**Case report****The curse of painlessness: unveiling a rare case of HSAN type VIII mutation****Abberaamee S*, Sujatha G P, Ashok L, Shambulingappa P, Pramod G V**

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Hereditary Sensory and Autonomic Neuropathy Type VIII (HSAN VIII) is an ultra-rare autosomal recessive neurogenetic disorder, caused by mutations in the PRDM12 gene, which leads to congenital insensitivity to pain. Pain perception is absent and affected individuals are prone to repeated trauma, self-mutilation, chronic infections, delayed wound healing and severe oral and maxillofacial complications. Oral manifestations can be important diagnostic clues and underline the role of dental professionals in the early recognition and prevention of complications.

Keywords: HSAN VIII, PRDM12 mutation, Congenital insensitivity to pain, Oral manifestation, Mandibular osteomyelitis, Hereditary sensory and autonomic neuropathy.

INTRODUCTION

Hereditary sensory and autonomic neuropathies (HSAN) are a rare group of inherited neurodegenerative disorders characterised by abnormal development and function of peripheral sensory and autonomic neurones resulting in decreased or absent perception of pain and temperature [1]. Pain is a significant protective mechanism that prevents tissue damage. Therefore patients with HSAN are prone to recurrent unnoticed trauma, which may cause chronic ulcerations, infections, bone destruction and delayed wound healing. An early diagnosis of this disease is often difficult since the affected children may be normal at birth except for a decreased response to painful stimulus. HSAN type VIII is a very rare autosomal recessive condition resulting from mutations in PRDM12, a gene that is essential for nociceptors, the sensory neurons that detect pain, to develop normally during embryogenesis. When PRDM12 does not function properly, neurons fail to differentiate correctly and the small myelinated A-delta fibres and unmyelinated C fibres are lost. The outcome is congenital insensitivity to pain [2]. Oral manifestations such as self-mutilation, premature tooth loss, traumatic ulcers, osteomyelitis, and pathological fractures are important diagnostic features that may be first recognized by oral

diagnosticians and pediatric dentists. Early recognition of these findings is important for timely diagnosis, multidisciplinary management and prevention of severe complications.

Case report

A 9-year-old male patient reported to the Department of Oral Medicine and Radiology with the chief complaint of decayed teeth in the left lower back region of the jaw for 1 month. The mother of the patient also reported progressive loss of multiple teeth in both jaws over the last three years. The child was from low socioeconomic status and had dropped out of schooling after first standard. Family history revealed consanguineous marriage of first degree. The patient had a history of self-extraction of erupted teeth which started 5 years ago. The mother gave a history of intermittent pus discharge from the left posterior mandible for 6 months and painless progressive swelling on the left side of the face for the last 3 months. The swelling slowly grew in size, and there was no pain or fever.

Medical history and birth history

Birth history was full-term, normal vaginal delivery. The child did not normally cry to painful stimuli until he was 6 months old. Ophthalmic abnormalities were early, with corneal opacity of the left eye at the age of eight months and total loss of vision of that eye by one year of age. The patient was hospitalised in infancy with

recurrent unexplained fever and persistent infections of the lower limbs. The patient was referred for genetic assessment in 2019 due to distinct clinical features. Genetic testing confirmed the diagnosis of Hereditary Sensory and Autonomic Neuropathy Type VIII, identifying a novel homozygous mutation in exon 5 of the PRDM12 gene. Associated systemic findings included double hemiplegia and severe anaemia, global developmental delay and failure to thrive. The medical history revealed that the patient was admitted for osteomyelitis of the ankle, knee and malleolus and treated with intravenous antibiotics. However, the patient was irregular for medical follow-up and was not on any medication at the time of dental examination.

Clinical examination

General physical examination revealed a poorly nourished child with short stature measuring 108 cm in height and weighing 18.5 kg. Pallor and oedema over the left ankle were noted. Abnormal equinus gait was present [Figure 1]. Ophthalmic examination showed microphthalmia in the right eye with corneal haziness and complete corneal opacity in the left eye. [Figure 2]

Blink reflex was absent bilaterally. Facial features included frontal bossing, excoriations over the midfacial region and reduced facial expression resulting in an open-mouth posture. Examination of extremities revealed traumatic ulcers with auto-amputation of thumbs due to repeated self-mutilation [Figure 3] and callosities over distal phalanges [Figure 4]. Extraoral examination revealed solitary diffuse swelling measuring approximately 3 × 4.5 cm on the left side of the face, extending superoinferiorly from the infraorbital margin to the lower border of the mandible and mediolaterally from the angle of the mouth to the preauricular region. Skin over the swelling appeared

stretched with no pulsations. On palpation, the swelling was soft in consistency, non-tender, with no local rise in temperature. A step deformity was palpable along the inferior border of the mandible suggestive of pathological fracture. A healed sinus tract was observed at the right angle of the mandible, presenting as a shrunken, scarred orifice without discharge, indicating previous chronic osteomyelitis.

