HEREDITARY SENSORY NEUROPATHY WITH NEUROTROPHIC KERATITIS

DESCRIPTION OF AN AUTOSOMAL RECESSIVE DISORDER WITH A SELECTIVE REDUCTION OF SMALL MYELINATED NERVE FIBRES AND A DISCUSSION OF THE CLASSIFICATION OF THE HEREDITARY SENSORY NEUROPATHIES

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SUMMARY

A Kashmiri family with 3 members affected by a congenital sensory and autonomic neuropathy and corneal opacification is described. The 3 affected cases were offspring of consanguinous marriages in two generations; autosomal recessive inheritance is therefore probable. Pain and temperature sensation was lost in the limbs with a resulting mutilating acropathy. Sudomotor function was also impaired. Motor function, tendon reflexes, kinaesthetic sensation and sensory nerve action potentials were normal. Sural nerve biopsy showed a selectively reduced small myelinated nerve fibre population. Corneal histology revealed neurotrophic keratitis.

The classification of the hereditary sensory and autonomic neuropathies is discussed. This family represents a previously unrecognized variant.

INTRODUCTION

The early literature contains reports of familial cases in which the salient clinical abnormality was the development of a mutilating acropathy, predominantly affecting the lower limbs. Such cases were frequently ascribed to lumbosacral syringomyelia (Nélaton, 1852; Bruns, 1903; Göbell and Runge, 1917; Schultze, 1917; Weitz, 1924; Riley, 1930; Van Epps and Kerr, 1940). They are difficult to assess in retrospect because of the lack of pathological documentation, but probably represent instances of hereditary sensory neuropathy. The recognition that such cases could be due to a hereditary sensory neuropathy came with the report by Ogryzlo

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(1946) on 4 affected individuals from a sibship of 12 from Newfoundland, the parents being clinically normal. The inheritance was probably autosomal recessive. The onset of symptoms was in early life with distal sensory loss affecting all modalities. Nerve biopsy demonstrated loss of nerve fibres.

The fact that the sensory loss in some cases mainly affected pain and temperature sensibility was the reason why many earlier authors had attributed this to 'lumbosacral syringomyelia'. In these cases, the inheritance was usually autosomal dominant. The first demonstration that they were also due to a sensory neuropathy was provided by Jughenn et al. (1949) in a single case that came to autopsy. Loss of myelinated nerve fibres, perineurial thickening and Schwann cell proliferation were observed. Subsequently Denny-Brown (1951), again in a dominantly inherited family previously reported by Hicks (1922) as hereditary perforating ulceration of the feet, considered that the primary defect was a degeneration of dorsal root ganglion cells and introduced the term 'hereditary sensory radicular neuropathy'.

In an attempt to classify hereditary sensory neuropathies in terms of their genetic and clinical features, Dyck and Ohta (1975) later categorized these former cases which showed autosomal recessive inheritance and congenital sensory loss affecting all modalities distally in the limbs as hereditary sensory neuropathy (HSN) type II. Those with autosomal dominant inheritance and an onset of symptoms most frequently during the second and third decades of life and who showed a predominant loss of pain and temperature sensibility were classified as HSN type 1. Nevertheless there is considerable clinical overlap between the two conditions (Asbury and Johnson, 1978).

The term congenital insensitivity to pain was formerly employed to indicate the absence of recognition of pain and a lack of reaction to painful stimuli from birth. In such cases in which there was accompanying anhidrosis, Swanson et al. (1965) and Bischoff and Curti (1977) established that there was a selective loss of unmyelinated axons in the peripheral nerves and a deficiency of Lissauer's tract. Similarly, congenital insensitivity to pain in association with familial dysautonomia was shown by Aguayo et al. (1971) to be related to a severe deficiency of unmyelinated axons and a lesser depletion of large myelinated axons. Both of these conditions are of autosomal recessive inheritance and were classified by Dyck and Ohta (1975) as HSN IV and III, respectively.

In the present study, a family is described in which a sensory neuropathy, probably congenital and of autosomal recessive inheritance was found to be associated with loss of small myelinated fibres. The family is unique in that the neuropathy was consistently associated with neurotrophic keratitis.

