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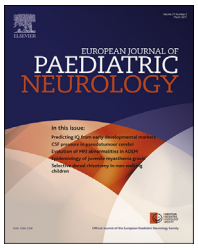

Original article

Orthopaedic manifestations of congenital indifference to pain with anhidrosis (Hereditary Sensory and Autonomic Neuropathy type IV)

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ABSTRACT

Background: Congenital indifference to pain with anhidrosis (CIPA) is a rare hereditary neuropathy, which is associated with defective sensation to noxious stimuli and autonomic dysfunction. The objective of the study was to report on the orthopaedic manifestations of this condition and provide an evidence-based approach for management.

Methods: Retrospective review of 14 consecutive patients with CIPA referred to a single tertiary centre. Mean age of diagnosis was 2.5 years (range 0.5 to 11 years).

Results: Patients presented with a range of orthopaedic problems including fractures, infections, growth disturbance, joint subluxation and Charcot joints affecting the limbs and spine. Conservative treatment with closed reduction and cast immobilisation was satisfactory for stress fractures of the lower extremity and Charcot joints. Posterior instrumented correction of scoliosis was associated with a high-risk of infection requiring reoperation for debridement and removal of posterior instrumentation. Growth disturbance leading to leg-length discrepancies were managed with shoe raises and corrective osteotomies. Aspiration and cultures may be used to differentiate between acute fracture and infection.

Conclusions: Preventative treatment strategies with appropriately padded shoe-wear, gait and posture modification, parental education regarding environmental thermoregulation, and behavioural support are essential for improving prognosis and reducing long-term complications.

Abbreviations: CIPA, congenital indifference to pain with anhidrosis; HSAN IV, Hereditary Sensory and Autonomic Neuropathy type IV; MRI, Magnetic Resonance Imaging; ADHD, attention deficit hyperactivity disorder.

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1. Introduction

Congenital indifference to pain with anhidrosis (CIPA) is a rare hereditary neuropathy, which is also known as Hereditary Sensory Autonomic Neuropathy type IV (HSAN IV) or hereditary sensory neuropathy. The disease is caused by a mutation in the nerve growth factor receptor tyrosine kinase 1 (NTKR1) coded on chromosome 1q21-q22.[1] This leads to a deficiency of the nerve growth factor (NGF) dependent myelinated Aδ and unmyelinated C-fibres, which clinically manifests as defective sensation to noxious stimuli and autonomic dysfunction.[2–4] Absent cholinergic sympathetic innervation to sweat glands results in anhidrosis and defective thermoregulation,[2–4] which is fatal in up to 20% of patients before the age of three years.[4]

Patients with CIPA often have varying levels of mental retardation and behavioural problems, which combined with defective sensation to pain leads to a wide-range of clinical presentations and conditions. Reported clinical manifestations include corneal ulceration, buccal trauma, onychopagia, self-mutilation, autoamputation, hypotonia and maxillofacial complications.[5–10] There is also an increased risk of orthopaedic complications such as fractures, nonunion, osteomyelitis, joint instability, avascular necrosis, and Charcot joints.[6,11,12] Patients often present late in the disease process making diagnosis and treatment more challenging. Arthrodesis, corrective osteotomy, and limb-lengthening are the most commonly performed procedures in CIPA.[12]

Studies to date on CIPA are limited to case reports or small cases series that pool findings from various systemic diseases and hereditary neuropathies. The objective of this study was to report on the orthopaedic manifestations and treatment of 14 patients with CIPA at a single referral centre and provide an evidence-based approach for the management of these patients.

2. Material and methods

The electronic database at our tertiary referral centre was searched for all patients diagnosed with CIPA, HSAN IV or congenital sensory neuropathy between 1990 and September 2014. This search identified 30 patients and the records of each patient were then reviewed by two of the authors (BK and AO). Of these, thirteen patients were excluded from the study as the underlying neuropathy was related to a different hereditary neuropathy (n = 6), diabetes mellitus (n = 3), alcoholism (n = 3) or syringomyelia (n = 1). A further three patients were excluded from the study as the patients were followed-up at another hospital or moved abroad during the follow-up period. The results of the remaining 14 patients were reviewed and included in this study.

All 14 patients included in this study were referred from their local secondary referral centres. Each patient was reviewed by our multi-disciplinary team, which included an orthopaedic surgeon, paediatrician, neurologist, geneticist, anaesthetist, microbiologist, physiotherapist, and social worker. A full history was obtained for each patient and complete orthopaedic and neurological examinations of the upper limbs, lower limbs and spine were performed. Each patient's level of mental retardation was assessed using the revised Leiter International performance scale.[13] Plain radiographic films and adjuvant imaging including Computerised Tomography and Magnetic Resonance Imaging (MRI) were organised as appropriate. These were reviewed and reported by a consultant musculoskeletal radiologist.

Diagnosis of CIPA was based on establishing three clinical criteria[14]: 1. Absent pain sensation since birth, 2. Whole body involvement, 3. Absent pain apprehension with preservation of deep tendon reflexes and other sensory modalities. Diagnosis was confirmed by the presence of a positive intradermal histamine skin test in all 14 patients. This involved the intradermal injection of 0.05 ml of 1/10 000 solution of histamine phosphate. Patients that developed an erythematous flare extending 1–3 cm were classified as normal, whereas patients with an absent flare were described as positive. Sural nerve biopsy was performed in 11 patients and findings reported by a consultant musculoskeletal pathologist. All of these patients had decreased myelinated Aδ and unmyelinated C-fibres on histological examination. DNA was prepared and confirmed for mutations in the NTKR1 gene as described by Shatzky et al.[15] in six patients. The remaining eight patients did not undergo genetic analysis, as the results would not affect the diagnosis or subsequent management.

The medical notes, pathology reports, diagnostic results and imaging findings were reviewed to collate data on the following outcomes of interest: Age at presentation, presenting symptoms, family history, consanguineous parents, mental retardation, orthopaedic complications, associated diseases, conservative treatment, surgical treatment, complications of treatment, and mobility at most recent follow-up. The results were tabulated and the outcomes of interest displayed for each patient included in this study. Due to the limited number of patients, statistical analysis to test p values was not performed as it would not generate meaningful results or add any value to the existing data. The study included eight male and six female patients with an average age of 21.4 years (range 11–31 years) at most recent follow-up.

3. Results

The clinical findings and outcomes of interest for patients included in this study are presented in Table 1. The mean age of diagnosis was 2.5 years (range 0.5–11 years) with twelve of the 14 patients diagnosed with CIPA before the age of 3.5 years. One patient (Case 1) immigrated to England at the age of nine years and was diagnosed with CIPA at our institution at 11 years of age.

This study included two separate pairs of siblings (Cases 4 & 5; Cases 10 & 11) and both of these groups had consanguineous parents who were first cousins. Each of these pair of siblings had one other healthy sibling who was not affected by any type of hereditary neuropathy. A further six patients had consanguineous parents, which included three parents who were first cousins (Cases 1,7,13) and three parents who were second cousins (Cases 6,9,12). The parents of the remaining four patients were not related to each other. Two patients had gastro-oesphageal reflux disease (Cases 2 & 10) and two