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**Case Report**

# Osteomyelitis or myositis ossificans: a diagnosis in disguise in a case of hereditary sensory and autonomic neuropathy type 4

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## ABSTRACT

Hereditary Sensory and Autonomic Neuropathy Type IV (HSAN-IV), also known as Congenital Insensitivity to Pain with Anhidrosis (CIPA), is an extremely rare condition with loss of peripheral unmyelinated and small myelinated nerve fibres, leading to the absence of pain sensation and inability to sweat. Affected patients require careful care in order to prevent debilitating consequences and potential morbidity as a result of recurrent trauma and self-mutilating behaviour. We report a case of 4 years and 10 months old boy who has been diagnosed with HSAN-IV at 6 months of age, which was confirmed by genetic testing. This study was conducted in the largest tertiary medical complex in the Kingdom of Bahrain. He had multiple hospital presentations with various upper and lower extremity injuries requiring a multidisciplinary approach for different management strategies. The diagnosis can be extremely challenging due to an exhausting list of differential diagnosis and limited number of cases provided in the literature.

**Keywords:** Hereditary sensory and autonomic neuropathy, Congenital insensitivity to pain with anhidrosis, Self-mutilation, Myositis ossificans, Osteomyelitis

## INTRODUCTION

Hereditary sensory and autonomic neuropathies (HSAN) comprises 5 subtypes of rare autonomic recessive genetic diseases, each with varying severity of sensory and autonomic dysfunction. Our case was diagnosed with HSAN type IV, also known as congenital insensitivity to pain with anhidrosis (CIPA), an extremely rare subtype.

The loss of small myelinated and unmyelinated fibres in peripheral nerves manifest as absence of pain sensation and inability to sweat.[1-4] This in turn leads to challenges and complexities in the diagnosis and management of such patients. This case report covers the condition thoroughly and sheds light on the clinical course associated with this rare genetic disorder.

## CASE REPORT

A retrospective analysis of clinical records, imaging studies, and management approaches was conducted on a 4-years and 10-months old boy. He was born through an uncomplicated spontaneous vaginal delivery at 40 weeks gestation, with normal APGAR scores, and to first degree consanguineous parents. This research took place in Salmaniya Medical Complex, Government Hospitals, the Kingdom of Bahrain, the largest tertiary medical center.

At 6 months of age, the patient presented to the hospital with excessive irritability and head hitting behaviour. A brain MRI was performed to rule out structural and metabolic abnormalities, however, it was unremarkable.

Notably, the child's developmental milestones were normal to his age.

At 1 year of age, the child had multiple presentations to the hospital with the complaints of limb biting and scratching of extremities. An array of diagnostic tests was performed including lab tests and imaging modalities which came back to be negative. Furthermore, genetic testing using whole exome sequencing (WES) was performed and revealed neurotrophic receptor tyrosine kinase 1 (NTRK1) gene mutation confirming the diagnosis of hereditary sensory and autonomic neuropathy type 4 (HSAN 4).[5,6] The patient had recurrent hospital admissions for complications resulting from his self-mutilating behaviour.

This led to bilateral fingers and toes inflammation with signs of infection requiring meticulous wound care, surgical debridement and intravenous antibiotics. Despite interventional efforts, the condition gradually advanced, leading to auto-amputations in bilateral fingers and toes (Figure 1 and 2). At 4 years of age, he was brought to the emergency department with right lateral foot swelling, erythema, and blackish discoloration.

Hence, he was admitted under orthopaedics surgery care for surgical debridement and was discharged on antibiotics. He was lost to follow-up and presented 2 months later with surgical site infection and was readmitted for extensive surgical debridement and intravenous antibiotics (Figure 3). 2 months later, he presented to the emergency department with left knee swelling, erythema and no fever.

X-ray showed proximal tibia metaphyseal fracture that was managed conservatively with casting and discharged with follow-up in the OPD (Figure 4).

On follow-up, serial x-rays were taken during an interval of 2 weeks (Figure 5) and 6 weeks (Figure 6), which showed excessive callus formation. Swelling was noted to increase in the left knee and leg (Figure 7). Therefore, ultrasound was done to rule out collections and was unremarkable. MRI was done afterwards and reported as acute osteomyelitis by a paediatrics radiologist consultant (Figure 8).

