An hereditary sensory and autonomic neuropathy transmitted as an X-linked recessive trait

J V JESTICO,* PA URRY,† J EFPHIMIOU‡

From the Essex Regional Neurology Unit, Oldchurch Hospital, Romford,* Royal Free Hospital,† Department of Medicine, The Rayne Institute, University College Hospital,‡ London, UK

SUMMARY Five members of a single family presented with neuropathic deformities and ulceration of the feet developing in the first and second decades of life, and progressed slowly over many years. In this form of hereditary sensory and autonomic neuropathy, there was minimal tendon reflex impairment, cutaneous sensory impairment was restricted to the feet, and there was no autonomic dysfunction. The only neurophysiological abnormality was that of reduced or absent sural nerve sensory action potentials. Sural nerve biopsies taken from two affected family members showed changes of a chronic neuropathy with loss of myelinated fibres, particularly affecting those of small diameter. Unmyelinated fibres were present in normal numbers. This condition differed from other forms of hereditary sensory and autonomic neuropathy having an X-linked recessive mode of inheritance.

Five types of hereditary sensory and autonomic neuropathies are recognised according to their individual clinical, neurophysiological and histopathological characteristics, together with a type and severity of any autonomic dysfunction.1

Type 1 is a rare disorder presenting with progressive trophic lesions of the feet resulting in severe and disabling bony destruction and deformity. Early reports described its occurrence in siblings who developed perforating ulcers of the feet during their late teens,2 families in which ulceration of the feet affected successive generations,3 and others with sensory impairment of the feet and absent lower limb reflexes.4 The family described by Hicks in 1922 contained ten affected members in four generations who also complained of shooting pain throughout the body and deafness.5 Although sporadic cases have been reported,6 it was clear from large family studies that the condition was inherited as a Mendelian dominant trait.7

When Denny Brown* reported detailed post mortem findings of an affected member of the family previously described by Hicks,8 he designated the condition hereditary sensory neuropathy. He considered the principal pathology to be a primary degeneration of the dorsal root ganglia with the most severe changes affecting the lumbo-sacral region. However, he noted Wallerian degeneration with patchy and sometimes considerable neuronal loss within the nerve roots and peripheral nerves. Subsequently histological and neurophysiological studies have left no doubt that the condition should be classified as a peripheral neuropathy.9 10

Type 2 also presents with penetrating ulceration of the feet, but in addition trophic changes affect the fingers and hands. Numerous clinical reports have described the progressive recurrent whitlows and neuropathic ulceration of the fingers and feet associated with areflexia and distal sensory loss in all limbs. Family studies have shown this condition to be transmitted as an autosomal recessive trait.11 12

Type 3 is characterised by insensitivity to pain and autonomic failure, being inherited as an autosomal recessive trait.13 14 Type 4 presents with insensitivity to pain associated with anhidrosis and mental retardation.15 16 Type 5 is also associated with insensitivity to pain, but has additional impairment of pain and temperature sensation in the limbs, similar to that of Type 2.17

This report describes five members of a single family who presented with painless deformities of the feet. As the mode of inheritance of this condition differed from that of other recognised forms of hereditary sensory and autonomic neuropathy, we report the clinical features, electro-physiological,
and pathological changes, for comparison with the other types of inherited neuropathies.

