Dermatologic Manifestations in Vitamin B12 Deficiency: A Review

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Abstract

Vitamin B12, also known as cobalamin, is a water-soluble vitamin primarily obtained from animal-based foods. It is crucial for hematopoietic cell formation, with methylcobalamin and adenosylcobalamin being its active forms. The metabolic process involves stomach release, binding to proteins, and absorption in the ileum with intrinsic factor. The liver stores B12, but deficiency can occur due to dietary, absorption, transportation, or metabolic issues.

Causes of low B12 levels include dietary choices, gastrointestinal diseases, and medications like metformin. Dermatological changes associated with deficiency, such as hyperpigmentation, can occur, possibly due to decreased glutathione and increased melanin production.

Vitamin B12 deficiency has a wide range of symptoms, from asymptomatic to severe neurological impairments, but its dermatologic effects have been under-represented in literature."

Keywords: Vitamin B12 deficiency, dermatologic manifestations

Background

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is essentially found in food of animal source. It has an important role in hematopoietic cell formation (Brescoll, 2015; Taleb, 2020). Vitamin B12 is present in different forms in the human body, with methylcobalamin and adenosylcobalamin being the two metabolically active forms (Brescoll, 2015).

Several coenzymes are involved in the metabolism of cobalamin. The release of cobalamin from ingested food proteins takes place in the stomach under the effect of pepsin; it then binds to haptocorrin. When it reaches the duodenum, cobalamin is released from its protein complex with the effect of pancreatic proteases and binds to intrinsic factor. The latter is needed to ensure the absorption of cobalamin in the terminal ileum. Cobalamin then reaches the portal circulation, and is delivered mainly to the liver, as well as other tissues. The storage of cobalamin in the liver is sufficient to last a long time (2-5 years) before its deficiency leads to clinically relevant pathology (Brescoll, 2015; Kannan, 2008). B12 deficiency can happen at any level such as ingestion, absorption, transportation, and metabolism (Brescoll, 2015; Demir, 2013).

Vitamin B12 is not synthesized in the human body, hence, it should be retrieved from external sources, particularly animal sources, such as meat, poultry, fish, eggs, and dairy products (Agrawala, 2013; DiBaise, 2019). It is also obtained from fortified cereals (DiBaise, 2019).

Common causes of low vitamin B12 can be divided into dietary, organic and drug related. Dietary causes of vitamin B12 deficiency are restrictive vegetarian diet and malnutrition. Organic causes include gastrointestinal tract diseases including autoimmune disease e.g. pernicious anemia and H-pylori infection, malabsorption syndromes, congenital diseases and surgical causes i.e. gastrectomy, ileectomy. Drug induced causes are metformin, proton pump inhibitors and histamine receptor antagonists. Other causes are - advanced age, alcoholism (Chiang, 2013; Dibaise, 2019, Mori, 2001; Rzepka, 2018; Kuenyefu, 2020; Gravina, 2018).

The exact mechanism of low vitamin B12 causing dermatological changes is unknown (Kaur, 2018). Hyperpigmentation of skin with megaloblastic anemia associated with low vitamin B12 was first observed by Cook in 1944. Pigmentation can manifest in any part of the body, however it is usually seen in feet and hands, particularly over interphalangeal joints. Facial hyperpigmentation has also been described (Tayem, 2016). Gilliam and Cox postulated that low levels of vitamin B12 causes decreased intracellular levels of reduced type glutathione which has a tyrosinase inhibiting effect that leads to increased melanin produced by epidermal melanocytes. This reduced type glutathione also retards mitosis and reduces DNA synthesis leading to dermal atrophy and hyperpigmentation. However the exact mechanism of this hyperpigmentation over certain areas of the body is still unclear and there are no theories to support it (Chiang, 2013). The same hypothesis is discussed in (Demir, 2013 and Mori, 2001).

Vitamin B12 deficiency can manifest in different ways (Table 1) ranging from completely asymptomatic patients to patients with severe disability due to nervous system involvement (Chiang, 2013; DiBaise, 2019; Jangda, 2022).

Despite vitamin B12 deficiency being a relatively common problem in several communities, its dermatologic effects remain one of the less published areas in both dietetic and dermatologic literature.

Search strategy

We searched different online databases: Google Scholar, PubMed, and UpToDate. Advanced search was used, including articles from 1950 to 2023, based on the following search strategy:
((B12 or cobalamin) AND (deficiency)) AND (skin or derm* or cutaneous).

We excluded articles published in languages other than English, duplicates, and articles discussing the skin manifestations of B12 intake rather than B12 deficiency. The research team members then reviewed the retrieved articles to select those with clinical relevance.