Based on the aforementioned MRI findings, he was admitted and started on IV antibiotics. A week later, follow-up MRI was done which raised the suspicion of myositis ossificans (Figure 9). Moreover, this finding was supported on plain radiograph, given the presence of calcifications within the surrounding musculature exhibiting dense periphery and lucent centre, and kept progressing over time (Figure 10).[7,8]

After multidisciplinary team discussion, an ultrasound guided aspiration was done to rule out infection. Culture and gram stain came back to be negative which supports the diagnosis of myositis ossificans. Finally, the patient was discharged on a cast with a close follow up.

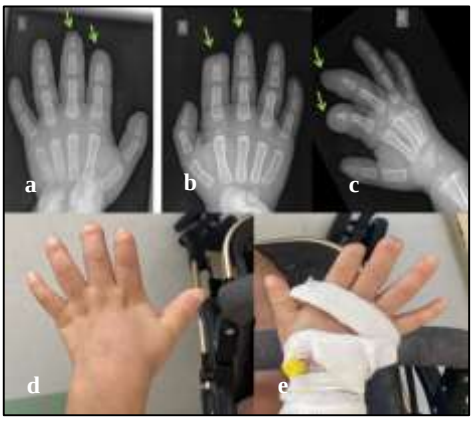


**Figure 1 (a-e): Radiographs and clinical photographs showing progressive resorption of bilateral index and middle fingers as a result of self-mutilation resulting in amputations (green arrows).**

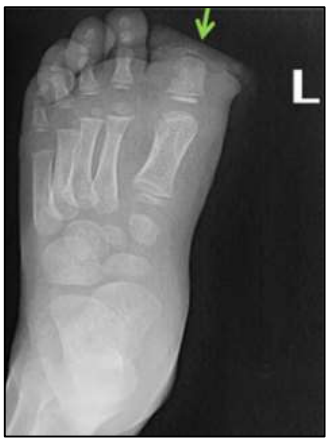


**Figure 2: Amputation of the left big toe (green arrow).**

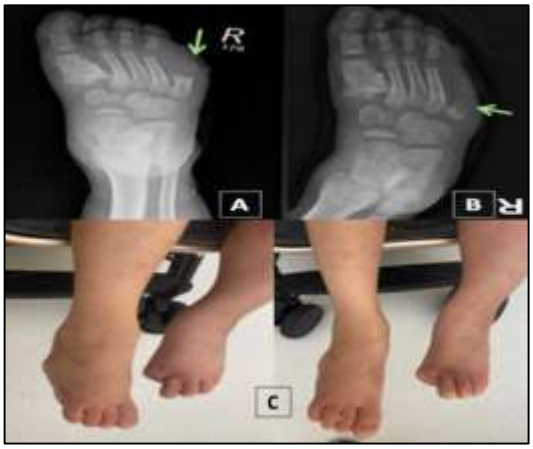


**Figure 3: (A) Evidence of partial resorption of the right 5th metatarsal bone, pre-op (B). Post-surgical debridement with excision of the infected bone (C). Clinical photographs of bilateral feet with healed scars.**

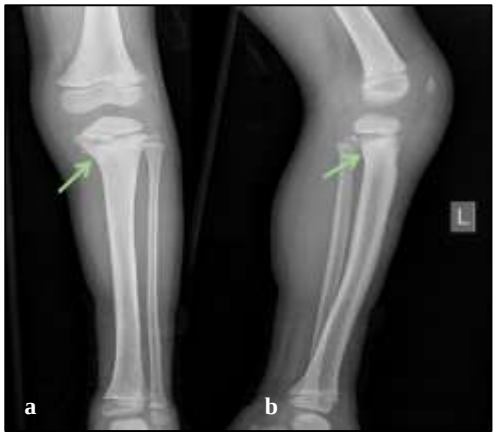


**Figure 4 (a and b): Radiographs of initial follow up visit showing left proximal tibia metaphyseal fracture (green arrows).**

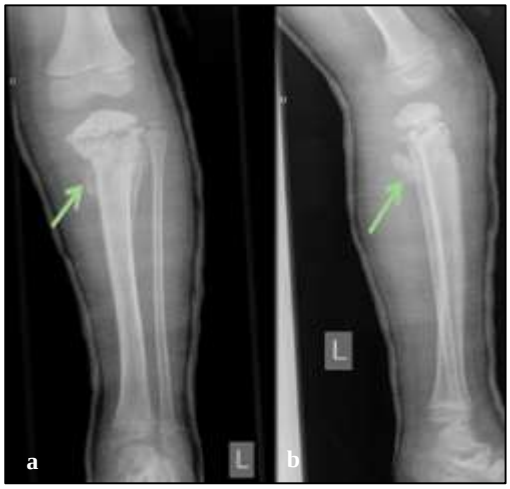


**Figure 5 (a and b): Radiographs of the left proximal tibia metaphyseal fracture at 2 weeks follow up, showing callus formation (green arrows).**

