IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 7, May 2023

A Review of Comprehensive Study Oncongenital Insensitivity to Pain with Anhidrosis

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Abstract: *In this article, we have demonstrated the signs and symptoms of children that refer to the pediatrics and assay about their complications with this disease. The current study's goals are to confirm the anti-inflammatory properties. Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV, is a relatively rare illness. Just a few hundred instances of CIPA have been documented globally, affecting 1 in 125 million infants. The bulk of cases are documented in Asian countries. Now, three clinical characteristics—mental retardation, a lack of perspiration, and pain sensitivity—were used to describe the illness. The human TRKA gene (NTRK1) is located on chromosome 1q21-q22 and is responsible for producing the nerve growth factor receptor tyrosine kinase. CIPA is caused by the TRKA gene. When a young female youngster with CIPA and a tibia fracture attended our centre for consultation, it served as inspiration for us to thoroughly review the literature and assess the therapeutic possibilities. The therapeutic approach is the only therapy strategy for CIPA that is yet unproven. In our research, we found that staphyloccus aureus is the most prevalent pathogen and that the skin and bones are the main sites of infection in children with CIPA. Here, we review the condition, including its history, case studies and treatment*

Keywords: CIPA Syndrome, Congenital Pain Insensitivity, pseudoarthrosis, Arthropathy, HSAN type 4

I. INTRODUCTION

Two symptoms of congenital insensitivity to pain with anhidrosis (CIPA) are present: the inability to feel discomfort, feel hot, or sweat less or not at all (anhidrosis). Type IV inherited sensory and autonomic neuropathy is another name for this disorder. Early CIPA symptoms and indications show up. Normally, although under cautious medical supervision, during birth or during infancy. Patients with CIPA frequently experience inexplicable fever episodes, engage in self-mutilation, are intellectually disabled, do not react to unpleasant stimuli, have anhidrosis, palmoplantar keratoderma, humoral immunodeficiency, and develop early-onset renal disease. The NTRK1 gene, which codes for neurotropic tyrosin receptor kinase, has been linked to CIPA. Tropomyosin-related kinase A (TrkA), which is encoded by NTRK1, binds to nerve growth factor (NGF). Unintentional self-harm is frequent among CIPA patients. Commonly by biting the fingers, lips, or tongue. It can result in the afflicted region being amputated on its own. Moreover, injuries to the skin and bones heal slowly in individuals with CIPA. Repeated trauma can cause osteomyelitis, a persistent bone infection, or Charcot joints, which are destroyed.About half of people with CIPA show signs of hyperactivity or emotional instability.Morphologic studiesrevealed that insensitivity to pain and anhidrosis result from the absence of sensory and sympathetic postganglionic neurons.Congenital insensitivity to pain is a rare disorder, first described in 1932, a clinician describes a 54 year old man who reported never having felt pain despite a list of injuries including “a blow in the face with a pickaxe, a bullet through a finger, a broken nose, severe loceration of the knee and a burned hand,etc. all without apparent pain.’’ The man named Edward Gibson, by Deaborn as congenital pure analgesia. Mardy was the first to study CIPA in depth. Published in 1999 in the American Journal of Genetics, Mardy identifies the cases of CIPA. Another study was done by Guo on two Taiwanese brother both diagnosed with CIPA. The incidence of this disorder is about 1 in 125 million with few cases reported worldwide to date. Nowadays, there are only around 20 cases have been reported in scientific literature. CIPA is very rare disease: there are only around 60 documents cases in the United States and around 300 worldwide and only handful of this condition is being reported in India. As per report a

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2.5 year old boy with clinical features as the first case in Iran, in 1963. As per research, nearly 20% of patients with this disorder die within the first 3 years of life because of hyperpyrexia.

