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Diffuse Palmoplantar Keratoderma Associated with Acrocyanosis

A Family Study

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Four members of a family, in which 8 suffered from diffuse palmopantar keratoderma associated with an uncommon form of acrocyanosis, are reported. Acrocyanosis and palmoplantar keratoderma do not always occur together and, therefore, an autosomal dominant inheritance for this association is suggested.

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Hereditary palmoplantar keratoderma of the diffuse variety is a frequently encountered genodermatosis with an autosomal dominant inheritance. It is the most frequently reported keratoderma and occurs worldwide, with equal distribution between the sexes. The keratinization disorder was first described by A. Thost in 1880 (1) and in 1883 P. G. Unna described its hereditary nature (2).

Diffuse palmoplantar keratoderma of the Unna Thost variety is generally evident in early infancy and is often fully developed by the age of 6 months (3). Hyperkeratosis is diffuse, smooth and uniform, and is strictly limited to palmar and plantar surfaces, but hyperkeratotic lesions have been described elsewhere (4). According to Thost's original description, demarcation towards normal skin may be surrounded by a band of erythema (1), but a variety with a papular border has also been described (5). Hyperhidrosis is frequently present and a high prevalence of dermatophyte infections often results in painful fissuring and scaling (6, 7). The thickening persists throughout life, but spontaneous remissions have been reported (3).

The frequency generally quoted is that of Northern Ireland of 1 : 40 000 (8). It has, however, recently been reported to be 1 : 12 000 in Slovenia (Yugoslavia) (9), 1 : 300 among adolescents in the county of Västerbotten (Sweden) and 1 : 200 among school children in Norrbotten, the northernmost county of Sweden (10, 11).

The cause of the disorder is not known, but a dual influence of genetic and environmental factors may trigger the disease in many cases (12). A strong association between diffuse palmoplantar keratoderma and manual labour has even been postulated. According to the literature, associated features are generally rare, and most often reported as sporadic cases. Features following a dominant mode of inheritance in association with hereditary palmoplantar keratoderma of the Unna Thost variety are less frequently reported in the literature (Table I). It was therefore considered of interest to report a family study of hereditary palmoplantar keratoderma of the Unna Thost variety, associated with acrocyanosis.

CASE REPORTS

Case no. 1 (III,4)

The proband, unmarried farmer, born 1938, was admitted to the Department of Dermatology in 1988 because of hyperkeratotic eczema on palms and soles. He was noted to have diffuse palmoplantar keratoderma associated with a dusky, well demarcated acrocyanosis limited to the lower third of his arms and legs. Family history confirmed a dominant inheritance for an association between hereditary palmoplantar keratoderma and acrocyanosis (Fig. 1).

He had suffered from diffuse palmoplantar keratoderma associated with acrocyanosis from infancy, more livid in colour than has been usually reported. There was no history of cardiovascular disorders. Apart from on his hands and feet, he had normal perspiration, and sensibility was normal.

From 1953 to 1963 he suffered from severe scaling with painful fissuring and hyperhidrosis of the hands and feet. In 1963 hyperhidrosis decreased and the thickness of the solar hyperkeratosis diminished. It remained unchanged on his palms, probably because of manual labour. Gentle trauma to the acrocyanotic skin resulted in hemorrhagic blisters 3–5 mm in diameter and a delay of 2–3 days. Blisters persisted for about a week and disappeared without scars or colour variations characteristic for extravasated blood. During childhood and when he did his military service, he had non-hemorrhagic blisters, which appeared on the soles of his feet from May to September, but have never recurred.

At the clinical examination a diffuse palmoplantar keratoderma of the Unna Thost type was found. Demarcation to normal skin was distinct and no papular border between the

Table I. *Diffuse palmoplantar keratoderma of the Unna Thost variety, with associated features*

Sporadic	Familial
Skeleton	
Clinodactyly (13)	Clubbing and skeletal deformity of terminal phalanges of hands and feet (15)
Mutilating palmoplantar keratoderma (14)	
Skin, hair and nails	
Hailey-Hailey disease (16)	Hyperpigmented spots (27)
Icthyosis vulgaris (17)	Vitiligo (28)
Psoriasis vulgaris (18)	Heliotrichie (23)
Atopic dermatitis (19, 29)	
Darier's disease (20)	
Incontinentia pigmenti (21)	
Alopecia areata (22)	
Heliotrichie (23)	
Hydrocystomas, miliary cysts xanthelasmas, nail and dental dystrophies (24)	
Basal cell epitheliomas (24)	
Multiple lipomas (25)	
Knuckle pads, leukonychia and deafness (26)	
Onychodystrophy (22)	
Ear and eye	
Perceptive hearing loss and atopic dermatitis (29)	Progressive sensory-neural hearing loss (32)
Grey cataracht (30, 31)	Deafness (33, 34)
	Corneal dystrophy (35, 36)
Mucous membranes	
Reticular degeneration (37)	Oral leukoplakia (41)
Lip keratoses (38, 39)	Carcinoma of esophagus (42, 43)
Esophageal carcinoma (40)	
Micellaneous types	
Charcot-Marie Tooth' disease (44)	Acrocyanosis
Winer's calcinosis (45)	
Spinal myoclonus with dermal and retinal changes affected by myelitis (46)	

