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HYPOMELANOSIS OF ITO

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Abstract. Hypomelanosis of Ito appears to be a disorder of hypopigmentation. Findings from histochemical and electronmicroscopic studies indicate that pigment cells from the hypopigmented areas have short dendrites and synthesize less than normal amounts of melanin. The syndrome may have two forms; a cutaneous and neurocutaneous variety. In the more severe neurocutaneous variety, the phenotypic pigmentary abnormalities probably reflect a biochemical defect in all tissues derived from the neuro-ectodermal anlage.

Key words: Melanin; Pigment disease; Hypomelanosis; Congenital

Hypomelanosis of Ito is a rare disorder of the pigmentary system. Discussion persists about whether this disease should be classified as a disorder of hyper- or hypopigmentation (1) or whether it is a variant of incontinentia pigmenti (2). We believe the features of hypomelanosis of Ito are sufficiently characteristic to distinguish it easily from incontinentia pigmenti.

We should like to report another case, with unusual clinical findings, and contribute new data on the histology of the hypopigmented areas, which indicate that pigment cells of the hypopigmented areas are not producing normal quantities of melanin.

We divide hypomelanosis of Ito into two different syndromes; a more common cutaneous type in which the disease is limited to pigmentary changes and mild abnormalities of perspiration; and a neurocutaneous variety in which the patients manifest severe nervous system defects and bony abnormalities in addition to the hypopigmentation and sweating abnormalities.

CASE REPORT

The patient, a 23-year-old female, was the first of three siblings. The mother, who was 19 years old at delivery, had moderately severe toxemia and hypertension during the pregnancy but the delivery was normal. For the child

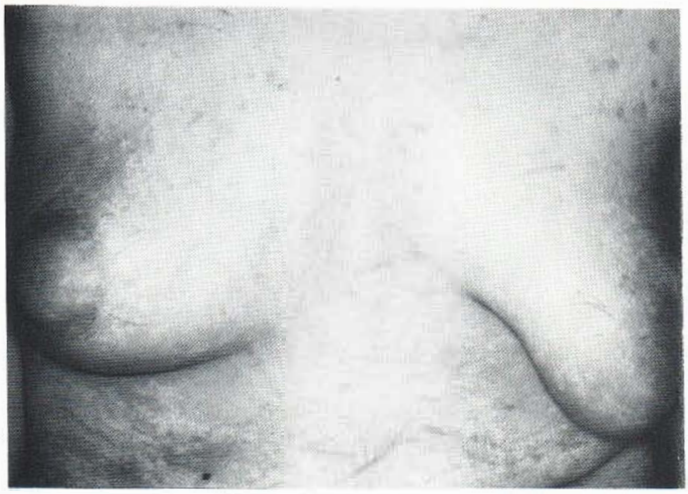

Fig. 1. The breasts are asymmetric. Whorls of depigmented skin are visible on the flanks.

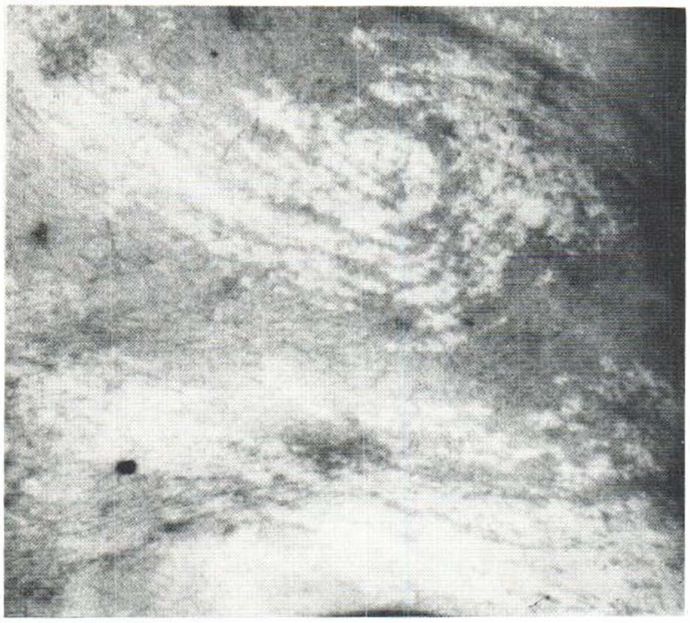

Fig. 2. Close-up view showing sharply demarcated swirls of depigmented skin.

