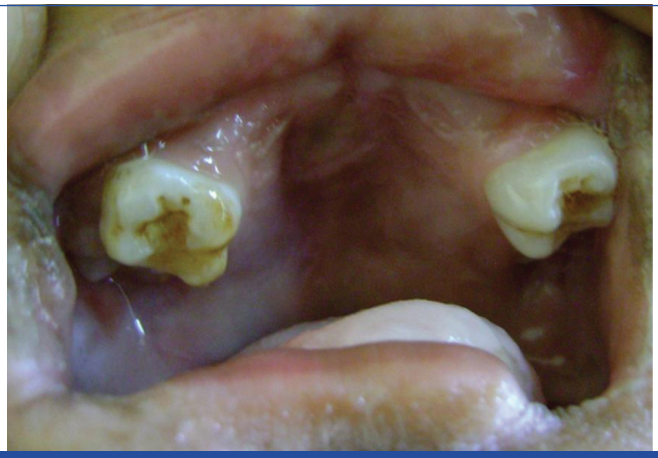
[Table/Fig-2]: Self-induced injury over nasal aspect.



[Table/Fig-3]: Trauma over angle of mandible.



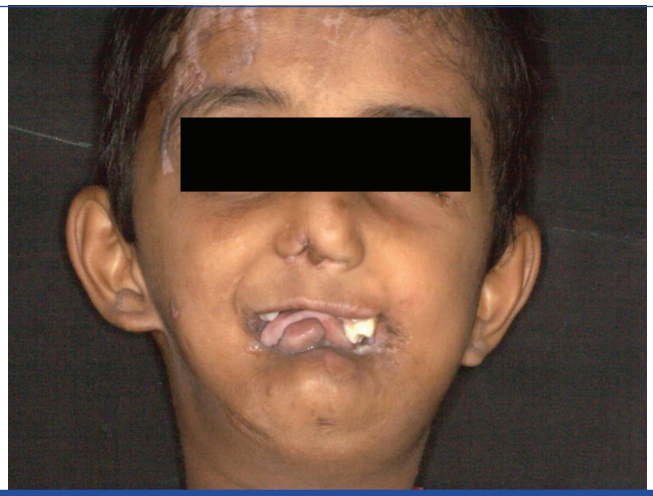
[Table/Fig-4]: OPG showing missing teeth and mandibular fracture.



[Table/Fig-5]: Photograph showing missing teeth, increased vertical height of occlusion and oral trauma.

of a geneticist, chromosomal study showed a mutation of the Neurotrophic Tyrosine Kinase Receptor type I (NTKR1) gene located on the 8.3-Mb region on chromosome 1 (p13.2-p11.2), NGF locus. This helped us diagnose the condition as HSAN V.

The treatment approach involved giving great importance to motivating and carefully instructing the patient and his parents to achieve good compliance. The sharp surfaces of the molars were eliminated by grinding, and pit and fissure sealants were added. Overdentures to improve the vertical height and aid in mastication were considered but not used as the relatives did not consent to the management. Hence, sharp ends of the teeth were drilled and canines were blunted. Custom-made headgear and a self-modeling mouthguard to prevent facial injuries and cheek self-biting were prescribed at the time of referral. Further follow-up to prevent digit mutilation was advised. On sequential follow-up, the number of injuries had significantly decreased. Corneal opacity had also reduced with good eye care by usage of eye patches [Table/Fig-6].



[Table/Fig-6]: Follow-up photograph.

DISCUSSION

HSAN V is a genetically inherited and rare disease that is characterised by repetitive autosomal recessive mutations of the Nerve Growth Factor beta (NGFβ) gene located on the 8.3-Mb region on chromosome 1 (p13.2-p11.2), which forms the basic convoy for both nociceptive and trophic functions. The incidence of this disease has been estimated at about 1 in 25,000 [1]. Genetic and ensuing biochemical studies have revealed a mutation in the NTKR type 1 gene located on chromosome 1 [2].

Inherited peripheral neuropathies usually manifest as congenital insensitivity to pain, where there is an impairment in the ability to perceive pain, or as congenital indifference to pain, where there is an absence of the affective response to pain perception [Table/Fig-7]. It is proposed that each HSAN disorder is caused by different genetic errors affecting certain parts of the small nerve fibers during neurodevelopment, resulting in variable phenotypic expression [3]. Most commonly seen in consanguineous marriages, among the other HSAN types, this type is not associated with cognitive impairment [4].

With this basic background in mind, we now consider the case of the four-year-old Indian male who presented with multiple painless oral ulcers, loss of permanent dentition, self-mutilation of fingers and nostrils, mandibular fracture, and failure of repeated corneal transplants. These symptoms can mainly be attributed to the loss of pain sensation, which predisposes the child to self-harm which may culminate in serious infections or self-amputation of respective body parts.

