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Hereditary Sensory Autonomic Neuropathy Type IV – A Rare Case Report

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Abstract

Background: Hereditary sensory autonomic neuropathy type IV (HSAN -IV) (also known as congenital insensitivity to pain with anhidrosis) is a very rare neuropathy that presents in infancy. It presents with anhidrosis, absence of pain sensation, self -mutilation, developmental delay and mental retardation. Pain insensitivity is manifested in biting of the tongue and hands or in painless fractures, bruises, and cuts.

Case description: This case report is of a 10 year old girl child with signs and symptoms of HSAN Type IV who reported to the OPD for a dental evaluation.

Conclusion: Self-mutilation in HSAN Type IV patients should be prevented and treated with a multidisciplinary approach including Pediatric dentists. Management of these patients is done by careful monitoring and treatment of injuries due to self-mutilation and eruption of teeth.

Keywords: HSAN, Congenital insensitivity to pain, Anhidrosis, oral manifestations, selfmutilation

Introduction

Pain is defined as "An unpleasant emotional experience usually initiated by noxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such."(Monheim)[1]. In normal individuals as a protective body mechanism there will be a reflex withdrawal from the source of damage in the form of pain and painful stimuli [2]. In the absence of pain, there is an increased risk of developing systemic illness associated with pain [3].

Hereditary Sensory Autonomic Neuropathies (HSAN) are a group of rare hereditary neuropathies first described by Dearborn in 1932 as “Congenital pure analgesia”. This neuropathies are charecterized by neuronal atrophy and degeneration affecting peripheral sensory and autonomic nervous system.[3]

Table 1: Other terms used to describe the HSAN [3]

Morvan syndrome
Mal perforant du pied.
Congenital pure analgesia
Congenital general pure analgesia (Dearborn, 1932)
Congenital universal insensitiveness to pain (Ford and Wilkins, 1938)
Congenital universal indifference to pain (Boyd and Nie, 1949)
Congenital absence of pain (Winkelmann, 1962)
Familial syringomyelia
Familial trophoneurosis

They are categorized into five main types based on the age of onset, clinical features, and inheritance [4]. Each HSAN disorder is likely caused by genetic errors that affect specific aspects of small fiber neurodevelopment, which result in variable phenotypic expression[5].

Congenital insensitivity to pain and anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (Nishida syndrome as it was first reported by Nishida in 1951) is the second most common HSAN. It is an extremely rare autosomal recessive disorder with a handful of case reports in India. It is an autosomal recessive disorder characterized by congenital lack of pain sensation, reduced ability to feel hot or cold, inability to sweat, episodes of recurrent hyperpyrexia, mental retardation, blood pressure fluctuations, and gastrointestinal disturbances,[5] and self-mutilating behaviour[6].They suffer from burns and fractures leading to orthopaedic problems and secondary osteomyelitis[7]. The incidence of this disorder has been estimated to be 1 in 25,000 population[2]. This case report is of a 10 year old girl who had visited our department for a dental evaluation.

Case Report

A 10 year old girl reported to our department of Pediatric and Preventive Dentistry for dental evaluation. History revealed that patient was born preterm at 8 months through cesarean delivery to parents of a second degree consanguineous marriage. Patient is the youngest of two siblings. The parents and the elder sister were normal with no history of similar complaints.

The patient was diagnosed with congenital pneumonia and hyperbilirubinemia at birth. At 10 months her CT brain showed diffuse cerebral atrophy. Parent also reported that child did not cry during immunization or any other painful stimuli. At 2 years,the patient underwent ophthalmic procedures for self inflicted corneal ulcerations on the right eye due to absence of blink reflex and corneal sensation. The parents also gave a history of delayed developmental milestones and they reported that currently patient is studying in a special school.

On examination patient was conscious, active and cooperative (Frankl behaviour rating 3), height of 114 cm and weight of 22kg. Her gait and posture were normal. Patient exhibited multiple scars on her extremities.[Figure 1] The nails of both the hands were dystrophic in nature with the left index finger more severe than the right [Figure 2]

On extra oral examination, patient’s head shape was mesocephalic, euryprosopic facial form with a concave facial profile. Patient was also found to have corneal opacity on both eyes ,[figure 3] limited mouth opening (18 mm) due to fibrosis of lower lip and angular chelitis on both corners of the mouth. [figure 4], dry ,coarse and thick skin.