Cutaneous manifestations of B12 deficiency

The pattern of hyperpigmentation is generalized with accentuation in flexural areas, palms, soles, and the oral cavity. It may also be accentuated in areas of pressure, such as the terminal phalanges, knees, and elbows. Pigmentation due to vitamin B12 deficiency can manifest in any part of the body, but mainly on the hands and feet, interphalangeal joints, and occasionally in the toenails and fingernails. Hyperpigmentation can be the initial manifestation of vitamin B12 deficiency. Excessive

Table 1. Common signs and symptoms of vitamin B12 deficiency

Body system	Common signs and symptoms
Hematologic	Megaloblastic anemia
Neurologic	Subacute combined degeneration of spinal cord
Psychiatric	Apathy, agitation, hallucinations
Cardiovascular	Tachycardia
Dermatologic	Hyperpigmentation, graying hair, hunter glossitis, vitiligo, angular stomatitis

melanin is found in the basal layer of the epidermis in hyperpigmentation due to B12 deficiency. In one patient with a reddish hyperpigmentation due to chronic cobalamin deficiency that resolved with the treatment of parenteral vitamin B12, biopsy showed an increased number of dermal blood vessels. It has also been speculated that the increase in melanin could be due to the influence of cobalamin decreasing the level of reduced-type glutathione, which normally inhibits tyrosinase. Glossitis, glossodynia, recurrent ulcers, cheilitis, stomatitis can manifest due to deficiency of cobalamin (Brescoll, 2015; Chiang, 2013).

Dermatologic diseases associated with B12 deficiency

Vitiligo: Other than in hyperpigmentation, cases vitiligo has also been reported with cobalamin deficiency in various studies (Brescoll, 2015; Chiang, 2013; Demir, 2013; Jangda, 2022; Jithendriya, 2013; Kannan, 2008; Rzepka, 2018; Sarwar, 2019).

One study (Wolffenbuttel, 2019), identified vitiligo linked with pernicious anemia as both autoimmune conditions.

Recurrent aphthous stomatitis: Recurrent aphthous stomatitis is also reported with low vitamin b12 levels, although it's not as common as atrophic glossitis. In a randomized, double-blind, placebo-controlled trial, a 1,000-mcg dose of sublingual vitamin B12 was an effective therapy for the treatment of recurrent aphthous stomatitis regardless of the patients' serum vitamin B12 level [32] (Brescoll, 2015).

Treatment of cutaneous manifestations

Cyanocobalamin and hydroxocobalamin are both synthetic forms of vitamin B12 and both are used in the treatment of vitamin B12 deficiency. However, a significant difference in their administration is their maintenance dose interval. Cyanocobalamin, which contains a cyanide group, is administered monthly, whereas hydroxocobalamin is given every two-to-three months.

For that reason, hydroxocobalamin was preferred over cyanocobalamin as first-choice therapy in vitamin B12 deficiency. The administration routes are various, including oral, sublingual, intramuscular (IM), intranasal, intravenous, and deep subcutaneous formulations, with parenteral administration usually reserved for severe cases of deficiency in practice. However, a Cochrane review in 2018 concluded that low-quality evidence suggests oral and IM vitamin B12 have similar effects regarding normalizing serum vitamin B12 levels, with an advantage for oral treatment being less expensive (Taleb, 2020).

Early diagnosis and treatment of vitamin B12 deficiency is the key, as if left untreated it can lead to irreversible manifestations especially neurological deficits. Normal dose is 1000 µg cyanocobalamin IM injection once per week until the deficiency is corrected (DiBaise, 2019; Sabatino, 1998; Taleb, 2020). The duration of treatment with vitamin B12 depends on cause of deficiency.

The treatment of vitamin B12 deficiency in pernicious anemia is 1000 µg of vitamin B12 by intramuscular injection every day or every other day for 1 to 2 weeks, followed by monthly injections for 3 months, and thereafter every 3 months for life Those who are deficient for nutritional reasons can be maintained on oral cobalamin tablets after their course of vitamin B12 injection (Kannan, 2008).

With treatment, hyperpigmentation resolves in 6-12 weeks. Neurological response usually starts in the first week and is completely evident within 6 months (Sarwar, 2019).

Conclusion

In case of unexplained hyperpigmentation B12 deficiency should be considered as an underlying cause. There are links between cobalamin and dermatologic diseases such as vitiligo, atopic dermatitis, and aphthous stomatitis. Pigmentation due to vitamin B12 deficiency can mimic Addison's pigmentation, but it's not a usual presentation. After ruling out Addison's disease, a vegetarian diet should be kept in mind for vitamin B12 deficiency. It is vital for physicians to understand the atypical manifestations of B12 deficiency, as prompt diagnosis and early intervention can prevent some serious neurological complications.

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