

Case Report

Hong Kong J Orthop Res
2021; 4(1): 4-7
ISSN (e): 2663-8231
ISSN (p): 2663-8223
Received: 25-03-2021
Accepted: 13-04-2021
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www.hkorthopaedicjournal.com
DOI: [10.37515/ortho.8231.4102](https://doi.org/10.37515/ortho.8231.4102)

Congenital Insensitivity to Pain and Anhidrosis: A painful experience by a painless child

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Abstract

A three-year-old boy with congenital insensitivity to pain and anhidrosis (CIPA) was first presented with transphyseal separation of distal left humerus. Surgical treatment with closed reduction and k-wiring of transphyseal separation of distal humerus resulted in devastating surgical site infection and osteomyelitis. Multiple surgical debridement and application of external fixator to eliminate infection were futile. At the age of four years, he refused to bear weight as a result of left hip dislocation. Closed reduction and spica cast was unsuccessful, resulting in recurrent left hip dislocation. He has since not been able to walk. At the age of five years, the right hip was dislocated followed by ipsilateral subtrochanteric femur fracture. Appropriate treatments such as hip spica and titanium elastic nail were not possible due to extensive bruising and skin ulceration over the right thigh. This child ended up with functionless left upper limb, bilateral hip dislocation and malunited right femur fracture. Conservative treatment and watchful neglect might be the ideal treatment for patients with CIPA.

Keywords: CIPA, Transphyseal separation of distal humerus, Hip dislocation.

INTRODUCTION

Congenital insensitivity to pain and anhidrosis (CIPA) is a rare autosomal recessive disease with a reported incidence of one in 125 million newborns [1]. This neuropathy, also known as hereditary sensory and autonomic neuropathy type IV, is characterized by the absence of pain and temperature sensation, inability to sweat, hyperpyrexia, mental retardation, and self-mutilating behavior. Clinicians must have a high index of suspicion when toddlers present with multiple fractures as CIPA may mimic osteogenesis imperfecta.

CASE REPORT

A 3-year-old boy presented with unexplained swelling of the left elbow for 5 weeks before he was referred to our center. His parents did not notice obvious trauma or injury to his left elbow. Antenatal history was uneventful. Family history did not reveal any inherited diseases or bone fragility. He displayed global developmental delay involving all aspects of fine motor, gross motor, language, social and cognitive skills. He started walking at the age of 2 years 6 months. Upon further history, he had multiple episodes of high fever between ages one to three but this unexplained hyperpyrexia did not raise clinical suspicion. Clinical examination drew closer attention when he showed no response to pain. Radiographs revealed left distal humerus transphyseal separation with abundant new bone formation along the distal humeral shaft (Figure 1a). A genetic study was performed and diagnosis of CIPA was made after paediatric consultation. We proceeded with close manual reduction and percutaneous pinning of left distal humerus (Figure 1b). Unfortunately, the fixation was complicated with severe pin tract infection and osteomyelitis. More than 10 further surgeries were performed to eradicate infection. Among the procedures performed include multiple debridements, trans-elbow external fixation, antibiotic cement spacer insertion and revision of external fixator. Intra-operative culture grew multiple organisms namely *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The fulminant infection resulted in a loss of the distal half of left humerus and a functionless upper limb (Figure 1c). At 4 year 10 months old, he refused to bear weight on his left lower limb. Radiograph revealed a dislocated left hip. Despite achieving a concentric reduction after close manual reduction and hip spica, the left hip dislocation recurred six months later (Figure 2a, 2b, 2c). He has since not been able to walk. Within a year, this patient had a right hip dislocation (Figure 3a) followed by subtrochanteric fracture of the right femur (Figure 3b). Ideal fixations such as hip spica and titanium elastic nail were not possible as he developed blisters and necrotic skin over the distal right thigh

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that took two months to heal. This child ended up with a functionless left upper limb, bilateral hip dislocation and malunited right femur fracture (Figure 3c).



Figure 1: (a) Left elbow transphyseal separation with abundant callus formation at the distal half of humerus. (b) Close manual reduction and percutaneous pinning of distal humerus. (c) Complete resorption of distal half of left humerus.



Figure 2: (a) Left hip dislocation. (b) Close manual reduction of left hip and hip spica. (c) Redislocation of left hip 6 months after reduction.



Figure 3: (a) Right hip dislocation, which occurred one year after left hip dislocation. (b) Close fracture of right subtrochanteric femur following right hip dislocation. (c) Malunited right femur fracture.