**CASE REPORTS**

All the family members originated from Kashmir. The 3 members affected by sensory neuropathy and corneal opacification (IV.4, IV.7, V.4) result from two first cousin marriages (fig. 1). Family members III.4, IV.3,6,7,8,10,12,13 were all normal on examination and were unaware of any other affected family members.
Case IV.4

This 26-yr-old man had a normal birth and did not suffer unexplained fevers during infancy. Bilateral corneal opacification had been noted at about 4 months of age. Ulceration of the tip of the tongue developed at the age of 3 yrs. A sore on the lip became a cleft through which drinking fluids would leak until the defect was closed surgically (fig. 2). From the age of 5 yrs he was aware that he did not feel pain if he cut his hand and that wounds took a long time to heal. He has never been able to feel pain or temperature with his hands or feet. Frequent whitlows have led to loss of terminal finger pulp and deformities of the toes, and autoamputation of one toe. Skin ulcers requiring grafting have affected his feet (fig. 3). He can feel pain and temperature on the trunk and face, has experienced abdominal pain and suffers discomfort if foreign objects lodge in his conjunctivae. Deteriorating vision due to corneal opacities led to a corneal transplant to the right eye at the age of 25 yrs.

Examination revealed mutilating acropathy affecting the feet (fig. 3) and fingers with loss of terminal digital pulp. The tip of the tongue was absent (fig. 2). Mentation, muscle bulk and power, the tendon reflexes, light touch, vibration and joint position sense, and 2-point discrimination were normal. The painful elements of pin-prick sensation, and tickle sensation, were totally absent in the limbs below the elbows and knees, over the tip of the tongue and on the scalp. Mild hyperpathia to pin prick was present on the trunk. Temperature sensation was impaired over the whole body. The corneal reflex was normal on the left but absent from the right-sided corneal graft. Tear secretion was normal.

Ophthalmological examination. Visual acuity was 6/12 in the left eye. The left cornea showed scarring affecting the mid and deeper zones of the stroma with cysts, clefs and pigment spicules within it, and clumping of pigment on the endothelium in the region of the scar (fig. 4). The corneal epithelium was intact and there was no clinical evidence of vascularization of the scar.

Laboratory investigations. The following were normal: routine haematology, plasma urea and electrolytes, blood sugar, serum immunoglobulins and protein electrophoresis, thyroid function, blood lead, vitamin B_{12} and syphilis serology, 24 h urinary vanillyl mandelic acid excretion, audiometry and psychometry.
Fig. 2 (left). Case IV.A, showing traumatic amputation of the tip of the tongue and perioral scars. The right cornea is cloudy, related to chronic rejection of a corneal graft.

Fig. 3 (right). Case IV.A, showing chronic ulceration of the feet and loss of the left hallux.

Fig. 4. Case IV.A, showing opacification of the central portion of the left cornea.
Neurophysiological investigations. Sensory and motor nerve conduction, and needle electromyography of the first dorsal interosseous muscle of the hand and the tibialis anterior were normal (Table 1), as were somatosensory evoked potentials on stimulation of the posterior tibial nerve at the ankle (N20 lumbar 25 ms, 12 μV; P40 cortex 39 ms, 0.9 μV).

Autonomic function. Sweating was examined on the ventral surface of the body and limbs which were coated with Edicol Pinceau 4R 1G starch BPC and inspected for discoloration after raising the body temperature by 1°C. Sweating was incomplete and occurred only in the areas recorded in fig. 5.

Blood pressure lying was 122/74 mmHg and with 60° tilt was 115/64 mmHg. Sinus arrhythmia was present during deep breathing (55 to 85 beats/min). Carotid massage caused bradycardia.

