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Case Report

Congenital insensitivity to pain with anhidrosis and multiple Charcot joints in a child: A case report

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ABSTRACT

Congenital insensitivity to pain with anhidrosis (CIPA) syndrome is a rare autosomal recessive condition affecting various tracts in the peripheral and autonomic nervous system. CIPA has an incidence of 1/125,000,000. The only known causative gene to date is neurotrophic tyrosine receptor kinase 1 (*NTRK1*), which is located on chromosome 1q21-q22. The mutation in the *NTRK1* gene is associated with consanguineous marriages. Manifestations of this condition are highly variable, with insensitivity to pain being the mainstay. Patients are commonly presented with bruises, joint dislocations, multiple fractures, oral manifestations, and disfigured joints. We present a rare case of a CIPA patient manifested with Charcot's joints. A 15-year-old male presented with multiple destructed joints in both knees, ankles, and wrists. He uses walking aids and has a loss of response to painful stimuli. The condition started at the age of 7 years. Other manifestations were fever, anhidrosis, mental retardation, and self-mutilating behaviors. The parents have a consanguineous marriage. Nerve and muscle biopsies were obtained and revealed no significant pathological abnormalities. However, imaging showed grossly disorganized joints and the clinical diagnosis of CIPA was confirmed. As illustrated in this case, the occurrence of CIPA syndrome, hereditary sensory and autonomic neuropathy Type IV, remains highly unprecedented and genetic testing is mandatory for the diagnosis. In addition, nerve and muscle biopsy should be obtained, and advanced imaging such as magnetic resonance imaging is needed to evaluate the case fully. There is no definitive therapeutic intervention for this condition, therefore, education and prevention are important to improve the quality of life of a CIPA patient.

Keywords: Arthropathy, Congenital insensitivity to pain with anhidrosis, Insensitivity to pain, Neurotrophic tyrosine receptor kinase 1, Hereditary sensory and autonomic neuropathies, Self-mutilation

INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA) was first described in 1963 by Swanson. Congenital insensitivity to pain is a rare condition affecting various tracts in the peripheral nervous system.[1] The constant features of CIPA are unexplained fever, insensitivity to pain, anhidrosis, mental retardation, and self-mutilating behaviors. Other features may include bruises, joint dislocations, multiple fractures, oral manifestations, and aggressive behaviors causing painless injuries to the extremities.[2] CIPA is a very rare autosomal recessive disorder and although there are no data about the prevalence of this syndrome, which is not commonly

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seen in clinical practice.[2] The incidence of 1/125,000,000 is reported. It is believed to be caused by a mutation in the neurotrophic tyrosine receptor kinase 1 (*NTRK1*), which affects the nerve growth factor in the embryonic period and is located on chromosome 1q21-q22.[2] In most patients, the autonomic nervous system might be affected as well.[1] This condition is known as hereditary sensory and autonomic neuropathy (HSAN). It is divided into five subtypes: Sensory radicular neuropathy (HSANI), congenital sensory neuropathy (HSANII), familial dysautonomia or Riley–Day syndrome (HSANIII), congenital insensitivity to pain with anhidrosis (HSANIV), and congenital indifference to pain (HSANV).[3,4] In all these cases, the main pathology is in the small diameter C and A-δ fibers responsible for pain conduction.[1,4] This could be further classified based on different parameters such as the inheritance pattern, natural history of the disease, pathological alterations, neurophysiological characteristics, and biochemical disorders.[1,3,4] The widely used classification is the one proposed by Dyck who divided those neuropathies into five types of hereditary sensory and autonomic neuropathies, as described earlier.[3,4]

In these patients, pain perception is significantly impaired and autonomic functions are lost while pressure and touch sensations remain intact.[2] Growth impairment and mental retardation at various levels have been reported.[2] CIPA is characterized by the inability to perceive painful stimuli in the extremities, joints, or oral mucosa, which may lead to ulcers in the lips, gums, and tongue.[1] Due to anhidrosis, inability to sweat, fever might occur secondary to hyperpyrexia. The development of the small nociceptive neurons in the dorsal root ganglia will be impaired which could be responsible for the pain insensitivity observed.[2] As a result, these patients are more prone to have multiple and recurrent injuries, which may lead to bone fractures and joint dislocation or deformities. There is no standard treatment and surgical reconstruction remains the only invasive intervention in regard to CIPA with joint deformity.[5,6] Those patients are more prone to have multiple infections, most commonly *Staphylococcus aureus* infection.[5] Orthopedic problems and complications such as autoamputation, self-mutilation, septic arthritis, osteomyelitis, and scoliosis are pretty common.[7] Severe complications have been reported in joint reconstruction surgeries and conservative management with close follow-up is preferred to lower the risk of complications.[5,7] However, progressive scoliosis requires operative intervention, while fracture may be treated conservatively with cast immobilization. Osteomyelitis and septic arthritis are treated accordingly with antibiotics.[7] This report aims to describe a case of a pediatric patient with CIPA who presented with multiple Charcot joints involving both knees, ankles, and wrists.

