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CONGENITAL INSENSITIVITY TO PAIN WITH ANYHYDROSIS: MORPHOLOGICAL STUDIES OF SKIN AND PERIPHERAL NERVES*

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Congenital insensivity to pain with anhydrosis is one of a group of diseases termed hereditary sensory neuropathies (HSN), which is characterized by the absence of pain, heat sensation, and perspiration[1]. The principal findings are episodes of fever, inability to perspire despite the presence of normal functioning sweat glands, lack of response to fainful stimuli, self-injury, painless fractures, and mental retardation. Since first reported by Gillespie and Preccua[2] in 1960, nineteen additional cases have entered the literature. This report deals with two male siblings in whom skin and sural nerve biopsies were investigated by light and electron microscopy.

Case Reports

Case 1

Two male siblings, aged five and two years, were the first and second products of consanguineous parents. The family history was non-contributory and the pregnancies were uneventful and full-term. Both subjects had frequent unexplained episodes of fever beginning in the neonatal period. After the age of one self-mutilations were noticed. The mother also became aware that the children did not experience pain on accidental injury and on being burned. It was also reported that they were unable to sweat, but lacrimation was present when the subjects were extremely upset. Developmental milestones were delayed.

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Physical examination revealed their height and weight to be between the 3rd and 25th percentiles. Both had dry skin and hair and some tissue loss was observed in the lower labium and tongue due to self-multilation (Fig. 1). The subjects did not have front teeth. There were many scars and ulcers on the extensor surfaces of the extremities which could be subject to trauma. The ends of almost all fingers and big toes were calloused and ulcerated with partial resorption of the terminal phalanges. All the nails were deformed (Fig. 2). The respective blood pressures were normal and did not change with posture. The examination of the other systems were within normal limits.

Neurological examination revealed subjects with mild retardation who were sociable but emotionally labile. Neuro-muscular development appeared to be retarded. Deep tendon and corneal reflexes were normal. The children reacted normally to strong olfactory, auditory and visual stimuli. Taste and tactile sensations were present. No pain response was observed from pinpricks, or from hot or cold stimuli to the skin of all major regions of the body. Pinching of the Achilles tendon and testicular compression provoked no protest. The subjects could not distinguish sharp and blunt objects.

Laboratory studies revealed normal biochemical and immunological findings along with a normal hemogram. Spinal fluids, electromyographies, electroencephalographies and computerized tomographies were within normal limits. Intradermal injection of 0.1 ml 1/1000 pilocarpine solution produced no sweating.

