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Eccrine Sweat Glands Are Not Innervated in Hereditary Sensory Neuropathy Type IV

An Electron-microscopic Study*

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Summary. The ultrastructural study of a skin biopsy in a patient afflicted with hereditary sensory neuropathy type IV (congenital insensitivity to pain with anhidrosis) did not reveal any unmyelinated axons or axonal terminals around eccrine sweat glands but only processes, partially covered by a basement membrane and therefore resembling Schwann cell processes. The absence of such unmyelinated axons in close proximity to eccrine sweat glands where they normally occur appears to be the morphological equivalent to the anhidrosis and also corresponds to the deficiency of unmyelinated axons in the sural nerve of the same patient, as previously reported.

Key words: Hereditary sensory neuropathy – Sweat glands – Unmyelinated axons – Ultrastructure

Introduction

Hereditary sensory neuropathy type IV, as separated by Dyck and Ohta (1975), is marked by congenital analgia and anhidrosis due to the lack of unmyelinated nerve fibers in peripheral nerves. This has recently been confirmed by electron microscopy (Goebel et al. 1980). Clinically, the inability to recognize painful stimuli is usually more apparent than the inability to sweat. However, the latter may be more dangerous to the patient's life indeed.

As sudomotor fibers are carried among unmyelinated axons in cutaneous nerves, an ultrastructural study of skin from a patient afflicted with hereditary sensory neuropathy type IV may reveal non-innervation of eccrine sweat glands. It is the purpose of this paper to report such an observation.

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Material and Methods

A skin biopsy was fixed in buffered glutaraldehyde, washed in the same buffer, osmicated, dehydrated in increasing concentrations of ethanol, and embedded in araldite. One micrometer thick toluidine blue-stained sections served to localize eccrine sweat glands for ultrathin sectioning which was followed by uranyl acetate and lead citrate staining. For control purposes, eccrine sweat glands were studied in skin biopsies obtained to diagnose or rule out lysosomal diseases of various kinds for which eccrine sweat glands represent diagnostically valuable cells.

Case Report

The clinical and laboratory findings of our patient have been reported previously (Goebel et al. 1980).

This infant boy, born to unrelated German parents, had several bouts of high fever during the first 3 months of his life. Insensitivity to pain became later apparent, but he did not appear mentally retarded. He could produce tears but never sweated. Minor's sweat test was negative. He did not react to painful stimuli and had numerous scars on his hands and tongue. Conduction velocities of motor and sensory nerves were within normal limits. He died suddenly at the age of 15 months during another bout of high fever. Autopsy was not consented.

Results

Normal Controls

Eccrine sweat glands are surrounded by a discontinuous ring of mesenchymal and Schwann cells and processes which often run parallel to the surface of the glands. They are separated by the epithelial basal lamina, collagen fibers, and fine fibrillar material from the abluminal surface of the sweat gland epithelial cells. Schwann cells usually contain several unmyelinated axons. Not infrequently, such axons carry small clear vesicles representing axonal terminals (Fig. 1). How-

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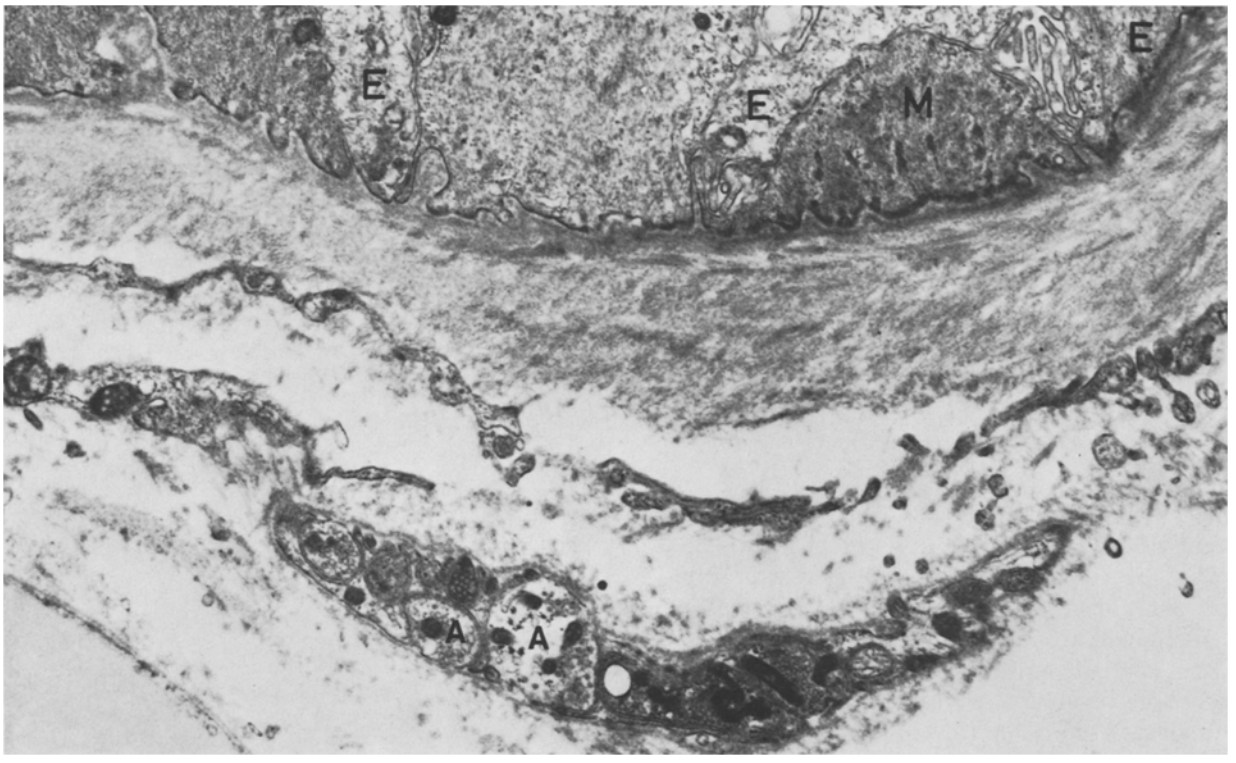