![FIG. 5. Case IV.4. Sweat test. The shaded areas indicate residual areas of sweating.](image)

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MCV = motor conduction velocity, m·s⁻¹; DL = distal motor latency, ms; F = F wave latency, ms; Amp. = amplitude, μV; Latency = latency to peak, ms.
Case IV.7

This 11-yr girl, sister of Case IV.4, had a normal birth and infancy. Bilateral corneal opacification was noted at 1 yr of age. An ulcer appeared on the tip of the tongue at the age of 3 yrs and even when she subsequently bit off the tip of her tongue she appeared free of pain. At the age of 4½ yrs bilateral keratitis with perforation and adherence of the iris to the cornea on the right was recorded at ophthalmological consultation. By the age of 5 it was clear that she could not appreciate pain or temperature with her hands, feet, anterior tongue or around the nose. Trophic skin ulcers and bony deformity subsequently appeared in the feet. Muscle bulk, power, tendon reflexes and joint position sense were normal. Histamine flare was normal in the areas of reduced pain sensation. There was no postural hypotension and sinus arrhythmia was normal. The cornea and conjunctivae of both eyes were anaesthetic. Tear secretion was normal.

Ophthalmological examination. The visual acuity was no light perception in the right eye and 6/60 in the left. The periphery of the right cornea was clear but its centre bore a dense scar that was superficially vascularized. The iris was adherent to the scarred area. A penetrating keratoplasty had been performed on the left cornea and the specimen was available for histological examination.

Nerve conduction studies. Motor conduction velocity and sensory nerve action potentials were normal (Table 1).

Case V.4

This girl had a normal birth. The eyes were said by the family to have been normal at birth but bilateral corneal opacification was noted at 6 months of age. She may have had a seizure when aged 6 months. When examined at 18 months of age she walked normally, did not speak, and had early trophic changes on the lips and fingertips. A response to pin prick was absent from the hands and normal from the trunk. Both conjunctivae were anaesthetic.

Ophthalmological examination. By 2 yrs of age penetrating keratoplasty for central corneal opacity had been performed on both eyes and one cornea was available for histological examination.

MORPHOLOGICAL INVESTIGATIONS

Nerve Biopsy

Sural nerve fascicular biopsy from a site immediately posterior to the lateral malleolus was obtained under local anaesthetic from Case IV.4 in February, 1985.

Methods. The specimen was fixed for 3 h at 4°C in 3% glutaraldehyde in PIPES buffer (Baur and Stacey, 1977), washed in buffer and postfixed in 2% osmium tetroxide in PIPES buffer. After dehydration through graded concentrations of ethanol, the specimen was embedded in Araldite using 1, 2 epoxypropane as an intermediary. Semithin sections (1 μm) for light microscopy were stained with thionin and acridine orange (Sievers, 1971). Thin sections for electron microscopy (JEOL 100 SX) were stained with 12.5% methanolic uranyl acetate and lead citrate. Myelinated fibre density and size-frequency distributions were obtained using a Kontron Videoplan image analysis system connected to a Leitz Ultraphot. Morphometry of unmyelinated axons was undertaken on electron microscope montages of approximately 10% of the fascicular area at a final magnification of ×8000. Single fibre preparations were obtained by teasing in Araldite, employing the method described by Spencer and Thomas (1970); 136 fibres were isolated.
Fig. 6. Case IV.4. Transverse section of portion of sural nerve biopsy specimen showing relative lack of small myelinated nerve fibres. Thionin and acridine orange stain, × 530.

Fig. 7. Case IV.4. Size-frequency distributions of myelinated nerve fibres (A) and unmyelinated axons (C) in the sural nerve. B shows the myelinated nerve fibre distribution from a control subject aged 38 yrs.
Results. Transverse sections of the nerve biopsy specimens showed a lack of small myelinated fibres (fig. 6). Myelinated fibre density was reduced at 4726/mm$^2$ (normal range 7500–10 000/mm$^2$, Jacobs and Love, 1985). A fibre size-frequency histogram confirmed a striking selective reduction in the smaller diameter myelinated fibre peak (fig. 7A, B). No active fibre degeneration or demyelination was seen in the semithin sections, but occasional regenerative clusters, in slightly excessive numbers for the patient’s age, were present. No hypertrophic changes were encountered. The teased fibre preparations showed a normal relationship between internode length and fibre diameter, apart from three fibres with intercalated remyelinated segments and one regenerated fibre with uniformly reduced internode length. This amount of abnormality is within normal limits for the patient’s age.

