Short Communication
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Acromelanosis, as a clinical manifestation of Vitamin B12 deficiency

Abstract

Cyanocobalamin (vitamin B12) is essential for cell growth and reproduction, also for hematopoiesis due to its role in the synthesis of folates, as well as in the synthesis of nucleoproteins and myelin. The effects of this vitamin deficiency are usually seen first in the red blood cells and in marked deficiency pancytopenia may appear.1; in addition to affecting other systems such as the central nervous system and bone marrow as well as the skin, being acromelanosis a rare clinical manifestation. A 5-year-old 10-month-old girl is presented, referred to our Unit with pancytopenia, neurological involvement, and skin hyperpigmentation on the back of the hands and feet. Given the clinical suspicion of vitamin B12 deficiency, laboratories are carried out in which a marked decrease in cyanocobalamin is confirmed, which is why replacement treatment with it is indicated. Skin hyperpigmentation stands out as a clinical manifestation that guides the diagnostic presumption of Vitamin B12 deficiency, and its rapid resolution after the establishment of adequate treatment.

Keywords: vitamin B12, deficiency, skin hyperpigmentation, acromelanosis

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Introduction

Dietary vitamin B12 deficiency is usually the result of insufficient absorption, the most frequent causes in adults include: inadequate daily intake (e.g., in vegans, patients with malnutrition), alterations in absorption due to intrinsic factor deficiency or pernicious anemia (infrequent in children), achlorhydria and autoimmune metaplastic atrophic autoimmune gastritis, partial or total gastrectomy, celiac disease, Crohn's disease and pancreatic insufficiency. In the pediatric population, the most frequent causes are: lack of intake, malabsorptive syndromes such as celiac disease, cystic fibrosis, gastric and intestinal resections and inborn errors of metabolism such as methylmalonic acidemia and homocystinuria.

The deficiency causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, peripheral neuropathy 2. Cutaneous hyperpigmentation is found within the range of manifestations 3. The following is the case of a female patient 5 years 10 months old with the presence of acromelanosis as one of the clinical manifestations secondary to Vitamin B12 deficiency.[1–3]

Case presentation

Female patient aged 5 years 10 months, native and resident of Cuilapa, Santa Rosa, student, who was referred from the National Unit of Pediatric Oncology, UNOP, for pancytopenia under study, non-neoplastic. Ten days prior to consultation, she started with diarrheal stools, 3 per day, abundant, liquid, associated with vomiting and fever, treated with acetaminophen without improvement, so she consulted the hospital of Cuilapa, Santa Rosa, where she was admitted and laboratories were performed, showing pancytopenia, being necessary to transfuse packed cells and platelets. She was referred to UNOP where they performed a bone marrow aspirate and immunophenotyping, which did not show a process suggestive of neoplasia, so she was referred to the Hospital Infantil de Infectología y Rehabilitación, HIIR, for evaluation and follow-up. The girl with a medical history of infection at 3 years of age, was referred to the Infectious Diseases and Rehabilitation Hospital, HIIR, for evaluation and follow-up.[4,5]

She was admitted to the hospital in Cuilapa and was later transferred to a nutritional recovery center for 2 months in Guazacapan. At the time of her admission to this unit her diet was based on grains, fruits and vegetables and although she consumes meat and chicken, only 1-2 times a month; describing up to this moment a normal growth and development and the complete national vaccination schedule for her age. On physical examination, weight: 13.6 kg (with edema) and estimated weight: 11 kg; height 95 cm; SCT: 0.54; with T/E: -3; P/T: 0. HR: 86 bpm; FR 22 rpm BP: 111/ 65 mmHg; T: 37OC and SO2: 93%. The girl appears apathetic and indifferent to the environment, sparse brittle hair, with glossitis and cheilosis, presence of flat bluish hyperpigmented lesions on the tongue and oropharynx, hepatomegaly 4 cm below the costal ridge. Hyperpigmented external genitalia. Symmetrical mobile extremities, edema with pitting, hyperpigmentation in distal phalanges of hands and feet, generalized petechiae (Figure 1).[6]

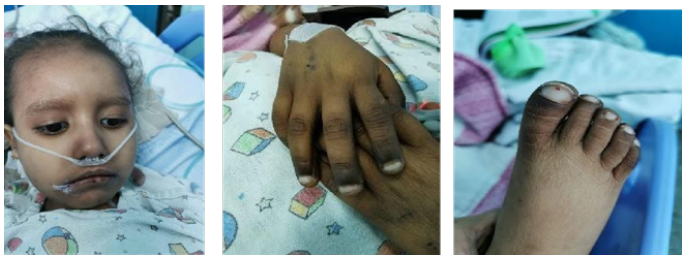

Figure 1 Glossitis, cheilitis and acromelanosis in a patient with megaloblastic anemia due to vitamin B12 deficiency.