Pathophysiology

CIPA is brought on by an NTRK1 gene mutation. The NGF-B receptor protein is made using instructions from the NTRK1 gene. Cells' exteriors include the NTRK1 receptor. Especially the neurons responsible for transmitting pain, temperature, and touch sensations (Sensory neurons). Signals that aid in cell survival are sent when the NGF-B protein interacts to the NTRK1 receptor. Neurons die by a process of self-destruction known as apoptosis when the NTRK1 gene is mutated, resulting in a protein that is unable to convey messages without adequate signalling. Those with CIPA are unable to experience pain due to sensory neuron loss. Those who have CIPA also lose the nerves that lead to their sweat glands. This results in anhidrosis in the afflicted person.Dorsal root ganglia (DRG) neurons of the trigeminal ganglia (V) neurons are NGF-dependent primary afferents. Most likely, a portion of the neurons of the vagus nerve (X) and glossopharyngeal nerve (IX) are NGF-dependent neurons. Blood vessels, the piloerector muscle, the sweet glands, as well as other target organs or tissues in the body, are all innervated by sympathetic postganglionic neurons. Cholinergic postganglionic fibres connect to sweat glands. The main afferents that depend on NGF may be stimulated directly or indirectly by triggering stimuli. These neurons emit (SPA and CGRP) in response to stimulation, which controls itch, pain, and inflammation. Postganglionic sympathetic neurons can also affect inflammation. Calcitonin gene-related peptide (CGRP), dorsal root ganglia (DRG), sympathetic ganglion (SG), substance P (SP), and spinothalamic tract (STT) are some of the related compounds.

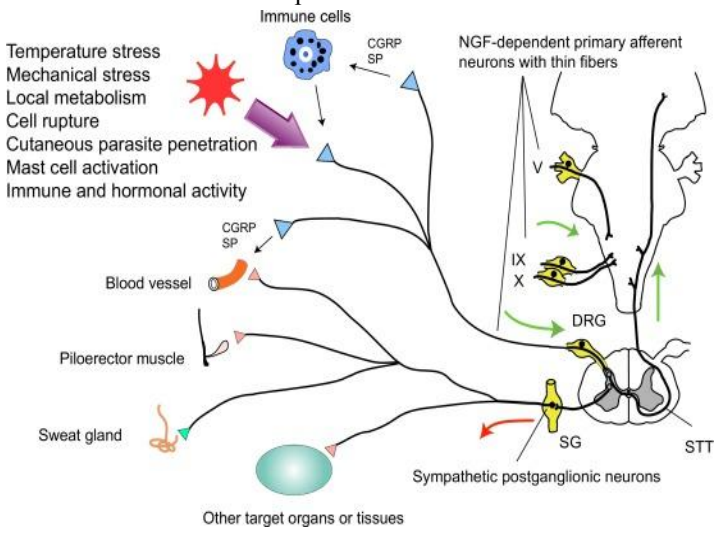

Fig. No.1Patients with congenital insensitivity to pain with anhidrosis

Inheritance

This syndrome has an autosomal recessive inheritance pattern. This indicates that the gene has been altered in both copies in each cell. One copy of the defective gene is carried by each parent of a person with an autosomal recessive disorder, however they normally do not exhibit the signs and symptoms of this condition. The diagnosis of CIPA is often made following the whole course of development in babies who have recurrent fevers. Who bites their tongue, fingers, or lips a lot? If elderly people continue to have catastrophic injuries, an evolution is necessary. Clinical diagnoses are formed via evaluations of sensory and autonomic functioning.

Treatment

CIPA cannot be cured, hence the main goal of treatment is safety. Avoiding injuries is crucial, and any wounds should be checked for infection. For social support and advice on coping with CIPA, support groups might be useful. Congenital insensitivity to pain linked with channelopathy has been treated with an opioid antagonistic drug called Naloxone, which has shown some partial efficacy uncertain patient.