On electron microscopy, the unmyelinated fibres were morphologically normal (fig. 8). The density of unmyelinated axons was increased at 76 000/mm$^2$ (normal range 30 000–40 000/mm$^2$, Jacobs and Love, 1985), this presumably being related mainly to the reduction in numbers of small myelinated fibres. As a whole nerve biopsy was not performed, total fascicular area and hence an estimate of the
absolute unmyelinated axon count could not be obtained. The size distribution of unmyelinated axons was normal (fig. 7c). The presence of regenerative clusters derived from myelinated fibres was confirmed (fig. 9). There were also occasional stacks of flattened Schwann cell processes of the type that follow the degeneration of Remak fibres (Ochoa, 1978). No giant vacuolated fibroblasts of the type reported by Schoene et al. (1970) in hereditary sensory neuropathy were observed.

**Corneal Histology**

Corneal tissue was available for histological study from Cases IV.7 and V.4, obtained at the time of corneal grafting performed at the ages of 13 yrs and 18 months, respectively. The specimens were fixed in formalin, embedded in paraffin wax and stained with haematoxylin and eosin and the periodic acid-Schiff technique.

**IV.7.** The epithelium was variable in thickness with atrophy in several places and loss of much, but not all, of Bowman’s zone. There was some stromal vascularization and scarring with a very few scattered lymphoctyes. Descemet’s membrane and the endothelium were normal.
Case V.4. Cross-section of the full thickness of the cornea showing a slightly thickened epithelium in direct contact with the substantia propria, the normal acellular Bowman's zone between these two structures having failed to develop. There is focal hypercellularity of the collagenous stroma associated with some vascularization (arrows). Descemet's membrane is narrow and difficult to identify at this magnification. Haematoxylin and eosin, ×180.

V.4. The corneal epithelium was acanthotic and thickened, but without keratinization, and rested on a basement membrane that was in direct apposition to the lamellar collagen and the substantia propria, there being no identifiable Bowman's zone (fig. 10). A few lymphocytes were present in the stroma, chiefly in the vicinity of infiltrating blood vessels. Descemet's membrane was intact if slightly narrow (fig. 11). Oxytalan fibres were not present (these are an elastic tissue precursor normally found in Descemet's membrane in early childhood which disappear in later life). The endothelium was morphologically normal and of normal density.

DISCUSSION

Hereditary Sensory Neuropathy with Neurotrophic Keratitis

The cases described in this report, from a single family, may represent a unique disorder. All affected individuals exhibited insensitivity to pain, manifested from childhood and possibly congenitally, related to a sensory neuropathy. Clinical examination showed selective loss of pain and temperature sensation which was maximal distally. This had led to a mutilating acropathy and also to facial and tongue injury. Motor function and large fibre sensory modalities were preserved.
The only detectable autonomic manifestation was widespread anhidrosis. This may have contributed to the acropathy by causing dryness and fissuring of the skin.

Sural nerve biopsy revealed selective loss of small myelinated fibres and a normal density of unmyelinated axons. The presence of occasional stacks of flattened Schwann cell processes unassociated with axons suggests that some degeneration of unmyelinated axons may have occurred. No evidence of active myelinated fibre breakdown was encountered, but the finding of occasional regenerative clusters indicates that some degeneration and subsequent regeneration of myelinated fibres had also occurred. These appearances were not frequent but were considered to be excessive for the patient's age. Some continued progression of the neuropathy is therefore implied although, clinically, there was no positive indication of this. The development of increasing mutilating changes may merely represent the consequences of persisting pain and temperature sensory loss.


**Fig. 11.** Case V.4. Deep aspect of the cornea showing an even but marginally narrow Descemet's membrane (2.5 μm compared with the 3–4 μm usual at this age). The endothelial lining is continuous and not unduly sparse. Periodic acid-Schiff, ×450.

