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DIAGNOSIS AND MANAGEMENT OF VITAMIN B12 DEFICIENCY ANEMIA IN PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This systematic review article aims to compile and analyze the scientific evidence on the diagnosis and management of Vitamin B12 Deficiency Anemia in pediatric patients, providing a comprehensive and up-to-date view, identifying gaps in research, and guiding future investigations and clinical practices. Methodology: The systematic review used the PVO strategy (population, variable and objective) to formulate the guiding question. The searches were performed in the PubMed Central (PMC) database with five descriptors combined with the Boolean term "AND": Vitamin B12 Deficiency, Child Growth, Child Development Disorders, Malnutrition, pediatrics. A total of 150 articles were found, of which 23 were selected after applying the inclusion and exclusion criteria, and 13 were used to compose the collection. Results: Essential for DNA production, methylation, and neurotransmitter synthesis, vitamin B12 plays a crucial role in neurological and hematopoietic development. Deficiency can lead to disorders such as megaloblastic anemia and irreversible neurological damage, especially in children and during pregnancy. Laboratory evaluation should include serum cobalamin measurement, methylmalonic acid, and homocysteine. Clinical trials show that supplementation improves motor development in children with suboptimal levels of vitamin B12. Conclusion: Early identification and prompt treatment of vitamin B12 deficiency are essential to prevent serious complications. Proper supplementation is crucial for at-risk populations, such as pregnant women, young children, and individuals following vegan or vegetarian diets. The relationship between maternal vitamin B12 levels and neonatal outcomes still requires further investigation. Vitamin B12 deficiency is a public health problem that needs continued attention and additional research to improve diagnostic and therapeutic approaches.

Keywords: Supplementation, Diagnosis, Complications, Pediatrics, Vitamin B12.

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INTRODUCTION

Vitamin B12 (B12) or cobalamin (Cbl) is a water-soluble vitamin contained exclusively in foods of animal origin, such as dairy, eggs, meat, and fish (WIRTHENSOHN et al., 2023). The dietary absorption of vitamin B12 is a complex process that begins with the production of haptocorrin (also called transcobalamin I or ligand R) by the salivary glands. When food is broken down in the stomach by gastric acid and pepsin, free vitamin B12 is released and associates with haptoracen. Simultaneously, the parietal cells of the stomach release intrinsic factor, which cannot bind to the vitamin B12-haptocorrin complex. Only when the food advances into the duodenum, where trypsin and other pancreatic enzymes degrade haptoracen, does vitamin B12 become available to bind to intrinsic factor (SOCHA et al., 2020).

The complex formed by vitamin B12 and intrinsic factor attaches to the receptor on the mucosal surface of enterocytes in the ileum. From there, vitamin B12 is transported into the bloodstream by multidrug resistance protein 1, where it rapidly binds to its transport protein transcobalamin II. The vitamin B12-transcobalamin complex then binds to transcobalamin receptors on hematopoietic stem cells and other cell types, allowing absorption of the complex, followed by lysosomal degradation of transcobalamin. Free vitamin B12 then becomes available for cellular metabolism (SOCHA et al., 2020).

Vitamin B12 participates in erythropoiesis, the synthesis of DNA and fatty acids, energy generation, and the functioning of the nervous system. A deficiency results in megaloblastic anemia and nervous system problems. In infants with nutritional vitamin B12 deficiency, the first clinical signs are irritability, growth retardation, and food refusal, accompanied, in the most severe cases, by damage to the central nervous system, which may be irreversible (PANZERI et al., 2024).

The vitamin B12 levels of newborns depend on the B12 levels of their mothers. However, after the 6th month, with the introduction of additional nutrients, the external intake of B12 begins. As vitamin B12 is mainly found in animal products, deficiency is frequent in children, especially in developing countries, in those who do not consume sufficient amounts of this type of food (TANDON et al., 2022). The recommended daily intake of B12 is 0.5 µg/d for infants in the first three months, 1.4 µg/d from 4 to 12 months, 4 µg/d for adults, 4.5 µg/d during pregnancy, and 5.5 µg/d for women who are breastfeeding (WIRTHENSOHN et al., 2023).