On intra oral examination tongue size appeared normal, pale pink in color with depappillation and loss of tongue tip. The lower arch showed partial anodontia(history of self extraction) with abscence of permanent root stumps , root stump in relation to 36, and ulcerations along the entire length of the ridge [figure 5]. On hard tissue examination, teeth present in the maxillary arch were 11,15,55,16,21,22,24,26. Patient was found to have deep dentinal caries in relation to 26, root stump in relation to 52 and dental caries in relation to 55 and 16 . [figure 6].OPG revealed severe bone loss and absence of permanent tooth buds in the entire length of mandible , there were also missing 12 and 14,tooth buds of 17,23,25, 27and 28 can also be appreciated. [figure 7]

A provisional diagnosis of congenital insensitivity to pain was made based on her past medical records and clinical findings. Further investigations were required for a confirmed diagnosis.

Differential Diagnosis: Different neurological syndromes associated with oral self mutilation include Lesch Nyhan syndrome, Cornelia de Lange syndrome,Tourette syndrome, HSAN III or Riley-Day syndrome and Ectodermal dysplasia.

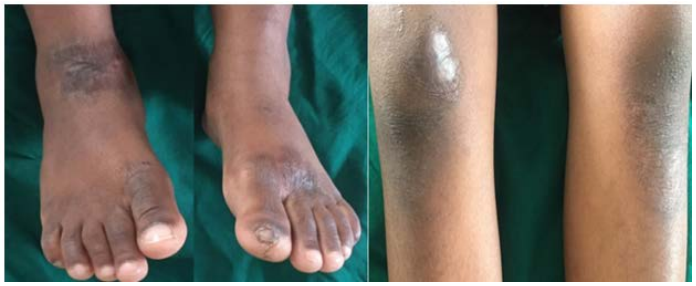

Figure 1: Showing scars of self mutilated injuries in lower extremities.

Figure 2: Showing dystrophic nails.

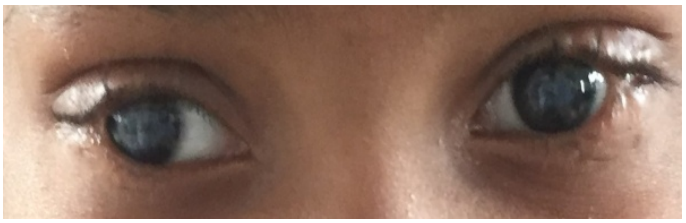

Figure 3: showing corneal opacities.