the neonatal period was uneventful. At 3 months of age the infant's pediatrician thought the baby might have suffered a brain injury at birth. At 6–8 months, whorled hypopigmented areas began to appear over her trunk without a preceding rash. At 16 months a diaphragmatic hernia was repaired surgically. The child had two seizures associated with tonsillitis and fever around the same time. At age 4 years the child was thought to have a peptic ulcer, but no radiographic studies were performed. At age 5 years the patient had chicken pox, possibly complicated by mild encephalitis.

Her intellectual and motor development were retarded. The child sat at 5 months and crawled at 7 months. She could not walk until 18 months. Her gait was clumsy and she fell frequently, sustaining a skull fracture in early childhood. She spoke only six to eight words at 4 years of age. Psychologic examination at age 9 indicated an I.Q. of 21. She was placed in a state training school for the mentally retarded and remains there to the present time. At age 10 she was started on sodium phenobarbital (Luminal®; Winthrop Lab., N.Y., USA) and diphenylhydantoin sodium (Dilantin®; Parke, Davis & Co., Detroit, Mich.,

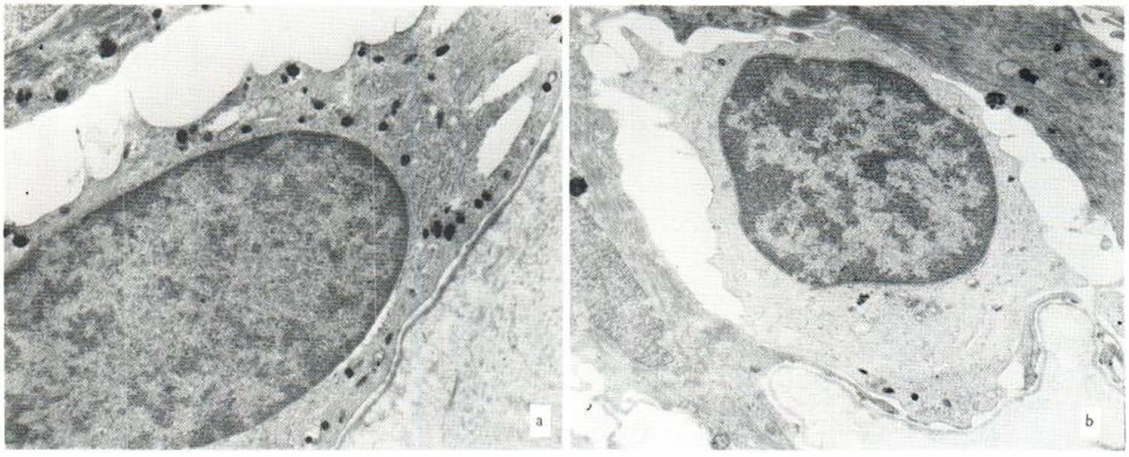

Fig. 3. Representative sections of normal (*a*) and hypopigmented skin (*b*) examined by electron microscopy, showing the relative decrease in melanosome in the hypopigmented area (×23 000). The epidermal basement membrane is visible at the bottom of each photomicrograph. The nucleated cells in both illustrations are melanocytes surrounded by keratinocytes.

USA) by mouth to control akinetic seizures which were causing frequent falls. The medications have decreased the number of seizures.

Two younger brothers are normal. The mother and father are high school graduates. A maternal great-grandmother had epilepsy. A paternal uncle and his son are retarded. No relatives are known to have pigmentary abnormalities.