In a representative sample of Brazilian children under 5 years of age, it was found that 14.2% of children between 6 and 59 months had vitamin B12 deficiency, and this frequency was even higher (25.3%) among younger children (6 to 23 months) with greater

socioeconomic vulnerability. Regional variations were also observed, with a more unfavorable scenario in the North and Northeast regions of the country. More than 1 in 4 children (28.5%) living in the North region had vitamin B12 deficiency, that is, 2.9 times higher than that found in the South region (9.7%). It is relevant to note that, in the North region, the highest rates of nutritional deficiencies and child malnutrition continue to be observed. This data reveals individual inequalities in micronutrient deficiencies between Brazilian regions. It is reinforced that vitamin B12 deficiency should be included in the public policy agenda for this region and in other places where social inequalities can impact vitamin B12 levels (SALVATTE et al., 2023).

This systematic review article aims to compile and analyze the scientific evidence on the diagnosis and management of Vitamin B12 Deficiency Anemia in pediatric patients. The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the clinical manifestations resulting from vitamin B12 deficiency in pediatric patients, as well as to demonstrate the main methods used in the diagnosis and treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate anemia due to vitamin B12 deficiency in the pediatric population, as well as what are the diagnostic and therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Five descriptors were used in combination with the Boolean term "AND": Vitamin B12 Deficiency, Child Growth, Child Development Disorders, Malnutrition, pediatrics. The search strategy used in the PMC database was: Vitamin B12 Deficiency AND Child Growth, Vitamin B12 Deficiency AND Child Development Disorders, Vitamin B12 Deficiency AND Malnutrition AND pediatrics. From this search, 150 articles were found, which were later submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and

experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 150 articles were found. After applying the inclusion and exclusion criteria, 23 articles were selected from the PubMed database, and a total of 13 studies were used to compose the collection.

DISCUSSION

Vitamin B12 is a cofactor involved in DNA production, methylation, and neurotransmitter synthesis. In addition, it acts as a cofactor for the enzyme methylmalonyl-CoA mutase and methionine synthase, and its deficiency leads to increased plasma levels of MMA and homocysteine. Thus, vitamin B12 deficiency during periods of accelerated growth, such as neonatal and childhood, results in much more severe symptoms than the signs of anemia seen in other phases (TANDON et al., 2022) (SHARAWAT et al., 2023). Adequate levels of vitamin B12 in early childhood favor growth and prevent cognitive impairment (SUGAPRADHA et al., 2024).

Vitamin B12 has different forms that are cofactors for complex reactions within the cell. Methylcobalamin and adenosylcobalamin are active forms of cobalamin. Methylcobalamin is the cofactor for methionine synthase, and its lack causes megaloblastic anemia. Adenosylcobalamin is also a cofactor for methylmalonyl-CoA mutase, and this pathway is responsible for the neurological effects of vitamin B12 deficiency. Vitamin B12 binds to some proteins in the blood. About 20% of circulating cobalamin is connected to transcobalamin (TC). The cobalamin-TC complex, known as holo-transcobalamin (HoloTC), delivers vitamin B12 to cells. HoloTC stands for the metabolically active form of vitamin B12. Most circulating cobalamin is bound to haptocorrin (VARKAL; KARABOCUOGLU, 2021).

The vegan diet is the most restricted and excludes all foods of animal origin, as well as products that contain ingredients derived from these foods. The biggest problem with the vegan diet is the total absence of vitamin B12 in foods of plant origin. Severe vitamin B12 deficiency in the first 1000 days of life has been associated with impaired neuronal myelination, which causes damage to the auditory and visual systems and interferes with learning and social interaction. Signs and long-term prognosis vary according to the severity and duration of the deficiency. All mothers and babies who follow vegetarian or vegan diets should use supplements. Newborns born to mothers with vitamin B12 deficiency usually

have no symptoms at birth, but develop clinical signs between 4 and 6 months of age, ranging from megaloblastic anemia to irreversible neurological damage (PANZERI et al., 2024).