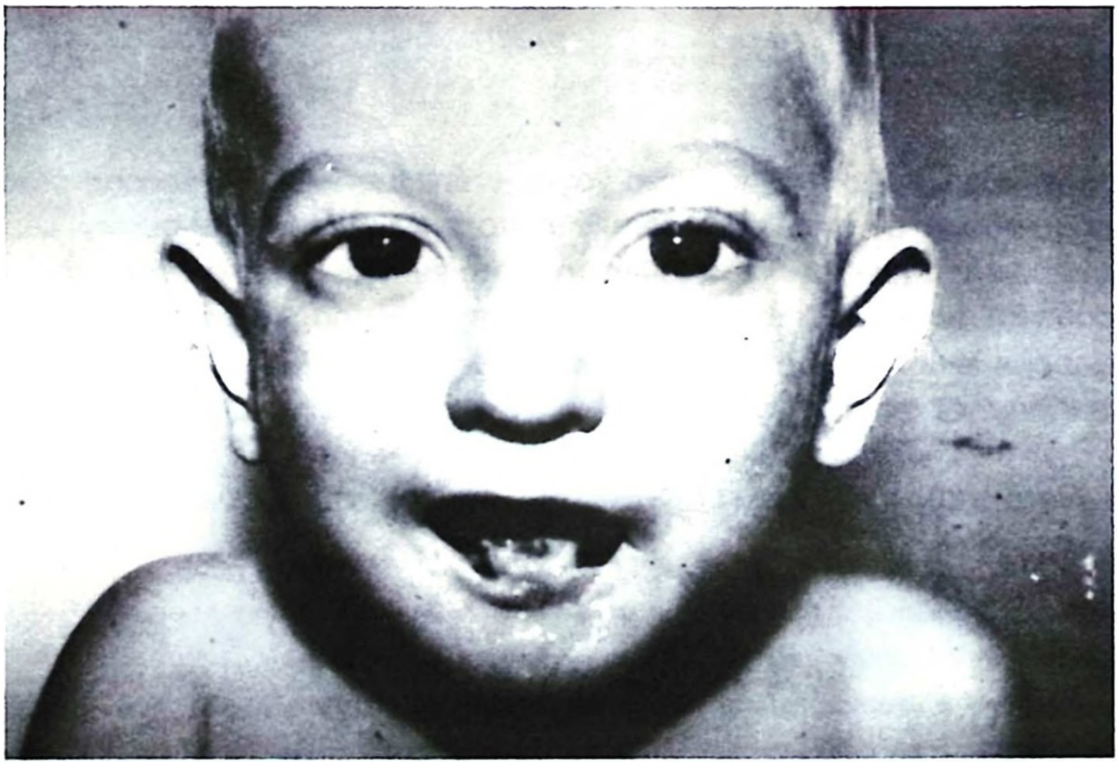

Fig. 1: Tissue loss in the lower labium and tongue due to self-mutilation.

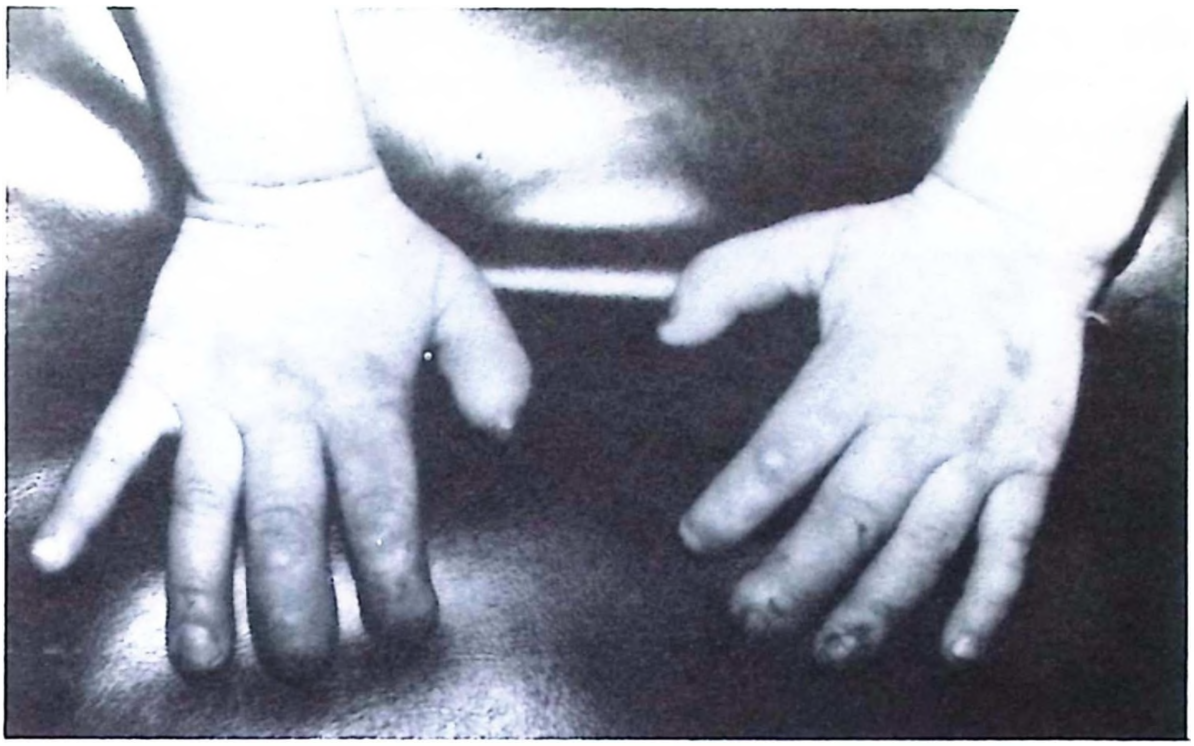

Fig. 2: Calloused and ulcerated fingers, partial resorption of terminal phalanges, deformed nails.

Roentgenograms of the hands revealed partial resorption of both thumbs, index and middle fingers (Fig. 3). The chromosomes were found to be normal with Giemsa-Trypsin-Giemsa (GTG) banding.