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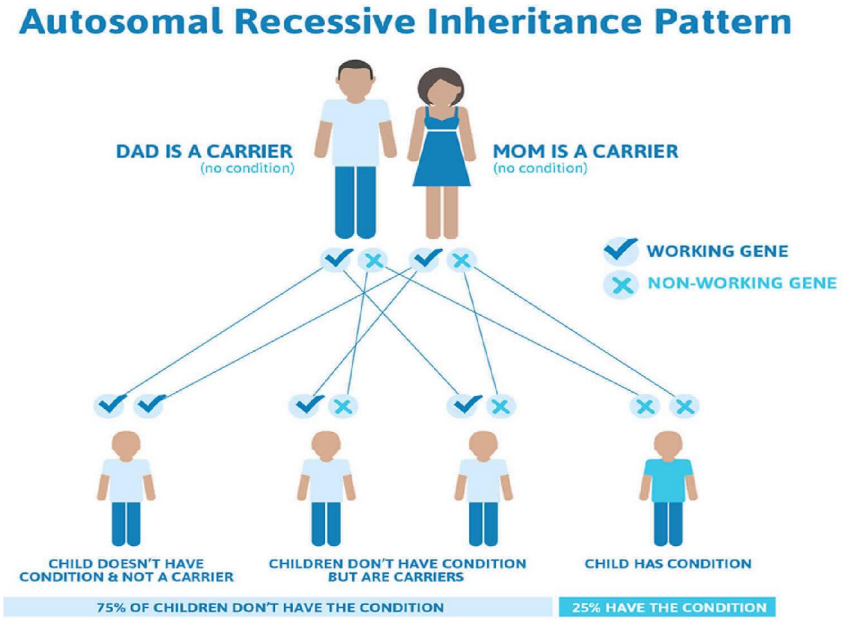

Fig. No. 2 Autosomal recessive inheritance pattern

Case Presentation

CASE 1:A 12-year-old child with persistent osteomyelitis presented. He was the sixth child of an Iranian couple who were consanguineous. His birth records revealed a poor Apgar score. There was no inherited or familial illness in the family. Becoming pregnant was common. He underwent many hospital stays as a result of osteomyelitis, fever, convulsions, and hell sores. He had no response to discomfort and was unable to feel either heat or pain. Results from the lumbar puncture and brain CT scan were both normal. The TORCH and metabolic studies came back empty. He has mental disabilities. The nerve conduction velocity and electromyography (EMG and NVC) were both normal. Complements, nitroblautetrazolium (NBT) assays, immunological globulins, blood gas, and serum uric acid testing for viral indicators such HBV, HCV, and HIV were all normal.

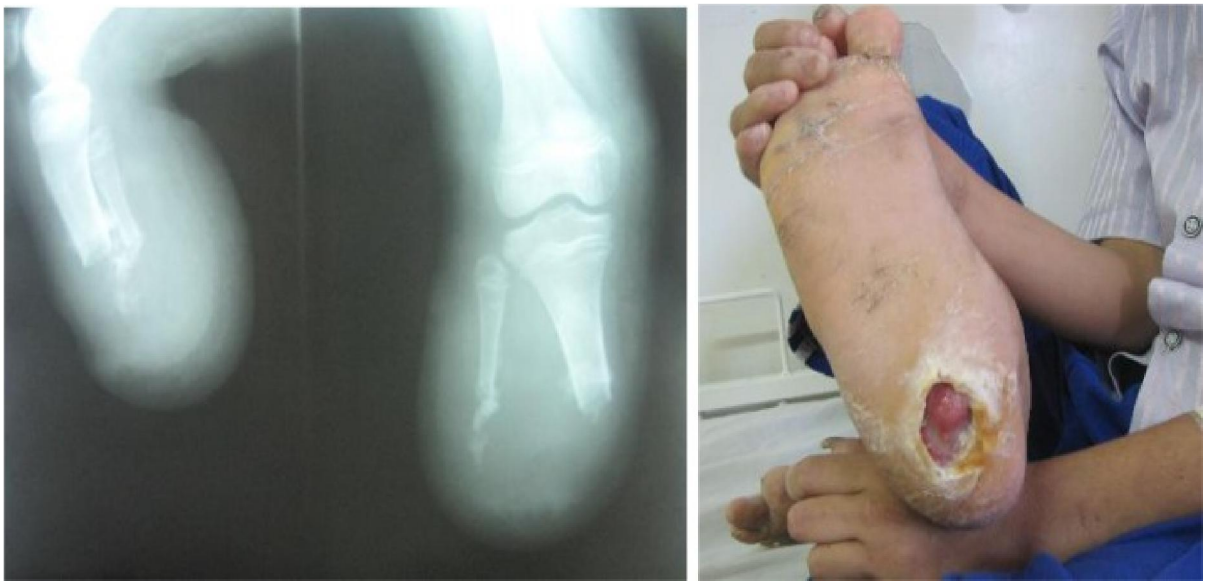

Fig. No. 3 Fingertip osteolysis (right) and painless heel sore (left) ina 12 year old boy with CIPA syndrome