hyperkeratotic and normal skin was seen. Neither knuckle pads on the dorsal aspects of the finger joints nor hyperkeratotic lesions on other parts of the skin were observed. Hyperkeratosis was smooth and uniform and conventional culture for dermatophytes proved negative.

The acrocyanosis was more livid than is generally seen. Elevation of the hands to above the level of the heart, heat, and physical activity resulted in return to normal skin colour. Lowering the hands immediately resulted in a return of the acrocyanosis. On the dorsal aspects of his hands, three or four hemorrhagic blisters with a diameter of 2–3 mm were seen (Fig. 2). A blister 5–6 mm in diameter was found near to the fourth toe of the left foot. There were no blisters on the palms or soles, and rubbing the skin did not induce blistering. Neurologic examination including testing of autonomic function was normal. Cardiologic examination showed a beat-to-beat variation in heart rate of 30:15 ratio and the Valsalva ratio was within normal limits. There was no orthostatic hypotension and blood pressure response to static exercise was normal. Plasma and urine catecholamine levels were normal.

Punch biopsy from hyperkeratosis of the right hand showed orthohyperkeratosis, hypergranulosis and acanthosis, which is the usual histopathologic picture of the Unna Thost variety. Subepidermal vessels were slightly dilated and there was an insignificant mononuclear cell infiltrate.

Punch biopsy of blisters from the dorsal aspect of the left hand showed extravasation of red blood cells into the orthohyperkeratotic layer and cavities representing older bleedings. Subcorneal cleavage or vacuolization and degeneration of basal cells indicating epidermolysis bullosa simplex were not found on histopathological examination. However, increased numbers of mononuclear cells were found in the subepidermal layer. In PAS-stained sections, no hyphae was

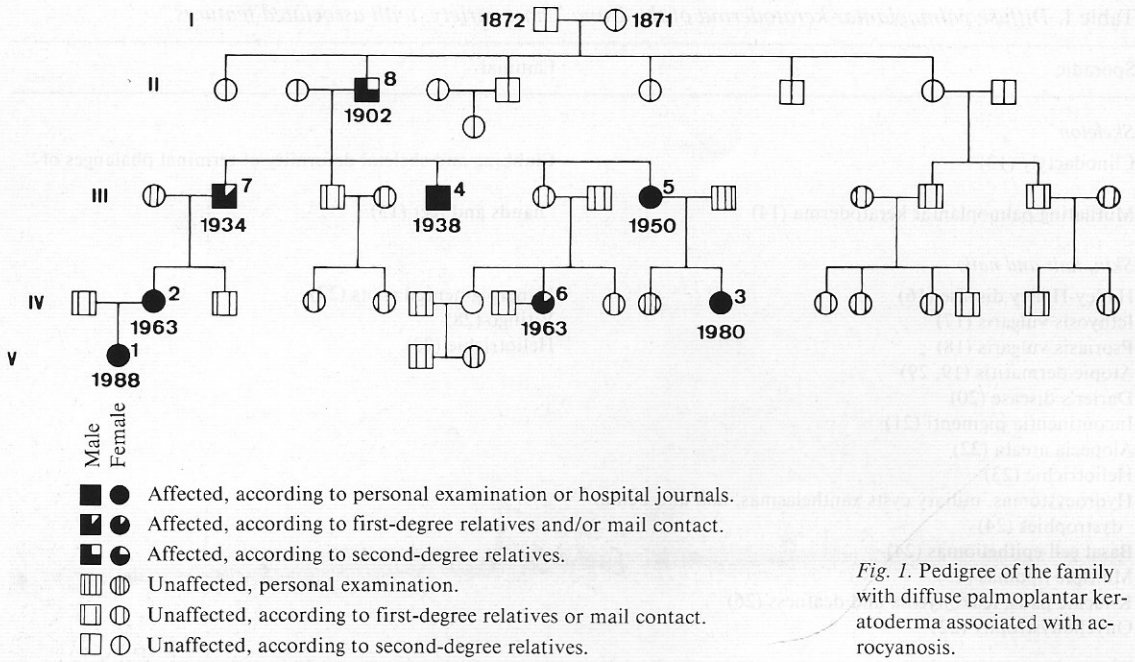

Fig. 1. Pedigree of the family with diffuse palmoplantar keratoderma associated with acrocyanosis.

found, and immunofluorescence technique failed to detect antibodies.

