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CLINICAL CASE

Vitamin B12 deficiency in an infant child of a mother with pernicious anemia

Déficit de vitamina B12 en un lactante hijo de madre portadora de anemia perniciosa

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What do we know about the subject matter of this study?

Vitamin B12 deficiency in infants is one of the major causes of potentially irreversible neurological damage. The most frequent etiology is maternal deficiency linked to vegetarian diets.

What does this study contribute to what is already known?

Maternal pernicious anemia can lead to vitamin B12 depletion in the mother and, consequently, deficiency in the infant. This rare etiology should be considered, especially in mothers who do not follow a vegetarian diet.

Abstract

In infants, vitamin B12 deficiency is mainly due to nutritional deficiencies related to maternal deficit. Most cases of maternal deficiencies are associated with vegetarian diets. Pernicious anemia is an autoimmune disease that affects the absorption of this vitamin. Although it is less common than nutritional deficiency, is also an important cause of maternal deficiency. **Objective:** to report a case of an infant with vitB12 deficiency, secondary to pernicious anemia in his mother, and to review the most important aspects of this disease in childhood. **Clinical Case**: Nine months-old male infant, without pathological perinatal history, exclusively breastfed, with persistent rejection of solid food from 6 months of age. One month before hospitalization, he progressively presented hyporesponsiveness, with fluctuating state of alertness, regression of motor development milestones, and vomiting. The blood count showed macrocytic anemia and neutropenia. Vitamin B12 deficiency was confirmed in the patient. He received treatment with intramuscular vitamin B12 with good clinical and laboratory response. Maternal B12 deficiency was confirmed as the cause of the infant's deficiency. Since the mother reported no dietary restrictions, anti-intrinsic factor and anti-parietal cell antibodies were measured, leading to the diagnosis of pernicious anemia. **Conclusions:** Early recognition is essential to prevent the development of potentially irreversible neurological damage. Maternal pernicious anemia should be considered in children with megaloblastic anemia, especially in those whose mothers do not follow vegetarian diets.

Keywords:
Megaloblastic Anemia;
Vitamin B12 Deficiency;
Pernicious Anemia;
Neonatal Screening;
Vegetarian Diet

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Introduction

In recent decades, the role of micronutrients, such as vitamin B12 (cobalamin) and folates, as well as the consequences of their deficiency, has been the subject of research[1]. In developing countries in Southeast Asia, Africa, and Central America, vitamin B12 deficiency is considered a common nutritional deficiency[1,2]; in contrast, in developed countries and South America, the prevalence is estimated to be low; however, there are no studies on the subject.

In infants, vitamin B12 deficiency is mainly due to nutritional deficiencies related to maternal deficiency or, more rarely, to genetic defects in the absorption or metabolism of the vitamin[2,4-7]. Maternal deficiency can be caused by diets with inadequate amounts of this vitamin, which is present in animal products, such as poorly conducted vegetarian or vegan diets, or in the context of food deprivation[2,3,6-9]. Pernicious anemia is an autoimmune disease that produces intrinsic factor antibodies, compromising the absorption of this vitamin. Although it is less frequent than nutritional deficiency, it is also an important cause of maternal deficiency, which can lead to depletion in the infant.[4,5,10,11]

After birth, both breast milk and supplemental formulas are adequate sources of B12 for the infant. At this stage, the levels of this micronutrient are strongly related to maternal levels. In the maternal deficiency state, levels in the infant will be affected by both decreased placental transfer and low levels in breast milk[12].

Vitamin B12 is a fundamental factor for DNA synthesis, acting as a cofactor in two enzymatic reactions. First, at the methionine synthase, which converts homocysteine to methionine. The decreased activity of this enzyme results in homocysteine accumulation. Secondly, at the methylmalonyl-CoA mutase, which catalyzes methylmalonyl CoA to Succinyl CoA. Its deficiency results in methylmalonic acidemia and deficient amino acid synthesis. Clinically, these alterations produce megaloblastic anemia and neurological alterations[2,6].

While hematological alterations are completely reversible, neurological symptoms may not be. Long-term follow-up is a priority to determine the extent of this entity. Few studies include this aspect, but it has been suggested that the duration and severity of the deficit may be associated with an evolution with irreversible sequelae[11,13-15].

The objective of this work is to report a case of vitamin B12 deficiency in an infant secondary to pernicious anemia in his mother, to reinforce the importance of a timely diagnosis to prevent potentially irreversible neurological damage.