Intraoral findings

Intraoral examination revealed a solitary swelling measuring approximately 2 × 2 cm involving the left posterior mandibular alveolus, extending from the distal aspect of the 36 regions to the 34 regions, involving the buccal vestibule. Overlying mucosa appeared stretched. Bilateral angular cheilitis was present. Tongue appeared smooth and depapillated, consistent with bald tongue. Microstomia was observed. Hard tissue examination revealed only teeth 16 and 26 present clinically. All other teeth were missing due to repeated self-extraction. The other teeth had extensive structure loss due to caries and trauma. Dental findings clearly indicated the lack of a protective pain mechanism, resulting in repeated oral injury and tooth loss. [Figure 5 & 6]

Radiographic examination

Orthopantomogram showed impacted teeth 15, 17, 24, 25, 27 and 44. Bilateral bodies of the mandible show diffuse, ill-defined radiolucent areas with altered trabecular bone pattern. There was significant thinning of the cortical plates with fragmentation and displacement suggestive of bilateral pathologic fracture secondary to chronic osteomyelitis. Horizontally impacted 44 and delayed eruption of multiple teeth indicated developmental disturbance associated with underlying neuropathy. Hematological investigation revealed hypochromic microcytic anemia. [Figure 7]

Figure 1: Equines foot



Figure 2: Ocular examination revealed right microphthalmia with corneal haziness and corneal opacity of the left eye



Figure 3: Bilateral autoamputation of the thumbs



Figure 4: Callosities involving the nails and distal phalanges, with associated traumatic ulcers



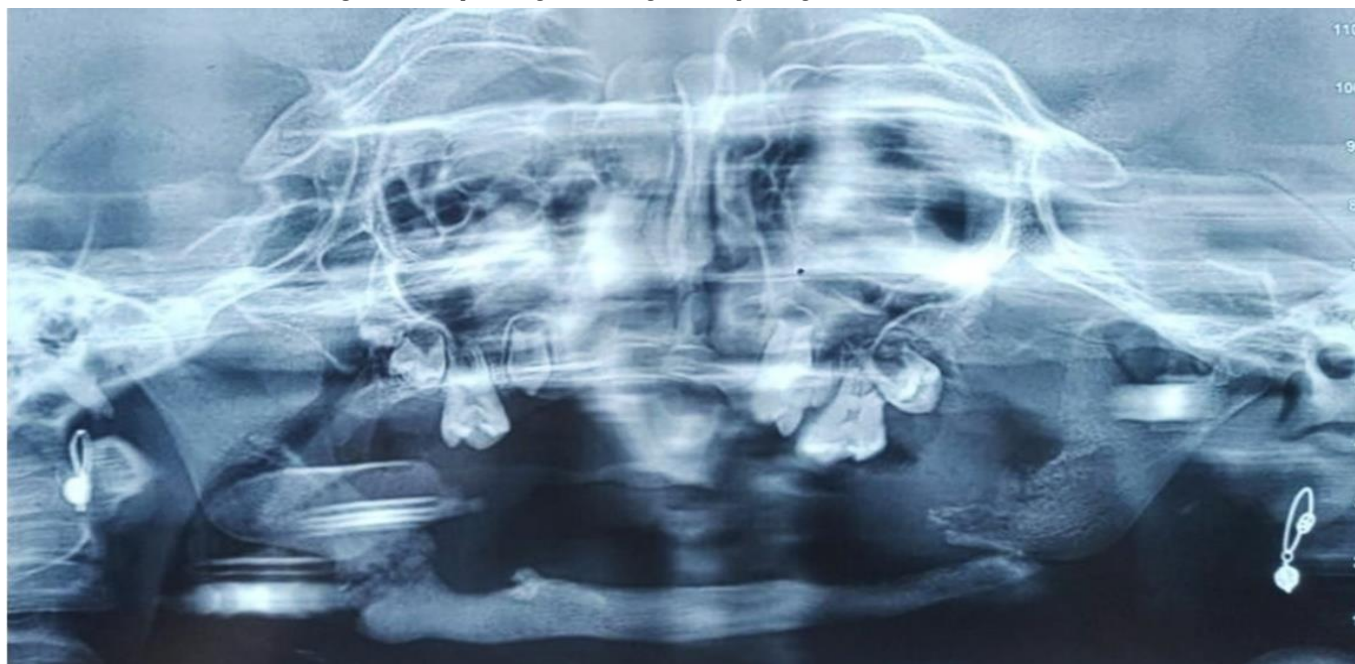
Figure 5: The maxillary arch exhibited multiple missing teeth**Figure 6:** Mandibular arch showing multiple missing teeth**Figure 7:** Orthopantomogram showing bilateral pathological mandibular fractures

