IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2023 Vol.:27, Issue:3

A Brief Review on Congenital Insensitivity to Pain and Anhydrosis (CIPA)

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 22 May 2023
Accepted: 29 May 2023
Published: 30 June 2023

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Congenital Insensitivity, Pain, Anhydrosis (CIPA)

ABSTRACT

Congenital insensitivity to pain with anhydrosis (CIPA) syndrome is a rare autosomal recessive disorder that affects various tracts of the peripheral and autonomic nervous systems. CIPA include recurrent childhood-onset hyperthermia and unexplained fever, anhydrosis (inability to sweat), severe loss of pain sensitivity, neurodevelopmental delay, unconscious self-mutilation of fingers, lips, and tongue, corneal abrasion, palmar hyperkeratosis, no.-painful fracture and joint deformities in the right ankle. Torn, deep tendon reflexes and motor and sensory nerves. CIPA is very dangerous and in most cases the patient does not live more than 25 years. The pathophysiology of CIPA is not completely clear, but it is believed to occur through improper differentiation of fibroblasts into bone cells. It mostly occurs in areas with a high risk of injury, such as the quadriceps, arm flexors, and abductors [7]. Patients of CIPA have homozygous mutations in the NTRK1 gene. The purpose of reporting this syndrome is to help physicians become familiar with this condition, avoid unnecessary surgery or amputation, use conservative treatment, and facilitate diagnosis of this syndrome without additional laboratory requests. That's it. Unfortunately, there are no facilities in our country to confirm the diagnosis by genetic testing, so treatment must be initiated based on clinical and preclinical findings to improve patient quality of life.

INTRODUCTION:

Congenital insensitivity to pain with anhydrosis (CIPA) syndrome is a rare autosomal recessive disorder that affects various tracts of the peripheral and autonomic nervous systems.[1]Congenital anhydrosis with anhydrosis (CIPA) was first described by Dearborn in 1932 and systematically described by Swanson in 1963. It was Dyck who in 1984 introduced hereditary sensory autonomic neuropathy (HSAN) as an entity and classified it into five types (HSAN-I to HSAN-V) based on clinical presentation, mode of inheritance, pathology and molecular basis.[2]Hereditary sensory and autonomic neuropathy (HSAN) is a group of disorders characterized by insensitivity to noxious stimuli and dysfunction of autonomic functions, associated with pathological abnormalities of the peripheral nerves.[3]Type IV congenital insensitivity to pain (CIPA) is characterized by unexplained febrile episodes at an early age, in addition to insensitivity to pain and self-injury.[4] CIPA include recurrent childhood-onset hyperthermia and unexplained fever, anhydrosis (inability to sweat), severe loss of pain sensitivity, neurodevelopmental delay, unconscious self-mutilation of fingers, lips, and tongue, corneal abrasion, palmar hyperkeratosis, no. -painful fracture and joint deformities in the right ankle. Torn, deep tendon reflexes and motor and sensory nerves.[5]

OTHER NAMES[6]

- CIPA
- Hereditary insensitivity to pain with anhydrosis
- Hereditary sensory and autonomic neuropathy type IV
- Hereditary sensory and autonomic neuropathy, type 4II
- HSAN type IV
- HSAN4
- Familial dysautonomia Type IV

EPIDEMIOLOGY-

CIPA is very dangerous and in most cases the patient does not live more than 25 years. Although some can lead a more or less normal life, they must constantly look for cuts, bruises, self-mutilations and other undetectable injuries.[7]CIPA has an incidence of

1/125,000,000.[1]Cases of CIPA have been reported from various parts of the world, but most cases are from Japan. American and Bedouin Israelis.[2]More than 300 cases have been reported from Japan, about 60 cases from the US.[8]Cases of congenital insensitivity to pain in anhidrosis (CIPA) are very rare and only a small percentage of this condition has been reported in India.[9]

PATHOPHYSIOLOGY-

The pathophysiology of CIPA is not completely clear, but it is believed to occur through improper differentiation of fibroblasts into bone cells. It mostly occurs in areas with a high risk of injury, such as the quadriceps, arm flexors, and abductors [7]·patients of CIPA have homozygous mutations in the NTRK1 gene. This gene codes for receptors for a nerve growth factor that normally promotes the survival of embryonic sensory and sympathetic neurons . Dysfunction of this factor leads to sensory and sympathetic dysfunction, leading to CIP and anhidrosis.[10]

CLINICAL REPRESENTATION OF CIPA-In general, all HSAN patients with congenital insensitivity to pain present with repetitive, painless, and often unrecognized musculoskeletal injuries beginning in early childhood, sometimes misdiagnosed as nonaccidental injuries. The repetitive and unconscious nature of these injuries can lead to untreated fractures, joint destruction, osteomyelitis, septic arthritis, avascular necrosis, and Charcot arthropathy. Many patients also suffer self-inflicted injuries.[10]

ETIOLOGY-

GENETICS-

The only known causative gene so far is **neurotrophic receptor tyrosine kinase 1 (NTRK1),** located on chromosome **1q21-q22**. A mutation in the NTRK1 gene is associated with consanguineous marriage.[1]

- The **NTRK1** receptor is important for nerve cell survival. The NTRK1 receptor is found on the surface of cells, especially the neurons that send messages to pain, temperature and touch (sensory neurons). When the **NGFβ** protein binds to the NTRK1 receptor, signals are sent inside the cell that help it grow and divide and help it survive. Mutations in the NTRK1 gene create a protein that cannot send signals. Without the proper signal, neurons die through a self-destructive process called apoptosis. loss of nerve leads to an inability to feel pain in

people with CIPA. In addition, people with CIPA lose the blood vessels that supply the sweat glands, so people suffer from dehydration.[6]

