Hereditary Sensory Neuropathy: A Case With Pain and Temperature Dissociation

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SUMMARY: *A case of hereditary sensory neuropathy is described resembling Dyck's Type I hereditary sensory neuropathy. Sensory testing revealed marked pain impairment in feet and hands shading at mid calf to normal at mid thigh and shading above the wrist to normal at the elbow. Other sensory modalities including temperature were intact except painful heat and painful cold and they produced very little if any discomfort. Stimuli at 0° C or 45° to 70° C elicited a temperature response but not pain. Sural nerve biopsy findings (including electronmicroscopy) were consistent with a diagnosis of Type I hereditary sensory neuropathy, but also showed evidence of abortive axonal regeneration and profound Schwann cell vacuolation.*

RÉSUMÉ: *Nous décrivons un cas de neuropathie sensitive héréditaire ressemblant au type I de Dyck. L'examen sensitif montre une atteinte marquée de la sensation à la douleur qui s'atténue à mi-jambe pour devenir normale à mi-cuisse et au poignet pour une réponse normale au coude. Les autres modalités sensitives, sauf la chaleur et le froid douloureux, étaient intactes et ne produisaient que peu de trouble. Les stimuli à 0° C ou de 45° à 70° C élicitaient une réponse type température, mais aucune douleur. L'étude d'une biopsie du nerf sural (y compris la microscopie électronique) confirme le diagnostic de neuropathie sensitive héréditaire de Type I, mais également démontre des signes de regénérescence axonales avortés et une vacuolation marquée des cellules de Schwann.*

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The term hereditary sensory neuropathy (HSN) refers to a group of disorders characterized by a primarily sensory neuropathy but differing from each other in the mode of inheritance, the sensory modalities involved, and the age of onset of the disease.

The sensory neuropathy designated as Type I HSN by Ohta and Dyck (1975) was originally described as Hereditary Perforating Ulcer of the Foot (Hicks, 1922), Acropathic Ulcer-Mutilante Familiale (Thevenard, 1953), or Hereditary Sensory Radicular Neuropathy (Denny-Brown, 1951). Attributed at one time to lumbosacral syringomyelia (Verhoogen, Vanderveld, 1894), this theory was dispelled by Denny-Brown in 1951 when an autopsy on a case revealed degeneration of the dorsal root ganglia, dorsal roots , and peripheral nerves, with greater involvement of unmyelinated than of myelinated fibers. Subsequent autopsy reports confirmed these findings.

In this report, we describe a case of HSN occuring in a young woman with no obvious family history but with one parent minimally affected and with dissociation between temperature and pain sensation. We include the histopathologic and ultra-structural findings of a sural nerve biopsy with a brief review of recent work on this subject.

CASE REPORT

The patient was a 23-year old Caucasian female. Since early adolescence she was aware of a loss of pain sensation in both feet. At about age 12, she developed painless blistering of the planter surface of both big toes followed by breakdown of the skin and ulcer formation. The ulcers slowly healed but recurred during her teen

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years. On occasion she experienced sudden sharp leg pains with a twisting sensation lasting seconds and followed by a throbbing sensation. These bouts of pain lasted up to 24 hours and had increased in frequency so that she was experiencing approximately one bout every one to three weeks.

All members of the family were sent a questionnaire and none of them had any problems with ulcerative lesions of their feet nor had any member had a problem with pain or temperature sensation in the extremities. The patient's mother and the patient's 26-year old brother were examined and no neurological abnormality could be found. Because of slight foot deformity, however, the patient's mother had a peripheral nerve biopsy done by Dr. P. Dyck and mild changes were found in keeping with a mild sensory neuropathy.

Physical examination revealed a healthy looking young woman. Abnormalities on examination were limited to the lower limbs. On the planter surface of each big toe was a round ulcer, 1 cm in diameter and 5 mm in depth. On the tips of the second toes of each foot, a circular area of dry hyperkeratosis with a central blackish discoloration was present. There were no pigment changes nor evidence of arterial insufficiency. Peripheral pulses were normal. There was no motor weakness nor wasting and reflexes were all 2+ and symmetrical. Sensory testing was completely intact to touch, vibration, and joint position sense. Pain as tested by pin prick and pressure was markedly impaired over the fingertips bilaterally and over the hands to the wrists and above this level shaded to being normal just below the elbows. In her feet, pain was markedly impaired and this extended up to the mid tibial area and from there shaded so that in mid thigh it was normal. Tickle sensation was normal in the upper and lower extremities except over the lateral aspect of the right leg where a nerve biopsy had been taken. Temperature was carefully tested with various gradations from very cold to very hot. The areas tested were her fingers, hands, feet, and legs. Over the fingers she was able to distinguish temperatures with a difference of as little as 2° C. Over the feet she was able to distinguish temperatures with a difference of as little as 3° C. At 0° C applied for one to five minutes she reported the sensation as very cold. She did not feel any pain. 10° C was reported as cold. Between 10° C and 25° C she reported the sensation as cool. At 35° C she reported the sensation as warm. At 45° C she reported the sensation as hot. From 50 to 70° C applied from one to three minutes, she described the sensation as very hot but was unable to appreciate any pain although she described the sensation as being very uncomfortable.