On physical examination the patient has hypertelorism and an epicanthal fold. She has an alternating strabismus. The fundi are normal but she requires spectacles to correct a moderate myopia. Her gums are hypertrophic and her cheeks and chin hirsute, all side effects of the diphenylhydantoin sodium.

Her heart, lungs, and abdomen are normal. Her breasts show a striking asymmetry (Fig. 1). She has required braces to walk since 1973 when her gait became more uncoordinated and shuffling. Adjustments in the diphenylhydantoin sodium therapy did not improve her gait. The muscles of her leg are flabby. The fourth metacarpals are short.

Her face and extremities are normally pigmented. Whorls of depigmentation are present on the trunk (Fig. 2). The depigmented areas are sharply defined and appear less pigmented than any other area of the body. Measurements with a reflectometer (Photovolt Reflectometer Model 610) (5) confirm this observation. No differences were found by means of a starch-iodine assay in the quantity of sweat produced by the normally pigmented and hypopigmented skin. Patches of dermatitis periodically appear over the chest and upper back. These clear with topical steroids, leaving the skin normal except for hyperpigmented scratch marks. No hypopigmentation develops in these areas of scratching.

X-rays of the skull are normal. An upper GI series showed no evidence of previous ulcer disease. An EEG contained multiple atypical spikes and waves in frontal and parietal areas. Routine complete blood count, urinalysis, blood urea nitrogen, serologic tests for syphilis were normal. A karyotype analysis showed a normal female chromosome pattern.

Histologic Studies: A shave biopsy of contiguous normal and hypopigmented skin was removed for examination by routine hematoxylin and eosin (H&E) staining, dopa stains and electronmicroscopy. Skin for H&E was fixed in Bouin's solution, and for electronmicroscopy in glutaraldehyde. On H&E sections, depigmented areas appear normal. Dopa stains (4) show that the hypopigmented areas contain fewer, smaller pigment cells, with sparse, short dendrites. Electronmicroscopy photographs confirm the presence of pigment cells in the hypopigmented areas (Fig. 3*a* & 3*b*), but they seem to contain less melanin than does the normal skin.

COMMENT

The syndrome of hypomelanosis of Ito has also been termed Incontinentia Pigmenti Achromians. We agree with others (2) that incontinentia pigmenti achromians is a meaningsless term and should be discarded in favor of hypomelanosis of Ito.

Hypomelanosis of Ito probably has two forms, cutaneous and neurocutaneous. Approximately two-thirds of the patients have the cutaneous variety manifested mainly by mild abnormalities of perspiration and depigmentation. In this group the pigmentary loss begins late in childhood, persists until early adulthood, and then may disappear. Other than the mild cosmetic disfigurement, these children seem to be normal. In the patients with the neurocutaneous syndrome, depigmentation develops earlier in infancy and is accompanied by severe, central nervous system dysfunction, seizures, and bone abnormalities. In a previous paper (6), we suggested that cutaneous pigmentary abnormalities, especially if present at birth, might be a manifestation of a more generalized defect of all neuro-ectodermal derivatives. A genetic or enzymatic defect of the neuroectodermal anlage present during the critical developmental stages of the embryo could affect all organs derived from the neural crest. Thus mental retardation, seizures, and coordination defects, which are so easily attributable to trauma at birth, anoxia or infections, are in fact more probably due to a biochemical injury in the first or second trimester of pregnancy.

Others have examined the appearance of pigment cells in several different forms of congenital hypomelanosis (3). A patient with probable hypomelanosis of Ito was grouped with other patients who had a nevus depigmentosus. The findings were similar to ours. Split-dopa preparations showed the pigment cells to be clumped, with short, sparse dendrites. Preparations examined by electron microscopy had a significant decrease in the numbers of melanosomes within pigment cells and keratinocytes. Thus our study indicates that the pigmentary abnormality of patients with the neurocutaneous variety of hypomelanosis of Ito cannot be distinguished from that of the more benign form of cutaneous hypomelanosis of Ito, although the genetic defects in these two disease forms must differ greatly. The findings of our study indicate that hypomelanosis of Ito is a disease of hypopigmentation.

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