Case Report

Congenital Insensitivity to Pain with Talar Avascular Necrosis and Neuropathic Arthropathy of the Ankle Joint

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ABSTRACT

Congenital insensitivity to pain with anhydrosis (CIPA), is a very rare genetic disorder characterized by recurrent episodes of unexplained fever, inability to feel pain and temperature, generalized anhydrosis, self-mutilating injuries and mental retardation. We present a case of a 8-year-old boy with these criteria who presented with gross right ankle swelling, collapse and avascular necrosis of the talus that was treated conservatively with non-weight-bearing cast.

KEY WORDS: anhydrosis, insensitivity, pain, talus

INTRODUCTION

Congenital insensitivity to pain with anhydrosis (CIPA) is a very rare autosomal recessive disorder; it is also known as hereditary sensory and autonomic neuropathy (HSAN) type four. CIPA is characterized by inability to feel pain and temperature. This often leads to repeated injuries sometimes unintentional or self-mutilating (*e.g.,* biting the tongue, lips or fingers).

Normally, sweating helps cool the body. However, in CIPA patients there is generalized anhydrosis often causing recurrent attacks of hyperpyrexia and seizures. They also develop characteristic emotional behavior and many affected individual have mental retardation. The touch and pressure sensations are preserved[1].

CIPA is caused by mutation of the NTRK1 gene. This gene is responsible for encoding the receptor tyrosine kinase (TrKA) for nerve growth factor (NGF) which is critical for the formation of autonomic neurons and the small sensory neurons in the dorsal root ganglia[2,3].

On skin biopsy, in CIPA, the sweat gland appears to be normal, but an ultrastructural study of skin biopsies revealed non-innervation of the eccrine sweat gland which affect the ability of the individual to sweat[4].

CASE REPORT

A 8-year-old boy was referred to the outpatient department because of gross right ankle swelling. He was a single child out of a consanguineous marriage between healthy parents of Iranian origin with no family history of a similar disease. The child was born after full term normal pregnancy *via* a normal vaginal delivery. His birth weight was 2.6 kg. The parents gave history of recurrent attacks of unexplained fever, insensitivity to pin prick and previous fractures.

The child was averagely built and his skin was dry. There was a healed ulcer over the lower lip and tongue, a healing ulcer over the base of the first metacarpal of the right hand (Fig. 1), and multiple healed scars of self-mutilating injuries over the areas of the lower left forearm ,wrist and left hand (Fig. 2).

A local examination showed gross right ankle swelling with mild hot skin and scars of previous healed heel ulcer. A plain X-ray showed recently healed fracture with exuberant callus over the first metatarsal bone (Fig. 3), and sclerosis of the dome of the talus with subchondral fracture and collapse of the articular surface (Fig. 4, 5). A real time ultrasound showed significant right ankle joint effusion. A magnetic resonance image (MRI) showed right ankle joint effusion, subchondral talar dome fracture and low signaled non-enhanced sclerosis of the posterior half of the talus (consistent with avascular necrosis) (Fig. 6).

His white cell count was 8.6 x 10^9/l with a normal differential count. His hemoglobin (Hb) was 12.3 g/dl, C reactive protein (CRP) was 19 mg/l, erythrocytic sedimentation rate (ESR) was 45 mm/hr, blood culture was negative and the tests for sickling and brucella agglutination were negative.

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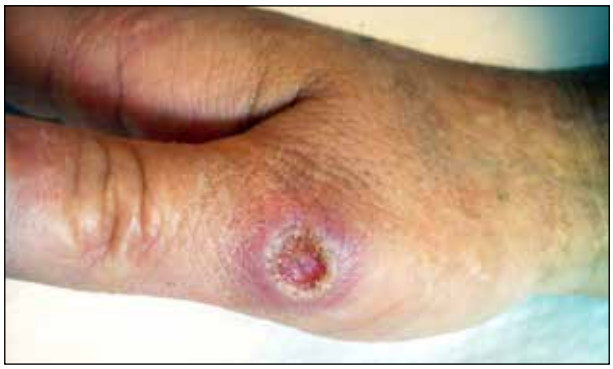