The following laboratory findings were normal. CBC, differential count, platelets, peripheral smear, SMA 18, glucose tolerance test, serum B12 and folid acid, T4, ANA, RF, VDRL, urinalysis, chest and lumbosacral spine x-ray and audiogram. X-rays of both feet showed small radiolucent areas in the distal phalanx of the left big toe suggestive of osteomyelitis. Nerve conduction studies were consistent with a sensory polyneuropathy of primarily unmyelinated and thinly myelinated fibers (C and A — delta fibers).

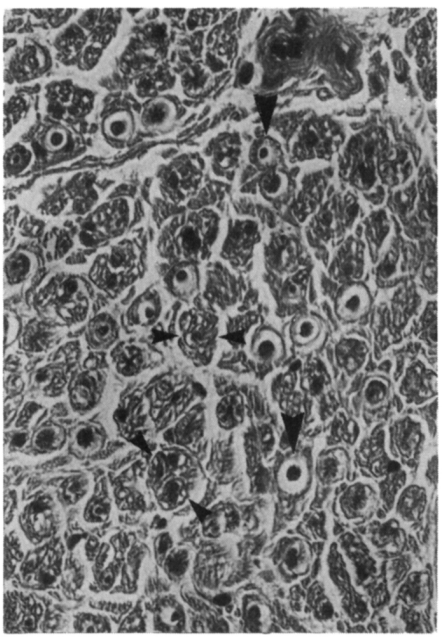

Figure 1 — TS of sural nerve, HE x 750. Well-preserved AB fibers (large arrows) mingled with cords of vacuolated Schwann cells (small opposed arrows). No "onion-bulbs" are seen. Schwann cell nuclei are increased.

SURAL NERVE BIOPSY

The nerve was grossly normal. Light microscopic examination (Fig. 1) showed substantial loss of myelin affecting the small rather than the large fibers. Schwann cells were increased in number and size with formation of numerous cords of cell-processes devoid of myelin, but showing increased acid phosphatase activity. There was mild endoneurial fibrosis.

Teasing showed many strands of tissue with no myelin but with increased collagen (bands of Bungner). All large myelin sheaths teased were normal. Only a few thinly myelinated fibers were found and all were irregular in thickness and internodal length: rare short chains of myelin ovoids were present.

Electronmicroscopy showed moderate numbers of thick myelinated fibers with well formed regular lamellae and a few thin fibers with vacuolated myelin and irregular periodicity. Many clumps of irregular Schwann cell processes were seen, separated from adjacent structures by a rather wide endoneurial space with some increase in collagen fibers. Although occasionally basement-membrane was lacking where two cell-processes abutted closely, all cells showed basement-membrane for most of their periphery and each clump of processes was completely surrounded by basement-membrane. Their cytoplasm was markedly vacuolated and showed few organelles: occasional distended mitochondria, fragments of endoplasmic reticulum, and cytoplasmic fibrils were seen. No normally invaginated unmyelinated axons were found and there were very few axonal structures. They tended to occur in clusters of very small processes with many neurofilaments, lying on the surface of Schwann cell processes and incompletely surrounded by basement-membrane (Figs. 2 and 3). Occasional collagen pockets were present. There were few fibroblasts, almost all near the perineurium, and they were morphologically normal.

DISCUSSION

The case reported here most closely resembles HSN Type I in the age of

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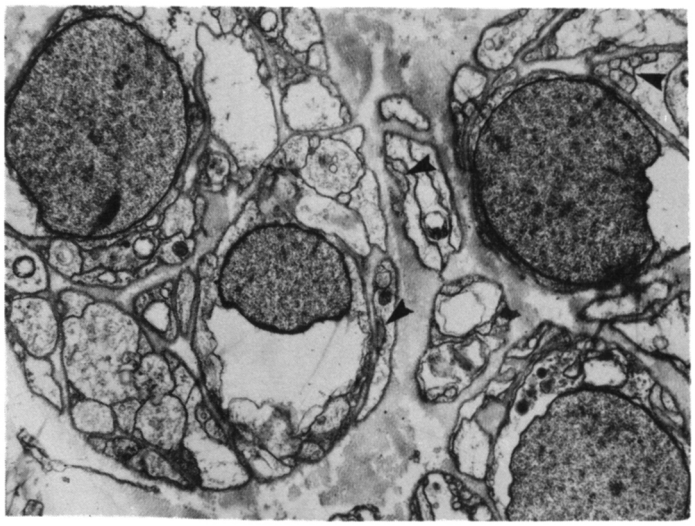

Figure 2 — TS of sural nerve, x 12,000. Parts of adjacent Schwann cell cords composed of vacuolated processes, with increased nuclei. Collagen is mildly increased. Fine non-myelinated axons (arrows) are in clusters or individually on the surface of some processes, without invagination.