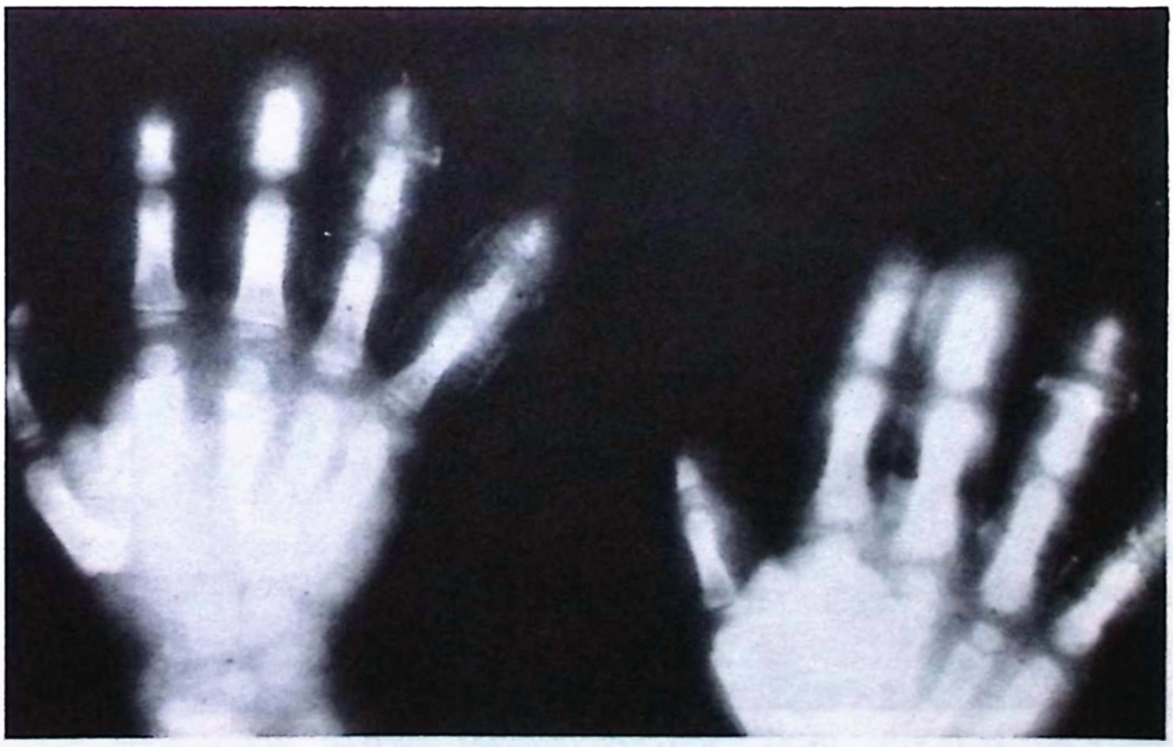

Fig. 3: X-ray examination of the hands.

Skin biopsies by light and electron microscopy demonstrated free dermal nerve networks and normal sweat glands (Fig. 4). Electron microscopy of the sural nerves revealed extreme paucity of unmyelinated fibers. Separation between axons and myelin shells were also noted (Fig. 5). An increase in collagen tissue between the fibers was an additional pathological finding (Fig. 6).

Fig. 4: All normal epidermal layers and excretion channels of sweat glands.

Fig. 5: Electron micrograph of the patients' sural nerve showing an almost complete absence of unmyelinated fibers.