Clinical Case

9-month-old male Caucasian infant, born at 39 weeks of gestational age with a birth weight of 3320g. He did not present any pathology in the perinatal stage. Regarding feeding, he was exclusively breastfed from birth, and from the age of 6 months he rejected solid foods, not being able to incorporate them into his diet; however, his growth was normal. His mother reported that she regularly included foods of animal origin in her diet. In relation to family history, her mother was affected by hypothyroidism, without other relevant data.

One month before consultation, the patient started with food refusal and concomitant vomiting 2-3 times a day. He showed hyporeactivity, less energetic crying, loss of social smile and connection with the environment, with fluctuation of the level of consciousness over time. In addition, at the time of consultation, he was unable to perform some of the motor milestones acquired at 6 months of age, when he was able to sit with assistance and attempt to grasp objects.

The anthropometric evaluation showed weight of 8,300 kg (weight/age P15-P50), length of 68 cm (length/age P15), and head circumference of 47 cm (head circumference/age P85), considering the child growth patterns of the World Health Organization. On physical examination, he was lethargic, without hemodynamic impairment, and marked cutaneous and mucosal pallor. There were no alterations in the tongue or the mucous membranes. Heart rate was normal with no heart murmur. There was no hepatosplenomegaly. Neurological examination showed marked hypotonia of the trunk and limbs. Osteotendinous reflexes were present. The rest of the examination was normal.

Blood analysis showed macrocytic aregenerative anemia, with hemoglobin (Hb) 5.62 g/dL (10.5-13.9), mean corpuscular volume (MCV) 91 fL (71-85.5), mean corpuscular hemoglobin (MCH) 31.7 pg (25-31), erythrocyte distribution width 36.1% (11.6-15), reticulocytosis 20700 cells/mm^3 (0.9%). He also had leukopenia with neutropenia [leukocytes 4800 cells/mm^3 (6000-17500), neutrophils 490 cells/mm^3 (1500-8500)], and platelets were normal [156000 cells/mm^3 (150-500000)]. Blood smear showed anisopoikilocytosis.

Venous blood gases showed metabolic acidosis with hyperlactatemia (pH 7.37, pCO2 27.5 mmHg, HCO3 17.3 mmol/L, BE -8.8 mEq/L). Lactate 4.1 mmol/L. Ionogram and hepatogram were normal.

Given the clinical suspicion of megaloblastic anemia, vitamin B12 and folic acid levels were evaluated, identifying low plasma vitamin B12 levels [<50 pg/ml (618-925)], elevated homocysteine [58 mol/L (4.68-5.97)], elevated urine methylmalonic acid [557 umol/

mmol creatinine (0.11-0.17)], and folic acid within reference values (>20 ng/ml). Head MRI was normal. Laboratory data (low vitamin B12, elevated homocysteine, and elevated methylmalonic acid) confirmed vitamin B12 deficiency in the infant.

Treatment was started with vitamin B12 1000 mcg/day intramuscularly for one week and then once a week for 4 weeks. After 10 days of treatment, he presented homocysteine levels, urine methylmalonic acid, and vitamin B12 within normal ranges. When treatment was started, there was a clear improvement in reactivity and interaction with the environment, appetite, and muscle tone. He presented hematologic improvement with normal Hb and MCV values after 2 months of treatment. Treatment was continued with a monthly dose of 1000 mcg of vitamin B12 for 6 months. Table 1 shows the evolution of hematological and biochemical parameters.

Vitamin B12 levels were measured in the mother which were lower than 50 pg/ml, identifying the etiology of the deficit in the infant. The mother's hemogram did not show anemia (Hb 12.7 g/dl) and the MCV and the rest of the hematological parameters were normal (88.9 fL, MCH 29.6 pg, platelets 232000 cells/mm^3, leukocytes 6700 cells/mm^3). Since there were no dietary restrictions to explain the deficiency, an anti-intrinsic factor and anti-parietal cell antibodies count was performed and was positive, leading to a diagnosis of pernicious anemia.

Discussion

Although megaloblastic anemia is the most characteristic feature of vitamin B12 deficiency, the identification of nonspecific initial symptoms is essential for early diagnosis[13].

As in the clinical case presented, persistent refusal to incorporate solid foods may be the initial onset of symptoms and usually precedes the development of hypotonia or clinically evident anemia. Initial symptoms may be detected early in the first trimester of life. Clinical manifestations in the infant may appear while the mother remains symptom-free and even without anemia[8,13].

Different authors have postulated that vitamin B12 deficiency should be included in the differential diagnosis of patients who present a failure in the acquisition of behaviors or regression of psychomotor development, as occurred in our case[7].

The rest of the elements that complete the clinical picture, such as growth retardation, vomiting, hypotonia, hyporeactivity, and megaloblastic anemia, usually appear in the evolution. Less frequently, the appearance of seizures and extrapyramidal symptoms have been described at the neurological level[13].