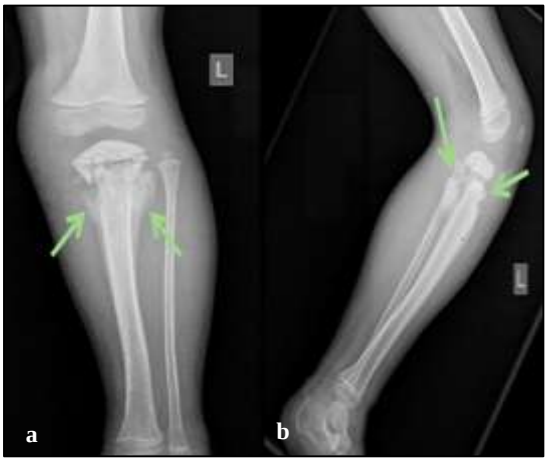


**Figure 6 (a and b): Radiographs of the left proximal tibia metaphyseal fracture at 6 weeks follow up, with further increase in the callus formation (green arrows).**

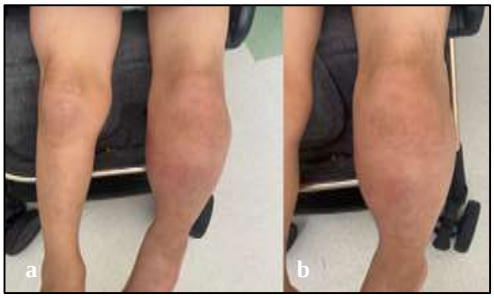


**Figure 7 (a and b): Clinical photographs of increased swelling in the left knee and leg at 6 weeks follow up.**

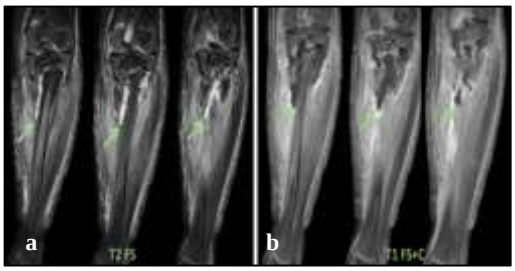


**Figure 8 (a and b): Features concerning for acute osteomyelitis with adjacent muscles myositis and rim enhancing fluid collection/abscess formation within the proximal left tibial metaphysis (green arrows).**

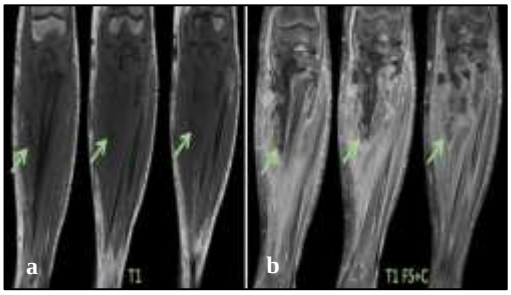


**Figure 9 (a and b): 1 week follow-up MRI, interval worsening in proximal tibial destruction, with interval development of callus within the regional musculature representing myositis ossificans (green arrows).**


**Figure 10 (a and b): 1 month Follow-up radiographs showing interval increase in calcification within the surrounding musculature representing myositis ossificans, showing the characteristic, dense periphery and lucent centre (green arrows).**

## DISCUSSION

HSAN Type 4 is a subtype of a rare spectrum of diseases involving 5 subtypes, also known as CIPA, which usually presents early in infancy with specific features.[4] This arises after a mutation in the neurotrophic receptor tyrosine kinase receptor 1 (NTRK1) occurs in the genome of the chromosome 1 (1q21/22). This genome, specifically, consists of 17 exons and measures at a length of 23 kb, which encodes for nerve growth factor (NGF) and is the gene responsible for the development of CIPA. This gene abnormality further produces a loss of function effect that disrupts the structure and impairs survival of sympathetic and sensory neurons.[6,9,10] The clinical course of the disease revolves around the impairment of pain sensation and markedly decreased/ or even absent sweating. Furthermore, the anhidrosis causes cutaneous changes and the sensory insensitivity, which is much more profound, may result in self-mutilation, auto-amputation, and corneal scarring.[11] Also, the synergistic effect of the anhidrosis and thermoregulation system may result in hypothermia which may propagate to seizures.

