Congenital insensitivity to pain with anhidrosis

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Abstract

Congenital Insensitivity to Pain with Anhidrosis (CIPA) is characterised by disruption of sensory neurons caused by genetic mutations in the Neurotrophic Tyrosine Kinase 1 (NTRK1) gene which leads to impaired pain sensation, accompanied by anhidrosis (the inability to sweat) and varying degrees of intellectual disability.

Herein, we report a case of CIPA that presented with infection of an amputated left toe, with prior admissions due to various injuries. The patient had no apparent intellectual disability. A general physical examination yielded various scars with a predilection for the elbows, knees, and shins as well as an early loss of teeth (front incisors of the lower jaw). The patient exhibited anhidrosis, a self-injurious behaviour, and an abnormal response to painful stimuli, all of which led to a clinical diagnosis of CIPA.

Keywords: Congenital insensitivity to pain with anhidrosis, Loss of teeth, High body temperature.

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Introduction

Congenital insensitivity to pain with anhidrosis (CIPA) is an extremely rare condition,[1] with a prevalence of one in 125 million new-borns.[2] It is also known as hereditary sensory and autonomic neuropathy type IV, part of a group of neuropathies sub-classified as types I, II, III, IV, and V.[3]

Persons with CIPA exhibit insensitivity to pain, the inability to sweat (anhidrosis), and intellectual disability. Given the complete insensitivity to pain, including visceral pain, individuals with CIPA have multiple injuries, often with very dramatic presentations but they seem to be unaffected by it.

This disease is inherited in an autosomal recessive manner, and has been isolated as the NTRK1 gene mutation.[2] In resource poor countries, like Pakistan, extensive testing for diseases is often impractical with limited access to genetic testing. To the best of our knowledge, no case of CIPA has previously been reported in the literature from Pakistan. Given Pakistan's high rate of consanguinity and earlier research suggesting a genetic component to the disease, we expect the prevalence to be higher as compared to the global figure.

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Case Report

Herein is a case of a six-year-old female diagnosed with congenital insensitivity to pain with anhidrosis syndrome at two years of age. The case was first seen at a local clinic in Rawalpindi in June 2019 and was then transferred to CMH Lahore for further treatment and follow-up. The patient's mother did not remember the exact dates due to the extensive number of check-ups.

The patient is born of a consanguineous marriage, born at term via a caesarean section after a normal pregnancy, as per the mother, and stayed in the neonatal intensive care unit for one day due to a viral infection which resolved soon after.

Upon enquiry, the parents reported that their child never cried due to any injury. Self-mutilation of the tongue with loss of the front incisors of the lower jaw (Figure 1A), followed by pulling of hair was also noticed after the age of one. The patient had a history of impaired wound

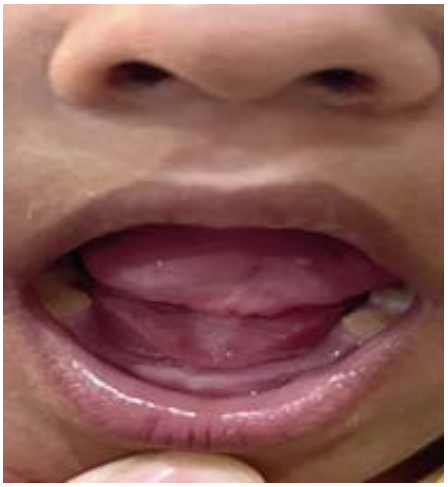

Figure:-1A : Loss of front incisors

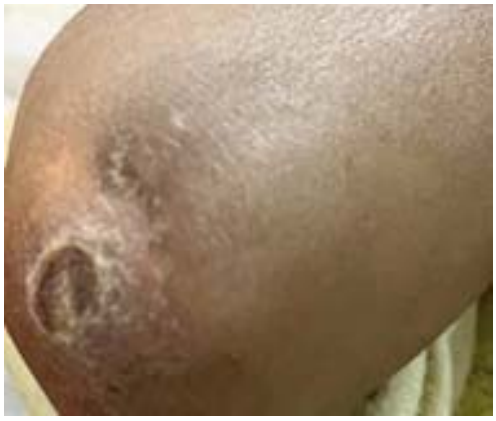

Figure:-1B: Signs of impaired wound healing and multiple scars.