CASE REPORT

A 15-year-old male presented to the orthopedic clinic with multiple destructed joints. The joints involved were both knees, ankles, and wrists. He has a loss of response to painful stimuli, anhidrosis, but no cutaneous neuropathies, and no muscle weakness. The patient's parents reported a previous history of bilateral knee swelling 6 years ago, following a trauma, and right ankle swelling 3 months back. The patient started to have signs and symptoms at the age of 7 years. No other siblings suffered from a similar problem. The parents have a consanguineous marriage. The patient was evaluated thoroughly by both a rheumatologist and neurologist who suggested nerve and muscle biopsy as part of the workup.

His examination showed that he was having difficulties in mobilization and came to the clinic walking with walking aids. His higher mental functions were normal, with no facial asymmetry and no cutaneous manifestations or pigmentations. Both knees, ankles, and wrists revealed swollen and deformed joints [Figure 1]. Blood investigations, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, creatine phosphokinase, and lactate dehydrogenase, were all within normal range. Plain radiography of both knees and ankles revealed the presence of bilateral ankle dislocation, disorganized and destructed joints, suggestive of Charcot joints [Figure 2]. Plain films of the right leg and femur showed dislocation with overriding ends of the tibia and femur [Figure 3]. Magnetic resonance imaging (MRI) of the spine ruled out syringomyelia, and brain MRI was normal. MRI of the knees revealed severe joint disfigurement with loose bony fragments within the joints, and the diagnosis of bilateral Charcot joints was made [Figure 4]. The diagnosis of CIPA syndrome, HSANIV, has been made with multiple Charcot joints. Nerve conduction studies of the upper extremities were normal. The nerve conduction of the lower extremities could not be technically performed due to the presence of homogenous Charcot deformities. Gene

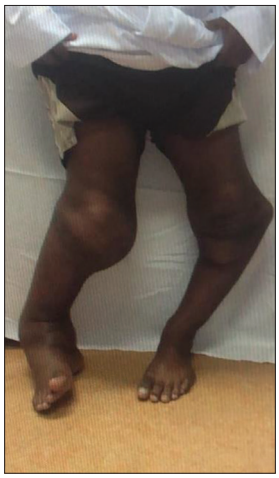

Figure 1: Photo showing bilateral joint deformities of both knees and ankles.

studies were conducted and revealed mutation of the *NTRK1* gene. He had a muscle biopsy from the right vastus lateralis and nerve biopsy from the right sural nerve. The results revealed no significant pathological abnormalities. Siblings' screening was negative. He was started on physiotherapy and occupational therapy. Parents were educated about their child's condition. Preventing and monitoring further self-inflicted injuries is a key to avoid infections and deterioration of his difficulties. The patient unfortunately lost follow-up.

DISCUSSION

The prevalence of CIPA is approximately 1 in every 125,000,000 according to recent reports.[2] The mutation in the *NTRK1* gene was associated with consanguineous marriages like in the current case.[6] However, another study that was published in 2013 reported a case of a patient with CIPA of nonrelated parents.[2] In the current case, the patient had the insensitivity to pain, which is considered the main sign of this disease. However, a study done on two identical twins with CIPA reported multiple presentations of the twins with indifference to painful stimuli, yet abdominal pain was present, and recurrent episodes of fever of unknown etiology not responsive to antipyretics.[5] Although our patient's mental function was normal, many patients with CIPA develop mental retardation.[1] Innervated sweat glands were reported by one of the studies, but anhidrosis remains predominant.[2,5] Regarding diagnosis, many studies reported no reaction to pain with having unexplained episodes of hyperpyrexia after birth accompanied by skin dryness. Some studies, including the current case, support the evidence of a delayed diagnosis of CIPA in childhood due to the occurrence of symptoms at a later age.[2,5,6] Usually, an extensive workup is needed for a definitive diagnosis. While the role of nerve biopsy remains controversial, it has been affirmed that CIPA is accompanied by the loss of unmyelinated and reduction of small, myelinated fibers in the sural nerve, which could explain these manifestations.[2,5] Genetic counseling should discourage consanguineous marital relations, especially if there is a positive history of CIPA syndrome in the family.[2]