This extensive involvement of ectodermal structures including skin, bone and nervous system contributes to injuries and complications.[12,13] Myositis ossificans is an abnormal overgrowth of benign heterotopic tissue, specifically lamellar bone, which occurs in extra skeletal soft tissues. The pathophysiology is still poorly understood. However, the existing literature enlists that the heterotopic tissue calcification occurs due to a defective proliferation of fibroblasts which forms osteogenic cells. It initially arises after a localized inflammatory reaction occurring due to muscle injury.[14,15] As a result, cytokines are released including bone morphogenetic protein 2 and 4 (BMP 2 and 4) and transforming growth factor (TGF). This leads to the conversion of vascular endothelial cells to endothelial-derived mesenchymal cells, which may differentiate into osteoblasts and chondrocytes. The end result is the formation of heterotopic bone and cartilage.[15-17]

The disorder manifest clinically as pain, stiffness, swelling or redness. It can also be suspected after an incidental finding on an X-ray.[18,19] Classically, an inciting event, such as trauma due to a fall or blow is reported by the patient, however, it is not always the case. As the clinical presentation of such cases is variable, it can mimic other entities such as tumours or infections.[7,19] Myositis ossificans takes several weeks of development until reaching mature lamellar bone. This can be described through three stages; early, intermediate and late, nevertheless the duration of each stage varies.[15] In the early stage, plain radiographs may show faint peripheral calcification. In the intermediate stage, an outer shell of lamellar bone with a main osteoid core develops. Finally, in the late stage mature lamellar bone forms. The lesion is described to be evolving in a centrifugal zonal pattern which helps in differentiating it from other diagnoses including malignant conditions.[19,20] Histopathological examination may be misrepresentative of sarcoma.[15] Pathological samples under microscopy displays a mixture of immature loosely appearing fibroblasts and myofibroblasts showing cellular pleomorphism classified as mild degree. A numerous amount of chronic inflammatory cells and macrophages can be present. In addition, mitotic figures may be absent or seen in few amounts.[19,21,22] This case report presents a young boy who is diagnosed with HSAN Type IV at 6 months of age and myositis ossificans at the age of 4 years and 10 months. It helps provide valuable insights into the clinical presentation, disease progression, diagnostic modalities and management strategies for this complex condition through retrospective data collection. In this special case, a multidisciplinary approach was necessary to provide optimum patient care involving orthopaedic surgeons, paediatricians, neurologists, physical therapists, radiologists, pathologists, and wound care specialists. The main goal was early detection and prompt intervention to prevent injuries and complications. Wound care and infection control had special emphasis to minimize the risk of severe infections and further worsening of symptoms.

Throughout the case, imaging modalities were crucial in tracking the disease course and evaluating associated complications. But firstly, a comprehensive review of history and clinical examinations was compulsory to understand that these recurrent fractures and injuries were not due to child abuse or non-accidental injuries. Moreover, this is an important differential diagnosis that has to be excluded with such a clinical course. Radiographs were necessary to evaluate skeletal injuries and facilitate comparison in follow-ups. Ultrasound was used to identify soft tissue changes. MRI was important to assess for the presence of acute osteomyelitis and guiding surgical planning when necessary.

The rarity of HSAN, particularly Type IV, represents the primary limitation of this case report, which limits the size of the patient cohort and the availability of literature on the topic. In addition, myositis ossificans is a rare entity and studies on the course of the disease itself are scarce. Nevertheless, the findings presented herein offer valuable insights into the diagnosis and management of HSAN Type IV and provided a foundation for future research and case studies in this field.

## CONCLUSION

HSAN type 4 is rare and the key for a proper management is early diagnosis. There is no specific management plan for this disease. However, with early diagnosis, good understanding of the disease, parent's education and patient training, a positive impact can be made. This can aide in prevention of injuries, such as traumas to the limbs or head, corneal scarring from dehydration and their complications. Also, regular follow-ups are mandatory with head-to-toe examinations and early prompt management of any injury in order to prevent serious complications.

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