Congenital Insensitivity to Pain with Anhidrosis (CIPA): Report of a Case of Saudi Female Infant with Oral Manifestation

Khaled M. Mohamed BDS, MDS, PhD.

Assistant Professor of Oral & Maxillofacial Rehabilitation Department – Division of Oral & Maxillofacial Surgery ,Faculty of Dentistry - King Abdulaziz University- KSA. (Lecturer of Oral & Maxillofacial Surgery.. Oral & Maxillofacial Surgery Department, Faculty of Dentistry - Suez Canal University - Egypt).
k_kamel25@hotmail.com

Abstract: Congenital insensitivity to pain with anhidrosis (CIPA) is a rare hereditary autosomal recessive disorder. The causative gene neurotrophic tyrosine kinase receptor 1 (NTRK1) is located on chromosome 1 and encodes tyrosine kinase receptor which is stimulated by nerve growth factor (NGF). Clinically, CIPA is characterized by insensitivity to pain, anhydrosis, repeated attacks of fever at very young age, self mutilation, defective or absence of tears and mental retardation. Orthopedic, maxillofacial, dermatological and ophthalmic complications are common. Absence of pain leads to self mutation that begins after eruption of teeth and manifested in tongue, lip and finger biting. In addition to early diagnosis, medical, physiological and social support and guidance of those patients' families is important, dental preventive measures are crucial for prevention of early self mutilation.
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1. Introduction:

Congenital insensitivity to pain with anhidrosis (CIPA), or hereditary sensory and autonomic neuropathy (HSAN) type IV is a rare and severe recessive autosomal disorder, that was first described by Swanson in 1963 [(1)].

According to Dyck classification [(2)], congenital insensitivity to pain with anhidrosis (CIPA) is categorized as HSAN type IV: type I is relatively mild, mainly affects the lower limbs and manifests in the second to fourth decade. Type II is more severe and presents in infancy. Type III is familial dysautonomia or Riley-Day syndrome. It is multi-systemic and affects mainly Ashkenazi Jews. Type IV features insensitivity to pain, heat intolerance, and mental deficiency. Type V affects nociception selectively.

Insensitivity to pain associated with defective development of nociceptive neurons in dorsal root ganglia and abnormal innervations of eccrine sweat glands by cholinergic sympathetic fibers that are responsible for anhydrosis and hyperthermia [(3)]. Indo *et al.,* 1996 [(4)], identified the causative gene neurotrophic tyrosine kinase receptor 1 (NTRK1) that is located on chromosome 1 and encodes tyrosine kinase receptor which is stimulated by nerve growth factor (NGF). Neutrophins bind to tyrosine kinase receptors: TrkA, TrkB, or TrkC and a common neutrophin receptor p75 (p75NTR) that has no tyrosine kinase domain. Mutated receptors lead to defect in NGF signal transduction and to impaired support to sympathetic ganglion neurons and nociceptive sensory neurons in dorsal root ganglia. Inability to transduce NGF into growing sympathetic and sensory neurons leads to death of these neurons of neural crest origin and is NGF dependant [(5-7)].

Clinically, CIPA manifested mainly by recurrent episodes of fever starting in infancy, 20 % of children die during the first three years of life. Additional characteristic of the condition is anhydrosis (lack of tearing accompanied by superficial punctuate keratopathy and corneal opacity), absence of reaction to pain, and mental retardation. All these features lead to self-mutilating behavior, such as biting tongue, lips and fingers, extremities' injuries as fractures and dislocation, and recurrent infections. Delayed wound healing, loss of primary teeth, palmar hyperkeratosis and cardiovascular complications [(1, 8, 9)].

Diagnosis of CIPA is based on clinical findings, which is characterized by history of recurrent fever, dermatological sings, insensitivity to pain, multiple infections, fractures and joint dislocations, self-mutilating behavior and learning disabilities. Pharmacological test (intradermal injection of 1:10,000 histamine) and skin and nerve biopsy (absence of unmyelinated axons, decrease in the number of small myelinated axons and normal distribution of large myelinated axons) [(10)]. Deoxyribonucleic acid (DNA) analysis for detection of NTRK1 gene mutations is the most definitive diagnostic tool [(4)].