Case reports

Case 1

A 13-year-old schoolboy presented with a four month history of painless deformities of the feet. He had been a normal infant born at term following an uneventful pregnancy. There was no parental consanguinity. His early developmental milestones and scholastic record were normal. He enjoyed sports, particularly football at which he excelled playing regularly for the school team. He could not recall having injured his feet, and he denied weakness, numbness or other sensory symptoms in the feet or legs. There was no bladder dysfunction. His general health was good. On clinical examination both feet were deformed with prominent bony enlargements of the metatarsal bones and flattening of the pedal arches. There was no ulceration of the skin. There was excessive painless movement of the tarsal joints. Higher cerebral functions, cranial nerves, and fundi showed no abnormality. There was no wasting, weakness or ataxia of the limbs. The ankle reflexes required reinforcements, other tendon reflexes being brisk and symmetrical. The plantar responses were flexor. Perception of light touch, pain and temperature was impaired over the dorsal aspect and soles of both feet. Vibration was appreciated at the ankles, and position sense preserved. Deep pain was appreciated when pressure was applied to the Achilles tendons. There was normal sweating in both feet. Tests of autonomic function were normal. The peripheral nerves were not thickened. Normal haematological and biochemical investigations included: full blood count, ESR, serum B12 and folate levels, urea, electrolytes, glucose, calcium, phosphate, phytic acid, creatinine kinase, liver and thyroid function tests, plasma lipids, protein and haemoglobin electrophoresis, immuno-globulin and complement levels, urinary porphyrins, and amino acid electrophoresis. VDRL, TPHA and autoantibody screen were negative. The plasma alkaline phosphatase was elevated at 910 IU/l, and electrophoresis showed this to be predominantly the bone isoenzyme. 24-hour urinary protein excretion was 0.11 g/l (normal less than 0.08). Midstream urine, creatinine clearance and excretion urrogram were normal. A rectal biopsy specimen was normal. CSF examination including electrophoresis was also normal. Radiological examination of the feet showed changes typical of neuropathic joints, (fig 1). In the left foot the calcaneo-cuboid joint was involved and there was sclerosis of the cuboid bone. However, the most severe changes in this foot comprised of sclerosis and fragmentation of the tarso-metatarsal joint surfaces with new bone formation extending distally between the first and second metatarsals. There was thickening of the shafts of the first and second metatarsals, and some periosteal new bone formation. Similar changes were seen in the right foot in the medial aspect of the tarso-metatarsal joint with considerable thickening and sclerosis of the first metatarsal, and subluxation of the joint. There was less severe thickening of the second metatarsal. Early sclerotic changes were also seen in the first metatarsophalangeal joint.

Electrophysiological studies in the upper limbs showed normal median and ulnar nerve sensory action potentials and motor conduction velocities. There was no evidence of denervation on sampling the small hand muscles. In the lower limbs the sural nerve action potential was reduced to 5 μV (normal 10-35). Motor conduction velocity in the common personal nerve was normal at 41 m/s. Muscle sampling of the tibialis anterior and extensor digitorum brevis muscles showed no abnormalities.

A sural nerve biopsy specimen was examined by light and electronmicroscopy. On light microscopy of methacrylate embedded tissue the specimen consisted of five fascicles associated with epineurial connective tissue. There was

Fig 1 Case 1: radiograph of feet showing neuropathic joint disease particularly affecting the tarso-metatarsal joint surfaces.

Fig 2 Transverse section of two fascicles of sural nerve from Case 1 showing severe depletion of myelinated fibres particularly those of small size. (Methacrylate Haematoxylin Eosin × 200).
An hereditary sensory and autonomic neuropathy transmitted as an X-linked recessive trait

Fig 4 Kinship of patients affected with this hereditary sensory and autonomic neuropathy. Affected males are shown as solid squares.

Similar though less severe changes were seen in the left foot.

Electrophysiological studies in the upper limbs showed normal radial and median mixed nerve action potentials and conduction velocities. The left sural nerve action potential was reduced in amplitude at 5 μV (normal 10–35) but sensory conduction velocity was normal at 48 m/s. Conduction velocity in the medial popliteal nerve was normal at 44 m/s. Only a semi thin epoxy resin imbedded preparation of the sural nerve biopsy was available for study. By light microscopy the specimen comprising of five fascicles showed a generalised paucity of myelinated fibres with absence of fibres in some areas, (fig 3). Measurement of 500 myelinated fibres showed a more severe loss of small diameter fibres. The proportion of small (1–7 μm) to large (8–14 μm) fibres was 34% to 66% (ratio 1:1.9). Unmyelinated fibres were present in normal numbers.

Case 2 (Brother of Case 1)

This patient developed painless deformities of the left foot at the age of three years, with calcaneo-valgus and flattening of the pedal arch. Walking had always been difficult, but he was nevertheless able to walk for several miles. At the age of nine years he complained of pain in the right foot following exercises at school, and was first investigated at that time. Examination revealed gross deformities of both feet with bony prominences and flattening of the pedal arches. There was excessive painless movement involving the right ankle and dorsum of the foot. There was no wasting or weakness of the lower limbs. The ankle jerks were absent, other reflexes being normal. Pain appreciation was impaired symmetrically in both feet. Light touch and vibration sensibilities were normal. Routine haematological and biochemical investigations were normal. Radiology of the feet demonstrated soft tissue calcification anterior to the right ankle joint, with evidence of destruction of the subtalor and talonavicular joints. The talus showed evidence of avascular necrosis with collapse.