Case no. 2 (III,5)

The proband's sister, who was born in 1950, had had diffuse palmoplantar keratoderma associated with acrocyanosis from the age of 2 years (Fig. 1). Acrocyanosis extended 10 cm proximal to the hyperkeratosis. Apart from hemorrhagic blisters, she had the same clinical findings as the proband. She was married to a gardener, who had hyperkeratotic lesions on both hands, but not on his feet. There was no evidence of inheritance of hereditary palmoplantar keratoderma and his palmar hyperkeratosis was probably due to manual labour.

Case no. 3 (IV,3)

This couple had two daughters, born 1973 and 1980. From 1 year of age the younger girl had had a diffuse palmoplantar keratoderma associated with acrocyanosis, which reached about 15 cm proximal to the hyperkeratosis (Fig. 1). Teeth, hair and nails were normal and hemorrhagic blisters had never appeared. *T. mentagrophytes* was cultured from soles, but scaling and fissuring were insignificant. Dermatophytosis was successfully treated with econazole–propylene glycol cream, which had previously been used for this particular complication (47). Punch biopsy from the hyperkeratotic margin of the left foot showed orthohyperkeratosis and hypergranulosis, but there was no subepidermal mononuclear cell infiltrate. Hyphae were not demonstrated in PAS-stained sections.

Case no. 4 (V,1)

An affected cousin of case 3 (IV,3) gave birth to a daughter in 1988, who was born with palmoplantar keratoderma and acrocyanosis, sharply demarcated 5 cm proximal to the hyperkeratosis. Nails were normal but hyperkeratosis had a scaly and greasy appearance (Figs. 1, 3). *Aspergillus fumigatus* was found on conventional culture, but was considered to be a coincidental finding. Hyperkeratotic papules bordered the plantar keratoderma and there were no blisters.

According to the first- and second-degree relatives, the clinical picture of cases II,8, III,7 and IV,6 did not differ from cases 1, 2, 3 and 4, though blisters were not reported.

DISCUSSION

The acrocyanosis associated with palmoplantar keratoderma in these patients had a different clinical picture than generally seen, as it was only present on the lower third of arms and legs and had a distinct demarcation from normal skin. It was unusual that the cyanosis disappeared completely when arms and legs were raised. The cause of the acrocyanosis is still unknown, but microcirculatory studies have shown that the peripheral arterioles are unduly sensitive to cold and the smaller vessels, espcially those of the subpapillary plexus, are dilated. Impaired platelet function together with changes in blood viscocity have been surmised as a pathogenetic factor (48, 49).

Normal functioning of the autonomic nervous system does not exclude impaired tonus of peripheral vessels and may explain in part the pathogenesis of

