

KNUCKLE HYPERPIGMENTATION IS A MARKER OF VITAMIN B₁₂ DEFICIENCY IN VEGETARIAN POPULATION

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ABSTRACT

BACKGROUND

B₁₂ deficiency is common in India as is Vitamin D, folic acid, or iron deficiency. Megaloblastic Anaemia due to vitamin B₁₂ deficiency is extremely common in the predominantly vegetarian population. The symptoms are modified also by the underlying disorder causing its deficiency. Knuckle hyperpigmentation is one of the essential features of it. In spite of being a common disorder, its recognition is delayed or missed because the manifestations are diverse in nature, and is often subclinical. Laboratory estimations of B₁₂ levels are also not reliable. The ways of picking up those with clinical or subclinical B₁₂ deficiency and the reasons and solutions are very much needed. Here we emphasize the clinical sign of knuckle hyper pigmentation as an important clue towards the aetiology of Megaloblastic Anaemia.

The aim of the study is to know the correlation of knuckle hyper pigmentation with serum vitamin B₁₂ deficiency in vegetarian population.

MATERIALS AND METHODS

40 patients with knuckle hyperpigmentation, all were vegetarian screened for serum vitamin B₁₂ deficiency.

RESULTS

Out of 40 patients, 28 females and 12 males, 32(80%) patients showed decreased levels of serum Vitamin B₁₂.

CONCLUSION

Vitamin B₁₂ deficiency is not uncommon in vegetarian population and knuckle hyperpigmentation is an early marker of this and need larger studies to know it better. Knuckle pad hyperpigmentation is much more frequent than diffuse pigmentation of the palms and/or soles in such patents. Few patients with vitamin B₁₂ deficiencies do present with severe anaemia requiring blood transfusions and often have skin hyperpigmentation.

KEYWORDS

Knuckle hyperpigmentation, Vitamin B₁₂ deficiency, Vegetarian.

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BACKGROUND

Megaloblastic anaemia is not uncommon in the Indian subcontinent as well as other parts of Asia; with females and vegetarians being more susceptible to Vitamin B₁₂ (cobalamin) deficiency. Vitamin B₁₂ is the only vitamin that contains a trace element (cobalt) that is why it's called cobalamin. Cobalamin is produced in the gut of animals and we can't get it from plants or sunlight. Plants don't need B₁₂, so they don't store it, that's why this deficiency is common among vegetarian population.¹ The hallmark pathophysiologic mechanism of megaloblastic anaemia is an impairment of DNA synthesis. Two vitamins, cobalamin

(vitamin B₁₂) and folic acid are essential for DNA biosynthesis. Megaloblastic anaemia results from abnormal maturation of hematopoietic cells due to faulty DNA synthesis.² Vitamin B₁₂ deficiency occurs in four stages, beginning with declining blood levels of the vitamin (stage I), progressing to low cellular concentrations of the vitamin (stage II), an increased blood level of homocysteine and a decreased rate of DNA synthesis (stage III), and finally, megaloblastic anaemia (stage IV). There is evidence that the disease is more common than was previously believed.³

Some of the described cutaneous manifestations associated with B₁₂ deficiency include characteristic mucocutaneous hyperpigmentation, vitiligo, angular cheilitis, and hair-nail changes, which are often missed or overlooked in early, asymptomatic phases of the disease.⁴ The first description of hyperpigmentation of the extremities-especially over the dorsum of the hands and feet, with accentuation over the interphalangeal joints and terminal phalanges (knuckle hyperpigmentation).⁵ But anaemia is the final stage of B₁₂ deficiency. Long before anaemia sets in, B₁₂ deficiency causes several other

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problems, including fatigue, lethargy, weakness, memory loss and neuro-psychiatric problems.

Knuckle hyperpigmentation (Figure 1) is an essential and early feature of vitamin B₁₂ deficiency among vegetarians;⁶ the relationship of knuckle hyperpigmentation with degree of vitamin B₁₂ deficiency is not well studied. We did a prospective study from April 2017 to March 2018 to document the incidence of knuckle hyperpigmentation with serum vitamin B₁₂ deficiency among vegetarian population in our hospital.



Figure 1. Patient's Both Hands Showing Knuckle Hyperpigmentation

MATERIALS AND METHODS

Total 40 patients of age group between 25 to 45 years were enrolled for this prospective study from April 2017 to March 2018, out of which 28 were females and 12 were males. The inclusion criteria for this study were the vegetarian people with knuckle hyperpigmentation. Pregnant and lactating women, patients having any systemic diseases, those who received blood transfusions within one month prior to presentation and those already on vitamin B₁₂ supplementations were excluded. Detailed history regarding demography, clinical presentation with special reference to pallor, organomegaly, nervous system examination (tingling, numbness, paresthesia etc.), jaundice, history suggestive of malabsorption, drug history and family history were documented. All were screened for hemoglobin, Mean corpuscular volume (MCV), WBC count, platelet count, peripheral blood smear (PBS) findings, and serum B₁₂ (ref.: 180 to 800 pg/ml), serum folic acid (ref.: 4 to 20 ng/ml). Other causes of hyperpigmentation such as Addison's disease were ruled out. Cases with B₁₂ level <180 pg/ml were considered as B₁₂ deficient and those with levels < 100 pg/ml were considered as severe B₁₂ deficiency.² Similarly, cases with folate levels < 4 ng/ml were considered as folate deficient. All cases where a diagnosis of megaloblastic anaemia was made, they received parenteral (intramuscular) cyanocobalamin (1000 µg/day) for 7 days, followed by a weekly dose of the same for a minimum of 8-12 weeks depending upon the serum B₁₂ level.