This pattern of fibre loss, namely a selective reduction in the small myelinated nerve fibre population with preservation of the large myelinated and unmyelinated axons, has been observed previously in 2 cases, both of whom had a congenital sensory neuropathy. The first (Low et al., 1978) was a 6-yr-old girl with recurrent ulceration of her extremities dating back to the age of 7 months, associated with degenerative arthropathy of the ankles. There were no motor abnormalities, the
tendon reflexes were preserved and the only detectable sensory loss was for pain and temperature distally in the lower limbs and for pain distally in the upper limbs. Autonomic function was normal, including sweating, apart from anisocoria, and defective pupillary reaction to light on one side. Nerve conduction studies were normal. The second case (Dyck et al., 1983) was a 14-month-old child with selective and universal loss of pain sensation but no other apparent neurological abnormalities except for some evidence of reduced sudomotor function and probable psychomotor retardation. Neither case had a positive family history and there was no definite evidence of consanguinity. It was assumed by Dyck et al. (1983) that these 2 cases were likely to have a genetic basis, although it would not be possible to exclude an environmental factor operating in utero in the absence of a family history and evidence of a progressive neuropathy.

The unique features of our family are, first, that this form of sensory impairment with the same pattern of nerve fibre loss on nerve biopsy has been observed as an autosomal recessive trait. The second feature is its association with bilateral corneal opacification, the corneal periphery remaining clear. This corneal opacification was probably not present at birth but developed simultaneously in both eyes of each patient during the first few months or years of life.

A major question is whether the corneal abnormality was merely secondary to the neuropathy or whether it was a separate manifestation of the abnormal gene which caused the neuropathy. Since the relatives recalled that the corneas of Case V.4 were initially clear, a congenital disorder such as sclerocornea or Peter's anomaly has to be discounted. Definite clinical evidence of a traumatic keratitis was only obtained for one of the six corneas, the right eye of Case IV. The nature of the stromal scarring and vascularization, together with the presence of a few scattered leucocytes, is consistent with a postinflammatory disorder. So far as the pathogenesis is concerned, the bilateral simultaneous onset observed in all 3 patients points to an underlying endogenous disturbance, as opposed to a simple infective or traumatic episode. In view of the evidence in other tissues of a sensory nerve defect it is conceivable that the basic pathogenesis of the corneal changes is also neurotrophic, the precise mechanism being obscure but possibly an outcome of vasomotor disturbance at the periphery and associated metabolic consequences (Sigelman and Friedenwald, 1954). Certainly the histological findings compare with those previously described in neurotrophic keratitis (Spencer, 1985).

Of the numerous reported cases with hereditary sensory neuropathy, only one sibship apart from our own has exhibited central corneal opacification. A disorder in Navajo Indian children with the autosomal recessive inheritance of corneal opacity associated with mutilating acropathy, painless long bone fractures, cutaneous ulceration, areflexia, abnormal nerve conduction and severe loss of myelinated fibres in the sural nerve was described by Appenzeller et al. (1976). The corneal opacification in these cases was attributed to trauma rather than developmental anomaly. Corneal histology was not reported. Moreover, the pattern of nerve fibre loss resembles that of type II HSN (Ohta et al., 1973) rather
that the selective diminution in the small myelinated fibre population seen in our family.

The rarity with which corneal opacification is encountered in hereditary neuropathy suggests that it is not an automatic consequence of the neuropathy. Its invariable association with the neuropathy in our cases and those of Appenzeller et al. (1976) raises the possibility that it is a postnatal anomaly of the cornea caused by the abnormal gene responsible for the neuropathy, or by a closely linked gene. The association of the neuropathy and the keratopathy in two generations in our family makes it unlikely that more than one gene is involved.

Classification of the Hereditary Sensory Neuropathies

The classification of the hereditary sensory neuropathies has so far been based on a combination of the clinical and genetic features (Dyck and Ohta, 1975; Thomas, 1975; Asbury and Johnson, 1978). These conditions may be associated with autonomic manifestations which are sometimes the salient aspect of the clinical presentation. Dyck et al. (1983) therefore suggested that this group of disorders could appropriately be termed the hereditary sensory and autonomic neuropathies in view of the overlap between these two manifestations. Ultimate characterization will depend upon identification of the abnormal genes and gene products. Until then it is clinically useful to categorize them in terms of their pattern of inheritance in combination with their clinical and pathological features. Autosomal dominant, autosomal recessive and possible X-linked recessive pedigrees have been identified. A tentative classification is given in Table 2. Occasional patients with peroneal muscular atrophy display a severe distal sensory loss leading to a mutilating acropathy (England and Denny-Brown, 1952; Dyck et al., 1965;

