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Case Report

A case of hereditary sensory and autonomic neuropathy type 4 presenting with chronic trophic ulcers

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ABSTRACT

Hereditary Sensory and Autonomic Neuropathy (HSAN) is a rare group of diseases involving varying degrees of peripheral nervous system. It is classified into five main types. HSAN type 4 is associated with insensitivity to pain and temperature and anihidrosis. The method of this study was to authors present a case report of a 3 year-old boy with Hereditary Sensory and Autonomic Neuropathy Type 4 presenting with chronic ulcers. Conclusions of this study was to HSAN type IV is a rare condition. There is no definitive treatment available presently for this condition.

Keywords: Anhihidrosis, Hereditary Sensory and Autonomic Neuropathies, pain, Ulcers

INTRODUCTION

Hereditary Sensory and Autonomic Neuropathies (HSAN) are a heterogeneous group of extremely rare hereditary neuropathies that affect mainly the sensory and autonomic parts of the peripheral nervous system.[1] Nelaton first described the condition in 1852 as a case report of three brothers who presented with neurotropic plantar ulcers.[2] In 1975, the term, "hereditary sensory and autonomic neuropathy," was coined to emphasize the autonomic involvement in these diseases.[3] There are variations in the clinical presentations among patients with HSAN.

Some present with pure sensory involvement, some with a mixed motor and sensory involvement and others with autonomic disturbances of varying degrees.[1,4] Mostly, the patients with HSAN present with loss of temperature and pain sensations that leads to chronic ulcers on the limbs. Later, these ulcers may progress and cause serious soft tissue infections and osteomyelitis resulting in limb amputation as the final outcome.[1] Recently, the availability of genetic testing has allowed HSAN to be classified into five main types based on various factors like the age of onset, clinical features, inheritance patterns and genetics.[1,5] HSAN IV is also known as congenital insensitivity to pain with anhidrosis (CIPA), a rare autosomal recessive condition that presents in childhood. CIPA is associated with mutations in the NTRK1 gene.[6] In this case report, authors present a case of a three-year-old male child, who presented with chronic non-healing ulcers on the lower extremities with total loss of pain sensation and anihidrosis.

CASE REPORT

Authors present a three-year-old patient who presented to us with chronic non-healing ulcers on the lower limbs since two years. The patient was born to a healthy non-consanguineous Indian couple. There was no similar history in the family and the patient is the only child of the parents. His developmental milestones were delayed

since birth in all the domains. The mother complained of self-mutilating habits in the child that began in infancy and presented initially as lip biting and teeth extraction.

The mother also complained of chronic ulcers over the lower limb. The biggest one was on the heel of the right foot which was approximately 3cm*3cm in size, and about 3 cm deep. The ulcer had grown and spread deeply to a size where the underlying bone was visible and palpable. The child also had a newly developing lesion near the lateral malleolus of the right foot which was about 3cm*1cm in size and about 0.5cm deep. There was a third ulcer with a size of 2cm*2cm on the left knee which was superficial without deeper invasion.

There was also one superficial ulcer on the dorsal aspect of the penis which was about 1cm*0.5cm in size. The mother gave a history of the phalanges of the toes of the right and left feet undergoing automatic amputation. There were no visibly intact toes on either of the feet since they were lost either due to auto-amputation or self-mutilation. The child had no sensation to pain. The mother also complained of absence of sweating in the child since birth.

The patient had destroyed all teeth due to extraction and had bitten his lips due to his self-mutilating behaviors and also had frequent episodes of head banging. On clinical examination of the child, the patient looked moderately well, and had an average body built (BMI= 19). He was in no significant distress.

The patient had a body temperature of 98.8 F, pulse rate of 100beats/ min, respiratory rate of 25 cycles/min and a blood pressure of 92/71 mm Hg. On further examination, the patient had a normal examination involving the respiratory, cardiovascular and abdominal system.

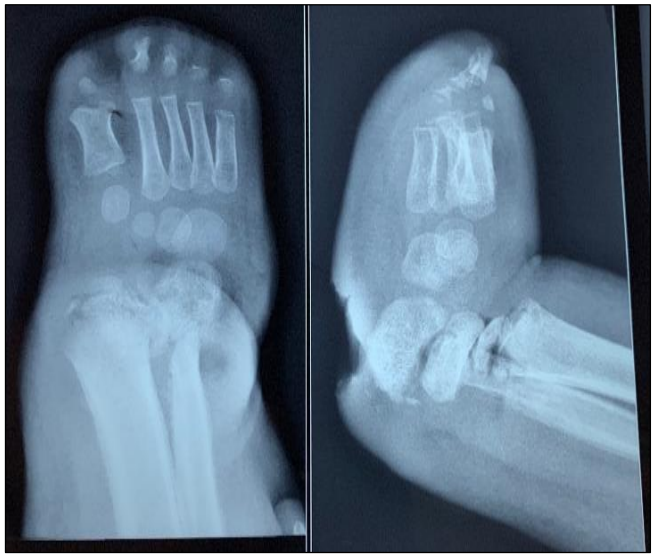

Figure 1: X ray of the right foot ulcer with bone extension.