To treat the infection of a hill sore, this patient is recommended (an ulceration). He used the proper medications and the debridement of necrotic tissues to manage the infection in order to prevent limb amputation and maintain the highest quality of life. Moreover, there was severe osteolysis in his mandible, where attempts were attempted to perform the

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necessary dental operations. Evident self-mutation was seen, particularly in his fingers. Moreover, radiographs of him showed osteolysis. During the physical examination, the other locations, including the lung, heart, abdomen, and eyes, were all normal.

CASE-2: A male patient aged 15 arrived at the orthopaedic clinic with many damaged joints. Knees, ankles, and wrists were among the joints that were affected. He exhibits anhidrosis and a lack of pain tolerance, but neither cutaneous neuropathies nor muscular weakness. The patient's parents revealed a prior history of right ankle swelling three months before and bilateral knee swelling six years prior following a trauma. Around the age of 7, the patient started exhibiting signs and symptoms. No other siblings experienced the same issue. The marriage between the parents is consanguineous. Both a rheumatologist and a neurologist extensively examined the patient and recommended nerve and muscle biopsies as part of the workup. His evaluation revealed that he had mobility issues despite arriving at the clinic using a cane. His higher cerebral processes were normal, and he had no cutaneous symptoms or pigmentations, nor did he have any facial asymmetry. Swollen and malformed joints might be seen in the wrists, ankles, and knees [Figure 1]. The results of all blood tests, including lactate dehydrogenase, creatine phosphokinase, C-reactive protein, complete blood count, and erythrocyte sedimentation rate, were all within the normal range. Ankle dislocations on both sides were seen on plain radiographs of the knees and ankles, as well as disordered and damaged joints that might be Charcot joints [Figure 2]. The right femur and leg were dislocated, with the tibia and femur's ends protruding [Figure 3]. Syringomyelia was ruled out by magnetic resonance imaging (MRI) of the spine, and an MRI of the brain came out normal. The diagnosis of bilateral Charcot joints was obtained after an MRI of the knees revealed extensive joint deformity and loose bone fragments within the joints [Figure 4]. With the aid of many Charcot joints, the CIPA syndrome, HSANIV, has been identified. Upper-extremity nerve conduction tests were normal. Due to the homogeneous Charcot abnormalities present, it was technically impossible to conduct nerve conduction in the lower extremities. The NTRK1 gene has a mutation, according to gene research. He had right vastus lateralis muscle and right sural nerve biopsy procedures. The findings showed no obvious pathological anomalies. The siblings' screening came back empty. He began receiving physical and occupational therapy. Parents received information regarding their child's illness.

