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Hyperpigmentation as a symptom of Vitamin B12 deficiency: A review

Nikhat Naaz
Senior Resident, Department of Community Medicine, Rajshree Medical & Research Institute, Bareilly, Uttar Pradesh, India

Abstract
Introduction: Vitamin B12 (Cobalamin) deficiency is one of the most common vitamin deficiencies and is an important nutritional public health problem. Vitamin B12 deficiency presents as a variety of signs and symptoms. However, cutaneous manifestations of Vitamin B12 deficiency are often neglected. Skin hyperpigmentation is the most common cutaneous manifestation associated with vitamin B 12 deficiency. The article reviews the current knowledge on link between hyperpigmentation and vitamin B 12 deficiency
Material and Methods: Pubmed database and Google scholar database were searched for Case reports, case series and mini reviews related to hyperpigmentation as a symptom of vitamin B12 deficiency.
Results & Conclusion: Many studies mainly case reports have found an association of hyperpigmentation with vitamin B 12 but majority of them state it as a rare combination.
From this review we find that pigmentation disorders due to vitamin B12 deficiency may be much more common than earlier thought. Therefore, all cases of hyperpigmentation should also be evaluated for Vitamin B12 deficiency. Studies have shown that hyperpigmentation due to vitamin B12 deficiency is reversible with adequate Vitamin B12 supplemental therapy.

Keywords: vitamin b12 deficiency, hyperpigmentation, cobalamin deficiency

1. Introduction

Vitamin B12 (Cobalamin) deficiency is one of the most common vitamin deficiencies and is an important nutritional public health problem which could be affecting millions of people worldwide [1]. Vitamin B12 is a water-soluble vitamin and its deficiency may present as some well-known symptoms like anaemia, paraesthesia and abnormal gait to some lesser known symptoms like stomatitis (inflammation of mouth and lips) and pigmentation disorders in skin, hairs and nails [2]. Additionally, some other dermatologic conditions, like vitiligo, acne, and atopic dermatitis may be linked with cobalamin deficiency [3]+.

Cutaneous manifestations of Vitamin B12 deficiency, first described by Dr Bramwell Cook (1944) are often neglected. Dr Brook first pointed out the association of pigmentation of knuckle, tongue, lips and area around neck with anaemia related to vitamin B12 deficiency (macrocytic anaemia). Other common areas of hyperpigmentation are nasolabial folds, under eyes, forehead, dorsum of ankle, back of wrist and legs [4]. Skin hyperpigmentation is manifested in 19 % of individuals with vitamin B12 deficiency [5] and is the most common cutaneous manifestation associated with vitamin B 12 deficiency [3]. This hyperpigmentation is commonly observed on dorsum of hands and feet, and on creases of palm and soles. The hyperpigmentation is more exaggerated on the interphallangeal joints and may also appear on nails as hyperpigmented streaks [6, 7].

Hyperpigmentation as a primary symptom of B 12 deficiency is very rarely reported in literature [8] despite this being an important manifestation of B12 deficiency [9]. Strict vegan or vegetarian diet and malabsorption of vitamin B12 are among the most common causes of Vitamin B12 deficiency [10, 11].

Blackish discoloration of nails (known as Melanonychia) has also been reported in few cases of vitamin B 12 deficiency [12, 15].

The article reviews the current knowledge on link between hyperpigmentation and vitamin B 12 deficiency. It will mainly focus on the pigmentation in various parts of body which may result due to vitamin B 12 deficiency.

1.1 Prevalence of vitamin B 12 deficiency:

Prevalence of vitamin B12 deficiency varies from 3% to 5% in the general population and 5% to 20% among people older than 65 years [16]. Due to the high variability of cut-off values across laboratories, vitamin B 12 deficiency prevalence ranges from 3% for people aged ≥3 years to 67.6% for elderly (71–74 years) [17, 18]. Deficiency rates based on specific population groups are: pregnant women-62%, children-25% to 86%, adolescents-21 % to 41%, elderly- 11% to 90 [19].

1.2 Recommended Dietary Allowance (RDA) for Vitamin B12:

The main sources of vitamin B12 constitute dairy products, meat and poultry. Table 1 shows recommended dietary allowance of vitamin B 12 for different age groups [20].

Table 1: RDA of vitamin B 12 for different age groups.

Age	Male	Female	Pregnancy	Lactation
0-6	0.4 mcg	0.4 mcg		
7-12	0.5 mcg	0.5 mcg		
1-3	0.9 mcg	0.9 mcg		
4-8	1.2 mcg	1.2 mcg		
9-13	1.8 mcg	1.8 mcg		
14+	2.4 mcg	2.4 mcg	2.6 mcg	2.8 mcg

1.3 Causes of Vitamin B 12 deficiency

Vegetarians develop B12 deficiency regardless of age, sex, place of residence, age, or type of vegetarian diet. Therefore,

strict vegetarians should take preventive measures including Vitamin B12 supplements, balanced diet to avoid Vitamin B 12 deficiency states [19].