On examining the Neurological System, the patient had absent responses to variations in temperature and painful stimuli. The sensations of touch, position, and vibration were intact.

Tendon reflexes and plantar responses were normal. There was no cranial nerve palsy. There was a global delay in his development. He could not follow commands completely and was unable to speak.

On investigation, serum uric acid levels were normal. Blood investigations revealed a hemoglobin level of 8 g/dL, a total leukocyte count of 10,400/mm3 and an adequate platelet count. The Erythrocyte sedimentation rate was 18 mm/hour.

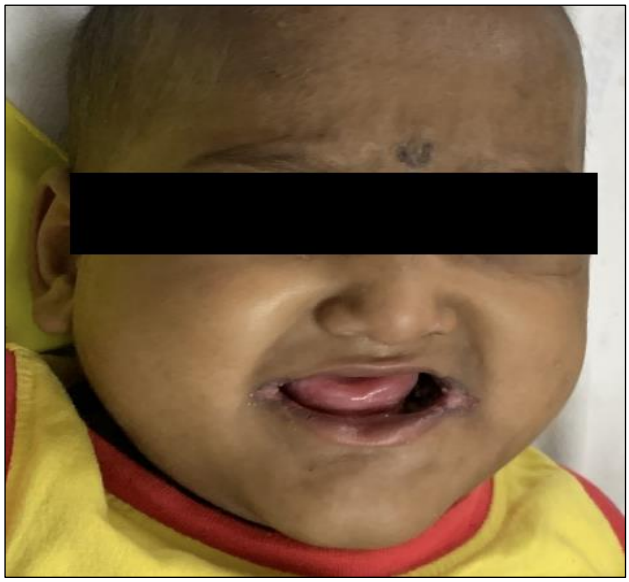

Figure 2: Lip biting and loos of teeth due to self-mutilating behaviors.

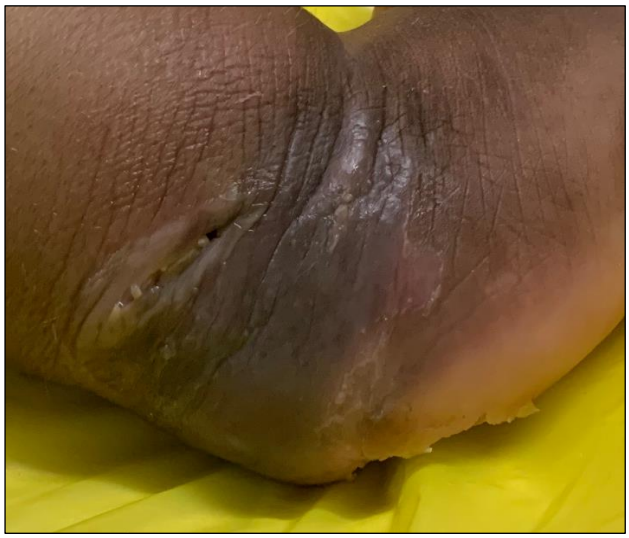

Figure 3: Newly developing ulcer near the lateral malleolus of the right foot.

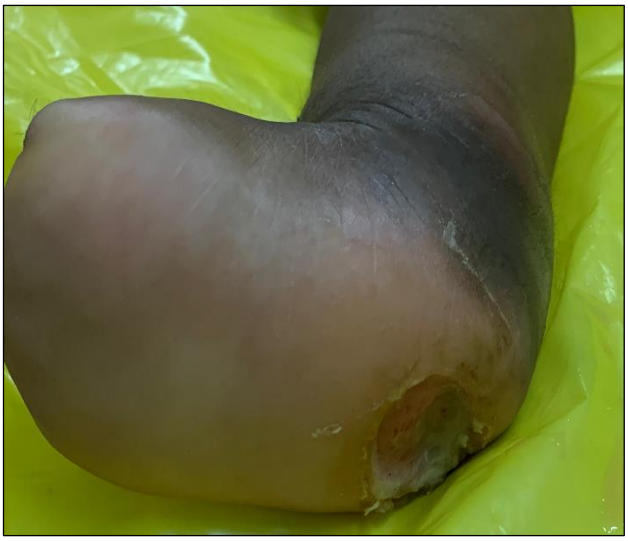

Figure 4: The large ulcer on the right heel with loss of toes.