Fig. 1. A Schwann cell carrying numerous unmyelinated axons (*A*) and axonal terminals close to eccrine (*E*) sweat gland and myoepithelial (*M*) cells. Control patient, ×13,720

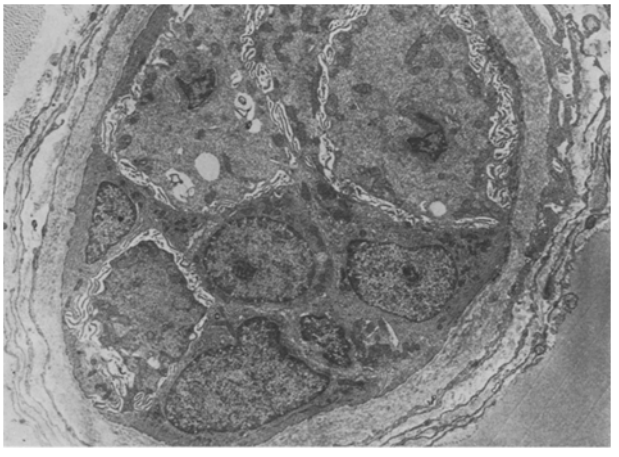

Fig. 2. Eccrine sweat gland surrounded by parallel layers of loosely arranged processes. These processes do not harbor any unmyelinated axons. Patient with hereditary sensory neuropathy type IV. ×2,565

ever, even the axonal terminals are separated from sweat gland epithelial cells, including myoepithelial cells, by interposed processes and a fuzzy fibrillar coat outside the basal lamina (Fig. 1).

Sensory Neuropathy Type IV

At low magnification, sweat gland structures including myoepithelial cells were often surrounded by a fuzzy coat of granular and fibrillar material outside the basal laminae and numerous cell processes running parallel to the abluminal surface of the gland (Fig. 2). These processes were often loosely packed in layers (Fig. 3). However, at higher magnification such processes and their cells, also forming discontinuous rings around the glands, never contained axons of unmyelinated or myelinated character or axonal terminals (Fig. 3). At the surface of such cells and their processes a very thin discontinuous coat resembling a basement membrane was often present (Fig. 3).

Discussion

Our electron-microscopic studies are based on a single skin biopsy of a patient afflicted with hereditary sensory neuropathy type IV (Goebel et al. 1980), which may not encompass the entire spectrum of the sweat gland population in such patients. Normal eccrine sweat glands are surrounded by unmyelinated nerve fibers which do not penetrate their basal laminae (Ellis 1967; Bourlond 1968; Jenkinson et al. 1978). However, about sweat glands in this young boy's skin biopsy unmyelinated axons were never encountered. In normal human skin, unmyelinated axons show close spatial proximity to sweat gland epithelial cells and often contain clear vesicles as an indicator of axonal ter-

