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REVIEW ARTICLE

Diagnosis of some common and uncommon hyperpigmentation disorders in children

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ABSTRACT

Skin color is an important social and cultural characteristic, which explains why the parents of children with any deviations from normal pigmentation are concerned about this problem. This article discusses selected pigment anomalies present at birth or appearing in the first months of life. They may be transient or permanent, localized (as in café-au-lait spots) or segmental, or more rarely, complex or generalized. As with most pigmentary diseases, a physical examination, including Wood's lamp examination and a detailed history, is usually sufficient for diagnosis. Time of onset, distribution pattern, and associated clinical and sometimes histopathologic or molecular findings are helpful in differentiating these disorders.

Introduction

Skin color is an important social and cultural characteristic, which explains why the parents of children with any deviations from normal pigmentation are concerned about this problem. Troubles in skin color may raise considerable concern in black and Asian communities. Normal constitutive pigmentation is under the control of myriad genes, but recent studies in humans have attributed a major part of pigmentation variation across races to a limited number of genes. The human equivalent of the mutant golden zebrafish *SLC24A5/NCKX5* explains a major part of the shift observed from Negroid to Caucasian phenotypes, and has recently been related to oculocutaneous albinism type 6.[1] Other important human genes include *MATP/SLC45A2*, which when mutated is responsible for oculocutaneous albinism type 4,[2] and the *MRC-1* gene, several loss of function variants of which have been described to be associated with pale skin and red hair, indicating a skewing of melanin production toward that of pheomelanin. Although recreational sun exposure is contraindicated in babies, examination at birth may be misleading for congenital anomalies, because modifications of pigmentation are frequently revealed after the first outdoor exposures. Normal skin has essentially all its melanin in the epidermis and hairs. The color that one perceives when viewing the skin depends on several factors, especially the depth of pigment deposits. If melanin pigment is present in the dermis, the integument takes on a blue–gray hue that looks bluer as the pigment is deposited deeper. Melanin is not the only natural skin pigment. Diet carotenoids deposit in the epidermis and dermis, and contribute in a minimal way to the yellowish tint of the skin. However, a pronounced yellowing of the integument is common in babies on high carotenoid diets. Red and blue hues are the product of oxyhemoglobin and reduced hemoglobin in capillaries, arteries, and veins in the dermis. They may mix in some areas with abnormalities of the pigmentary system, such as in phakomatosis pigmentovascularis (Figure 1), and variations may depend on the maturation of the skin and its thickness.

This article discusses pigment anomalies present at birth or appearing in the first months of life. They may be transient or permanent, localized [as in café-au-lait (CAL) spots] or segmental, or more rarely, complex or generalized. In most pigmentary diseases, physical examination, including Wood's lamp examination and a detailed history, is usually sufficient. Time of onset, distribution pattern, and associated clinical and sometimes histopathologic findings are helpful in differentiating these disorders. Molecular diagnosis has become available for some rare entities, such as hereditary symmetrical dyschromatoses,[3] but the bulk of nevoid lesions has not yet been understood at the molecular level.

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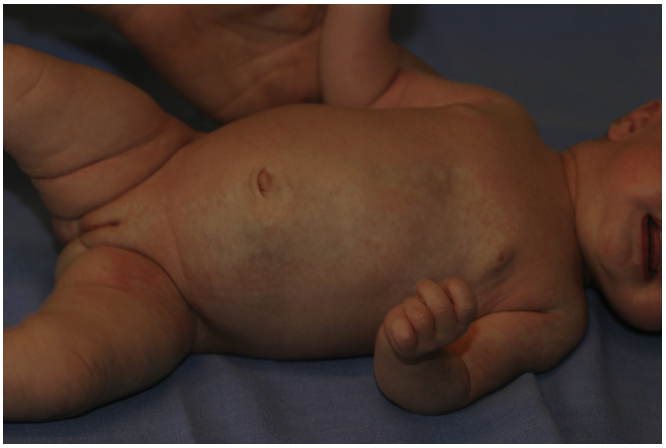

Figure 1 Phakomatosis pigmentovascularis. Note the mix of blue, red, and anemic macules.