Although the vegetarian population is at higher risk of deficiency, it is also common among non-vegetarians. Vitamin B12 deficiency is a major public health concern worldwide. Pregnant women and young children are at higher risk of facing this deficiency. Regional disparities in the prevalence of vitamin B12 deficiency during pregnancy have been observed, indicating varying levels of risk in different regions (SUGAPRADHA et al., 2024).

Vitamin B12 insufficiency during pregnancy has been linked to poor pregnancy outcomes, including miscarriages, stillbirths, neural tube malformations, intrauterine growth restriction, low birth weight, and early delivery. Vitamin B12 deficiency is also associated with an increased risk of gestational diabetes mellitus. Vitamin B12 levels in pregnant women are thought to influence vitamin B12 status in the fetus and infant (SUGAPRADHA et al., 2024).

In breastfed babies, the main cause is a lack of vitamin B12 in the mother. Babies who are breastfed receive vitamin B12 through breast milk during the first few months of life, and B12 levels begin to decline around the sixth month in babies fed exclusively with breast milk. Especially in mothers who follow a vegan diet or suffer from gastritis or other conditions that impair absorption, breast milk may not contain sufficient amounts of vitamin B12. In addition, congenital conditions, such as Imerslund-Gräsbeck syndrome, rarely cause cobalamin deficiency in infants (VARKAL; KARABOCUOGLU, 2021).

A lack of vitamin B12 causes a wide range of disorders, ranging from cases without symptoms to fatal conditions. The main tangible consequences of vitamin B12 deficiency are megaloblastic anemia and neurological problems. In children, frequently observed symptoms are developmental delay or regression, decreased muscle tone, lethargy, excessive irritability, tremors, and microcephaly (VARKAL; KARABOCUOGLU, 2021). One systematic review did not identify a clear linear relationship between birth weight and maternal vitamin B12 levels during pregnancy. However, deprivation has been linked to a higher number of low-birth weight infants. The relationship between maternal, neonatal, and infant vitamin B12 levels has been shown to be varied (SUGAPRADHA et al., 2024). Three randomised controlled trials (RCTs) looked at the impact of vitamin B12 supplementation on neurological development in children with suboptimal vitamin B12 status. Of these, two RCTs conducted in health facilities with infants born with low birth weight or developmental delay demonstrated that a high dose of vitamin B12 (400 µg of hydroxycobalamin intramuscularly) significantly improved motor development (STRAND et al., 2020).

Macrocytic anemia can be attributed to a lack of vitamin B12 (cobalamin, Cbl) and folic acid in children. Vitamin B12 deficiency is defined by: serum cobalamin levels less than 200 pg/mL and hemoglobin below 11.5 g/dL in children aged 1 to 5 years, or hemoglobin less than 11 g/dL in children aged 5 to 12 years, along with any of the following: mean corpuscular volume (MCV) greater than 84 + [age (a) x 0.6] fL, and peripheral blood smear showing hypersegmented neutrophils (5 lobulated nuclei in more than 5% of neutrophils) or bone marrow aspiration suggestive of megaloblastic anemia. In cases of severe deficiency, thrombocytopenia may be observed. A low reticulocyte index is typically seen. In cases of severe anemia, nucleated erythrocyte precursors, Cabot rings, and Howell-Jolly bodies may appear (CHANDRA et al., 2022) (SAXENA et al., 2023).

Specific laboratory evaluation for vitamin B12 deficiency begins with the measurement of total serum cobalamin levels. Vitamin B12 levels less than 200 pg/mL are strongly suggestive of deficiency, although both false positive and negative results may occur. A normal level of cobalamin makes deficiency unlikely. For borderline cobalamin levels (200–400 pg/mL), additional laboratory tests, such as measurement of methylmalonic acid and homocysteine, should be performed. Methylmalonic acid and homocysteine are intermediates in the metabolism of vitamin B12 and increase its deficiency. Homocysteine is also elevated in folate deficiency, as well as vitamin B12 deficiency (SOCHA et al., 2020).