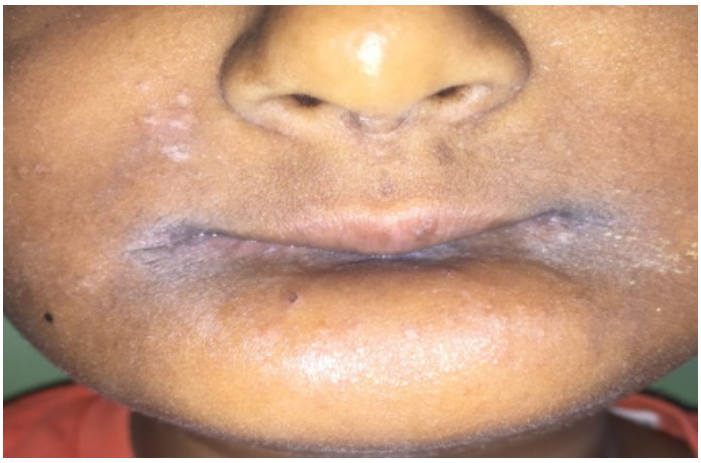

Figure 4: Showing angular chelitis

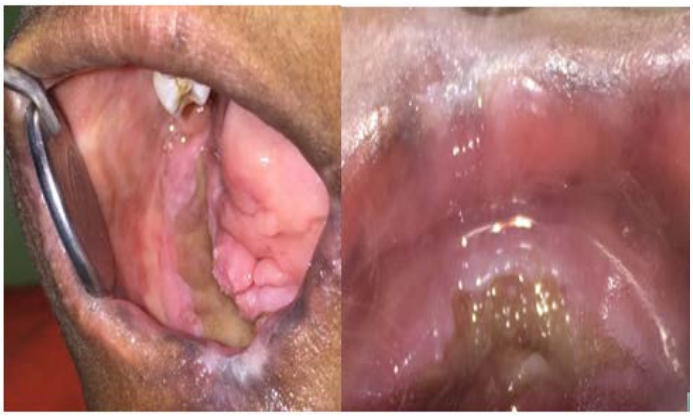

Figure 5: Showing ulcerations on the lower arch

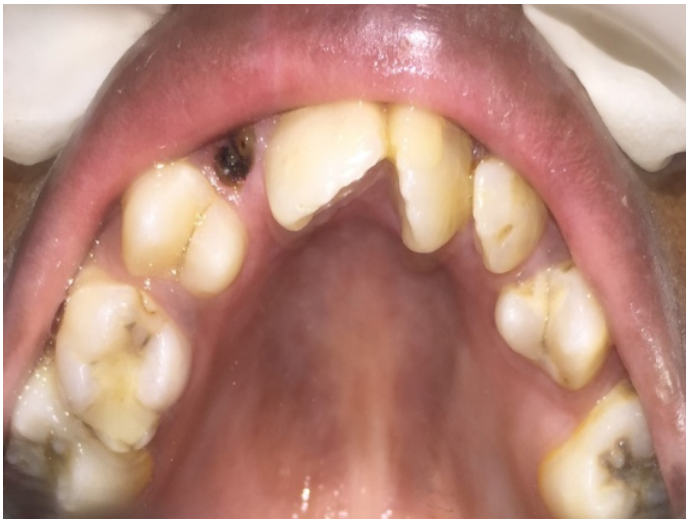

Figure 6: Showing upper arch with multiple caries and root stump.

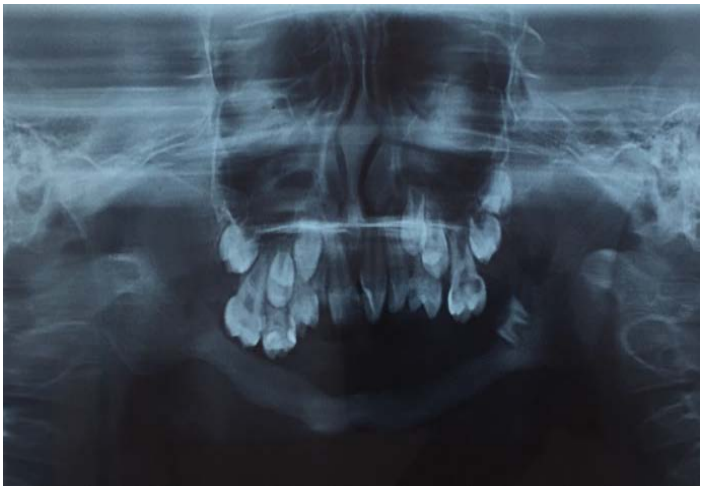

Figure 7: OPG of the patient

Discussion

In 1993, Dick et al recognized 5 types of Hereditary sensory neuropathies (HSN), [8]

HSN I – sensory radicular neuropathy,

HSN II – congenital sensory neuropathy,

HSN III – familial dysautonomia or Riley Day syndrome,

HSN IV – congenital insensitivity to pain with anhidrosis (CIPA),

HSN V – congenital indifference to pain. (HNNA)

All HSAN that produce abnormalities of pain sensation have involvement of the small-diameter C and A-delta fibers that transmit pain sensation. [7] It is due to mutation in the NTRK1 gene. Since neurotrophic receptor is a receptor for nerve growth factor there is a failure of differentiation and migration of neural crest cells resulting in the complete absence of small myelinated and unmyelinated nerve fibers in patients with CIPA [7].

Table 2: Genetics And Pathophysiology Of HSAN [9]

TYPE	TRANSMISSION	CHROMOSOMAL LOCATION	AGE OF ONSET	GENE	PATHO-PHYSIOLOGY
HSAN 1	Autosomal dominant	9q22.1-q22.3	20-50 year	Serine palmitoyl transferase (SPTLC)	↓Diameter of C and Aδ axons
HSAN II	Autosomal recessive	12p13.33	Infancy	Hereditary sensory neuropathy (HSN) 2	↓Number of myelinated fibers: Unmyelinated fibers preserved ↓Small myelinated fibers

HSAN III familial dysautonomia (FD) or Riley Day syndrome.	Autosomal recessive	9q31	Infancy	IKBKAP (Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex associated protein)	Severe loss of unmyelinated fibers: Complete loss of large diameter myelinated fibers
HSAN IV congenital insensitivity to pain with anhidrosis (CIPA) or Nishida syndrome	Autosomal recessive	1q21-q22.	Infancy	Neurotrophic tyrosine kinase receptor type-1 (NTRK1)	No myelinated fibers, ↓Small myelinated fibers
HSAN V	Autosomal recessive	1p13.2-p11.2	Childhood	Nerve growth factor B (NGFB)	Drastically ↓small myelinated fibers: ↓Unmyelinated fibers

Diagnostic Criteria[3]

Thrush suggested three criteria for diagnosing congenital insensitivity to pain:

i. Pain should be absent from birth.

ii. The entire body should be affected.

iii. All other sensory modalities should be intact or minimally impaired and tendon refl exes present.