Fig 3 A fascicle of sural nerve from Case 2 demonstrates severe loss and in parts absence of myelinated nerve fibres. (Epoxy-resin. Toluidin blue × 350)

a generalised reduction in the population of myelinated fibres, particularly those of small size, (fig 2). Measurement of 800 myelinated fibres confirmed the more severe deficit of those of smaller diameter. The proportion of small (1–7 μm) to large (8–14 μm) was 15-3% to 84-7% (ratio 1:5.5). Myelin sheath thickness appeared appropriate for the diameter of the axons. There was no evidence of active fibre break-down, nor were there degenerative clusters or ‘onion bulbs’. Unmyelinated fibres were present in normal numbers. Apart from some increase in endoneurial collagen the connective tissue appeared normal. There were no inflammatory infiltrates, Stains for amyloid were negative. Blood vessels incorporated in the section appeared normal. On electronmicroscopy the density of the unmyelinated fibres was calculated at 35,000/mm² (normal). The appearance were those of a chronic neuropathy with a generalised loss of myelinated nerve fibres, those of small diameter being more severely depleted.

Case 3

A male, (maternal uncle to cases 1 and 2) developed deformity and ulceration of the feet at 3 years of age. He was investigated in Jamaica where he was diagnosed as having a sensory neuropathy affecting only the feet. The condition progressed slowly with indolent painless ulceration and at the age of 19 years, the deformed left foot was amputated. He is now 20 years of age, and otherwise well.

Case 4

A male, (maternal uncle to cases 1 and 2) developed deformities of both feet with subsequent ulceration from the age of ten years. He is now 24 years of age and otherwise well.

Case 5

A male, (maternal uncle to cases 1 and 2) developed painless ulceration of a great toe at the age of ten years. The following year the affected digit was amputated. He is now 27 years of age and otherwise well.

(Cases 3, 4 and 5 were not examined by the authors.)

Unaffected family members

The parents and two sisters of cases 1 and 2 were each interviewed and examined. None had any neurological symptoms, and no abnormalities were found on examination. Nerve conduction studies were taken in each case and sensory action potentials and motor conduction velocities were normal in both upper and lower limbs. The family
Discussion

The clinical features of the hereditary sensory and autonomic neuropathy described in this report had some similarities with Types 1 and 2 including the development of ulceration of the feet. However, there were several differences which are discussed below, and it was clearly distinct from Types 3, 4 and 5, there being no generalised insensitivity to pain or autonomic dysfunction. As such these later conditions will not be considered further.

In all five patients described in this report the neuropathic lesions were confined to the feet. In one patient (case 1) there was no ulceration of the feet, but he had the shortest clinical history. In case 2, deformities of the feet preceded ulceration by 13 years. Cases 3 and 4 developed deformities of the feet and ulceration simultaneously. In case 5, ulceration was restricted to the great toe, but it was not known whether he subsequently developed foot deformities. Both case 1, in whom ulceration had not yet occurred, and case 2, in whom ulceration of the feet was a late manifestation of the condition, were both born and lived in England. The other affected family members, in whom ulceration was an early manifestation of the condition, all lived in poorer circumstances in Jamaica. The combination of poor hygiene and repeated unnoticed trauma to the feet are principally responsible for the development of such ulceration and may explain why this was such a prominent feature in those patients.

Four affected family members developed deformities of the feet within the first decade; in two, these changes occurred within the first three years of life. In one patient (case 1) such deformities did not develop until his mid-teens.

In all five patients in this study, the sensory impairment was restricted to the feet, even after symptoms had progressed for many years. In the two cases examined by the authors the cutaneous sensory loss was relatively slight compared with the gross neuropathic disease. In case 1, there was only a subjective blunting of cutaneous sensation affecting both touch and pain sensibilities equally. In case 2 there was a dissociated sensory loss with sparing of touch sensation.

In the two cases examined there was minimal tendon reflex involvement. In case 1, with the shortest clinical history, the ankle reflexes were depressed but could be obtained with reinforcement. In case 2, the ankle reflexes were absent, but other tendon reflexes were preserved. Case 3, investigated in Jamaica, was diagnosed as having a peripheral neuropathy restricted to the lower limbs, implying that impairment of reflexes if present was restricted to the legs.