Regarding hematologic alterations, the presence of macrocytic anemia is the key element that frequently guides the diagnosis. This is an aregenerative anemia, which sometimes associates laboratory alterations compatible with hemolysis, such as increased lactate dehydrogenase (LDH) and bilirubin, as a consequence of ineffective erythropoiesis and secondary hemolysis of erythrocytes that complete their megaloblastic maturation[16]. The association with neutropenia, as in this case, is observed in 17-49% of patients and the concomitance of plateletopenia is also frequent with 44-80%[1]. In some series in developing countries, due to frequent nutritional deficiencies, megaloblastic anemia is the most frequent cause of pancytopenia, with higher figures than aplasia or leukemia[1].

The patient of this case did not present MRI alterations. Although it is not known whether there is an association between the initial changes in the MRI and the development of neurological sequelae, it was identified that most of the cases reported with intellectual disability in the evolution had brain atrophy at the time of diagnosis[11,13,15,17].

Usually, the first test performed to confirm the diagnosis is vitamin B12 levels. This value is reliable when it is observed at very low levels (less than 100 pg/ml), but it is not useful to rule out this deficit if it has values close to the lower limit of normality. The diagnosis should include blood or urine methylmalonic acid and homocysteine levels, which are increased in 98% of patients with clinical manifestations of vitamin

Table 1. Hematological and biochemical evolution of the infant after the start of treatment with vitamin B12

	Day 0	Day + 10	Day + 60
Hemoglobin (g/dl)	5.62	6.9	11.5
Mean Corpuscular Volume (fl)	91	86	72
Vitamin B12 (pg/ml)	50	2000	320
Urinary Methylmalonic Acid (umol/mmol of creatinine)	557	0	0
Plasmatic Homocysteine (mmol/l)	58	7	7

B12 deficiency.[6] These also allow monitoring the response to treatment, since their values decrease rapidly after the start of supplementation[1,4,6,18].

The etiology proposed for the deficit in the infant was nutritional deficiency linked to maternal deficit. The absence of a vegetarian diet in the mother, as well as the presence of a history of autoimmunity, such as hypothyroidism in our case, makes it necessary to rule out pernicious anemia as the cause of the maternal deficit[4]. The differential diagnosis in the infant is made with congenital alterations in the absorption or transport of vitamin B12 and should be considered mainly when there is no maternal deficiency[5].

In the pediatric age group, evidence-based treatment for this pathology has not been established[19]. The classic treatment, which was applied in this patient, consists of intramuscular administration of vitB12 at 1000 mcg/day dose for one week, then the same dose weekly for one month, and finally monthly doses until recovery[2,20]. Some studies show that oral vitamin B12 at high doses could be equally effective, even in patients with pernicious anemia[19,21]. In pediatric patients, where in most cases vitamin absorption is not affected, this treatment can be considered, however, in infants, food refusal and the presence of vomiting can make the treatment less reliable. Clinical practice guidelines are required regarding this pathology in the pediatric age group.

Currently, there are no clinical guidelines for the diagnosis of vitamin B12 deficiency in pregnancy[22]. There is growing interest in the inclusion of this vitamin deficiency in national neonatal screening programs. In a recently published study in Germany, the prevalence of this deficiency was 1/5355 newborns, with maternal deficiency of this vitamin being more frequent than the inborn errors of metabolism studied in most of the panels[23]. Several screening strategies have been evaluated, including second-line studies, generally a measurement of homocysteine and methylmalonic acid in patients who presented low methionine or elevated propionyl-carnitine (C3) levels in first-line studies for inborn errors of metabolism. Since it is a relevant health problem, there are adequate tests to evaluate it, there is an effective treatment, and its detection in the subclinical stage could prevent potentially irreversible damage. This disease meets Wilson and Jungner's criteria for inclusion in screening programs[25].

Conclusions

From the analysis of the clinical case, we conclude that early recognition of vitamin B12 deficiency in infants is key to preventing potentially irreversible neurological sequelae. The initial clinical manifestations, as in this case, can be non-specific leading to diagnostic delays. Vitamin B12 deficiency should be considered in the differential diagnosis of infants with feeding difficulties, growth retardation, and hypotonia.

Maternal pernicious anemia is an uncommon cause of vitamin B12 depletion in the infant. However, it should be considered in the case of children with megaloblastic anemia whose mothers do not follow vegetarian or vegan diets.

The clinical usefulness and costs of including screening for vitamin B12 deficiency in neonatal screening programs could be evaluated in depth in our sphere.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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