1.4 Cut Off Values for Vitamin B12 deficiency

The cut off values for vitamin B12 deficiency may range from 100 pmol/L to 350 pmol/L. In many studies the cut off value of 148pmol/L was used. However, across literature there is no single consensus on the cut off values for serum B 12 levels.(21) However, Vitamin B12 deficiency is generally defined as a plasma concentration of <148 pmol/L (200 pg/ml) and marginal status defined as a concentration of 148-221 pmol/L. (10)

2. Material and Methods

Pubmed database and Google scholar database were searched through April 2019 for English language studies related to Hyperpigmentation as a symptom of vitamin B12 deficiency. Case reports, case series and mini reviews related to hyperpigmentation resulting from vitamin B12 deficiency were selected. However, cases of Vitamin B12 deficiency without any symptoms of hyperpigmentation were excluded.

3. Results

3.1 Case Reports

Hyperpigmentation as a symptom of vitamin B12 deficiency has been reported in the past in forms of case reports and case series. Some authors have mentioned it as a rare association. In a study among children Demir *et al* observed mucocutaneous manifestation of vitamin B12 deficiency among children. He found that hyperpigmentation was present in 85 % of the children with vitamin B 12 deficiency. In majority of these children (87.5%) hyperpigmentation improved with Vitamin B 12 supplementation. (22)

In a case series Aron *et al* reported that among 63 patients with vitamin B12 deficiency, skin hyperpigmentation occurred in 19% of them. (5) In another study of 198 adults, among 25 patients with megaloblastic anemia, 21(64%) had knuckle hyperpigmentation and 9 (36%) had diffuse hyperpigmentation of palms and /or soles. Six of these patients with hyperpigmentation were followed and it was found that the hyperpigmentation improved significantly with vitamin B 12 therapy. (23) Table 2 summarises different case reports of patients with hyperpigmentation as a manifestation of vitamin B 12 deficiency.

Table 2: Case reports of patients with hyperpigmentation due to Vitamin B12 deficiency

Age	Race	Symptoms	Causes	Serum B12	Treatment given	Histology/ Microscopy
25 y/F[24]	Indian	Blackish discoloration of skin over dorsum of proximal and distal interphallangeal joints of hands for 3 months.	Vegetarian diet	31.6 pg/ml	Oral vitamin B12	-------
34 y/F [7]	Indian	Skin lesions on feet bilateral for 1.5 months.	Unknown	113 pmol/l	IM B12 1000 mcg/d	-------
54 y/F[7]	Indian	Skin lesions on neck and upper and lower limbs for 4 months.	Vegetarianism	100pmol/L	IM B12 1000 micg/d	-------
54 y/M[25]	Haitian (African)	Darkening of hands, feet and tongue	Malnutrition	35 pg/ml	IM B 12 1 mg every week for 2 months, then every month for 3 months	-------
43y/M[13]	------	Increased skin pigmentation	Lack of intrinsic factor	34.34 pg/ml	IM (B12) 100 mg/day for 7 days, then 2x/week for 3 weeks, then 100 mg once a month	-------
40 y/F[26]	African American	Diffuse darkening of the palms of both hands for 3 to 4 months.	-Antibodies to Intrinsic factor (Pernicious Anemia) -Strict vegetarian diet	67 pg/ml	1,000 μg injections intramuscularly daily for 7 days followed by once a week and once a month for one year thereafter.	-------
65 y/F[26]	African American	Hyperpigmentation of both palms with dark discoloration of the nails	-High serum levels of Antibodies for Intrinsic factor -Malabsorption -Chronic gastric atrophy	55pg/ml	intramuscular injection of vitamin B12 (1,000 μg) daily for one week, then weekly for one month.	-------
28 y/M [27]	Muscat, Oman,	Diffuse brownish-black discolouration on both the palmar and dorsal aspects of both hands,more pronounced at the distal and proximal inter phalangeal joints for 2 months	Chronic gastritis and focal villous blunting- leading to Malabsorption	75 pmol/L	1,000 µg of intramuscular B every day for one week, followed by the same dose once a week for four weeks and then once a month for two months.	The duodenal biopsy also revealed mild chronic inflammation and focal villous blunting.
16 y/F[28]	Indian	Bluish nail discolouration	Strict vegetarian	100 pg/mL	Intravenous vitamin B12 injections.	Biopsy from a nail showed focal parakeratosis with