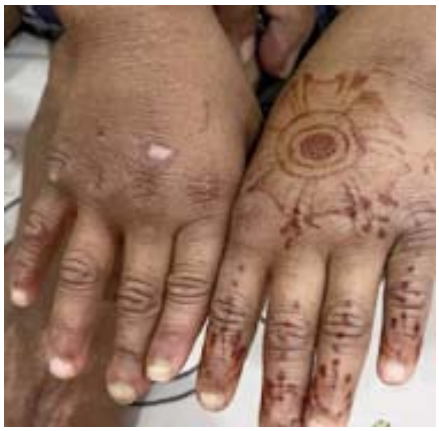

Figure:-1C: Misshapen fingernails and scars on hands.

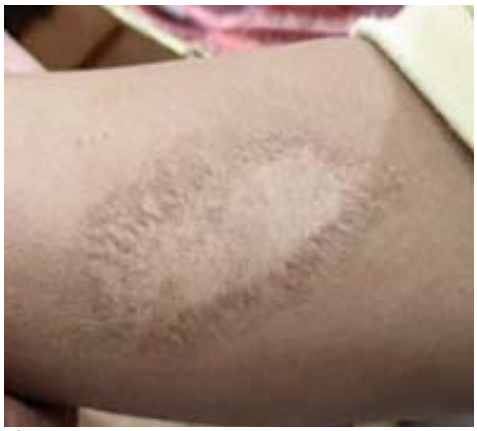

Figure:-1D: Scarring

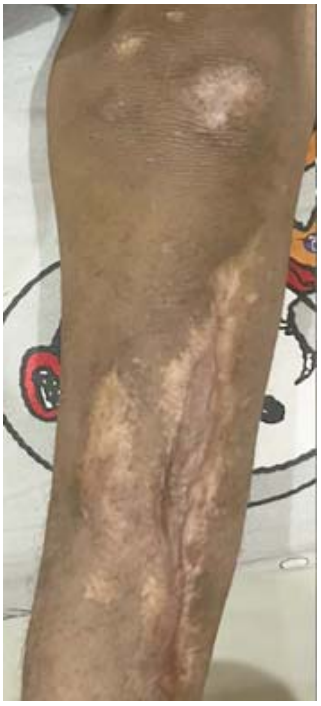

Figure:-1E: Multiple scarring.

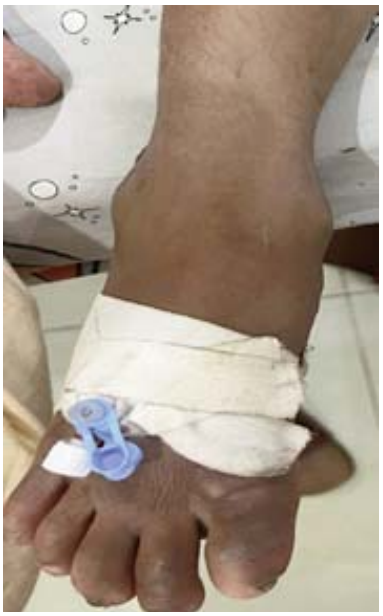

Figure:-1F: Loss of toenail due to recurrent infection of digits.

healing, multiple scarring (Figure 1B) along with misshapen fingernails (Figure 1C) and scars on hands and legs (Figure 1D and Figure 1E) which might be due to recurrent infections of the digits (Figure 1F). The patient was highly prone to injury—at times requiring surgical intervention. Fever was documented as almost 103 degrees Fahrenheit on many occasions and the parents reported that their child did not sweat even in summers.

By the age of four, she underwent a skin grafting procedure of the left toe due to earlier infection and placement of rods in the left leg due to a fractured tibia (Figure 1G). She received multiple antibiotics, paracetamol and symptomatic care throughout the years due to recurrent fevers and infections.

The patient achieved her milestones on time. Feeding

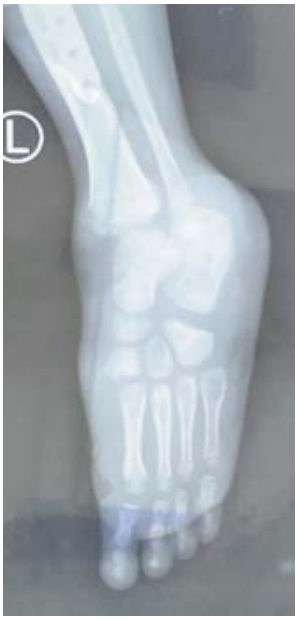

Figure:-1G: Rod in left leg after surgical correction of tibial fracture.
Legend: Physical Findings of Patient with CIPA.

habits are also normal and vaccinations are up-to-date.