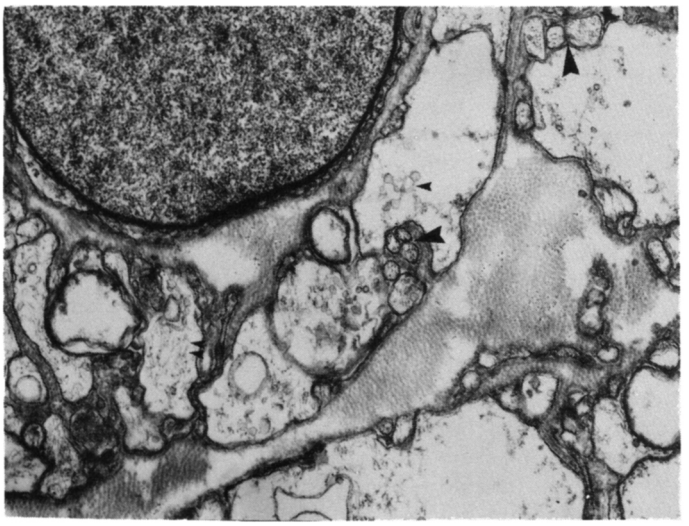

Figure 3 — TS of sural nerve, x 30,000. Clusters of axonal sprouts (large arrows) lie in shallow pockets. The vacuolated Schwann cell processes show fibrils (double arrow) and dilated endoplasmic reticulum (small arrow).

onset, the formation of neurotrophic ulcers, and the occurrence of lightning pains. The inheritance in Type I HSN has been reported as being dominant (Denny-Brown, 1951; Reimann et al, 1958; Veerhoogen and Vandervelde, 1894). Sporadic cases such as ours appeared to have been reported by others (Reimann et al, 1958), but as Ohta and Dyck pointed out (1975) it is possible that mild asymptomatic forms exist in family members as was the case in our patient's family. Our case is different from the reported cases of HSN Type I in that the patient could clearly distinguish gradations of temperature and yet had marked impairment of pain sensation. She was unable to appreciate painful cold or painful heat. It is well known that at about 0° C the pain fibers are stimulated and so the normal person does not feel cold but reports pain. Similarly, pain is reported above about 45° C so that freezing cold and burning heat feel similar. In our patient, even 0° C for five minutes or exposures to stimuli as hot as 50 to 70° C failed to elicit pain but were reported as very cold or very hot respectively. It is clear that we have no morphological criteria which might enable us to recognize either the peripheral nerve pathways or the receptors associated with temperature as opposed to those associated with pain. In our patient, at least in her sural nerve, there appeared to be such severe loss of C fibers that one might suppose her residual temperature sensation is being conveyed largely by A-delta fibers. Current research would support this in respect of cold sensation, though not yet of warmth. Whether the differential lesion in her case affects receptors or primarily sensory neurons cannot be decided. The possibility of initial involvement of the receptors in these cases, however, merits further study. In typical HSN Type I cases there seems to be degeneration of the neuron, manifested first as a dying-back of the peripheral process (axon) and later as disappearance of cell-bodies from the dorsal root ganglia; since the process is slow it is likely that degeneration would be associated with attempted regeneration of some axons and this probably accounts for the small clustered axonal processes seen in the present case, best interpreted as axonal sprouting.

To the best of our knowledge there have been no reports of electronmicroscopic studies in HSN Type I, specifically. The study by Schoene et al (1970) deals with two siblings affected by what would now appear to be HSN Type II with predominant loss of large myelinated (A-beta) fibers and no striking change in Schwann cells. Thus, it is difficult to assess the diagnostic significance of the profound vacuolation of Schwann cells seen in our case. Vacuolation of fibroblasts has been recorded in HSN Type II by Schoene et al and in hypertrophic neuropathy by Asbury et al (1971), so this does not appear to be a specific process. In the present case the presence of basement-membrane, the character of the nuclei, and the pattern of proliferation and relationship to axonal sprouts leaves no doubt that it is Schwann cells that are vacuolated and the very few fibroblasts seen were quite normal. Careful re-assessment of the handling of the specimen and examination of other nerve biopsies processed at about the same time gives no reason to suppose that the changes are artefactual, but final assessment will have to await the reporting of other HSN Type I cases.

CONCLUSIONS

It has been shown by Ohta and Dyck (1975) that, in all probability, the disorder in Type I HSN does not manifest itself primarily in the dorsal root ganglia as suggested by Denny-Brown (1951) but more peripherally as a dying-back process. Our findings in this case of a dissociation between pain

and temperature sensation leaves open the possibility that the disorder originates in the sensory receptor itself and points to the need for continued attempts to identify and study pain and temperature skin receptors in normal man and in the neurophathies.

In the presence of intact pain sensation, cold stimuli below 0° C and heat stimuli above 45° C produce pain. It would appear that this may be the result of competition between pain and temperature sensation with pain sensation extinguishing the temperature sensation since our patient with impaired pain sensation described stimuli as either cold at 0° C or hot at 45° C and above, but not painful.

Ultrastructural studies showed marked vacuolation in the Schwann cells. Whether these changes are unique for Type I HSN can only be determined by study of further cases.

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