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Dermatologic findings of vitamin B_{12} deficiency in infants

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Abstract

Background/Objectives: Vitamin B_{12} deficiency in infants is uncommonly reported from developed countries and generally lacks dermatologic manifestations. On the contrary, infantile vitamin B_{12} deficiency is common in India and cutaneous manifestations are a constant feature, although often overshadowed by neurologic and hematological manifestations. The aim of this study was to describe the skin changes of vitamin B_{12} deficiency in infants.

Materials and Methods: A retrospective chart review of vitamin B_{12} deficient infants for clinical and laboratory parameters was performed and data analyzed.

Results: Forty-three infants, 30 boys and 13 girls, aged 4 to 27 months, with vitamin B_{12} deficiency were identified. Skin hyperpigmentation was present in 41 infants; it was localized to the dorsa of hands and feet in 26. Fifteen infants had generalized hyperpigmentation; 10 had a reticulate pattern, and 5 had a homogeneous pattern. Brown and sparse scalp hair were present in all. Glossitis was seen in 5 infants and cheilitis in 3. Of the 32 infants who underwent laboratory investigations, 28 had anemia and 21 macrocytosis. Serum vitamin B_{12} was measured in 30 infants; it was low in 19. Of the 11 with normal serum vitamin B_{12}, 9 had received vitamin B_{12} before referral but had macrocytosis and low maternal serum vitamin B_{12}. The infants were treated with vitamin B_{12}. Skin pigmentation and mucosal changes resolved completely by 3-4 weeks, but hair changes were slower to reverse.

Conclusion: Cutaneous findings are a common feature of vitamin B_{12} deficiency in Indian infants and resolve with treatment.

KEYWORDS
angular cheilitis, glossitis, hair changes, hyperpigmentation, infants, vitamin B_{12}

1 | INTRODUCTION

Vitamin B_{12} deficiency is increasingly being recognized in infants, children, and adolescents.[1] In infants and young children, vitamin B_{12} deficiency is almost always secondary to maternal vitamin B_{12} deficiency and is, therefore, encountered in the exclusively breastfed infants of mothers who are either strict vegetarian or have an underlying pernicious anemia.[2-4] Early recognition and prompt treatment of this condition are extremely important to prevent the deleterious effects of vitamin B_{12} deficiency on the growing brain.[2,3]

The clinical picture of vitamin B_{12} deficiency in infants is dominated by neurologic symptoms of irritability, apathy, hypotonia, psychomotor regression, and involuntary movements.[2-5] Muco-cutaneous involvement occurs in the form of skin hyperpigmentation, glossitis, angular cheilitis, and hair abnormalities.[2,4] Skin hyperpigmentation has been reported to be distinctly uncommon in Caucasian infants with vitamin B_{12} deficiency.[6,7] Cutaneous manifestations are, however, consistently present in Indian[2,8] and Turkish[4,9,10] infants with vitamin B_{12} deficiency but are usually

Institutional Ethical Committee has given its approval for the conduct of this study.

eclipsed by the more serious neurologic or hematological symptoms and signs. Hyperpigmentation of skin as the presenting symptom of infantile vitamin B_{12} deficiency is uncommon. As a result, cutaneous manifestations of vitamin B_{12} deficiency in infants have not received due attention in the dermatology literature.

Skin hyperpigmentation associated with vitamin B_{12} deficiency in Indian infants has some distinctive features that have not been emphasized outside the Indian literature. The aim of this study was to describe the dermatologic manifestations of vitamin B_{12} deficiency in infants from India.

2 | MATERIAL AND METHODS

A retrospective chart review of infants and young children diagnosed with nutritional vitamin B_{12} deficiency between February 2010 and February 2017 at a tertiary care hospital of north India was carried out. Details of clinical (largely nondermatologic) and laboratory parameters of a part of the cohort of the infants included in this study have been previously reported.[2] For the current analysis, the presence, distribution, pattern, and other characteristics of cutaneous hyperpigmentation, and mucosal and hair findings were noted. Laboratory parameters analyzed included complete blood count, mean corpuscular volume, and serum vitamin B_{12} of the infants and their mothers. The extent of investigation was limited by the financial constraints in some cases. Vitamin B_{12} deficiency in infants was diagnosed on the basis of low serum vitamin B_{12}. In infants who had normal serum vitamin B_{12} because of administration of vitamin B_{12} prior to referral, diagnosis of vitamin B_{12} deficiency was inferred from the presence of peripheral macrocytosis and low maternal serum vitamin B_{12}.[2] Infants were treated with vitamin B_{12} and other supportive care as dictated by the general condition of the infant. The study was approved by institutional review board.