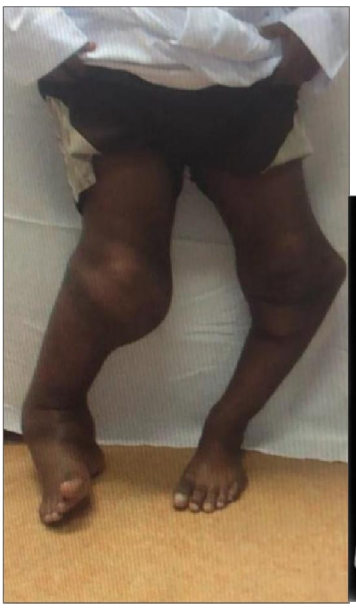

Fig. No. 4 Deformed joints

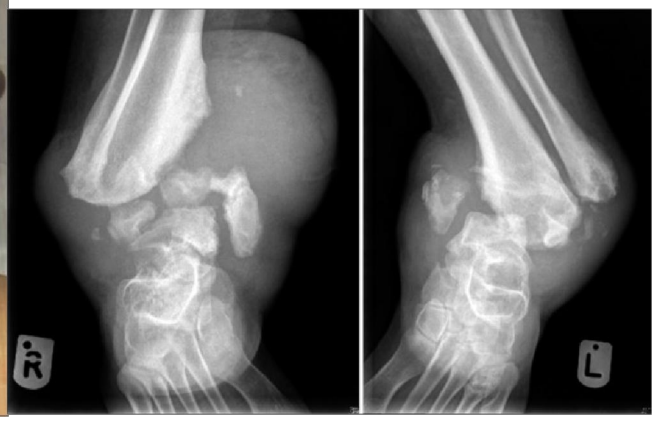

fig. No. 5 Charcot joint

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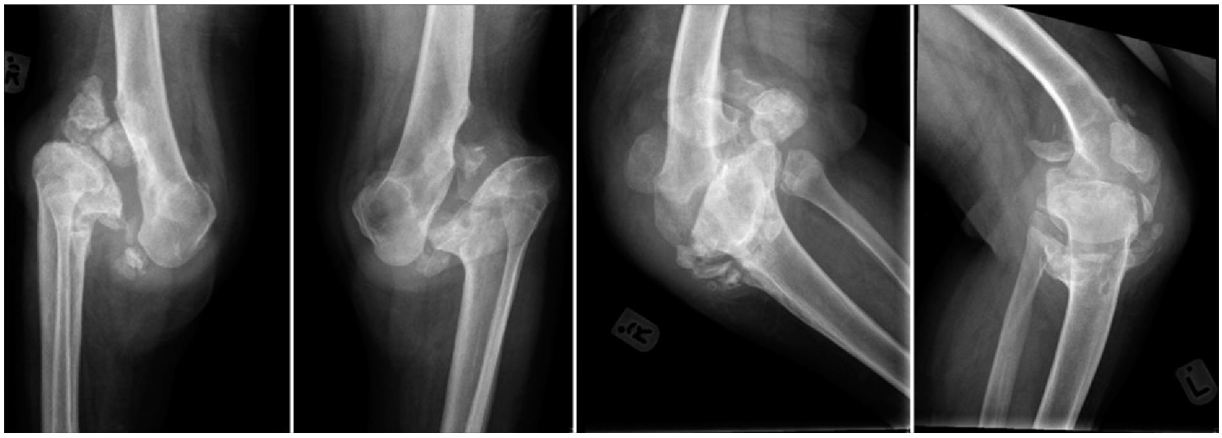

Fig. no. 6Dislocation with overriding ends of the tibia and femur

CASE 3:A 2.5-year-old boy was referred to the pediatrics clinic with severe self-mutilating injuries to his hands, feet, tongue and oral mucosa caused by unconscious biting (Figure 1).