Bone marrow aspirate

Bone marrow with evaluable marrow lump, hypercellular with 35% myelocytes, metamyelocytes, 28%, segmented/cayed, 14% erythroid, 20% mature looking lymphocytes, 3% monocytes and 1% immature cells. Dysplastic changes affecting the 3 cell lines are identified, granulocytes show maturational asynchronism, type and hypergranularity, segmented granulocytes show predominantly megaloblastic changes, with nuclear alterations such as hypersegmentation and hypergranularity. The erythroid series

with megaloblastic changes and nuclear abnormalities, and the megakaryocytic series, shows alterations in the cellular structure and the megakaryocytic series, with megaloblastic (Figure 2).

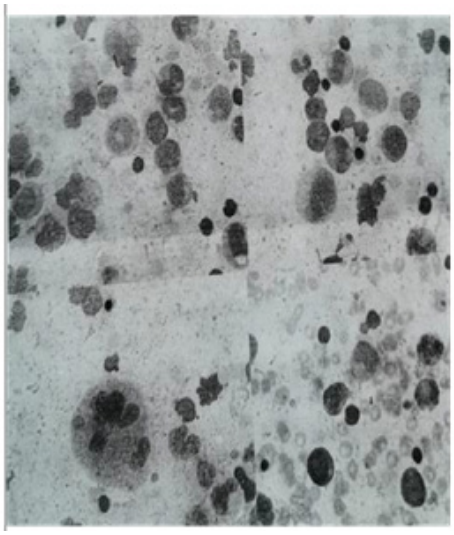

Figure 2 Bone marrow aspirate

He also presented with a generalized tonic-clonic seizure of approximately 1 minute duration. With labs: Hematology: WBC 2,780; Lymphocytes 74.80%; Neutral 20.90%; Hemoglobin 11.4 g/dL; Hematocrit 32.1%; MCV 87.1 fl; HCM 30.8 pg; Platelets 10,000 (previous transfusion due to hemodynamic compromise of packed cells and platelets) Vitamin B12 levels: < 148 pg/ml (VN: 213-816 pg/ml) FILM ARRAY (Real Time PCR): positive for Clostridium difficile toxi A/B, Shigella /EnteroInvasive. E.coli

Gastrointestinal sepsis due to EnteroInvasive E. coli (EIEC) carrying Shigella toxin 3. Severe Mixed Acute CPD (by Mclaren criteria) 4. Pseudomembranous colitis due to Clostridium difficile 5. Acromelanosis due to Vitamin B12 deficiency 5. Pancytopenia secondary to megaloblastic anemia.[7,8]

Treatment was started with protocol for severe acute protein-calorie malnutrition with antibiotic overture for isolated infectious agents. Vitamin B12 (1000mcg) daily for ten days intramuscularly, then 100 mcg orally weekly for another month with a plan to continue monthly for two more months. At 4 weeks the patient with resolution of clinical symptoms, resolves glossitis, cheilosis and diarrhea, as well as neurological symptoms and marked decrease of hyperpigmentation on the back of hands and feet and genital area (Figure 3). Hematology: WBC 8,760; Lymphocytes 40.25%; Neutrophils 53.2%; Hemoglobin 14 mg/dL; Hematocrit 38.9% MCV 80 fl; HCM 28.3 pg; platelets 250,000 and vitamin B12 levels: greater than 6,000.

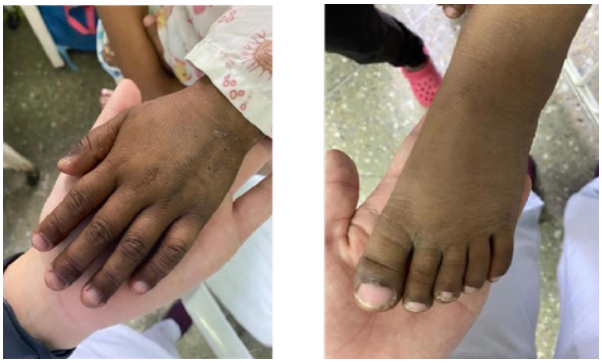

Figure 3 Decreased hyperpigmentation on hands and feet.

Discussion

Vitamin B12 or cobalamin plays a key role as a coenzyme in DNA synthesis and cell maturation, as well as in neuronal lipid synthesis. The human body is not able to synthesize it and must obtain it from the diet, mainly from foods of animal origin (meat, milk and dairy products, eggs, fish).