| TABLE 2. CLASSIFICATION OF HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSAN) |
|-------------------------------|---------------------|
| Autosomal dominant inheritance | Dominantly inherited sensory neuropathy (Denny-Brown, 1951) (HSAN I*) |
| | Dominantly inherited sensory neuropathy with paraplegia (Cavanagh et al., 1979) |
| Autosomal recessive inheritance | Recessively inherited sensory neuropathy (Ohta et al., 1973) (HSAN II*) |
| | Hereditary anhidrotic sensory neuropathy (Swanson, 1963) (HSAN IV*) |
| | Familial dysautonomia (Riley et al., 1949) (HSAN III*) |
| | Hereditary sensory neuropathy with neurotrophic keratitis (present family) |
| | Recessively inherited sensory neuropathy with spastic paraplegia (Cavanagh et al., 1979) |
| X-linked recessive inheritance | X-linked recessive sensory neuropathy (Jestico et al., 1985) |
| Uncertain status | Hereditary sensory neuropathy with dysautonomia (Nordborg et al., 1981) |
| | Congenital sensory neuropathy with selective loss of small myelinated fibres (Low et al., 1978; Dyck et al., 1983) (HSAN V*) |

* Classification of Dyck et al. (1983)
Ben Hamida et al., 1981). One such family was described by Thomas et al. (1974) in whom an earlier diagnosis of 'lumbosacral syringomyelia' was revised to dominantly inherited type I hereditary motor and sensory neuropathy (HMSN). The prominence of the motor signs in such cases makes it more satisfactory for them to be classified as HMSN. Whether families with severe sensory loss are genetically distinct is so far not established. Linkage studies have not yet been reported.

**Autosomal dominant forms.** The main disorder in this category is the form first adequately described by Denny-Brown (1951). It comprises a distal sensory neuropathy with an onset most commonly in the second or third decades. Sensory loss initially affects mainly pain and temperature appreciation. Dyck et al. (1971) and Dyck (1984) found loss of myelinated axons of all diameters and of unmyelinated axons. This was least for large myelinated fibres, intermediate for small myelinated axons and greatest for unmyelinated axons. Spontaneous pain is often a feature. This form has been designated type I hereditary sensory neuropathy by Ohta et al. (1973).

Cavanagh et al. (1979) reported the occurrence of a sensory neuropathy accompanied by a spastic paraplegia of probable autosomal dominant inheritance. As the salient clinical feature was the sensory neuropathy and the accompanying mutilating acropathy rather than the spastic paraplegia, it is appropriate for this condition to be included amongst the hereditary sensory neuropathies.

**Autosomal recessive forms.** The most important disorder in this category consists of those cases described as congenital sensory neuropathy (Murray, 1973), progressive sensory neuropathy of childhood (Johnson and Spalding, 1964) or type II hereditary sensory neuropathy (HSN) (Ohta et al., 1973). Recessive inheritance has been suggested by the involvement of more than one individual in a sibship with normal parents and, at times, parental consanguinity. Similar isolated cases are likely to represent the same condition (Linarelli and Prichard, 1970; Barry et al., 1974; Person et al., 1977; Nukada et al., 1982). In some cases the sensory loss is clearly present from birth or early life (e.g., Wadia and Dastur, 1960; Winkelmann et al., 1962; Johnson and Spalding, 1964; Haddow et al., 1970; Linarelli and Prichard, 1970; Murray, 1973; Barry et al., 1974; Person et al., 1977). All sensory modalities are affected. Because of the preservation of motor function and the early age of onset, distal mutilation tends to be particularly severe. Not all have symptoms from infancy. In some cases given this designation (Nukada et al., 1982) or with otherwise similar clinical features (Adams et al., 1973), disease manifestations have not appeared until the third decade. Ataxia rather than the occurrence of cutaneous sensory loss has at times been the initial feature (Nukada et al., 1982). Minor autonomic involvement occurs, including impotence and disturbances of bladder function (Murray, 1973; Nukada et al., 1982). Nerve biopsies show severe loss of myelinated nerve fibres of all sizes and some reduction in the number of unmyelinated axons (Ohta et al., 1973; Nukada et al., 1982).