The prognosis of vitamin B12 deficiency depends on the severity and duration of the deficiency. Therefore, the diagnosis should be made as soon as possible and treatment should be started immediately. It is crucial to consider, diagnose, and treat vitamin B12 deficiency in childhood. Although the cost of treatment is relatively low, delaying the start of treatment can result in serious complications such as profound anemia and irreversible neurological damage (TANDON et al., 2022).

Since clinical manifestations, dietary history, and laboratory results (anemia with elevated MCV) contribute to indicate nutritional macrocytic anemia, replacement treatment should be initiated with vitamin B12. The intramuscular (IM) route is the most widely used treatment method in infants today. In patients with severe vitamin B12 deficiency, this route is preferred, using different administration schedules. Similarly, the IM pathway is commonly chosen in infants (VARKAL; KARABOCUOGLU, 2021). Regarding dosage, it is recommended to start treatment with 25 µg of vitamin B12 administered daily IM (or deep SC or IV) in the first 2-3 days. Then, 100 µg (50 µg in infants) of vitamin B12 is applied parenterally daily for the next 7 days (or up to 3 weeks in children with neurological signs), continued with 100 µg of vitamin B12 IM/SC deep/IV every other day for the next 7 days,

and finally 1000 µg of vitamin B12 given IM/SC deep/IV weekly for 1 month (CHANDRA et al., 2022).

Vitamin B12 is absorbed quickly and effectively by this route. While this seems to be an advantage, amounts that exceed the binding capacity of transcobalamin are eliminated through the urine. In addition, this route also has some disadvantages, such as repeated and painful parenteral injections, bleeding, discomfort, the need for a health professional, and high costs. For these reasons, patient adherence is unsatisfactory. Thus, the oral route may be preferred in some situations (VARKAL; KARABOCUOGLU, 2021). There is accumulating evidence that treatment with high-dose oral vitamin B12 may be as efficient as cobalamin IM in terms of recovering vitamin B12 levels and haematological responses (VAN VLAENDEREN et al., 2021).

Just as the method of administration varies, so too does the dose and duration of vitamin B12 therapy in children depend on age (infant, child, adolescent). Daily oral vitamin B12 in doses between 100 µg and 1000 µg, and parenteral vitamin B12 in doses of 25-1000 µg, have been used to treat anemia due to vitamin B12 deficiency. Oral vitamin B12 needs to be ingested on an empty stomach, since food interferes with its absorption (CHANDRA et al., 2022).

Oral vitamin B12 therapy (500 µg in infants, 1000 µg in older children) can be used in the treatment of macrocytic anemia caused by nutritional vitamin B12 deficiency. This dose may be given daily for one week, every other day during the following week, twice a week, once a week, once every 15 days for a month, and then once a month to complete at least 3 months of treatment. Alternatively, daily oral therapy with vitamin B12, 500 µg in infants, 1000 µg in older children, can be given for 3 months (CHANDRA et al., 2022).

In view of these issues, the sublingual route (LS) is being considered for vitamin B12 administration. The sublingual method allows for the absorption of vitamin B12 under the tongue, preventing intestinal absorption. In addition, this method has several advantages, such as lower cost, high patient acceptance, eliminates the need for hospital visits, is not painful, and does not cause injection injuries. The SL route is as effective as the oral route in treating vitamin B12 deficiency. In a prospective, open-label study, 18 patients with vitamin B12 deficiency were treated. In this study, patients received 2000 µg of vitamin B12 sublingually daily for 7-12 days, and serum vitamin B12 levels normalized rapidly and significantly in all patients (TUĞBA-KARTAL; ÇAĞLA-MUTLU, 2020).