Upon general physical examination, the patient was comfortable. She had a bandage on her left foot, a cannula on her right foot, and multiple areas of healing scars on her legs and arms. Nails of the middle fingers were deformed. An oral exam revealed a loss of dentition with ulceration of the tongue.

The patient was playful and talkative and showed no signs of distress or pain; however, evidence of repeated trauma on the arms was noted. Vitals were normal. Temperature was 99 degrees Fahrenheit. She was 106 cm in height (10th percentile) and weighed 15kg (<5th percentile). The rest of the examination was normal except for slightly decreased reflexes.

The diagnosis was made on a clinical basis as both the skin and sural nerve biopsy were unremarkable.

The patient's parents gave consent to use the clinical information and past records.

Discussion

Congenital insensitivity to pain with anhidrosis is part of a group of autonomic neuropathies termed the "hereditary sensory and autonomic neuropathies" (HSAN). Type IV is characterised clinically by insensitivity to pain, anhidrosis, and intellectual disability.[4]

The first signs include a dysfunctional thermoregulation system leading to multiple episodes of hyperthermia or unexplained fever that may be associated with seizures beginning in early infancy. Other symptoms often include anhidrosis, profound loss of pain sensitivity, and mild to moderate mental retardation. Insensitivity to pain and mental retardation may cause self-mutilation, leading to auto-amputation in these patients. The fingers, lips, and tongue are commonly affected. Corneal lacerations, non-painful fractures, and Charcot arthropathies may also be seen. The current patient had a history of a tibial fracture in the left leg requiring several subsequent follow-ups due to suspected infection.[5,6]

The patient had pulled out her lower incisors, which is suggested to be the most common cause of early loss of teeth in patients with CIPA.[7] Self-mutilation in the form of tongue biting and biting of the tips of the fingers was also noted along with multiple signs of trauma on her limbs.

It was reported that many individuals with CIPA have thick, leathery skin on the palms and soles and areas of hypotrichosis on the scalp, but this patient did not have these signs.[6] Anhidrosis associated with CIPA contributes to the calloused appearance of the skin and dystrophic nails which would explain this patient's misshapen nails of the middle fingers of both hands.[8] Multiple other injuries like burns, bone fractures, and recurrent joint dislocations are common.

Mutations in the NTRK1 gene, located on chromosome 1q21–22 lead to manifestations of CIPA.[2] This encodes neurotrophic tyrosine kinase also called tropomyosin-related kinase A (TRKA), which is mutated in a way that interferes with the normal transcription of the gene, therefore, stopping signals of pain and temperature from being relayed to the brain.[9]

The patient under discussion had presented to the emergency department with fever on several occasions, observed to remain near 100 degrees Fahrenheit at each visit. It is speculated that the anhidrosis disrupts thermoregulation contributing to the recurrence of fever. The child seemed unbothered by her high temperature.

Conclusion

Congenital insensitivity to pain with anhidrosis is a rare disorder which is a plight to live with. With evolving medical education and clinical care, our goal should be to ease the life of these individuals and help them achieve a standard of living that is both comfortable and safe, keeping in mind their susceptibility to injury. Considering that genetic components have a strong association with the development of this disease, techniques of diagnosis along with further research into mutations and treatment should be kept in mind.

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Abbreviations:
Congenital Insensitivity to Pain with Anhidrosis (CIPA).
Hereditary Sensory and Autonomic Neuropathy (HSANs).
Tropomyosin-related Kinase A (TRKA).
Nerve Growth Factor (NGF).

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AUTHOR'S CONTRIBUTION:
MA: Took initial history and examination, concept, drafting, editing and final review.
NM: Helped writing initial draft, editing and final review.
SSK: Took initial history and examination, writing, drafting, editing and final review.
MA: Overall editing, discussion writing and final review.
SK: Overall editing and final review.
All authors contributed to literature search, critical revision, of the drafts and final edits.