Congenital insensitivity to pain and anhydrosis: a report of two cases

Maharajan Karthikeyan, Thimmaiah Sreenivas, Jagdish Menon, Dilip Kumar Patro
Department of Orthopedics, JIPMER, Puducherry, India

ABSTRACT

We report on 2 patients with congenital insensitivity to pain and anhydrosis. The first one was a 7-month-old boy who presented with non-traumatic, haematogenous septic dislocation of the right elbow with physeal separation of the distal humerus. The second one was a 3-year-old girl suspected to have Job syndrome with an altered immunological profile.

Key words: arthritis, infectious; hypergammaglobulinemia; hypohidrosis; pain insensitivity, congenital

INTRODUCTION

Congenital insensitivity to pain and anhydrosis (CIPA) is a rare disorder of the autonomic and sensory nervous systems, with a prevalence of about 1 in 25 000 persons.1 It is also known as congenital sensory neuropathy with anhydrosis, hereditary sensory and autonomic neuropathy type IV, and familial dysautonomia type II. Commonly it is grouped under hereditary motor and sensory neuropathies, and is characterised by multiple trophic ulcers, self-inflicted wounds, chronic osteomyelitis, neuropathic joint, fractures, pseudoarthrosis, and physeal disturbances with limb length discrepancy. These patients have a poor prognosis, owing to fixation failure, non-union, and instability. We report on 2 patients with CIPA; one had septic dislocation and physeal disruption of the distal humerus, and the other had an altered immunological profile.

CASE REPORTS

Patient 1

In March 2010, a 7-month-old boy presented with a 4-day history of progressively increasing swelling of the right elbow, pseudo-paralysis of the right upper limb, and high fever. The child appeared to be toxic. The elbow joint was warm and unstable and had effusion. During physical examination, associated pain was less than expected. Multiple ulcers were
noted over both hands and feet. The tongue appeared to be bifid (Fig. 1a) and had multiple ulcers on its surface. Pain perception appeared to be completely absent. The child’s parents gave a history of absent pain perception with absent sweating since birth, and a history of self-inflicted wounds over the hands, feet, and tongue. However, there was no history of any trauma or ulcer over the right elbow. His older sibling who died at the age of 4 months from aspiration pneumonia also had similar medical history. The children were born of grade-2 consanguineous parents, but none of the parents or other relatives had a similar medical history.

Radiography and computed tomography of the right elbow revealed septic dislocation of the humeroulnar and radiocapitellar joint and a periosteal reaction (Fig. 1b). Ultrasonography revealed the presence of pus. Blood examination yielded leukocytosis (13,500 cells/mm$^3$) [reference range, 4500–10500 cells/mm$^3$] with neutrophilia (74%), and both the erythrocyte sedimentation rate (64 mm) [reference range, 0–17 mm] and C-reactive protein level (10.2 mg/dl) [reference range, <1 mg/dl] were raised. The serum procalcitonin concentration of 2.2 ng/ml was highly suggestive of bacterial infection. Serology for human immunodeficiency virus and hepatitis B surface antigen were negative. Tests for immunoglobulins (IgG, IgA, IgM, IgE, C3, and C4) to rule out immunodeficiency disorder yielded no abnormality, as did nerve conduction studies. Intradermal injection of 0.1 ml of 1:1000 solution of histamine produced a wheal with no pain or axon flare responses.

The patient was treated with intravenous cloxacillin and gentamicin as per our hospital protocol. Under general anaesthesia, the patient underwent open arthrotomy of the right elbow through the posterior approach, and about 20 ml of pus was drained. The distal humeral physis was completely separated, together with humeroulnar dislocation and erosion of the articular cartilage (Fig. 1b). After thorough debridement and lavage, the humeroulnar joint and distal humeral physis were fixed with Kirschner wires. The limb was immobilised in a plaster cast for 4 weeks. Culture of the pus yielded methicillin-resistant *Staphylococcus aureus*, sensitive to vancomycin. Intravenous vancomycin for 2 weeks and oral Linezolid for further 4 weeks were administered.

Follow-up radiographs showed loss of fixation with signs of chronic osteomyelitis such as lytic lesion and periosteal reaction (Fig. 1c). At week 4, the Kirschner wires were removed but the elbow was noted to be unstable. The distal humeral physis had malunited. There was no active sinus or local infection. The child was prescribed a dynamic elbow brace (Fig. 1c).