Clinical manifestations of HSAN IV [5,6,7,10].

Symptoms begin early in infancy, which include

- Delay in development including height and weight
- Mild-to-moderate mental retardation
- Insensitivity to pain is profound and results in deep ulceration on the knees and elbows, overuse of bones and joints leading to recurrent fractures, osteomyelitis, joint dislocations, and joint deformities (Charcot joints).
- Self-mutilation(mutilation of the face , fingers and mouth)
- Episodic hyperthermia associated with seizures,
- Anhidrosis
- Septicaemia
- Hypotrichosis of scalp
- Death from hyperpyrexia within the first three years of life in 20% cases.

Oral Manifestations [3,11]

Majority of the patients with HSAN IV presents with oral manifestations which includes

- **Trauma to the tongue and lips**

Bite wounds causes laceration and chronic non-healing ulceration of lips, and other oral mucosa. There will be absence of tip of tongue due to repeated biting from early infancy. They also manifests decubital ulcer on the ventral surface of the tongue. The incisal edges of erupting mandibular primary incisors may cause tongue injury during sucking or nursing leading to tissue laceration with excessive bleeding, infection, fever, or malnutrition. With the eruption of maxillary and mandibular primary incisors, further oral trauma, such as tongue or lip biting, is induced in this infant which is one of the important diagnostic signs of HSAN IV.

- **Abnormal gastroesophageal motility** may cause feeding difficulties and recurrent vomiting in children leading to erosion of teeth.
- **Xerostomia** leading to increased incidence of dental caries, oral infections such as candidiasis resulting in recurrent fever.
- **Burns** of oral mucosa especially palate, due to hot food or beverages as they may not be aware of pain associated with high temperature.
- **Reduced mouth opening** due to thick fibrous scars as a result of severe cheek biting.
- **Premature loss of teeth** due to self-extraction or dental sepsis and Increased incidence of fractures and osteomyelitis of jaws.
- **Insensitivity to dental pain**, leading to space infections or dental sepsis.
- **Loss of taste sensation**, especially failure to identify sweet taste.
- **Angular chelitis** due to anhidrosis.
- **Dental attrition and cervical abrasions**.

Management of HSAN Type IV

Management includes control of hyperthermia by use of acetaminophen or ibuprofen or direct cooling in a bath or cooling blanket [5] .child may also need measures to prevent psychological stress by minimizing apprehension and anxiety[7].Treatment of orthopaedic problems has to be managed with braces on ankle to prevent injury to the weight bearing joint[5]. Patients and the parents have to undergo appropriate genetic counselling since no gene-based therapies are available till date for any variant of HSN. Prenatal genetic testing is available for these disorders. Recent advances in molecular genetics, about the sensory and autonomic neuropathies have brought about improved methods for diagnosis of the conditions and genetic counseling for affected families.[3,5,12].

Treatment of foot ulcers and infections has to be done in accordance to management of diabetic foot ulcers.[9]

Dental Management [3,8]

Depending on the degree of self-injury, an appropriate treatment plan and management can be considered such as:

• Enameloplasty - Elimination of sharp surfaces of the teeth by grinding. Composite restorations can be bonded to the sharp edges of the teeth if the enameloplasy fails.

• Use of mouth guards or tongue guards and other appliances to prevent injury to the tongue and other soft tissues. The appliance must be periodically replaced according to child's growth.

•Prevention of dental caries as it can progress to involvement of pulp without causing pain and can lead to chronic infection and tooth loss due to dental abscesses.

• Extraction of offending teeth, full mouth extraction is an extremely radical treatment and should be the last alternative.

Conclusion

HSAN type IV, rarely seen in pediatric population, is one of the most debilitating neuropathies of childhood with a high morbidity and early mortality. Prevention of self-mutilation in CIPA patients should involve a team of multidisciplinary physicians as well as pediatric dentist. Treatment of these patients is quite difficult and information regarding this issue is scarce in dental literature. Therefore, treatment of these patients is diverse and predicated upon individual cases. Thus, the dental team should therefore be involved in the management of these patients as soon as the diagnosis is made and careful monitoring of injuries due to self mutilation and eruption of teeth should continue throughout the lifetime of the patient.

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