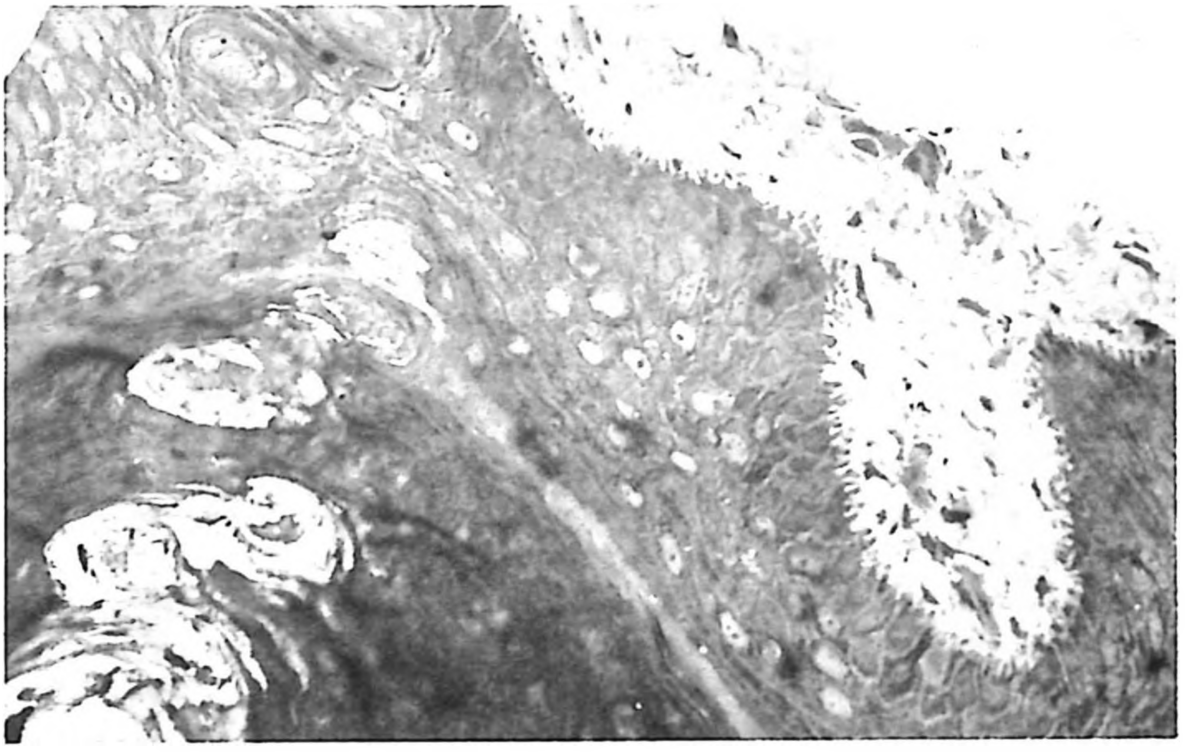

Fig. 6: An increase in collagen tissue.

Discussion

The main findings of the two brothers presented were congenital insensitivity to pain, self-mutilation, inability to sweat in spite of various stimulation, episodes of fever of unknown origin and mild mental retardation. Congenital absence of pain is the most important finding in hereditary sensory neuropathies of which there are at least four separate entities[3]. The genetic, clinical and morphological findings of these have been summarized in Table I, and have been compared to our cases. The genetic and clinical characteristics of our cases correspond mostly to HSN type IV or congenital insensitivity to pain with anhydrosis. This disorder is seen quite rarely, and 16 cases have been reported so far[1,2,4-13]. Morphological examination of the skin by light and electron microscopy was found to be normal in most cases, as in ours[1,4-7,9,11,12]. Peripheral nerves were found to be normal in all cases using light microscopy[1,5-9]. Swanson, et al[14], in a case in which necropsy had been performed, showed that there was an absence of small neurons in the dorsal ganglia, a lack of small fibers in the dorsal roots and the absence of Lissauer's tract. Based on the afore-mentioned observations, he suggested that the primary event regarding congenital insensitivity to pain with anhydrosis could be a migration defect in the neuron precursors and an interruption in maturation.

In all cases of HSN type IV in which the peripheral nerves could be examined by electron microscopy, similiar pathologies have been reported[1,10-13]. In 1980, Goebel et al[10] examined sural nerve biopsies by electron microscopy and

observed an almost complete absence of unmyelinated fibers and a slight decrease in small myelinated fibers. In the same year, Rafel et al[11] showed that both small myelinated and ummyelinated fibers were absent in morphometrical investigations. In 1981 Matsuo et al[12] reported an essential decrease in unmyelinated fibers and a slight decrease in small myelinated fibers in a two-month-old boy. In 1982, Verity et al[13] also observed the lack of unmyelinated fibers. Finally, in 1986, Itoh et al[1] noticed extreme paucity of unmyelinated fibers and a reduction in myelinated fibers, especially of small caliber. They also reported that the endoneurium consisted of abundant collagen fibers. None of the workers mentioned regeneration and degeneration in the axon and myelin shells, as had been reported in other HSN types.

In our cases, similar to the above-mentioned findings, the unmyelinated fibers had almost disappeared, while the collagen fibers had increased. Based on the fact that the unmyelinated fibers had almost disappeared and the small myelinated fibers had decreased in the peripheral nerves of all the cases reported, it is suggested that the insensitivity to pain and heat in HSN type IV might be due to a congenital defect in the formation of neurons.

Summary

Two male siblings born to consanguineous parents, with the diagnosis of congenital insensitivity to pain with anhydrosis are evaluated. The patients presented with unexplained bouts of fever, self-mutilation, repeated trauma and inability to sweat. Physical examination revealed both siblings to be insensitive to pain and temperature. The electron microscopic study of the skin was unremarkable whereas sural nerve biopsies yielded an essential lack of unmyelinated fibers.

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