Table 1: Review of case reports

Author	Year	Age/Sex	Clinical features	Gene	Diagnosis
Chen et al.	2015	13M/8F	Pain insensitivity, oral mutilation, corneal scarring	PRDM12	HSAN VIII
Zhang et al.	2016	4M	Reduced tears, corneal abrasions	PRDM12	HSAN VIII
Saini et al.	2017	2M	Oral trauma, global delay	PRDM12	HSAN VIII
Elhennawy et al.	2017	8M	Oral trauma, osteomyelitis	PRDM12	HSAN VIII
Moss et al.	2018	4M	Self-mutilation, skin lesions	PRDM12	HSAN VIII
Gaur et al.	2018	1M	Corneal scarring	PRDM12	HSAN VIII
Navya et al.	2019	1M	Oral mutilation	PRDM12	HSAN VIII
Kaur et al.	2020	1M	Corneal opacity	PRDM12	HSAN VIII
Suthar et al.	2022	1M	Corneal ulcer	PRDM12	HSAN VIII
Kusumesh et al.	2022	2F	Abnormal tooth development	PRDM12	HSAN VIII
Elsana et al.	2022	2M	Loss of corneal reflex	PRDM12	HSAN VIII
Pagare et al.	2026	10-month/F	Congenital insensitivity to pain, severe oral self-mutilation (near-amputated tongue tip), absent corneal reflex, hypohidrosis, alacrimia, recurrent osteomyelitis and skin infections	PRDM12	HSAN Type VIII

Based on clinical findings, radiographic features and genetic confirmation, the final diagnosis of Hereditary Sensory and Autonomic Neuropathy Type VIII with secondary chronic osteomyelitis of the mandible associated with bilateral pathological fracture was established. This case represents one of the rare documented presentations of HSAN VIII in a pediatric patient with comprehensive oral and systemic manifestations. The classic constellation of findings in HSAN VIII includes congenital insensitivity to pain, corneal opacity, developmental delay, recurrent infections and characteristic oral pathology. The PRDM12 gene mutation found in this patient adds to the growing evidence of association of this gene with severe sensory and autonomic dysfunction.

DISCUSSION

Hereditary sensory and autonomic neuropathies (HSAN) constitute a heterogeneous group of rare inherited neurodegenerative diseases. They are characterised by impaired or absent perception of pain and temperature due to dysfunction of peripheral sensory neurones. Pain perception is important to avoid tissue damage. It is a protective mechanism. Hence, loss of pain sensation exposes the affected to repeated unnoticed trauma, chronic ulcers, secondary infections, fractures and delayed wound healing. The rarity of HSAN often causes a delay in diagnosis, especially in early childhood, because affected infants may seem normal at first, apart from a reduced response to painful stimuli [1]. The tiny myelinated A-delta fibres and unmyelinated C fibres that are in charge of nociception and heat perception are the main targets of HSAN diseases. HSAN Type VIII, one of the newly discovered subtypes, is linked to mutations in the PRDM12 gene, which is crucial for nociceptor differentiation and embryological development. A transcriptional regulator required for the development and upkeep of sensory neurons involved in pain signalling is encoded by PRDM12. Congenital insensitivity to pain, self-mutilation behaviour, recurrent infections, corneal damage, and delayed wound healing are among the typical clinical manifestations of this gene mutation, which causes defective neuronal differentiation and impaired transmission of painful

stimuli [3].

Initially identified as congenital pure analgesia, HSAN can now be classified into several subgroups based on genetic factors thanks to advancements in molecular genetics. Mutations and clinical traits. According to Dyck's classification, there are five main forms of HSAN; other variants have recently been found through genetic research. Although the number of genetically

confirmed cases of HSAN Type VIII, an extremely rare illness caused by biallelic mutations in PRDM12, has increased, there are still few thorough publications detailing oral and maxillofacial features [4].

The clinical features of HSAN are usually manifest in infancy, when children with this disorder do not cry to painful stimuli such as injections, trauma or injury. Oral self-mutilation usually begins shortly after eruption of the deciduous teeth. The child may continue to bite or chew his tongue, his lips, the inside of the cheeks and his fingers. It can result in chronic ulcers, repeated infections, osteomyelitis and early tooth loss. Abnormal autonomic control of sweating and body temperature may also result in recurrent episodes of unexplained fever.

As a rule, intellectual development is normal, except for severe physical complications [5].