3 | RESULTS

A total of 43 infants, 30 boys and 13 girls, with vitamin B_{12} deficiency were identified. Mean age at presentation was 12.4 months (range 4-27 months). All were exclusively breastfed by vegetarian mothers belonging to economically deprived sections of society. Sixteen infants presented with involuntary movements, 11 with developmental regression, 7 with developmental delay, and 1 with seizures. Three children presented with failure to thrive and 3 with intercurrent illness. Only two infants first presented to a dermatologist because of skin hyperpigmentation.

Pallor was present in all of the children, glossitis in 5, and angular cheilitis in 3. One child had both angular cheilitis and glossitis, and 1 had tongue pigmentation. All infants showed a variable degree of hair changes with thin, light brown, and sparse hair (Figure 1). Characteristic dark brown/black skin pigmentation was noticed in 41 (95%) patients. Hyperpigmentation was localized to the dorsa of hands and feet with accentuation over fingers and toes in 26 infants

FIGURE 1 Sparse, thin, and brown scalp hair. Not all infants with vitamin B_{12} deficiency have severe changes shown here

FIGURE 2 Skin hyperpigmentation of the dorsum of foot with accentuation over phalanges

(Figure 2). Generalized hyperpigmentation was noted in 15 infants with a homogeneous pattern in 5 (Figure 3), and a reticulate or honeycomb pattern in 10 (Figure 4).

A complete blood count was available in 36 infants. Twenty-eight (77.7%) were anemic (Hb < 11 gm/dL). Macrocytosis (MCV ≥ 95 fL) was noted in 21 of 36 infants (58.3%) and three (8.3%) had borderline macrocytosis (MCV, 90-95 fL). Serum vitamin B_{12}, measured in 30 infants, was low (vitamin B_{12} < 200 pg/mL) in 19 (63%). Of the 11 infants with normal serum vitamin B_{12}, 9 had received vitamin B_{12} before referral but had other evidence of vitamin B_{12} deficiency in the form of macrocytosis or low maternal vitamin B_{12}. Maternal B_{12} was measured in 19 mothers and was low in 17.

The infants were treated with intramuscular vitamin B_{12} (500 μg for 3-5 days) in the acute phase followed by oral supplementation (15-30 μg per day) in the recovery phase (for 6-12 months). Follow-up details were available for 32 patients. General and neurologic improvement began within 48-72 hours. Dermatologic improvement

FIGURE 3 Generalized, reticulate, or honeycomb skin hyperpigmentation

FIGURE 4 Generalized, uniform, or homogeneous hyperpigmentation of the skin

was more gradual. There was progressive lightening of skin color becoming noticeable as early as 1 week after the treatment with resolution by 3 to 4 weeks. Progressive darkening and increased density of scalp hair were observed over weeks and months with complete recovery taking up to a year.

4 | DISCUSSION

Vitamin B_{12} deficiency is particularly common in Indian infants because of high prevalence of maternal vegetarianism on account of professed food habits or more commonly due to lack of resources to access foods of animal origin including milk.[11] Because tremors often dominate the clinical presentation, the term "infantile tremor syndrome" has been used in the Indian literature to describe this disorder.[2,5,12-20]

Skin hyperpigmentation was the most consistent dermatologic feature of vitamin B_{12} deficiency and was noted in 41 of the 43 infants in our study. Baker and colleagues from India were the first to describe skin hyperpigmentation and its causal relationship to vitamin B_{12} deficiency.[5,14] Later, several Indian studies attested to the almost universal presence of skin hyperpigmentation in vitamin B_{12} deficiency in infants.[2,17,20] Outside India, skin hyperpigmentation has been noted in Turkish infants with vitamin B_{12} deficiency.[4,9,10] Inexplicably, cutaneous hyperpigmentation is seldom observed in Caucasian infants with vitamin B_{12} deficiency.[6,7] It has been hypothesized that a certain degree of normal skin pigmentation may be necessary for hyperpigmentation to manifest.[5,14]