The question of progression in recessively inherited sensory neuropathy has
given rise to discussion. Murray (1973) considered that in his cases, the congenital neurological disorder was static, the advance in the mutilations that they showed merely being the result of persisting sensory loss. Other patients undoubtedly show progression of neurological signs; moreover, increasing severity of fibre loss of consecutive biopsies has been demonstrated (Nukada et al., 1982). Tamari et al. (1980) have suggested that two forms exist: (1) a congenital nonprogressive form, including the cases of Haddow et al. (1970) and Murray (1973); (2) a progressive form with an onset later in childhood, including the cases in the 3 families that they described and those of Johnson and Spalding (1964), Schoene et al. (1970), Ohta et al. (1973) and Jędrzejowska and Młczarek (1976). Not all published cases fall easily into one or other of these subdivisions. Nevertheless, in general, the available evidence makes this possibility worthy of further consideration.

The second clearly identifiable autosomal recessive form is sensory neuropathy with anhidrosis (Swanson, 1963; Brown and Podosin, 1966; Pinsky and DiGeorge, 1966; Vassella et al., 1968) or type IV HSN (Dyck and Ohta, 1975). Affected individuals show congenital insensitivity to pain, loss of sweating and mild mental retardation. There is a virtual absence of unmyelinated axons in the peripheral sensory nerves (Bischoff and Curti, 1977; Goebel et al., 1980), absence of small neurons in the primary sensory ganglia and a reduction in the size of Lissauer's tract (Swanson et al., 1965).

A third distinct condition is the Riley-Day syndrome (familial dysautonomia, Riley et al., 1949). Although autonomic manifestations are the predominant feature, individuals affected with this autosomal recessive disorder also display congenital insensitivity to pain. Aguayo et al. (1971), from a nerve biopsy study, demonstrated that there is a severe reduction in the number of unmyelinated axons and a lack of myelinated fibres of largest diameter. There are also reduced numbers of neurons in sympathetic, dorsal root and trigeminal ganglia (Pearson et al., 1971). Nordborg et al. (1981) described 3 sporadic cases of a nonprogressive congenital sensory neuropathy and dysautonomia with clinical features that differed in a number of respects from the Riley-Day syndrome. Nerve biopsy showed an almost total loss of myelinated axons and a reduction in the number of unmyelinated axons, this pattern more closely resembling that of type II HSN. It was considered that they probably represented a separate entity, distinct from the Riley-Day syndrome.

Finally, Cavanagh et al. (1979) described a sensory neuropathy associated with spastic paraplegia of probable autosomal recessive inheritance, the manifestations being more severe than in the autosomal dominant disorder that they also reported. A further family of this type has recently been identified (G. D. Schott and P. K. Thomas, unpublished).

X-linked recessive sensory neuropathy. There has been a single report of a sensory neuropathy with symptoms that developed during the second decade with possible X-linked recessive inheritance (Jestico et al., 1985). The clinical manifestations resembled those of dominantly inherited sensory neuropathy. Nerve biopsy
revealed a generalized loss of myelinated fibres, but particularly those of smaller diameter. Unmyelinated axons were present in normal numbers.

Pathological Basis for Hereditary Sensory Neuropathy

In dominantly inherited sensory neuropathy a progressive loss of dorsal root ganglion cells is assumed to occur (Denny-Brown, 1951). Whether there is a preceding distal axonal degeneration ('dying-back' neuropathy) is not established but this was suggested by the observations of Dyck et al. (1971) and Dyck (1984). The 'hyperplastic myelinopathy' affecting myelinated nerve fibres of medium or large calibre found in nerve biopsies from patients in a family with autosomal dominant insensitivity to pain (Comings and Amromin, 1974) represents artefactual myelin damage.

In recessively inherited sensory neuropathy, as already discussed, there is possible clinical evidence for genetic heterogeneity with both a congenital nonprogressive form, and a progressive form, usually with a later onset in childhood (Tamari et al., 1980). Nukada et al. (1982) have provided nerve biopsy evidence of continued fibre loss in the latter form.