		and knuckle hyperpigmentation over both hands and feet				adherent nail bed epithelium and the nail plate contained melanin pigment.
35 y/F[29]	Indian	Progressive hyperpigmentation on hands and feet (palmar & dorsal areas, knuckles, creases) tongue, oral mucosa and gluteal region over a period of one year	-Nutritional vit B12 deficiency -Anti parietal antibody weakly positive.	67pg/ml	Vitamin B12 therapy.	Skin Biopsy showed increased pigmentation in stratum spinosum and basal layer)
49 y/M[9]	Japanese	Hyperpigmentation on oral mucosa, forearms, elbows, palmar creases, periunguinal area, knees, and feet.	Malabsorption due to gastrectomy (10 yrs back)	---------	Vitamin B12 therapy	-On histology: Increase of melanin in the basal layer. -On Electron microscopic: Many melanosomes were observed in melanocytes and surrounding keratinocytes.
45 y/F[30]	Indian	Generalised hyperpigmentation for two years (first started on sun exposed areas later progressed as generalised hyperpigmentation on body, plam and soles.)	Vegetarian diet	81.3 pg/ml	Vitamin B12 injections.	-------
12 y/F[31]	Taiwanese	Diffuse progressive skin hyperpigmentation for 6 yrs	-Inborn metabolic disorder of vitamin B12 (cobalamin)		Oral Cobalamin 3mg daily.	-------
34y/M[32]	Indian	Gradual darkening of palms and feet which later progressed to face, gums and tongue. accentuated in palmar creases, on the dorsa of hands and feet, in intertriginous areas, on oral mucosa and in recent scars	Unknown	78pg/ml	Intramuscular injection of vitamin B 12 (1000 mg) daily for ten days, then weekly for one month and then monthly for two months.	Biopsy showed increased melanin in the epidermis.
21 y/F [6]	Caucasian	Hyperpigmentation over lower limbs whihc started from the inner thigh and had extended over the tibia over few years.	Strict vegetarian	100 pg/ml	Intramuscular B12 (1 mg daily for 7 days, 1 mg/week for 3 weeks and 1 mg/month for 3 months, for maintenance). Oral cyanocobalamin supplementation of 1000 µg daily for maintenance.	On Microscopy: increased numbers of basal cell layer melanocytes, as well as increased melanin granules in the basal layer and supral basal layer (Fontana stain)

3.2 Mechanism of Hyperpigmentation in B12 deficiency:

The mechanism behind hyperpigmentation in B 12 deficiency is not very well known. Some suggest that Vitamin B 12 is important for intracellular glutathione - which inhibits melanogenesis by inhibiting tyrosinase activity [33]. Some suggest that a defect in melanin transfer between melanocytes and keratinocytes may lead to pigmentation defects [9].

4. Discussion

Vitamin B 12 deficiency is quite common in developing countries [10]. It may be associated with neurologic, hematologic, gastrointestinal, dermatologic, and cardiovascular symptoms [7]. The dermatologic manifestations include: hyperpigmentation, vitiligo, hair changes, and angular stomatitis.

Vitamin B 12 deficiency may be associated with increased pigmentation in different parts of the body mostly on the dorsum of hands, feet, skin folds and mucosal surfaces [9, 25, 34]. From the past studies it may be suggested that hyperpigmentation as a symptom of vitamin B12 deficiency may be much more common than earlier thought and as a symptom of vitamin B 12 deficiency may precede the typical neurological signs and symptoms of vitamin B 12 deficiency [27]. The most common causes of vitamin B12 deficiency are strict vegetarian diet, malabsorption of Vitamin B 12, or impaired production or functioning of intrinsic factor [10, 11]. The mechanism suggested behind hyperpigmentation associated with vitamin B12 deficiency is suggested to be due to increased melanin synthesis [9].

Many studies mainly case reports have found an association of hyperpigmentation with vitamin B 12 but majority of them state it as a rare combination. In a case series Baker *et al* reported 21 patients who had hyperpigmentation with vitamin B12 deficiency. In another case series of 64 patients with vitamin B12 deficiency, Aaron *et al* reported that hyperpigmentation was the second most common (19%) mucocutaneous manifestations of Vitamin B12 deficiency followed by glossitis (31%) [5]+. Majority of patients with this hyperpigmentation get treated with vitamin B12 supplementation therapy.

From this review we find that pigmentation disorders due to vitamin B12 deficiency may be much more common than earlier thought. Therefore, all cases of hyperpigmentation should also be evaluated for Vitamin B12 deficiency. Studies have shown that hyperpigmentation due to vitamin B12 deficiency is reversible with Vitamin B12 supplemental therapy.

5. Conclusion

Hyperpigmentation due to vitamin B 12 deficiency is much more common than earlier thought. Vitamin B12 deficiency should always be considered while evaluating any patient with generalised or diffuse hyperpigmentation. Hyperpigmentation due to vitamin B12 deficiency is reversible with appropriate vitamin B12 supplementation.

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