RESULTS

Out of 40 patients, 32(80%) patients comprising 24 females (75%) and 8 males (25%) showed decreased levels of

serum Vitamin B₁₂. Out of these 32 patients, it was found that 21/32 (65.6%) were B₁₂ deficient (<180 pg/ml) and 11 had severe B₁₂ deficiency (<100 pg/ml). There was female predominance and the majority of the patients were in the age group of 25 to 30 years, who were students, living mainly in hostels or Jobseekers having only vegetarian diet, no animal food. Also, we noticed that inadequate intake of food, improper diet, stress were also contributing factors for the vitamin B₁₂ deficiency by questionnaires. Clinical evidence of neuropathy was present in 7/32 (22%) of patients. Fatigue was the most common clinical presentation noted in 19/32 (60%) cases.

Prominent knuckle pad hyperpigmentation in the dorsum of hands was documented in 26 of 40 (65%) cases whereas 14/40 (35%) cases had patchy or diffuse knuckle hyperpigmentation with dusky, brownish-black pigmentation over palms and / soles (Figure 2).

Ten of 32 cases, showed dramatic improvement in their hyperpigmentation following 8 weeks of parental B₁₂ therapy, whereas others are on follow-up.



Figure 2. Patient's Both Palms Showing Dusky, Brownish-Black Pigmentation

DISCUSSION

Vitamin B₁₂ deficiency affects all age groups and causes megaloblastic anaemia. Megaloblastic anaemia is a multisystemic disorder involving mainly the hematologic, gastrointestinal, and nervous systems.⁷ Other manifestations involve the cardiovascular system, skeletal system and skin and hair changes.⁸ Vitamin B₁₂ deficiency is common among vegetarian diet. The average Indian vegetarian diet is deficient in cobalamin.⁹ This study was performed to know correlation of cutaneous changes i.e. Knuckle hyperpigmentation with vitamin B₁₂ deficiency among the vegetarians as it was a very consistent finding found in 80% with decreased vit B₁₂ level. Vitamin B₁₂ deficiency commonly occurs in vegetarians as the important sources of vitamin B₁₂ are animal products.¹⁰ So the index of vitamin B₁₂ deficiency suspicion rises significantly in patients with knuckle hyperpigmentation.

In 1944, Dr Bramwell Cook first observed that hyperpigmentation of the skin was associated with a macrocytic anaemia and the anaemia responded to crude liver extract.¹¹ Sen K et al study showed 79% of vitamin B₁₂ deficient patients having knuckle hyperpigmentation.¹² Our study also showed 80% decreased levels of vitamin B₁₂ in vegetarian population with knuckle hyperpigmentation

which was statistically significant and needs further evaluation with large size samples. Since then, there have been sporadic case reports with descriptions of the peculiar skin-hair-nail changes in patients with megaloblastic anaemia.^{9,6,13}

In a recent study from southern India, hyperpigmentation has been observed to be an early and consistent feature of vitamin B₁₂ deficiency.⁶ Vegetarian diets can be classified as lacto-vegetarian, ovo-vegetarian, lacto-ovo-vegetarian, or vegan. Vegan diets have very low cobalamin content.¹⁴ Determining the cause of vitamin B₁₂ deficiency was not possible due to logistic constraints. In our study, we observed a strong association of cutaneous hyperpigmentation particularly the knuckle pad pigmentation with megaloblastic anaemia. A greater proportion of our cases were B₁₂ deficient (<190 pg/ml); and eight had significant B₁₂ deficiency (<100 pg/ml). In 1963, Baker and colleagues described characteristic reversible brownish-black pigmentation over dorsal aspect of interphalangeal joints of hands and feet (knuckle pigmentation) in a large series of 21 South Indian subjects with megaloblastic anaemia¹¹ following 8 to 12 weeks of parenteral cobalamin therapy. Our observation was in accordance with that published in the literature.^{6,11} Other studies by Kannan R. And Santra G et al also showed dramatic improvement of skin hyperpigmentation with parenteral cobalamin therapy.^{15,13}

Thus, cases with knuckle pigmentation were associated with a greater degree of B₁₂ deficiency; though this lacked statistical significance, but it has highlighted the importance of knuckle hyperpigmentation as a significant clinical marker in such patients. However, large-scale population-based studies are required to validate our findings.

The pathophysiologic mechanism associated with hyperpigmentation in B₁₂ deficiency seems to be complex and is poorly understood.⁴ However, the most accepted hypotheses are i) increased melanin synthesis, and ii) defective melanin transfer from melanocytes to adjacent megaloblastic keratinocytes. Reduced methylcobalamin causes a reduction in intracellular reduced glutathione which in turn, activates Tyrosinase enzyme in the L-phenylalanine - tyrosine - melanin pathway.¹⁶ Furthermore, hyperhomocysteinaemia in B₁₂ deficiency leads to increased cysteine level supplementing more melanin synthesis. Study by Mori K has suggested that hyperpigmentation is not due to a defect in melanin transport but is secondary to an increase in melanin synthesis.¹⁷ However, the reason for the localized hyperpigmentation over the knuckle regions among individuals of megaloblastic anaemia remains an enigma.

CONCLUSION

The present study reinforces the fact that Vitamin B₁₂ deficiency is not uncommon in vegetarian population. Knuckle pad hyperpigmentation is a reliable marker of megaloblastic anaemia and clinicians should be aware of these valuable clinical signs, but larger studies are required to know it better.

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