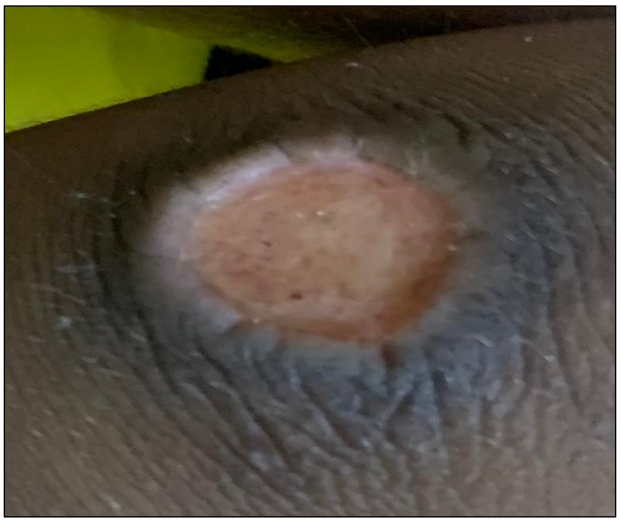

Figure 5: Ulcer over the left knee.

Total proteins were 4 gm % and Albumin was 1.3 gm%. Blood chemistry, liver profile, renal profile and other coagulation studies were found to be within normal limits. VDRL testing was negative and patient was Negative for Leprosy testing. X-ray of the right foot showed a lesion at the distal end of the tibia (Figure 1). MRI scan and EEG of the brain were normal. The child had an up-to-date immunization record.

A genetic testing was done for the patient. The results showed a heterozygous missense variation in exon 15 of the NTRK1 gene that results in the amino acid substitution of isoleucine for threonine at codon 653. The observed variation lies in the protein Tyrosine Kinase domain of the NTRK 1 protein.

Also, a heterozygous single base pair duplication in exon 15 of the NTRK 1 gene was noted, that caused a frame-shift and premature truncation of the protein 21 amino acids downstream to codon 683.

DISCUSSION

HSAN is a very rare condition with significant variability in its clinical presentation and hence it is often under diagnosed. The suspected pathogenesis involves a progressive degeneration of neurons that causes ulcerating wounds and other nervous disturbances. Based on the genetics and clinical presentation, HSAN has been classified into five different types. These have been summarized in Table 1.[1,7]

HSAN-I is a slow progressing disease usually seen in the age group of 20-50.[1,8] Patients with type 1 HSAN usually have loss of pain and temperature that begins in the lower limbs and gradually spreads proximally. Lancinating pain and ulcerations are also common. Autonomic changes are not very prominent and if seen, usually present with hypohydrosis.[1] Repeated osteomyelitis may cause Charcot joints in some cases.[8]

HSAN-II presents in infancy or early childhood and is characterized by the progressive loss of pain, temperature and touch sensations and involves both the upper and lower limbs4. Painless destruction of distal phalanges, undiagnosed fractures, slow pupillary responses, sweating and bladder complications are common in this type.[1, 8]

HSAN-III is also known as Riley-Day syndrome or familial dysautonomia and is a rare congenital variant. There are a number of autonomic disturbances including fluctuations in temperature and blood pressure, absence tears, recurrent lung infections, hyperhidrosis, taste abnormalities, loss of corneal reflex and impaired coordination due to cerebellar atrophy.[1,8, 9]

HSAN-IV usually is present since birth and is also called as Congenital Insensitivity to pain with Anihydrosis (CIPA). Patients usually present with absent responses to painful stimuli, mental retardation, decreased sweating. The neuropathy in this type usually involves the small nerve fibers (A-delta and C).[10] HSAN-V presents with absent responses to painful stimuli. Patients may have abnormal joints and hypohidrosis but have no mental retardation. There is another type known as HSAN with spastic paraplegia, which has Autosomal Recessive inheritance where the CCT5 gene is involved. It presents in early childhood with prominent sensory neuropathy with sensory loss of all qualities, mutilating acropathy and spastic paraplegia.[11]

This patient had HSAN type IV. He had no sensation at all to any painful stimuli. Also, he had no sensations to temperature changes and could not distinguish between hot and cold stimulants. He also had complete absence of sweating.