**Patient 2**

In December 2010, a 3-year-old girl presented with features of absent pain perception and anhydrosis since birth. She was born to grade-2 consanguineous parents. The first and third siblings died of sepsis, whereas the second was symptom-free. The patient experienced fever in the morning that subsided in the evening daily. The child had mild mental retardation and multiple trophic ulcers over the skull and extremities (Fig. 2a). There was a sinus over the proximal part of the left ulna discharging pus; radiography suggested chronic osteomyelitis (Fig. 2b). The child could not perceive any pain and was anhydrotic. Hot and cold sensation was preserved. Nerve conduction velocity testing revealed no

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**Figure 1**  Patient 1: (a) Bifid tongue, trophic ulcers over the left elbow and thumb, and healed trophic ulcer over the great toe, (b) septic arthritis of the right elbow, dislocation of the humeroulnar and radiocapitellar joint, and physeal disruption, and (c) loss of fixation and the use of a hinged brace for instability.
abnormality. Immunoglobulin profiling yielded elevated serum levels of IgG (19.3 g/l) [reference range, 9.5–12.5 g/l], IgE (1154 g/l) [reference range, <0.0003 g/l], and C3 (1.91 g/l) [reference range, 0.66–1.57 g/l], but IgA, IgM, and C4 levels were within normal limits. Grossly elevated IgE levels prompted evaluation for hyperimmunoglobulin E syndrome or Job syndrome, but the necessary features for these disorders were not fulfilled. Biopsy of the sural nerve showed a paucity of nerve fibres (predominantly of small diameter) with normal myelination (Fig. 2c).

**DISCUSSION**

In 2 cases of CIPA in male siblings, a defect in the gene NTRK1 (TRKA) was present in chromosome 1q. This encodes a high-affinity tyrosine kinase receptor for nerve growth factor (neurotrophic tyrosine kinase), a member of the neurotropin family that induces neurite outgrowth and promotes survival of embryonins and sympathetic neurons. The defect results in derangement of differentiation and migration of neural crests and the first-order-afferent system, which leads to formation of immature small myelinated (A delta) and unmyelinated (C) peripheral nerve fibres. An autopsy study confirmed the presence of immature nerve fibres in transmission of pain sensation. Mice lacking TRKA gene depicted similar phenotypic features of CIPA resulting in excessive neuronal loss in dorsal and sympathetic ganglia. CIPA was the first human genetic disorder implicated in the neurotropin transduction system. It is usually inherited as an autosomal recessive type, but sporadic types have also been reported.

Typically, CIPA manifests in infancy, with multiple episodes of fever, anhydrosis, and self-mutilation. Anhydrosis is due to non-innervations of eccrine sweat glands, although sweat gland histology is normal in skin biopsy. Hyperpyrexia secondary to anhydrosis accounts for the death in 20% of these children. Hence, their lifespan is usually short but long-term follow-up of such children has also been reported. They are usually mentally retarded. Touch, salivation, and lacrimation are preserved.

Hereditary sensory and autonomic neuropathy is classified into 5 types based on inheritance, course of the disease, clinical features, and nerve biopsy findings. Type 1 is a relatively mild condition affecting the lower limbs, and usually manifests in the second decade of life. Type 2 is more severe and involves all 4 limbs and usually manifests in infancy or early childhood. Despite non-sweating, temperature control is usually maintained. Type 3 is known as familial dysautonomia or Riley-Day syndrome. It is characterised by altered temperature and blood pressure control, manifesting with decreased pain sensation, hypertension, postural hypotension, recurrent episodes of aspiration (due to oropharyngeal dyscoordination), and disturbed gastropharyngeal mobility. Type 4 (CIPA) is characterised by anhydrosis, absent pain perception, defective temperature control, musculoskeletal problems, mental retardation, and severe behavioural disturbances. Type 5 is a relatively benign condition affecting only pain perception.

The differential diagnosis of CIPA includes hereditary anhidrotic ectodermal dysplasia, Fabry disease, and Lesch Nyhan syndrome. Hereditary anhidrotic ectodermal dysplasia is characterised by typical facies, scarce body hair distribution, anhydrosis, and dental abnormalities. It is differentiated from CIPA, as patients have intact sensation. Fabry disease involves paroxysmal pain, paraesthesia, fever, and multiple angiookeratomas. The typical presentation of Lesch Nyhan syndrome is self-mutilation and hyperuricaemia. All these are
X-linked inherited disorders. Patient 2 was suspected to have Job syndrome owing to high immunoglobulin E levels. The features of Job syndrome are characteristic facies, retained primary teeth, recurrent cold staphylococcal infections, eczema, recurrent pneumonia, and high concentrations of serum IgE. There is no convincing evidence correlating the levels of immunoglobulin with manifestations in CIPA, and it is not clear whether these could be the cause for recurrent infections.

Orthopaedic manifestations in CIPA are musculoskeletal infections, fractures, growth disturbances, avascular necrosis, Charcot arthropathy, joint dislocations, heterotopic ossification, and un-united fractures. Chronic or acute-on-chronic osteomyelitis and septic arthritis of haematogenous origin are the usual presentations. They often occur secondary to trophic ulcers and involve joints of the hand and foot and sometimes ankle and wrist. Septic dislocation with physeal separation (as in patient 1) is rare. This can be attributed to delayed presentation owing to absent pain perception. Prevention and training programmes play an important role in the management of these patients. Custom-fitted shoes and protective padding to prevent trophic ulcers should be provided. Prompt medical attention to minimise complications and if necessary early recourse to surgery should be emphasised. Regular follow-up and a brace should be provided.

DISCLOSURE

No conflicts of interest were declared by the authors.

REFERENCES