Similar characteristic presentations of self-mutilation and impaired sensation to pain are also observed in diseases like Lesch Nyhan syndrome, Fabry disease, phenylketonuria, and De Lange syndrome [5]. But the major differentiating factors between the listed differentials and HSAN V are the presence of partial anhidrosis, normal serum uric acid levels, absent peripheral nerve thickening and distorted features, histopathological studies indicating potential nerve loss which is confirmed by nerve conduction studies. Absence of cognitive impairment, neuropsychological problems, seizures, intellectual disability and hypopigmentation of the hair and skin are the discerning features found in untreated phenylketonuria, which is usually absent in classical cases of HSAN V. PKU is often diagnosed at birth by clinical features, neuroimaging, and biochemical tests, and the patient is treated immediately to prevent irreversible loss of neurological development [6].

A similar condition is hereditary anhidrotic ectodermal dysplasia, an X-linked hereditary disorder having complete clinical expression only in males. They are characterised by typical facies with scalp and eyebrow hypotrichosis, and major dental abnormalities; in contrast to HSAN, it is not accompanied by peripheral neurologic manifestations [7].

Despite the rarity of the disease entity, HSAN V can be managed with the combined efforts of a neurologist and an orthodontist. In the few cases reported, the most common presentation was oral and digital mutilation complaints; therefore, special attention should be paid to these symptoms [8]. Keeping in mind that oro-facial and other self-mutilation incidences decrease with age, the child could be counseled early on about the adverse effects of these actions and dental implantations can be used to ameliorate the dental damage. Ankle or knee braces could be advised prospectively to avoid injuries and decrease the occurrence of fractures to the respective joints.

With the long-term prognosis of the HSAN disorders improving with the advancement in genetic and molecular understanding, a larger number of individuals are reaching adulthood with minimal or correctable trauma [8]. But with the genetic aspect of the disease being obscure, further research and understanding of the disease

Classification	Inheritance	Sensory deficits	Autonomic deficits	Reflexes	Tissue Damage	Nerve fibers affected
HSAN I Hereditary sensory radicular neuropathy	Autosomal dominant	Distal loss of pain sensitivity Distal loss of thermal sensitivity Proprioceptive deficits Distal light touch deficits	None known	Absent/weak	Severe ulceration of extremities Painless injuries	All (smaller diameters affected more)
HSAN II	Autosomal I Recessive	Distal loss of pain sensitivity Distal loss of thermal sensitivity Distal proprioceptive deficits Diffuse light touch deficits	None known	Absent/weak	Severe ulceration of extremities Painless injuries	Myelinated fibers
HSAN III Riley- Day syndrome Familial dysautonomia	Autosomal recessive	Diffuse pain insensitivity Diffuse thermal insensitivity	Excessive sweating Defective lacrimation Postural hypotension Recurrent fevers Feeding problems	Absent/weak	corneal ulceration painless injuries	Unmyelinated fibers large myelinated fibets
HSAN IV Congenital pain insensitivity with anhidrosis	Autosomal recessive	Diffuse pain insensitivity Diffuse thermal insensitivity	Anhidrosis Recurrent fevers	Weak/normal	Ulceration of extremities Painless injuries Self- mutilation	Unmyelinated fibers Small myelinated fibers
HSAN V	Autosomal recessive	Distal pain insensitivity Diffuse thermal insensitivity	None known	Normal	Ulceration of extremities Painless injuries	Small myelinated fibers

[Table/Fig-7]: Classification of types of HSAN.

entity, pathogenesis and progression might aid in development of newer treatment aspects with orientation towards minimal physical limitations.

CONCLUSION(S)

HSAN V is a rare condition with a higher risk of orofacial deformities due to repetitive trauma. However, with all of the therapy options available, the prognosis of congenital insensitivity to pain and its accompanying problems is improving. Despite the elevated frequencies of injuries, the patient's long-term prognosis for achieving generally normal growth and development is highly dependent on strict adherence and frequent follow-ups.

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REFERENCES

[1] Davidson GL, Murphy SM, Polke JM, Laura M, Salih MAM, Muntoni F, et al. Frequency of mutations in the genes associated with hereditary sensory and autonomic neuropathy in a UK cohort. J Neurol. 2012;259(8):1673-85.
[2] Kalaskar S, Kalaskar A. Hereditary sensory autonomic neuropathy type V: a rare case report. Int J Contemp Pediatr. 2018;5(2):670.
[3] Axelrod FB, Gold-von Simson G. Hereditary sensory and autonomic neuropathies: types II, III, and IV. Orphanet J Rare Dis. 2007;2:39.
[4] Sung K, Yang W, Wu C. Uncoupling neurotrophic function from nociception of nerve growth factor: what can be learned from a rare human disease? Neural Regen Res. 2019;14(4):570-73.
[5] Prashanth GP, Kamate M. A case of hereditary sensory autonomic neuropathy type IV. Ann Indian Acad Neurol. 2012;15(2):134-36.
[6] Regier DS, Greene CL. Phenylalanine hydroxylase deficiency. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle; 1993.
[7] Deshmukh S, Prashanth S. Ectodermal dysplasia: a genetic review. Int J Clin Pediatr Dent. 2012;5(3):197-202.
[8] Suthar R, Sharawat IK, Eggermann K, Padmanabha H, Saini AG, Bharti B, et al. Hereditary sensory and autonomic neuropathy: A case series of six children. Neurol India. 2022;70(1):231-37.

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