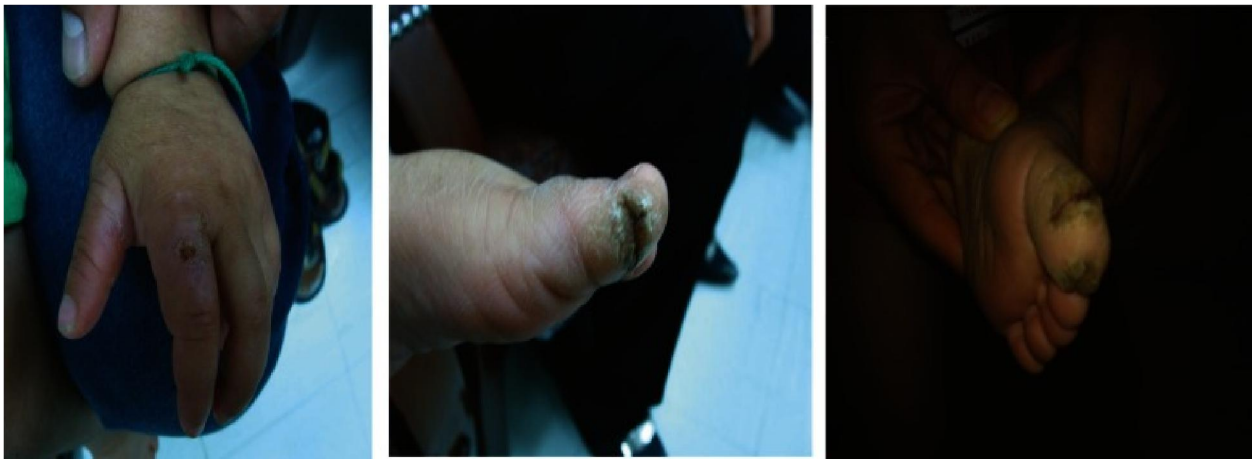

Fig. No. 7 the second child of cousin parents and the product of a term, normal vaginal delivery with a birth weight of 3300 gr.

He was institutionalized at the age of two months due to a fever and convulsion. The patient had a fever the entire time he was in the hospital. Evaluation was done to determine the cause of the prolonged fever, but none of the diagnostic tests—including blood cultures, CSF analyses and cultures, urine analyses and cultures, echocardiograms, blood smears, bone marrow aspirations and cultures, Wright and Vidal tests, abdominal sonography, and brain CT scans—showed abnormal results. He was eventually released from the hospital on phenobarbital, but the episodes of fever and hyperthermia kept returning. After his birth, his parents discovered that he had never perspired and that he did not enjoy warm weather or exposure to the sun. Under these circumstances, he became agitated and wept appropriately. The child's lack of reaction to any type of damage, including pricking, scorching, striking, and cutting, was another complaint made by the parents. The boy's hands or feet were regularly burnt by heater flames or hot water, yet he never complained about the discomfort. When he was 2.5 years old, he had an unrelated right third metatarsal fracture that was treated as an outpatient and left his right foot with swelling and a deformity.Teething had started at seven months of age, but because of biting and ulcerative lesions in the gums, his teeth had started to shed at 1.5 years of age.On examination, he had 12 kilograms weight (10th percentile), 92 centimeter height (75th percentile) and 48 centimeter head circumference (10th percentile) and a normal blood pressure without orthostatic hypotension. Ulcerative lesions were seen in his fingers, toes and mouth that were caused by self-biting (Figure 1)fungiform papillae on the tongue were present. In addition, keratosis and thick and dry skin in the palms of his hands and soles of feet were visible (Figure 1). He had red eyes and corneal ulcer. The deformity as Charcot joint (neuropathic osteoarthropathy) was observed in the right ankle due to repeated trauma (Figure 2).

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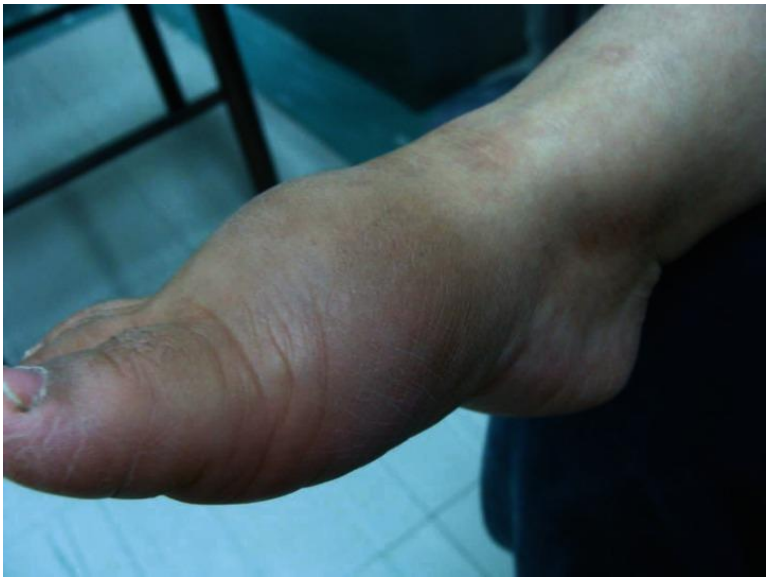