➢ Nociceptive sensory neurons and sympathetic autonomic neurons are under the surveillance of NGF and have a role in the activation and homeostasis of other cell types . Thus, NTRK1 mutations cause poor development of the somatic sensory system, which is located in the dorsal root ganglion sensory neurons for pain and temperature.[3]

➢ Defects in NGF signal transduction by the TRKA receptor result in failure to survive in sympathetic ganglion neurons and sympathetic ganglion neurons and crest-derived nociceptive sensory neurons.[11]

Mutation-A total of 37 different mutations were found in CIPA families from different countries. Mutations are found in the outer and inner domains of the cell.[12]

When do symptoms of congenital insensitivity to pain and anhidrosis start-

The age at which symptoms begin to appear depends on the disease from birth to childhood. Symptoms may appear at one age or at more than one age. Symptoms of some diseases begin at any age Knowing when symptoms start can help health care providers find the correct diagnosis.[13]

SYMPTOMS-

The patients may have signs of self-harm, mental retardation, as well as little or no sweating. The height and weight of these patients are below normal for their age. In addition to the loss of small myelinated fibers, patients with CIPA show a loss of myelinated fibers. As a result, there are no epidermal nerve fibers and the fibers around the sweat glands form the morphological basis of analgesia and anhidrosis in CIPA.[4]

Anhidrosis:- Abnormal response to heat Lack of sweat can be harmful because sweating allows heat to escape from the body. Anhidrosis may not be recognized until a significant amount of heat or exercise stops sweating. A general lack of sweating can be life-threatening because the body overheats.[14]

FOLLOWING SINGS ARE OBSERVED IN CIPA PATIENTS[13]–

➢ PREMATURE LOSS OF TEETH

- APLASIA OF SWEAT GLAND
- IMPAIRED TEMPRATURE SENSATION
- PAIN INSENSITIVITY
- SELF-MUTILATION
- ABNORMILITY OF HU8MORAL IMMUNITY
- FASCITIS (inflammation of fascia, tissue under the skin and the muscle.)
- NEUROPATHIC ARTHROPATHY
- NAIL BITING
- ABNORMILITY OF ANKLE
- ABONORMILITY OF ANS
- AVASCULAR NECROSIS
- DYSPHAGIA
- GROWTH DELAY
- SEPTIC ARTHRITIS
- SYNCOPE
- TOOTH ABSCESS
- HYPERSTHESIA- 20% of these patients usually die within the first three years of life due to repeated bouts of hyperkinesis.[2]

DIAGNOSIS-

There are no easy tests to identify CIPA, but providers have some tools to help make the diagnosis. For example, they can take a small sample of tissue and look under a microscope to look for underdeveloped nerves. The most accurate diagnostic test for CIPA is a genetic test to check for an abnormal TRKA (NTRKI) gene.[15] This syndrome can be diagnosed

through clinical tests and paraclinical tests, but it would be best to confirm it through genetic testing.[7]

Diagnosis of disease is based on clinical presentation, pharmacological test (intradermal response to 1:10,000 histamine), neuropathological examination in electron microscopy (lack of myelinated fibers, a small number of myelinated fibers and a normal distribution of large myelinated fibers) and the detection of a mutation in the NTRK1 gene represents the final diagnostic step.[5] Other tests are also done like axonal flare test and biopsy. In the cutaneous histamine injection flare test, a normal flare was not induced at the injection site in CIPA patients.[3]

The molecular test to evaluate the mutation of NTKR1 is a confirmatory test for the diagnosis of CIPA, but its utility is a great challenge.[15]

TREATMENT-

The treatment of CIPA varies patient to patient and depends on each individual case. There is no cure for CIPA and treatment is primarily about ensuring safety. It is important to prevent injuries and monitor wound infections Good health care and lifestyle changes are important ways to live safely with CIPA. These strategies should be implemented immediately after diagnosis and modified as needed throughout the child's life.[15]Prostheses improve the physical appearance and psychosocial adjustment of patients.[4]Definitive treatment should be considered as an alternative therapy of last resort. In elderly patients with mild to moderate mental retardation, conventional dental treatment (root canal treatment), restorative treatment (dental crowns) and/or orthodontic treatment may be considered. Rubber dams should be used for people with ADHD to avoid serious accidents.[4]In addition, research on CIPA may have clinical implications for the treatment of acquired "complex regional pain syndrome," including "causalgia" and "reflex sympathetic dystrophy."[12]

Because there are no treatments available for CIPA, prenatal screening is the only option to prevent the birth of an infected child in a family with the disease. Early identification of these patients, prevention of unintentional injuries, and timely diagnosis of orthopedic complications help limit the frequnyl, succinylcholine, atracurium, pancuronium, vecuronium, ketamine, propofol, barbiturates, benzodiazapines, and others. Surgery in CIPA patients is difficult to manage due to poor outcome and high complication rate .[2]

As there is no definitive therapeutic intervention for this disease, education and prevention are important to improve the quality of life of people with CIPA. There is no effective treatment for CIPA syndrome, and since most CIPA patients are young children, parents should be educated on simple precautions. Education, pain relievers, antibiotics, splints, prophylaxis, and regular follow-up are important to improve the quality of life of CIPA patients. Sibling screening is important for early intervention to slow disease progression to address these conditions.[1]

CONCLUSION-

The purpose of reporting this syndrome is to help physicians become familiar with this condition, avoid unnecessary surgery or amputation, use conservative treatment, and facilitate diagnosis of this syndrome without additional laboratory requests. That's it. Unfortunately, there are no facilities in our country to confirm the diagnosis by genetic testing, so treatment must be initiated based on clinical and preclinical findings to improve patient quality of life.

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