The dorsa of hands and feet displays the most pronounced pigmentation, with accentuation over the interphalangeal joints, the so-called "knuckle pigmentation."[2,10,14,16] Less commonly, the skin hyperpigmentation is generalized, extending over proximal areas of the limbs such as medial aspects of thighs and upper arms, axillae, perineum and perianal areas, neck, and trunk.[2,10,16] Pigmentation of palms, soles[5,18,19] as well as diffuse whole-body pigmentation[5,10] is also described. The involvement of skin tends to be bilaterally symmetrical.[14,17] Involvement of oral mucosa is rare.[18] Only one patient in our cohort had tongue pigmentation.

Morphologically, the hyperpigmentation is observed as either a homogeneous or uniform darkening of skin[10,16] or more commonly, as a network of light central areas and darker periphery, producing a peculiar reticulate or "honeycomb" pattern. This latter type of pigmentation has been reported only in Indian infants with vitamin B_{12} deficiency.[12,13,15-19] Unlike the transient, thermo-sensitive, purplish discoloration of the physiologic livedo-reticularis of infancy, reticulate pigmentation in vitamin B_{12} deficiency in our children was persistent, thermo-resistant, and dark brown/black in color.[21] Reasons for different patterns of hyperpigmentation are not known.

Despite being a common feature of vitamin B_{12} deficiency, infants are rarely brought to medical attention because of skin hyperpigmentation. Only 12 (11%) of 107 infants reported by Ramakumar and Pandove[19] and 13 (9.6%) of the 134 described by Bajpai et al[18] had presented with skin hyperpigmentation. In our series, only 2 (4.6%) of 43 infants had presented to the dermatologist. Natural dark complexion of Indian infants also makes it difficult for parents to discern gradual changes in the skin color. The dermatologic manifestations often get overshadowed by more worrisome neurologic manifestations in these infants.

Hair changes have been reported in 50%-100% Indian infants with vitamin B_{12} deficiency[8] and have also been described from Turkey.[10] Demir et al[10] found brittle and matted hair in 22.8% infants with vitamin B_{12} deficiency. Hair changes were present in all our infants. The majority had severe changes with only a few brown and short hairs remaining on the scalp. Eyebrows were similarly affected. We believe that other than vitamin B_{12} deficiency, malnutrition was also an important contributor to the hair changes in our patients.[22]

Angular cheilitis and glossitis are the other muco-cutaneous manifestations of infantile vitamin B_{12} deficiency.[4,10,12,17,18] In a prospective study by Demir et al,[10] 70% infants with nutritional vitamin B_{12} deficiency had glossitis and cheilosis. Others have reported much lower figures of 22%[9] and 40%[4] for glossitis. Similar changes have been noted in 5.2%[18] to 23.5%[16] Indian infants with vitamin B_{12} deficiency. Only in a small number of infants in our series displayed these mucosal changes, which is likely an underestimate given the retrospective nature of the study. The role of other vitamin and micronutrient deficiencies in angular cheilitis and glossitis cannot be entirely excluded in the absence of appropriate laboratory testing.

Many hypotheses including increased synthesis of melanin[23] and incontinence of melanin pigment due to defects in melanin transport to, or incorporation into, megaloblastic keratinocytes have been proposed to explain the skin hyperpigmentation,[24] but the exact mechanisms remain unknown.

Similar to what has been reported in the literature, the skin and hair changes in our infants responded very well to vitamin B_{12} treatment. Skin hyperpigmentation began to clear by the end of first week and completely resolved in 3 to 4 weeks. Hair changes were slower to discern and took weeks to become noticeable. Complete return of dense and dark hair occurred after several months, taking up to a year or even longer.

In conclusion, this report highlights the dermatologic changes of vitamin B_{12} deficiency in infants. The skin changes, often eclipsed by concomitant neurologic and hematological manifestations, provide an important clue to the diagnosis and rarely can be the presenting symptom. The dermatologist needs to be aware of this disorder to make the diagnosis and to provide appropriate advice on the etiology and course of skin changes.

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