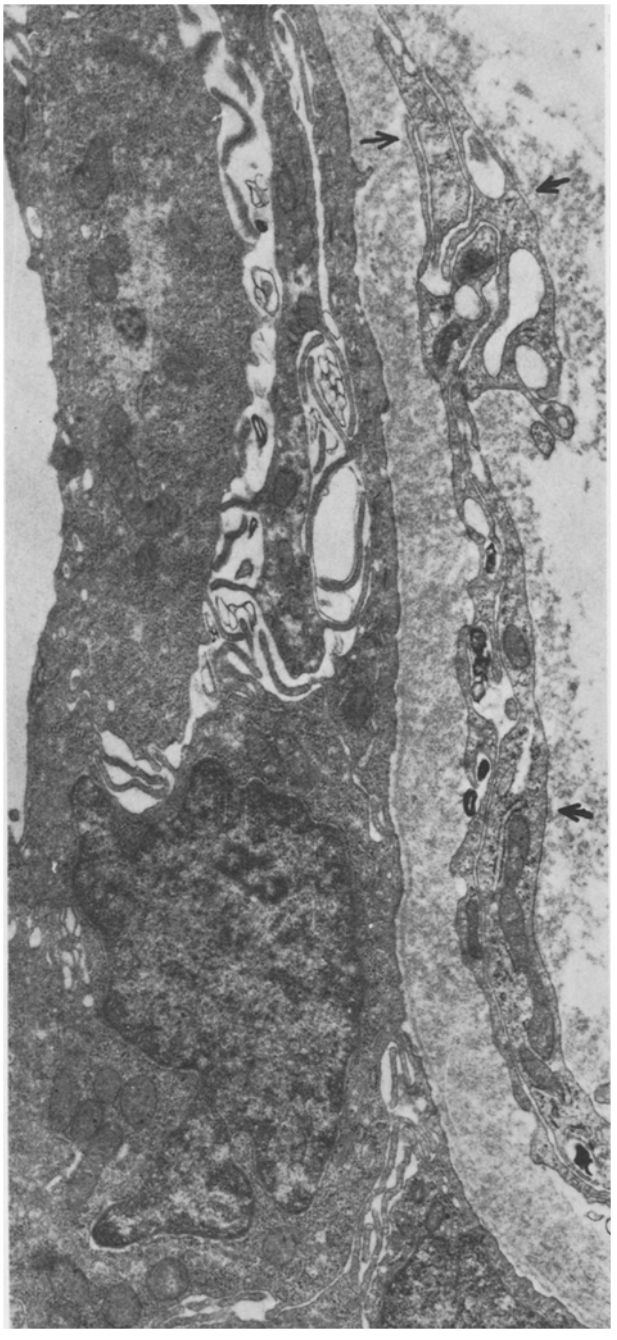

Fig. 3. Eccrine sweat gland in hereditary sensory neuropathy type IV. At high magnification, such processes do not contain any unmyelinated axons but are partially covered by a basement membrane (*arrows*). ×13,720

minals. This justifies the assumption that such unmyelinated nerve terminals may actually belong to sudomotor fibers. The absence of such unmyelinated axons and axonal terminals in the immediate vicinity of eccrine sweat gland cells in our patient's skin conforms to the marked deficiency of unmyelinated axons in his sural nerve, and appears to represent the morphological state of non-innervation of eccrine sweat glands. As unmyelinated axons in peripheral nerves do not carry a functional label, a marked deficiency of such unmyelinated axons in the sural nerve in hereditary sensory neuropathy type IV, clinically associated with analgia and anhidrosis, suggests that sudomotor fibers are also absent from the sural nerve. However, better evidence of such a deficiency of sudomotor nerves comes from our ultrastructural observations that unmyelinated axons or axonal terminals were consistently absent from cells and their processes about eccrine sweat glands in our patient's skin biopsy. Our findings confirm those recently reported on the skin and peripheral nerve in hereditary sensory neuropathy type IV (Rafel et al. 1980). Absence of unmyelinated axons and free nerve endings was noted in the prepuce of another patient afflicted with congenital sensory neuropathy with anhidrosis (Bischoff and Curti 1977).

The presence of a basement membrane, though discontinuous, covering cell processes around the eccrine sweat glands of our patient's skin biopsy seems to indicate that these processes belong to Schwann cells, although we cannot derive ultimate proof for such an assumption from our findings. Cytologic details of these cells were unlike those of neighboring fibroblasts and endothelial cells, which further supports the circumstantial evidence that the small processes partially covered by a basement membrane belong to Schwann cells.

The absence of unmyelinated sudomotor fibers around eccrine sweat glands and in the sural nerve indicates that there seems to be a primary deficiency of such fibers, possibly due to a developmental defect. To our knowledge, the sympathetic ganglia, normally containing sudomotor fiber neuronal pericarya, have not been sufficiently studied in patients with hereditary sensory neuropathy type IV to completely delineate the pattern of sudomotor pathways or their abnormalities in hereditary sensory neuropathy type IV.

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