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Congenital Insensitivity to Pain with Anhidrosis: A Review of Literature and Case Report

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ABSTRACT

Congenital insensitivity to pain with anhidrosis is a rare genetic disorder of peripheral nervous system characterised by recurrent episode of unexplained fever, generalized anhidrosis, insensitivity to pain and temperature and self mutilating behavior. We are presenting a eight year old female with CIPA who have pus discharge and pathological fracture of anterior mandible .Sural nerve biopsy revealed reduced number of unmyelinated and small myelinated nerve fibres ,consistent with characteristic feature of CIPA.

Key Words: *Pain insensitivity, Anhidrosis, ,Sural nerve*

INTRODUCTION

Congenital insensitivity to pain and anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy (HSAN) type IV, initially described by Swanson¹ in two brothers with changes in temperature control and insensitivity to pain, it is a rare autosomal recessive neuropathy of the

group of hereditary sensory and autonomic neuropathies, characterized by insensitivity to painful stimuli, changes in temperature control, and varying degrees of mental retardation. It is secondary to a mutation in the neurotrophic tyrosine kinase receptor type 1 (NTRK1) gene, located in chromosome 1. It encodes the tyrosine

kinase receptor type A that is autophosphorylated in response to nerve growth factor (NGF) activating several intracellular signaling pathways. Mutations in the NTRK1 gene inhibit the development of NGF-dependent sensory and autonomic neurons during the embryonic period². In adults, NGF is not necessary for cellular survival; however, it plays a crucial role in pain generation and hyperalgesia in acute and chronic pain. The expression of NGF is increased in traumatized and inflamed tissues, and activation of tyrosine kinase receptor type A in nociceptive neurons potentiates pain through several mechanisms³. Insensitivity to pain and mental retardation causes those patients to self-mutilation (especially fingers, lips, and tongue), corneal lacerations, non-painful fractures, arthropathies, and joint deformities leading to chronic osteomyelitis and septic arthritis^{4,5}.

In a study conducted in Japan with 15 patients, they all presented some degree of tactile sensitivity or hyperesthesia. Thermal sensitivity varies, but most patients have some degree of cold and heat sensitivity⁵. The reduction in the central and peripheral activities of noradrenaline and anhidrosis can lead to the development of perioperative hypotension and hyperthermia^{4,5}. The diagnosis of CIPA is based on the clinical presentation, pharmacological test (intradermic reaction to 1:10,000 histamine), and neuropathological exam: absence of unmyelinated fibers (C fibers), reduction in the number of small myelinated fibers (A δ fibers), and normal distribution of large myelinated fibers (A α and A β

fibers). The structure of the sweat glands is normal but they are not innervated. Genetic analysis looking for mutations on the NTRK1 gene represents the last diagnostic step⁴. Specific treatment is not available and due to the high morbidity associated with this disorder patients usually do not live past the second decade of life.

CASE REPORT

A eight year old female child weighing 19 kg , 79 cm height was referred to our department, whose chief complaint was a pus draining on lingual side of mandible in the anterior region. It started with swelling of lower face two months back which had regressed now after taking some antibiotic treatment. Patient also gave a history of recurrent fever since birth which is more during summer which is relieved by putting her in some cold water. There was also a history of self mutilating behaviour, i.e biting her Tongue, Nails fig 1, with a history of CIPA who was admitted for the surgical treatment of fracture mandible. Her family members reported a history of nonconsanguineous marriage and that the patient had one brothers, who is normal. Preoperative laboratorial exams were within normal limits. The patient was not taking any drugs and this was her first surgery. On physical exam she had a short neck, macroglossia, and Mallampati III indicating the possibility of difficult airways. She had diffuse lack of sensitivity to pain, and self-induced injuries in hands and distal extremities of the finger (Figure 2). Sural nerve biopsy suggests HSAN Type 4 (fig 3).

OPG reveals multiple carious teeth and permanent tooth buds multiple radiolucent areas with pathological fracture at parasymphyseal area.(fig 4).

The disease is managed as per the presentation. When presents with osteomyelitis of mandible all offending teeth to be extraction. Then ORIF to be done even though the child is having permanent buds under general anesthesia. Mandible has excellent healing results than other bones of the body in these patients.(fig 5).



Fig 3.Sural Nerve Biopsy



Fig. 1 Bifid Tongue



Fig 4.Pathologic Fracture Anterior Mandible



Fig.2 Digit Abnormality



Fig 5.ORIF done with miniplate and screws

DISCUSSION

According to Dyck and Otha (1975) hereditary sensory neuropathy (HSN) is divided into 4 types. Congenital insensitivity to pain (CIP) is added to this group as a similar neuropathy.

Hereditary sensory and autonomic neuropathies (HSAN) are a group of disorders characterized by insensitivity to noxious stimuli and autonomic dysfunction, associated with pathological abnormalities of the peripheral nerves. Five types of HSANs have been identified by Dyck.⁶ Type IV congenital insensitivity to pain with anhidrosis (CIPA) is characterized by inexplicable episodes of fever at an early age, in addition to insensitivity to pain and self-mutilation. Those affected do not sweat or cry.⁷

CIPA is secondary to a mutation in the neurotrophic tyrosine kinase receptor type I (NTRK1) gene. Mutation of this gene inhibits the development of nerve growth factor (NGF), and dependent sensory and autonomic neurons during the embryonic period.⁸ NGF is not necessary for cellular survival; however, it plays a crucial role in pain generation and hyperalgesia during episodes of acute and chronic pain.⁹ Insensitivity to pain can cause self-mutilating behavior for these patients. In most cases, bite injuries to the tongue, lips and fingers begin with the eruption of the primary teeth.¹⁰

Sometimes the self-mutilating behavior leads to severe injuries such as self-extraction of the teeth and nails. Oral self-mutilating behavior represents a challenge for dentists. Therefore, treatment of these patients is diverse and is predicated upon the

circumstances of individual cases. In the 1960s, dentists extracted the teeth of children diagnosed with CIPA in order to avoid oral self-mutilation and full denture therapy¹¹. Although those patients have insensitivity to pain, some of them have tactile hyperesthesia, which can cause an uncomfortable perception during surgical manipulation¹¹⁻¹². Perception of tactile stimuli and pressure can also cause complaints of postoperative pain. There are reports of surgical procedures without anesthesia in patients with CIPA, such as the case of a patient who underwent amputation of both feet under sedation, but without analgesia. He did not show any response to incision of the skin or disarticulation, and he only reacted to clamping of a nerve trunk with flexion of a limb¹³. An eight-year old patient with CIPA underwent reduction of a femur fracture with osteosynthesis under epidural block and sedation without complications during the procedure¹⁴.

Our patient having pathologic fracture of mandible, the disease was treated according to its manifestation. Involved teeth are extracted and granulation tissue are curetted out and fracture are reduced and stabilized with miniplates. In contrast to the slow healing reported in long bones, the mandible healed very quickly, possibly indicating that the osteoporotic mandible in this group of patients is different from that seen in the elderly. Furthermore, the standard ORIF technique can be safely used in this rare group¹⁵.

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