Fig. 1: Ulcer over base of the Rt. thumb

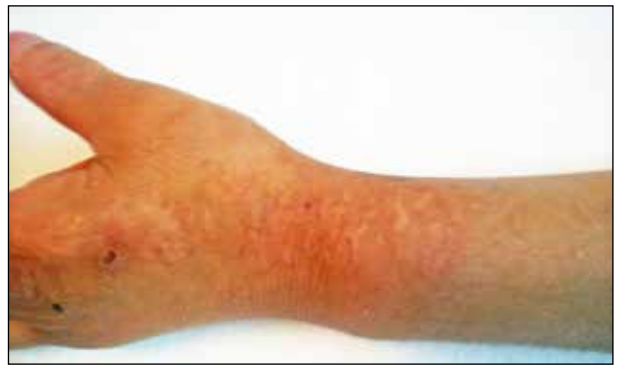

Fig. 2: Healed scars of self mutilating injuries of the wrist and forearm

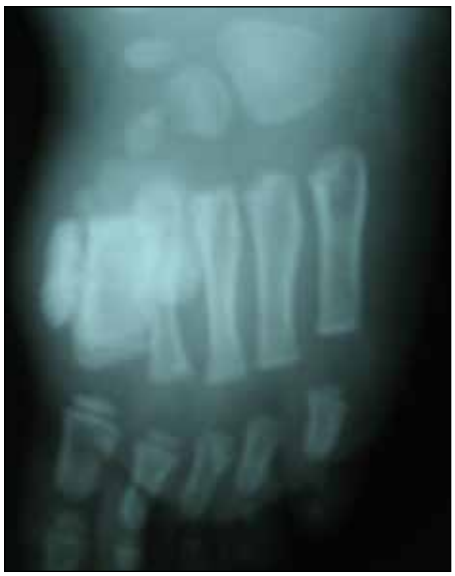

Fig .3: Exuberant callus formation of 1st metatarsal fracture

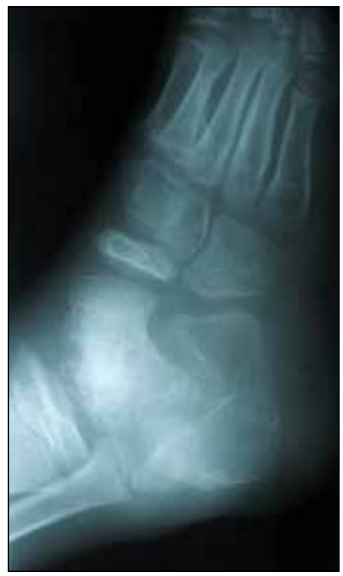

Fig. 4: Sclerosis of the talar body and irregularity of the talar dome

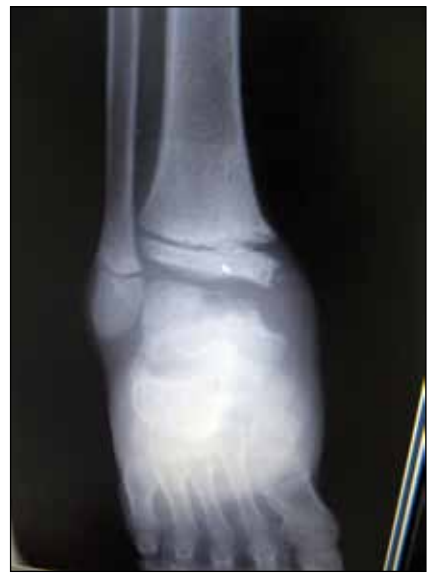

Fig. 5: Right ankle AP view showing subchondral fracture and collapse of the articular surface