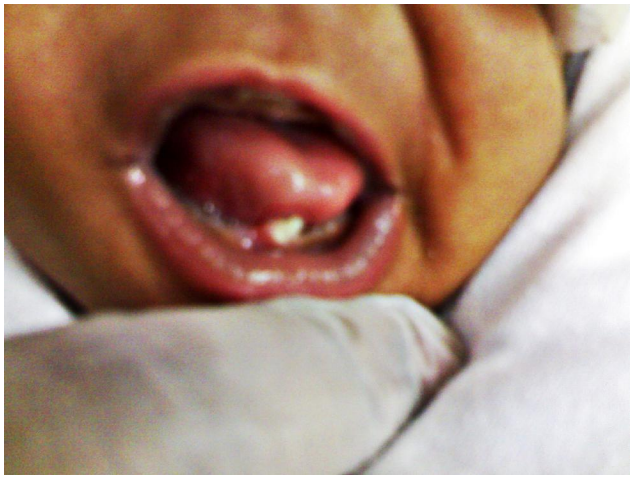
2. Case Report:

A 5-month-old female child was referred from family private pediatrician with a chief complaint of repeated ulcer in the tip of the tongue from ventral surface and loose prematurely erupted central incisors. She was born with a normal delivery. She was the first child of healthy parents of a consanguineous marriage. The child was diagnosed as having HSAN type IV at age of three months at a private hospital. There was no family history of neurologic or metabolic disease. The mother gave a history of her child of repeated attacks of fever started at the fourth week of life that she was hospitalized many times. The child was treated at the beginning as the cause of fever is infection until her condition was diagnosed by their pediatrician at private hospital.

The patient's history revealed an absence of normal reaction to painful stimuli during injection or cannula insertion. After the patient's mandibular central incisors erupted at age of four months and after eruption of tongue ulcer, the mother was advised to use a piece of rubber to avoid tongue biting till the teeth started to loosen.

Upon clinical examination the child physical appearance was normal with no dysmorphic features. The patient's skin was warm and dry (37.8 C). Oral examination revealed loose erupted deciduous central incisors with small ulcer in the ventral surface of tongue tip forming a red halo related to the incisal tip of the erupted incisors (Fig.1). On probing the labial mucoperiosteum, the child showed no response.

Although extraction is an extremely radical treatment, there was no other possibility to keep the loose teeth and treat the inflamed tongue tip. Extraction was performed using half cartridge of local anesthesia (mepivacaine HCL with epinephrine 1/100,000) for homeostasis. Anti-inflammatory was prescribed for the patient till the ulcer condition was improved and regeneration started.



3. Discussion:

CIPA is a rare autosomal recessive disorder of peripheral nervous system. The clinical presentation of the condition is quite characteristic with repeated episodes of fever in early life. The patients have dry and warm skin, suffer from anhydrosis and do not tear or sweat. Self mutilation is a serious complication of the disease that is mostly an outcome of insensitivity to pain. These complications include; tongue, lip and finger biting. Accidental injuries include bone fracture, joint dislocation and predisposition to deep infections as osteomyelitis. Progressive amputation might occur. Most of the children are mentally retarded, microcephalic and hypoactive.

Insensitivity to superficial and deep painful stimuli together with the absence of sweat and tears constitute the main and early features of the disease. Another rare autosomal syndrome "the triple "A", shares these manifestations, and characterized by another manifestation as alacrima, achalasia and adrenal insufficiency [(10)].

Bonkowsky *et al.,* 2003[(11)], suggested that diagnosis of CIPA by molecular means is not recommended due to large, unwieldy TRKA gene and considered the clinical presentation, electromyography (EMG), and skin biopsy are sufficient for making diagnosis. EMG excludes other peripheral neuropathies, while skin biopsy demonstrates absence of epidermal and sweat glands innervations. These represent a sensitive, reliable, and rapid means of diagnosis rather than DNA sequencing.

Primary dentition eruption is considered a pilot timing for self mutilation in CIPA disease. Frequently, the tongue and lips are affected with

resultant scarring and deformation [12]. Therefore, dental personnel should be involved of management of patients with CIPA. The parents should be taught the time of eruption of primary teeth in order to observe their child carefully particularly after eruption of teeth, take their child to dentist for preventive means. As in my case the mother used a piece of rubber that caused looseness of the central incisors that made it impossible to preserve the teeth. Preventive measures include grinding of incisal edge, use of mouth guards or other appliances [12]. Yet, extraction is an aggressive procedure, sometimes is unavoidable in cases where there is severe mutilation [13], or teeth are loose.

There is no treatment for CIPA and other autosomal neuropathies and the only treatment is symptomatic. Such families particularly, parents need continuous information, guidance and help by psychologist, medical and dental consultation that should be before teeth eruption to avoid self mutilation caused by erupting teeth.

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