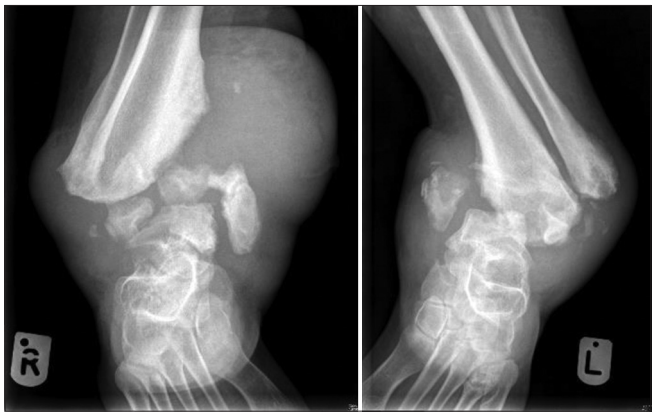

Figure 2: Plain radiography of bilateral ankle showing destructed joints and increased density of the articulating bones with associated enlarged periarticular soft tissue with increased density. Findings are suggestive of Charcot joints. The right ankle joint demonstrated comminuted fractures of the medial malleolus and distal end of the fibula with an associated soft-tissue swelling around the ankle joint. At the left ankle, there is a non-displaced fracture of the posterior aspect of the calcaneum.

There is no available curative treatment for CIPA syndrome, and most CIPA patients are young children, which requires educating the parents on simple preventive measures to deal with such a condition. Parents should avoid excessive wrapping to reduce hyperpyretic episodes and to hydrate them frequently.[2] During hyperpyretic episodes, parents should notify the general physician about the diagnosis to prevent unnecessary use of antibiotics and redundant

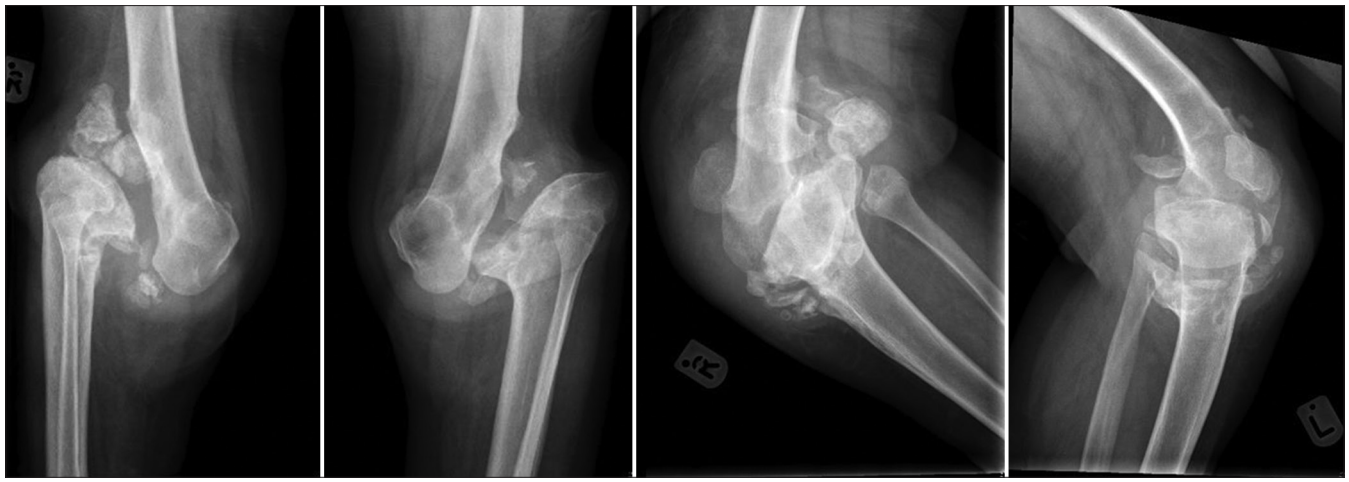

Figure 3: At the knee joints, there is a fracture and dislocation with overriding ends of the tibia and femur. The end of the femur is located posterior to the proximal end of the tibia. Multiple bone fragments are noted that may represent the patella and the condyle that are fractured.