DISCUSSION

Hereditary Sensory Autonomic Neuropathy (HSAN) was first described by Dearborn in 1932 [2]. Since then, various terms such as congenital universal indifference to pain, congenital pure analgesia, congenital analgia were used to describe this syndrome of congenital indifference to noxious stimuli [3]. A subtype of HSAN (type IV), also known as Congenital insensitivity to pain and temperature (CIPA) was first recognized by Swanson in 1963 when he reported a unique syndrome in two male siblings [4]. To date, there are around 300 cases reported worldwide. The pathogenesis of CIPA involves mutation of the NTRK1 gene that results in the alteration of tyrosine kinase A (an important nerve growth factor). This mutated gene is inherited in an autosomal

recessive fashion [5]. There is an infrequent non-Mendelian inheritance characterized by uniparental disomy of chromosome [6]. NTRK1 mutation will result in deficient development of afferent somatic sensory system for pain and temperature, autonomic sympathetic system and the central nervous system. Neurological laboratory tests may reveal a prolonged central conduction time on short-latency somatosensory evoked potentials and abnormal activity of somatic A-delta and C fibers in the nerves of the skin [7]. Typical presentations include insensitivity to pain, anhidrosis, mental retardation, self-mutilating behavior, unexplained fever, multiple infections, multiple fractures, osteomyelitis, growth disturbances, joint dislocation, Charcot's arthropathy, and avascular necrosis. Recurrent unexplained fever represents the first sign of CIPA. Failure of sympathetic neurons to

innervate eccrine sweat glands causes the inability to sweat and dissipate heat. Twenty percent of patients die of hyperpyrexia within the first 3 years of life [8]. CIPA patients become irritated and anxious rather than flustered when over heated. Gold standard test for diagnosis of CIPA is genetic study that reveals mutation of the NTRK1 gene located on chromosome 1 (1q21-q22) [9].

Fractures and dislocation begin to manifest as the CIPA child begins to mobilize. The combination of impaired bone metabolism and lack of nociceptive fibers tend to result in fractures. Fracture consolidation is impaired resulting in slow healing. Attempts to manage these fractures and dislocations are extremely challenging and are often futile. Surgical interventions risk surgical site infections and osteomyelitis. Dislocations are recurrent with unsatisfactory solutions. The incidence of soft tissue and bone infections is high, and recovery from injuries is often prolonged [10]. Staphylococcus aureus infections typically end with severe morbidity. The lack of pain and autonomic response to infection delays diagnosis, subjecting CIPA patients to multiple debridements in the effort to treat infection.

The ideal management for CIPA patients remains inconclusive. Kosmidis et al advocate performing external fixation for fracture management in lieu of its minimally invasive nature [11]. Pin tract infections were regarded as manageable via antibiotics and surgical debridements. However, Perez-Lopez et al advocate early surgery for long bone fractures to prevent pseudoarthrosis, demonstrating a case of elastic intramedullary nailing for femur and tibia fractures with no reported complications [12]. For lack of a definitive protocol, the general consensus is to treat fractures and infections via standard protocols.

CIPA patients with dislocations exemplify a treatment conundrum as the outcome is generally poor. Neuropathic hip dislocations are refractory to conservative methods, but often recur even with surgical intervention such as open reduction with femoral shortening and acetabuloplasty [13]. Koster reported a 6-year old girl with CIPA in 1999, for whom he treated a hip dislocation with multiple surgeries which resulted in a Charcot joint with femoral head fragmentation [14]. Wang et al and Delniotis et al in 2019 similarly reported failures to treat hip dislocation successfully despite multiple pelvic and femoral osteotomies [15,16]. Our experience is similar to these reported cases. Surgery with the intention of joint preservation is often futile resulting in a painless, dislocated Charcot hip. Base on these published records, we surmise that CIPA patients with joint dislocations are best treated conservatively with watchful neglect.

Another cause of concern in CIPA patients is with anaesthesia and its lack of experience described in view of a severely limited patient pool. Commonly encountered problems include malignant hyperthermia, unpredictable autonomic responses to surgery with labile blood pressures. Despite their insensitivities, anaesthesia remains a crucial aspect of surgery as CIPA patients react differently to noxious stimuli. Okuda et al emphasize the needs to address anxiety alleviation, temperature control and adequate pain control to maintain stable hemodynamics during surgery [17]. They reported no adverse reactions to intravenous or inhalational anaesthetic agents, opioids or succinylcholine.

CIPA patients have a short life expectancy. Parents to such children should be made aware of the implications of even trivial injuries, and therefore make extra effort to prevent these by close monitoring of activities and appropriate guidance and measures.

CONCLUSION

Congenital insensitivity to pain and anhidrosis is rare. Surgical treatment may be futile, associated with high incidence of treatment failure and complication. Parents must be counseled regarding the high incidence of skin infection, osteomyelitis and recurrent dislocation if surgical

intervention is employed. Conservative treatment and watchful neglect might be the treatment of choice.

Conflicts of interest

We declare that there is no conflict of interest.

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