The sensory neuropathy in the Riley-Day syndrome is probably nonprogressive. In this condition Aguayo et al. (1971) postulated a selective developmental arrest for both unmyelinated and large myelinated axons. This they related to interference with the second neuronal migration from the neural crest which gives rise both to small and large neurons. No evidence of degeneration of fibres in the nerve biopsy from their case was detected and thus a developmental failure was assumed.

A further possibility to be considered has been raised by Chimelli and Scaravilli (1986) in the rat mutant 'mutilated foot' (mf), which consists of a congenital sensory neuropathy. Here it has been shown that the pathological basis consists of a massive degeneration of dorsal root ganglion cells in the later fetal period which continues for a short time postnatally. It resembles, in excessive form, the 'programmed cell death' that occurs as a normal feature during development. Observations at the appropriate stage are so far not available in congenital sensory neuropathy in man to establish whether this could be the basis. In Case 1 of the series reported by Dyck et al. (1983), nerve biopsy at the age of 26 months showed no evidence of acute fibre breakdown, but it was not stated whether there was an excess of denervated Schwann cells to suggest previous fibre degeneration.

In Case IV.4 from the present study, the nerve biopsy appearances indicated a possible mild degree of continuing nerve fibre degeneration and regeneration. Surprisingly few denervated Schwann cells were present in relation to the magnitude of the depletion of small myelinated axons. However, if the fibre loss had occurred at an early age, the denervated Schwann cells may have disappeared (Weinberg and Spencer, 1978). The overall pattern suggests either a failure of development (aplasia) of the neurons giving rise to small myelinated axons, or a predominantly prenatal neuronal degeneration.
Hereditary Sensory Neuropathy

Congenital Indifference to Pain

Earlier descriptions refer to cases with congenital indifference to pain (Arbuse et al., 1949; Boyd and Nie, 1949; Westlake, 1952; Critchley, 1956; Fanconi and Ferrazzini, 1957; Silverman and Gilden, 1959), congenital universal insensitivity to pain (Ford and Wilkins, 1938; McMurray, 1950; Baxter and Olszewski, 1960), congenital pure analgesia (Dearborn, 1932) and asymbolia for pain (Schilder and Stengel, 1931). Such patients were stated to be able to distinguish sharp from blunt but not to recognize noxious stimuli as painful anywhere in their bodies, did not exhibit the usual physiological reactions to pain and retained their tendon reflexes (Ogden et al., 1959; Winkelmann et al., 1962). An agnosia for pain was postulated (Jewsbury, 1951).

Occasional cases were the product of consanguinous marriages (Durand and Belotti, 1957; Fanconi and Ferrazzini, 1957) or affected several siblings with normal parents (Thrush, 1973). Autosomal recessive inheritance might thus be suspected. Pathological changes were not recognized in the peripheral nerves, spinal cord or brain (Moffie, 1951; Feindel, 1953; Ogden et al., 1959; Baxter and Olszewski, 1960). These reports are now difficult to analyse and it is not clear whether indifference or asymbolia for pain remains an acceptable entity. No cases have been described in recent years which, after adequate study of the peripheral nerves, have proved not to have a sensory neuropathy. In the family reported by Thrush (1973), the site of the disturbance was considered to be in the CNS. The PNS was believed to be 'relatively intact'. Nerve biopsy was reported as showing some loss of large myelinated fibres with regenerative activity, but morphometry was not undertaken. Retention of the tendon reflexes, as in our cases, is typical of a 'small fibre' neuropathy; it does not exclude peripheral nerve disorder. Likewise, sensory nerve action potentials, which reflect conduction in large myelinated nerve fibres, may be preserved. Dyck et al. (1983) pointed out that their Case 1 and that of Low et al. (1978) would have been accepted as having normal peripheral nerve histology without morphometric study. The same is true of the present Case IV.4.

Acknowledgements

We wish to thank Miss Jane Workman for technical assistance and the Friedreich's Ataxia Group for financial support. The image analysis equipment was obtained with the aid of grants from Ciba Geigy Ltd., Basel, and the Central Equipment Fund of London University, and the electron microscope was provided by the Medical Research Council.

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(Received June 13, 1986. Accepted August 8, 1986)