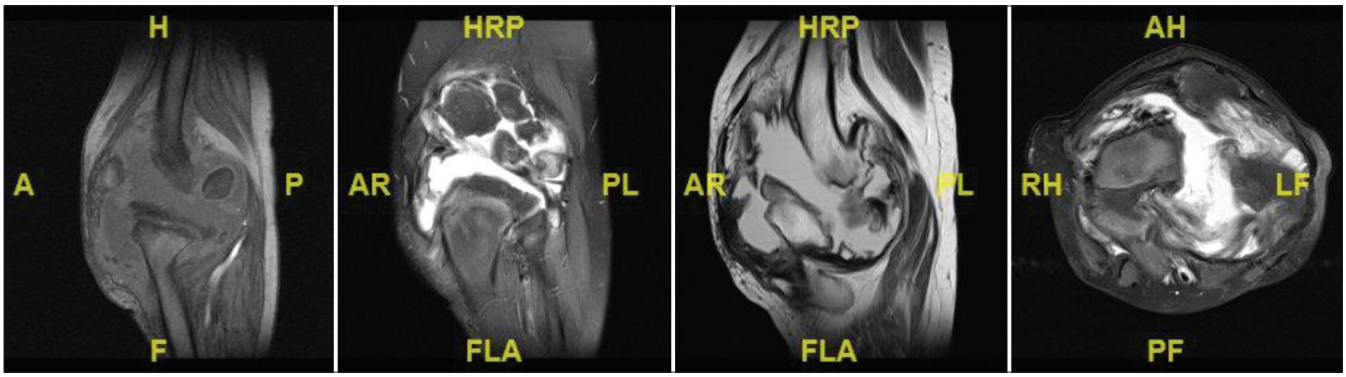

Figure 4: Magnetic resonance imaging of both knees showing significant soft-tissue swelling and significant joint effusion, as well as bony destruction involving femoral condyle and tibial condyle extending to the lower femoral metaphysis and upper tibial metaphysis with subluxation with significant loose bodies in the joint space.

investigations. Children with CIPA need to be closely monitored by the parents due to high susceptibility to traumatic injuries such as fractures, burns, corneal ulceration, and self-mutilation with no curative treatment in such patients.[8] Ankle fusion with vascularized autogenous bone grafting aiming at reduction of the destruction of joints and to improve mobility, which could have been performed if the patient presented earlier. It has been observed that metaphyseal fractures treated with surgical interventions are at risk of poor outcomes such as non-union and infections, unlike those who opted for conservative management of cast immobilization. These poor outcomes are the result of repetitive movement causing accidental injuries due to their inability to perceive pain.[9] Conservative management for this patient seemed to be the best option to prevent further complications caused by multiple surgeries. Preventive measures such as local foot care and custom-fitted shoes can help minimize the risk of injury and avoid the need for radical surgeries.[8-10] Local wound care and aseptic dressings should be applied to ulcerations on the elbows, knees, upper, and lower extremities.[2] This type of preventive measure to improve the quality of life was possible in our case due to the normal mental state of the patient. If these patients need surgical intervention, though they do not feel any pain, they may need an adequate dose of analgesia during surgery to prevent tachycardia and hypertension, which are unconscious physiological responses to pain.[2]

CONCLUSION

As presented in this case, the occurrence of CIPA syndrome, HSANIV, remains highly unprecedented and genetic testing is mandatory for the diagnosis. Nerve and muscle biopsy should be obtained due to the loss of unmyelinated and myelinated nerve fibers in the sural nerve, and advanced imaging such as MRI is needed to evaluate the case for any concomitant spine or brain pathologies, while always ruling out infections. There is no definitive therapeutic intervention for this condition and surgeries may further complicate the case, as these patients might need more than 1 surgery. Malunion, non-union, and infections are common complications as they are less likely to adhere to the management plan and prone to recurrent injuries. Education, analgesia, antibiotics, splinting, prevention, and regular follow-ups are significant to improving the quality of life of a CIPA patient. Sibling screening is crucial for earlier intervention to reduce the progression of the disease. Unfortunately, the prognosis of this condition is poor and such patients will have limitations in their mobility. For that very reason, these patients need regular follow-ups for a better quality of life.

AUTHORS' CONTRIBUTION

OAB conceived and designed the study. MMA conducted research, provided research materials, collected and organized data, and wrote the initial draft. MAS and BZA wrote the final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

ETHICAL APPROVAL

This case report was approved on April 8, 2021, by the Ethics and Research Committee of the National Guard Health Affairs, King Abdullah International Medical Research Center, Saudi Arabia (IRB number NRJ21J/065/03). All information collected were kept strictly confidential.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parent has given his consent for the patient's images and other clinical information to be reported in the journal. The parent understands that the patient's name and initials will not

be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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