The daily requirement of vitamin B12 is approximately 2 to 2.5 mcg, which is amply supplied by a balanced diet. Tissue stores of B12 are ample, between 3 to 10 mg, and can take decades to empty. The causes of its deficiency can be divided into three groups: low exogenous intake, poor digestion and malabsorption of the vitamin. In the last two groups we can mention in the pediatric population celiac disease, cystic fibrosis, gastric and intestinal resections, pernicious anemia due to intrinsic factor deficiency either congenital or due to alteration of its specific intestinal receptor (rare in pediatrics); lack of the transporter protein, transcobalamin II and disorders of intracellular metabolism of cobalamin with deficient production of its two active metabolites: methylcobalamin and adenosylcobalamin and among others inborn errors of metabolism such as methylmalonic acidemia and homocystinuria.

Vitamin B12 deficiency causes the appearance of various clinical manifestations such as megaloblastic anemia, digestive disorders (diarrhea, glossitis, anorexia), neurological manifestations (movement disorders, hypotonia, seizures and cerebral atrophy), alteration of anthropometric parameters (weight, height and head circumference in low percentiles) and skin manifestations such as acromelanosis or skin hyperpigmentation. Few cases of hyperpigmentation due to vitamin B12 deficiency have been reported in the world literature, characterized by a brownish-black coloration, affecting mainly photoexposed sites such as the back of the hands and feet, and being reversible once treatment is instituted.

Skin pigmentation will depend on the amount of melanin present, which is regulated by the enzymatic activity of tyrosinase and although the exact mechanism of hyperpigmentation due to vitamin B12 deficiency is unknown, several hypotheses have been put forward: 1. Patients with vitamin B12 deficiency have low levels of intracellular glutathione, leading to an increase in tyrosinase activity producing greater melanogenesis. Another hypothesis put forward by Griepp describes the influence of biopterin, a substance necessary for the hydroxylation of phenylalanine, which has a role in melanin synthesis, so that elevated levels of this substance could explain hyperpigmentation. Marks refers to a change in the distribution of melanin and affirms that in megaloblastic anemias there would be a defect in the transport or incorporation of melanin within the keratinocytes, which would cause pigment incontinence.

Although deficiency of this vitamin is not common knowledge in pediatrics and its deficit is usually only suspected and studied in relation to chronic pathologies that affect its absorption, and its deficiency is rarely thought to be due to low intake, the above case describes a patient 5 years 10 months old with a diet based on grains, vegetables and fruits and little consumption of foods of animal origin, such as meats, milk and eggs, only 2 times per month. In addition to this, she has a history of having been admitted to a Nutritional Recovery Center at the age of 3 years for 2 months. At the time of admission, she presented clinical manifestations of megaloblastic anemia, glossitis, cheilosis, anorexia, diarrhea, neurological involvement with apathy, seizures and movement disorders, as well as hyperpigmentation of the skin on the back of the hands and feet, genital area and oral mucosa, as well as severe growth retardation. The diagnosis, although well oriented by performing a bone marrow aspirate in this disease,

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can be made by determining serum vitamin B12 levels, which is accessible and inexpensive, with a sensitivity that varies between 65-95%. Among the differential diagnoses for acromelanosis and hyperpigmentation in the oral mucosa are diabetes mellitus, Addison's disease, Cushing's syndrome, heavy metal deposition, porphyrias, thyroid disorders, although most of these entities present generalized hyperpigmentation. The patient had a good response to treatment with vitamin B12, having a rapid

clinical recovery during the first days of the disease, reversal of signs and symptoms of hematological, gastrointestinal, skin and neurological involvement is observed, especially apathy, limitation of movement, anorexia is very striking, as described in the literature. Cerebral atrophy and demyelination usually reverses within several months. However, despite initiation of treatment, some children often suffer long-term cognitive and psychomotor developmental delay. The only prognostic factor so far described in case series appears to be the severity and duration of the deficiency.

We highlight the importance of the case we present, because through skin lesions, we can reach the diagnosis of systemic diseases, reversible with the appropriate specific treatment, avoiding irreversible neurological damage that these patients may present.[9,10]

Conclusion

Based on the literature studied, we can conclude that both folate and vitamin B12 are important components for the human body, so these nutrients can cause not only anemia, but also alterations at the cellular level, causing multiple clinical manifestations as our patient presented in the clinical case. Its deficiency, in turn, is a risk factor at the cardiovascular and oncological levels.

Prevention, correct diagnosis of the causes of the deficiency of these nutrients and the treatment established with the subsequent correction of eating habits are thus of great importance.

Acknowledgments

None.

Conflicts of interest

The author declares that there are no conflicts of interest.

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