Transient hypermelanoses of the newborn

At birth, maturation of the pigmentary system is not completed, and some areas, such as the scrotum in boys or dorsum of fingers (especially the distal phalanx), may look strikingly hyperpigmented in babies with otherwise pale skin.[4] Pigmentation of the genital area is probably influenced by sex hormone impregnation prior to birth, and friction or suction may partly explain finger hyperpigmentation (Figure 2). Some lighter phenotypes can be found with such transient birthmarks, babies belong usually to skin phototypes IV and darker, and this phenotype is normal in Asian and black babies. Transient pustular melanosis (TPM) is characterized by pustules present at birth that evolve into macular pigmentation (Figure 3). The content of the pustules is mostly neutrophilic, and the duration of the rash, especially the pigmentation, is longer. TPM is more common in black neonates, and is probably the cause of the so-called "freckling" or "lentigines neonatorum" noted in 15% of black neonates. The cause of both of these eruption types, which may coexist and are not linked to an infectious agent, is still unclear. Sterile transient neonatal pustulosis, a term that encompasses pustular rashes of erythema toxicum neonatorum and TPM, has been proposed. The fact that TPM is mostly diagnosed in black neonates may correspond to accelerated stimulation of negroid

Figure 2 Physiological finger pigmentation in a newborn.

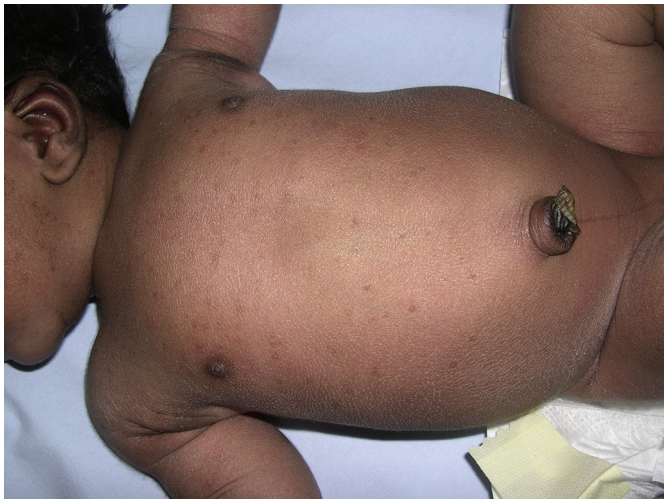

Figure 3 Neonatal freckling caused by transient pustular melanosis.

melanocytes caused by cytokines and growth factor release by inflammatory cells of the epidermal infiltrate. An increased amount of melanin in basal and suprabasal layers can be detected with the Fontana–Masson preparation. In pustules, erythema toxicum neonatorum-like features can be seen. Most characteristically, the subcorneal pustule contains polymorphonuclear leucocytes and scattered eosinophils. Keratinous debris, serous fluid, and fragmented hair shafts may also be present. Moderate acanthosis can be associated with this condition. In the dermis, eosinophils and neutrophils may be seen around capillaries and the upper portion of the hair follicle. TPM was originally described to be more frequent in black neonates when residual hyperpigmentation was included in its definition. The eruption is always present at birth. Lesions are located on the chin, neck, nape, upper chest, lower back, and buttocks, and also on the lower abdomen and medial side of the thighs. Rarely, the scalp, palms, and soles are involved. Clusters of pustules occur around the nipples and on pressure areas. In typical cases, pigmented macules coexist initially with flaccid vesiculopustules (1.5–3 mm in diameter) with no surrounding erythema that rupture easily and leave a collarette of fine white scales. Individual pustules dry out and may leave a flat, brownish crust that can be detached easily by gentle scratching. Unscratched crusts may persist for a few weeks, and pigmented freckles may persist for a few months in pigmented patients. Typical erythema toxicum neonatorum lesions occur in most patients in association with TPM in a typical time course.[5]

CAL spots

CAL spots present as uniform tan–brown round or oval macules with distinct margins and variable border contour. These lesions tend to enlarge in proportion to general body growth during the first several years of life and then stabilize. They do not regress in later years. Histologically, CAL spots have increased epidermal melanin without melanocytic proliferation. Ultrastructural examination reveals giant pigment granules (macromelanosomes) in lesions of patients with neurofibromatosis. CAL spots are commonly seen at birth or in early infancy and have been noted in up to 25% of children, particularly in black children.[6] Most children with CAL spots have no other associated abnormalities.

However, in children, multiple large CAL spots may be a sign of one of several syndromes. By far, the most common condition is type 1 neurofibromatosis. It is generally assumed that six or more