In one case reported in 2014, a child with short bowel syndrome was successfully treated sublingually. Subsequently, a study compared, for the first time, two substances administered sublingually (cyanocobalamin and methylcobalamin) and one IM

(cyanocobalamin) in children aged 5 to 18 years. In the study, 1 mg of cyanocobalamin IM was administered every other day for the first week and once weekly for the following three weeks, and 1 mg of cyanocobalamin or methylcobalamin, respectively, was administered sublingually daily for the first week and every other day for the following three weeks. Serum vitamin B12 levels increased significantly at the end of one month in all groups. In addition, sublingual methylcobalamin was considerably more effective than sublingual cyanocobalamin. In addition, all treatment routes resulted in significant hematological improvements (VARKAL; KARABOCUOGLU, 2021).

Children with hematologic manifestations due to vitamin B12 deficiency need treatment for at least 3 months. Children with neurological manifestations should be treated for at least 6 months. Children with an irreversible underlying cause of vitamin B12 deficiency (such as pernicious anemia, inherited disorders of vitamin B12 metabolism, underlying malabsorption disorders, or strict cultural practices such as strict veganism) that lead to vitamin B12 deficiency require lifelong therapy (CHANDRA et al., 2022).

Regarding the forms of vitamin B12, cyanocobalamin (CN-Cbl) is the synthetic form of vitamin B12, which needs to be converted into metabolically active coenzymes such as methylcobalamin (Me-Cbl) and 5'-deoxyadenosylcobalamin (Ado-Cbl). Hydroxocobalamin (HO-Cbl) is a long-acting form of vitamin B12, requiring fewer injections and therefore being preferred in children with persistent anemia or inherited disorders of vitamin B12 metabolism. Currently, there is insufficient evidence that the benefits of using Me-Cbl or Ado-Cbl compared to CN-Cbl or HO-Cbl emerged, in terms of bioavailability, biochemical effects, or clinical efficacy. Me-Cbl is the most readily available form on the market and can be prescribed to treat vitamin B12 deficiency anemia (CHANDRA et al., 2022).

Unlike oral forms, injections are more likely to trigger allergies. HO-Cbl is more allergenic than CN-Cbl, but allergic reactions can occur with all forms and pathways of cobalamin. Side effects such as nausea, pruritus, chills, fever, hot flashes, dizziness, or, rarely, anaphylaxis may occur. A history of sensitivity should be checked prior to parenteral administration of vitamin B12. In cases of allergic reactions, hydrocortisone can be used as a premedication or desensitization can be attempted. Intravenous vitamin B12 should be administered as an infusion over 45-60 minutes. Some children may even experience a temporary worsening of neurological symptoms. CN-Cbl should be avoided in children with optic nerve atrophy or Leber's disease, as it can cause damage to the optic nerve. It is important to monitor serum potassium levels in the first few days of treatment, as there is a risk of transient hypokalemia after initiation of vitamin B12 therapy, especially in patients with severe anemia (CHANDRA et al., 2022).

CONCLUSION

Vitamin B12 deficiency poses a significant challenge to global public health, affecting both vegetarians and non-vegetarians. This vitamin is essential for DNA production, methylation, and neurotransmitter synthesis, playing a crucial role in neurological and hematopoietic development. Vitamin B12 deficiency can lead to a wide range of disorders, from megaloblastic anemia to irreversible neurological damage, especially in children and during pregnancy.

Laboratory evaluation of vitamin B12 deficiency should begin with the measurement of serum cobalamin levels, supplemented by methylmalonic acid and homocysteine tests in cases of borderline levels. Proper supplementation is crucial, especially for at-risk populations such as pregnant women, young children, and individuals following vegan or vegetarian diets.

Clinical trials have shown that vitamin B12 supplementation can significantly improve motor development in children with suboptimal vitamin B12 status. However, the relationship between maternal vitamin B12 levels and neonatal and infant outcomes still requires further investigation.

In summary, early identification and prompt treatment of vitamin B12 deficiency are essential to prevent serious complications. Raising awareness of the importance of vitamin B12 and implementing supplementation strategies can significantly contribute to improving public health.

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