Oral manifestations are of particular importance for early diagnosis as dentists may be the first healthcare professional to identify unusual patterns of oral injury inconsistent with normal childhood trauma. Premature exfoliation or self-extraction of teeth, chronic ulceration, traumatic mucosal lesions, alveolar bone destruction, osteomyelitis, and pathological fractures are frequently reported oral findings in HSAN patients. Absence of pain may lead to extensive tissue damage before the patient seeks treatment.

Radiographic examination is useful for identifying impacted teeth, delayed eruption, bone loss, and pathological fractures caused by repeated trauma [6]. In this instance, the oral findings were significant and included several teeth that had been removed by the patient themselves, chronic osteomyelitis, impacted teeth, changes in the trabecular patterns, and pathological fractures

of the mandible on both sides. These findings demonstrate the need for a thorough clinical and radiographic evaluation in oral diagnosis. Hereditary sensory neuropathy should be considered in patients with atypical painless lesions in the oral cavity, unexplained tooth loss or recurrent infections. If identified early, these can be referred for molecular genetic testing and given appropriate multidisciplinary management. Differential diagnosis of hereditary sensory and autonomic neuropathy (HSAN) includes Lesch-Nyhan syndrome, congenital insensitivity to pain with anhidrosis (CIPA), ectodermal dysplasia and other hereditary neuropathies associated with self-injurious behaviour.

Molecular genetic testing is used to confirm the diagnosis by identifying mutations in one of the following genes: PRDM12, SCN9A, NTRK1, NGFB or DST. Genetic evaluation is particularly important in patients with consanguineous parents, since most HSAN subtypes are inherited in an autosomal recessive manner [6].

Management of HSAN is largely preventive and necessitates a team-based approach with oral medicine specialists, paediatric dentists, neurologists, ophthalmologists, orthopaedic surgeons and genetic counsellors. There is no definitive cure and management is directed at preventing self-inflicted injury, managing infection and maintaining oral health. Paediatric dentists have an important role in the use of custom-made protective mouthguards, smoothing of sharp tooth cusps, extraction of excessively mobile teeth when indicated, and regular follow-up to detect and manage complications. Control measures for the habit and for educating parents are equally important in reducing the self-mutilation behaviour. The oral diagnostician plays an important role in early recognition of the disease by correlating the clinical findings with the radiographic features and systemic manifestations. Early dental evaluation in childhood may prevent the progression of osteomyelitis and reduce the risk of pathological fractures and major maxillofacial destruction. Preventive care of this kind improves quality of life and lowers morbidity among affected children [7].

To date, few patients with a genetically proven diagnosis of PRDM12-related HSAN type VIII have been reported, and most share the same core features. These are early-onset self-mutilation, oral trauma, corneal abnormalities, recurrent infections and developmental delay. Kusumesh et al. (2022) reported a child with congenital insensitivity to pain, whose presentation included repeated injuries, corneal disease and oral manifestations and called for early diagnosis and team-based care [8]. A more recent genetically confirmed case by Pagare et al. (2026) reported near-total amputation of the tip of the tongue due to self-biting, recurrent osteomyelitis, absence of corneal reflexes and autonomic

dysfunction, emphasising the role of oral medicine specialists in early diagnosis and lifelong dental care [9].

The previously reported cases with comparable clinical presentation are summarised in Table 1. Compared with these reports, the present patient demonstrated multiple self-extracted teeth, diffuse chronic osteomyelitis, altered trabecular bone architecture, multiple impacted teeth, and bilateral pathological mandibular fractures, thereby expanding the spectrum of oral and maxillofacial manifestations associated with HSAN Type VIII.

Early recognition of characteristic dental manifestations plays a vital role in prompt diagnosis and prevention of severe complications. Oral medicine specialists and paediatric dentists are important in the early diagnosis of this condition, providing preventive care and long-term follow-up of affected patients. Genetic counselling is strongly recommended for consanguineous families to minimise the risk of recurrence in future offspring. Early multidisciplinary intervention improves prognosis, decreases morbidity and increases the overall quality of life of children with HSAN Type VIII [10-16].

CONCLUSION

This case report emphasises the role played by oral health professionals in the early diagnosis and management of HSAN VIII. Early diagnosis and prevention of severe complications are facilitated by the early recognition of characteristic dental manifestations. Oral medicine specialists and paediatric dentists play a major role in early detection, prevention of oral complications and long-term follow-up of patients. Early multidisciplinary management may reduce morbidity and improve clinical outcomes and quality of life in children with HSAN type VIII. The prognosis is guarded due to the progressive nature of the disease and the risk of recurrent infection, but optimal coordinated multidisciplinary care can substantially improve long-term outcomes and quality of life.

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Conflict of interest statement

The authors declare no conflicts of interest.

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