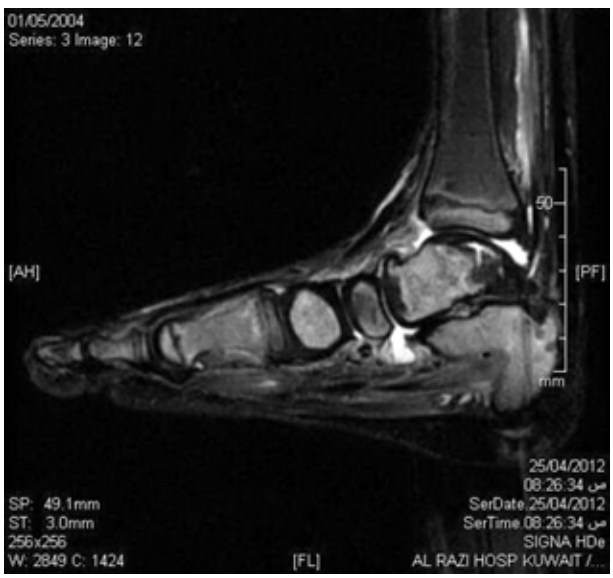

Fig. 6: Right ankle MRI showing joint effusion and avascular necrosis of the talus

The MRI of the brain was normal. The nerve conduction study (peroneal and posterior tibial) of both lower limbs was normal but the blink response of left and right supraorbital nerve was absent, sympathetic skin response to acoustic and electric stimuli in both upper and lower limbs were absent.

Psychiatric evaluation showed delay in motor, speech and play skills. His learning abilities were less than other peers. Wechsler intelligence scale for children (WISC) was performed and the result showed a total IQ: 61, verbal IQ: 58 and performance IQ: 69.

The patient was treated conservatively with non-steroidal anti-inflammatory drugs (NSAIDs), kept non-weight-bearing cast (protective splint) for nine weeks while he was an inpatient followed by POP cast after discharge" to reduce ankle swelling. Although, residual ankle swelling persisted after conservative treatment, the patient was kept in a protective weight bearing brace.

DISCUSSION

CIPA is a very rare hereditary disorder. It more likely occurs in homogeneous society. Dyck[5] recognized five types of hereditary sensory and autonomic neuropathies (HSAN). CIPA correspond to the fourth of the five types.

It is caused by lack of maturation of small myelinated and unmyelinated fibers of the peripheral nerves which convey sensation of pain and temperature[6]. Rafel *et al*[7] studied the cutaneous branch of the radial nerve by electron microscopy and they found complete absence of small myelinated (delta) and unmyelinated (C) fibers. Other studies confirm the same ultrastructure findings[8,9]. CIPA is caused by mutation in the NTRK1 gene which is responsible for encoding the receptor tyrosine kinase TrKA for nerve growth factor (NGF). It is a neurotrophic factor essential for survival and maintenance of sensory and sympathetic neurons. It is also an inflammatory mediator associated with pain and itching. NGF-TrKA system is essential for establishment of a neural network. NGF dependent neurons play a crucial role in the emotional experience, and cognitive and mental activity[10,11].

The sweat gland on skin biopsy in CIPA appeared to be normal but the ultrastructural studies of skin biopsies revealed non-innervation of the eccrine sweat glands which is the main reason of anhydrosis observed in these patients[4].

The clinical presentation could be classified according to Bar *et al*[12] into a) multiple infections, b) fractures, growth disturbances and avascular necrosis and c) Charcot arthropathies and dislocations.

Infection may be recurrent and destructive. Complications in wound healing and fracture treatment are also reported[13]. Most patients are mentally retarded with IQs varying from 41 to 78, the majority being in the range of 60s[7].

In our patient, diagnosis of CIPA was made on the basis of clinical features of insensitivity to pain and temperature, frequent hyperpyrexia and anhydrosis, scars of self mutilating injuries and frequent ulceration, multiple previous fractures that healed with exuberant callus formation (Fig. 3), absent sympathetic skin response to acoustic and electric stimuli of both upper and lower limbs associated with absent blink response of the left and right supra-orbital nerves. Delay in motor, speech, play skills and abnormal WISC are similar to the findings of Rosemberg *et al*[8].

CONCLUSION

Congenital insensitivity to pain with anhydrosis (CIPA) is characterized by absence of protective sensations that keep the body safe from injurious agents and prevents self-mutilation. CIPA patients require a team of multidisciplinary physician including dentist and educated parents. Absence of protective sensation from the joint leads to a continuous process of joint destruction. The treatment of this disorder consists of immobilization of the affected joint (brace or period of non-weight bearing cast), relief of pressure from weight-bearing areas and a weight relieving cast.

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