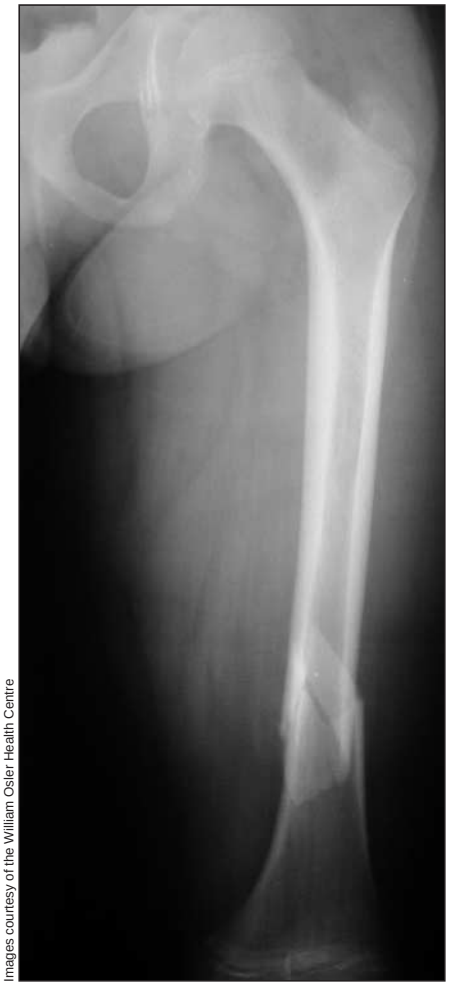
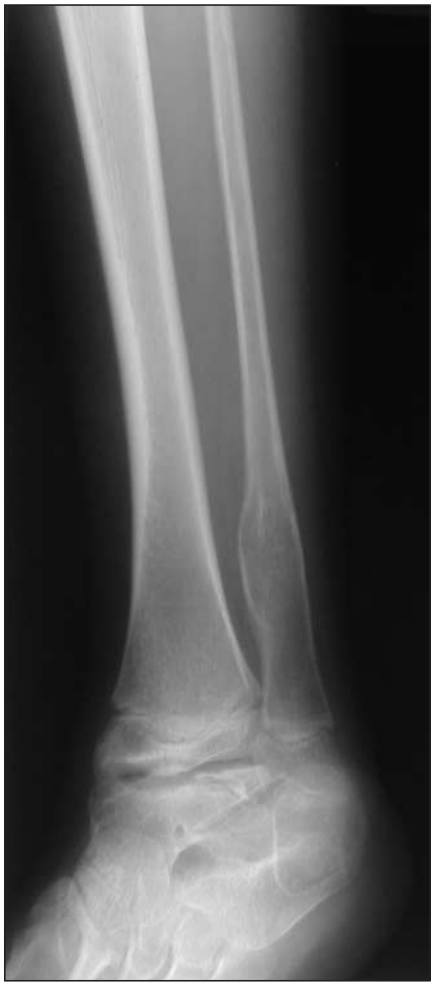
The mystery of the broken bones

A 15-year-old adolescent male presented with a decade-long history of recurrent fractures of the lower limbs. He had had an unremarkable prenatal and birth history and a normal development except for his height. His first fracture, of the left tibia, had occurred at the age of 4 years after only a minor trauma. Shortly thereafter he had fractured his right tibia after jumping off a chair. Toward the end of his seventh year he had complained of discomfort in his left hip; radiographs had revealed a recent fracture in that location and a healing fracture of the right hip. A radiograph taken when the boy was 11 years old had shown a fracture of the left femur (Fig. 1), and one taken at age 12 had revealed a healing fracture of his left lower fibula (Fig. 2). The patient had little recollection of the traumatic incidents that caused the fractures. Possible child abuse or osteogenisis imperfecta had been suspected, and the boy had been referred to a pediatric orthopedic surgeon and subsequently to a bone and calcium clinic at a tertiary care centre when he was 7 years old. A diagnosis of juvenile osteoporosis had briefly been entertained until one physician had noted the boy's insensitivity to pain. He was then referred to a pediatric neurologist.





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The patient had a family history of decreased sensativity to pain, first noticed in his 16-year-old brother at 10 years of age. The brother had chronic foot ulcers and a seizure disorder but no history of fractures. There was no family history of bone disease or other inherited metabolic or developmental problems.

The patient's weight was normal (50th percentile), but his height was just below the 5th percentile. The response to pain and light touch in his lower limbs was significantly decreased compared with the response in his upper limbs. Stereognosis was abnormal, and the results of a test for temperature sensation were inconclusive because the patient's answers were inconsistent. There was no ataxia. Peripheral deep tendon reflexes were normal.

Somatosensory-evoked potentials along the median and posterior tibial nerves and nerve conduction velocities were abnormal, which suggested the presence of a sensory polyneuropathy, probably on an axonal basis. Nerve conduction velocities in both parents were normal. Electromyography revealed intact motor neurons in the patient. Serum vitamin E and B_{12} levels were normal, as was the result of a skin histamine test. (The latter test often yields an abnormal result in certain types of hereditary sensory and autonomic neuropathy [HSAN].) Levels of serum ionized calcium, phosphate, creatinine and lead as well as the lipid profile were also normal. A urine amino acid screen was negative. An MRI scan of the brain and an ophthalmology assessment revealed no abnormalities. A biopsy of one of the patient's sural nerves showed complete absence of myelin fibres and large numbers of unmyelinated axons. HSAN was diagnosed.

HSAN comprises several peripheral neuropathies that affect the sensory nerves, autonomic nerves, motor fibres, or a combination of these, and that cause clinical features such as musculo-

Table 1: Classification of hereditary sensory and autonomic neuropathy (HSAN)[1,4]

Type	Mode of inheritance	Age at onset	Pathological and clinical findings
I	Autosomal dominant	Early adulthood	Mild sensory neuropathy of lower extremities
II	Autosomal recessive	Infancy	Severe neuropathy of all extremities; anhidrosis; myelinated fibre degeneration
III	Autosomal recessive	Infancy	Autonomic neuropathy
IV	Autosomal recessive	Infancy	Severe autonomic neuropathy; total loss of myelinated fibres; preservation of unmyelinated fibres; congenital insensitivity to pain and temperature, mild mental retardation, anhidrosis, unexplained fevers, musculoskeletal problems and behavioural disorders
V	Unknown	Any age	Pathophysiology not yet well defined; congenital insensitivity to pain and temperature in limbs, irregular areas of anhidrosis, abnormal nocioception, normal strength and normal tendon reflexes

skeletal manifestations (e.g., fractures, joint deformities, dislocations), or alterations in pain sensitivity, temperature discrimination, vibration sense or proprioception (Table 1).

HSAN type IV (also known as congenital insensitivity to pain[1–4]) is rare and occurs because of a mutation in the enzyme tyrosine kinase A, which is an important nerve growth factor.[4] The clinical presentation of HSAN type IV is variable; thus, a further subclassification has been established.[2] Patients with subtype A present with multiple infections, whereas those with subtype B present with multiple fractures, avascular necrosis and growth disturbances. Patients with subtype C present with multiple fractures, infections, joint dislocations, Charcot's arthropathy and mental retardation. Our patient's clinical features best fit those of HSAN type IV subtype B. Early diagnosis and injury reduction is the optimal method of treatment for these patients.

Congenital insensitivity to pain needs to be considered whenever young patients present with multiple fractures and bruises that are difficult to explain. Detailed physical examinations and medical and family histories will help to identify patients with this disorder, and appropriate investigations will help to determine the specific type and subtype of HSAN.

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