The rate of progression of the disorder appeared variable. The patient who developed foot deformity alone in childhood (Case 2) had deteriorated very slowly remaining mobile and without foot ulceration for many years, but more rapid deterioration occurred following the development of such ulceration. Another patient who developed simultaneous deformity and ulceration in childhood also deteriorated very slowly, amputation being necessary in his late teens. However in the patient developing the disorder in his teens (Case 1) the condition appeared to progress rapidly with extensive deformities occurring within a few months.

The electromyographic abnormalities seen in the two patients studied were restricted to the lower limbs, with a reduction or absence of the sural nerve action potentials. Neither patient showed slowing of motor conduction velocities in the common peroneal nerves and muscle sampling showed no evidence of denervation in the extensor digitorum brevis or anterior tibial muscles. In this study motor and sensory nerve conduction measurements were taken of unaffected family members, namely both parents and two of our patients sisters. These recordings were all normal, and from this the authors concluded that such studies would not be useful as means of detecting subclinical carriers of the condition.

The pathological changes in the sural nerve biopsy specimens taken from two patients in this study showed changes of a chronic neuropathy with selective loss of myelinated fibres, particularly affecting those of small diameter. These changes were similar to those reported from sural nerve biopsies taken from patients with hereditary sensory and autonomic neuropathy Type 1, with a relative sparing of large myelinated fibres. However, in our cases, unmyelinated fibres were present in normal numbers, whereas in Type 1, unmyelinated fibres are more severely depleted than myelinated fibres. Also, in Type 1 there may be discontinuity of myelin and increased Schwann cell nuclei, but these were not seen in our cases. This preservation of unmyelinated fibres had similarities with histological studies of sural nerve biopsies taken of patients with Type 2. In these there may be total loss of myelinated fibres with only unmyelinated fibres remaining.

The clinical features of the hereditary sensory and autonomic neuropathy described in this report had some similarities with both hereditary sensory and autonomic neuropathies Types 1 and 2 including the development of ulceration of the feet. It was clearly distinct from Types 3, 4 and 5, there being no
An hereditary sensory and autonomic neuropathy transmitted as an X-linked recessive trait

generalised insensitivity to pain or autonomic dysfunction. In all five patients the neuropathic lesions were confined to the feet as in hereditary sensory and autonomic neuropathy Type 1. The relatively mild cutaneous sensory impairment restricted to the lower limbs was also similar, one case (case 2) showing a dissociated sensory loss identical to that reported in patients with hereditary sensory and autonomic neuropathy Type 1. The neurophysiological changes were similar to those reported in other forms of hereditary sensory and autonomic neuropathy. However, despite the similarity of the clinical features, the onset of symptoms and early teens differed from type 1 in which typically develops from late teens or even at late as the third decade of life. This hereditary sensory and autonomic neuropathy certainly differed from type 2 which also begins in early childhood but which has prominent involvement of the upper limbs with recurrent infection and characteristic ulceration of the fingers.

Although the hereditary sensory and autonomic neuropathy described here had some clinical similarities with types 1 and 2, its mode of inheritance was unique. Whereas types 1 and 2 are transmitted as dominant and recessive traits respectively, this hereditary sensory and autonomic neuropathy was transmitted as a X-linked recessive trait, being carried by females and manifested in males. In family studies of the dominantly inherited hereditary sensory and autonomic neuropathy type 1, frequently more males than females are affected. Indeed, in one family study, only male members were affected, but the transmission occurred directly from father to son. Some of the earlier family studies of hereditary sensory and autonomic neuropathy Type 1 have been criticised in that all family members were not examined. For example, parents may have been dead at the time of the reports, or they had the disorder in a mild form and were asymptomatic, and therefore assumed not to have the disorder. Furthermore within affected families the severity of the neuropathy may vary considerably. However, in this report, neurological examination and electrophysiological studies of the mother and unaffected sisters of our patients were entirely normal. As such, the authors were confident that they were not affected by the condition. With its X-linked inheritance, we concluded that this condition was a distinct form of hereditary sensory and autonomic neuropathy, and have provisionally designated it hereditary sensory and autonomic neuropathy type 6.

The authors are grateful to Mr Francis Moll of the Royal Free Hospital, Histopathology Department, for his invaluable technical assistance.

References