Fig. No.8: Charcot joint in the right ankle

A neurologic evaluation showed that the cranial nerves were functioning normally. Deep tendon reflexes (DTR) and pupil light response were both normal, and the plantar reflex was bilaterally flexor. He was unable to assist with the sensory evaluation. According to the Denver Developmental Screening Test-II, the youngster experienced a neurodevelopmental delay. His parents and brother both had normal IQs and were in good health. They had no inherited illness symptoms and no bad family history. The results of the creatinine phosphokinase level, CBC, uric acid, serum glucose, liver, renal, and thyroid function tests, serum lactate, ammonia, and amino acid chromatography were all normal. Normal nerve conduction velocity (NCV) and minimal brain atrophy were detected by MRI.

II. RESULT AND DISCUSSION

The most prominent characteristic of autosomal dominantly inherited HSAN is type I. The first symptoms appear between the second and fourth decade of life and include gradual sensory loss, persistent foot ulcers that are perforating, and progressive bone deterioration. When NCV is normal, sweating is hindered. HSAN type II is an autosomal recessive condition that manifests as numerous injuries to the fingers and feet, persistent ulcerations, and loss of pain, temperature, pressure, and light touch sensibility in early infancy or childhood. Reduced deep tendon reflexes.
There are fewer or no action potentials in the sensory nerves. Familial dysautonomia, also known as HSAN type III, is an autosomal recessive condition that only affects Ashkenazi Jewish families. Hypotonia, hypothermia, and a weak or nonexistent sucking reflex are typical signs of nervous system failure that are present at birth. Tear production is low or nonexistent, there are no fungiform papillae, no corneal reflexes, anhidrosis, a reduced or absent DTR, postural hypotension, and reduced sensitivity to pain and temperature perception. Nevertheless, after a while, normal touch sensitivity becomes more noticeable. Recurrent pneumonia and cyclic vomiting are common in individuals. Intellect is still average. Many individuals pass away from the illness while they are young or infants.HSAN type IV is an autosomal recessive condition that is also known as congenital anhidrosis and pain insensitivity. Problems with thermoregulation, frequent bouts of hyperthermia, and unexplained fever that may be related to early-onset seizures are some of the first signs. Other symptoms include severe loss of pain sensitivity, anhidrosis (inability to sweat), and mild to moderate mental impairment. Microcephaly is a common condition. Due to their inability to feel pain and mental retardation, these people are more likely to self-mutilate, especially to the fingers, lips, and tongue. There are often Charcot arthropathies, painless fractures, and corneal abrasions. Joint abnormalities are the root cause of septic arthritis and persistent osteomyelitis. The palmar skin is dry, thickened, and hyperkeratotic. DTRs in children are regularly maintained and respond to tactile stimulus. Touch and pressure sensitivity are unchanged, but autonomic anomalies such the inability to sweat in response to heat or chemical stimuli (like pilocarpine) and the production of a wheal but not a flare after intradermal histamine injection are present. In contrast to other sensory neuropathies, the action

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potentials of the motor and sensory nerves are normal. HSAN type V is an autosomal recessive condition that has many traits with HSAN type IV, including anhidrosis and the loss of all other sensations in addition to pain and temperature senses. Tests for reflexes, strength, and nerve conduction are all within the normal range. The primary distinctions between types IV and V were thought to be the pattern of nerve fibre loss, the degree of anhidrosis in HSAN IV patients, and the absence of mental impairment in HSAN V patients.

III. CONCLUSION

According to this study, the diagnosis and medication of the infrequent medical illness CIPA are now being researched. Since this illness has no known treatment. In order to protect the patient's wellbeing, patients and their families can still manage the symptoms of this illness and alter their living arrangements

IV. ACKNOWLEDGMENT

I would like to our sincere thanks to Principal Dr. Yogesh Bafana Sir & Assistant Professor Mr. Ganesh Kardile for providing the required facilities for this article.

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