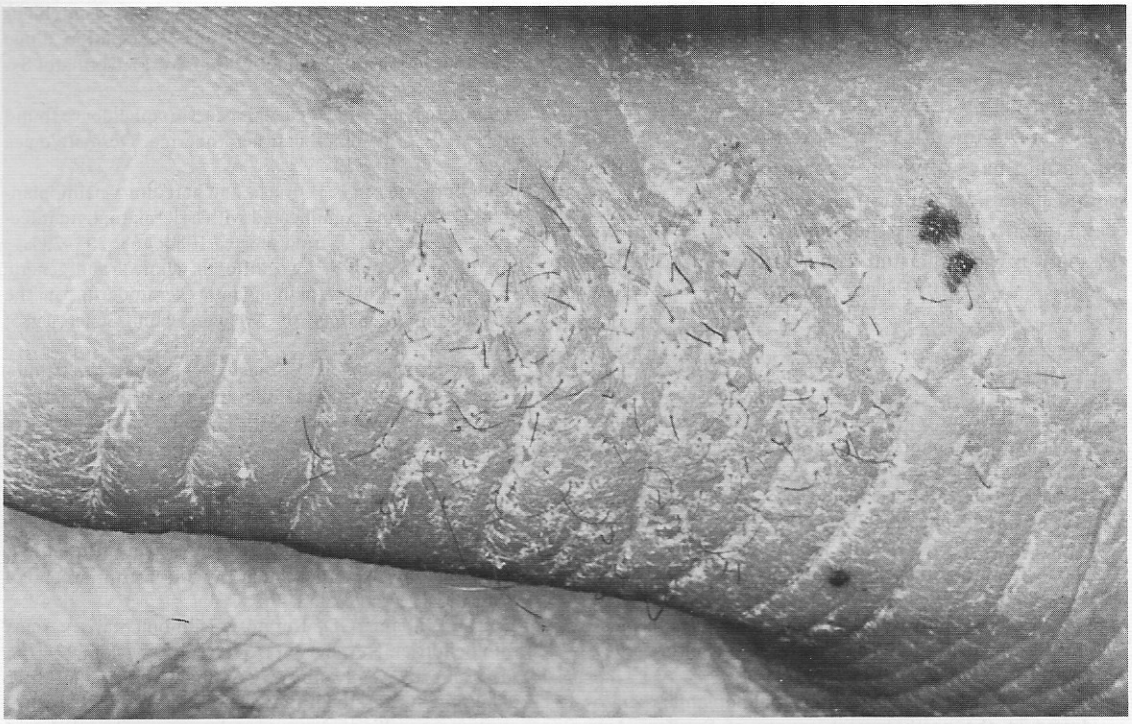

Fig. 2. Haemorrhagic blisters on dorsal aspect of a finger of the proband (Case no. 1,III,4).

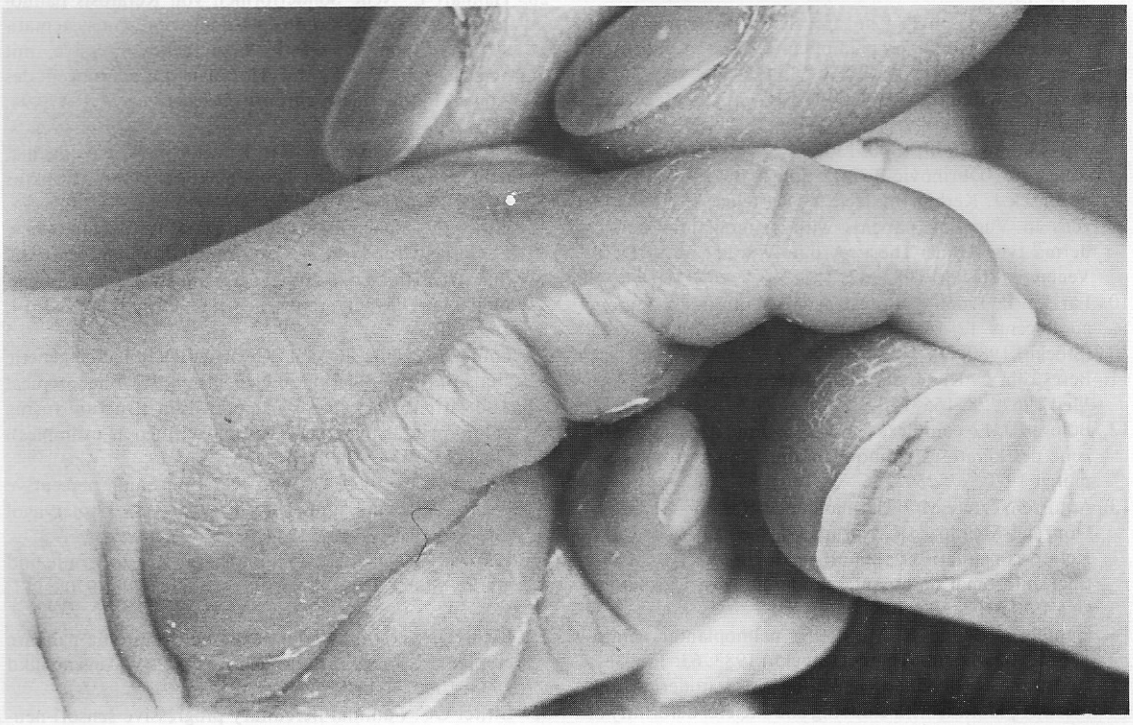

Fig. 3. Diffuse palmoplantar keratoderma associated with acrocyanosis, in a 3-month-old infant.

the acrocyanosis. According to the literature, acrocyanosis generally appears in early adolescence and a family history is common. Hereditary palmoplantar keratoderma of the Unna–Thost variety, however, usually starts in early infancy. Differences in age of appearance have often been reported and acrocyanosis and hereditary palmoplantar keratoderma do not occur together. It was therefore concluded that the association was inherited in an autosomal dominant manner.

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