Table 1: Types of HSAN.[1, 7]

Type of HSAN	Genes	Inheritance	Onset	Clinical features
I	SPTLC1 SPTLC2 ATL1 DNMT1 3p24-p22	Autosomal dominant	Adult	Loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement
II	WNK1 FAM134B KIF1A	Autosomal recessive	Childhood	Prominent sensory loss and mutilations in hands and feet, acropathy
III	IKBKAP	Autosomal recessive	Congenital	Familial dysautonomia, prominent autonomic, Disturbances and complications, absence of Fungiform papillae of the tongue, alacrimia, Excessive sweating
IV	NTRK1	Autosomal recessive	Congenital	No or reduced response to painful stimuli, anhidrosis, episodic fever, mild mental retardation, skin and cornea lesions, joint deformities
V	NGFB	Autosomal recessive	Congenital	Congenital insensitivity to pain, severe loss of deep pain perception, painless fractures, joint deformities, normal intelligence

The self-mutilating behaviors were evident and reported to be present from a very early age by the parents. Complete absence of sweating had resulted in this patient having a very dry skin. This patient had chronic ulcers, which were not healing.

Also, after reviewing literature, it is evident that most patients with HSAN type IV present with chronic ulcers. The most prominent ulcer was on the right heel, which had eroded to such an extent that the underlying bone was palpable on exam. Also, there were ulcers at many other sites. The patient had automatic amputation of his toes on both the lower extremities

This patient had a complete loss of all his teeth because of his self-mutilating tendencies. These patients often have tendencies of lip biting, manipulating and extracting teeth and hence, dental and oral rehabilitation should be considered.[12] This had caused this patient to have recurrent dental infections and halitosis on examination.

This patient had a certain degree of mental retardation. He could understand commands and follow them to some extent. However, his speech was significantly impaired and there was a delay in the developmental milestones. He had normal hearing.

Self-mutilation and impaired pain sensation can also be seen in other diseases like Lesch-Nyhan syndrome and de Lange syndrome. The normal uric acid levels and striking anihydrosis with complete loss of pain sensation led us to diagnose this as HSAN type IV.

CONCLUSION

HSAN is a very rare congenital disease and till date there is no specific and effective treatment to cure it. However, there is a need for appropriate supportive and preventive measures to reduce the chances of complications. The Patients and families need extensive counseling and constant support. They need to be trained and explained regarding proper ulcer care, dental and oral care and other types of rehabilitation. Also, the patient with the disease has a short lifespan and hence counseling and emotional support is detrimental.

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REFERENCES

1. Wright EJ, Garza RM, Wan DC. Hereditary Sensory and Autonomic Neuropathy: Case Report and Discussion. J Clin Med Case Reports. 2013;1(1):4.
2. Nelaton, M. Affection singuliere des os du pied. Gaz Hop Civ Milit. 1852;4:13-20.
3. Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF. Peripheral Neuropathy, 3rd Ed., WB Saunders, Philadelphia; 1094-1136.
4. Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol. 2012;8:73-85.

5. Khaledi M, Rezaei N. Hereditary and sensory autonomic neuropathies. Iran J Pediatr. 2012;22:567-8.
6. Suriu C, Khayat M, Weiler M, Kfir N, Cohen C, Zinger A, et al. Skoura - a genetic island for congenital insensitivity to pain and anhidrosis among Moroccan Jews, as determined by a novel mutation in the NTRK1 gene. Clin Genet. 2009;75(3):230-6.
7. Rotthier A, Baets J, De Vriendt E, Jacobs A, Auer-Grumbach M, Lévy N, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. Brain. 2009;132(Pt 10):2699-711.
8. Azadvari M, Emami Razavi SZ, Kazemi S. Hereditary Sensory and Autonomic Neuropathy Type IV in 9-Year-Old Boy: A Case Report. Iran J Child Neurol. 2016;10(2):83-5.
9. Axelrod FB. Familial dysautonomia. Muscle Nerve. 2004;29:352-63.
10. Prashanth GP, Kamate M. A case of hereditary sensory autonomic neuropathy type IV. Ann Indian Acad Neurol. 2012;15(2):134-6.
11. Bouhouche A, Benomar A, Bouslam N, Chkili T, Yahyaoui M. Mutation in the epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct5) gene causes autosomal recessive mutilating sensory neuropathy with spastic paraplegia. J Med Genet 2006;43:441-3.
12. Kim W, Guinot A, Marleix S, Chapuis M, Fraisse B, Violas P. Hereditary sensory and autonomic neuropathy type IV and orthopaedic complications. Orthop Traumatol Surg Res. 2013;99(7):881-5.

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