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Case Report

A mother's deficiency, a baby's challenge: vitamin B12 deficiency-related seizures and pancytopenia in an infant

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ABSTRACT

Anemia is prevalent in pediatric age and it stems from diverse factors. While iron deficiency is a common cause above six months of age, other nutritional deficits contribute to the disease burden. During pregnancy, anemia due to nutritional deficits is associated with adverse outcomes for the newborn. Precise diagnosis of dietary deficits in the pediatric population is vital to avert negative health consequences. We describe the case of a six-month-old exclusively breastfed infant with a mother having unspecified anemia under folic acid supplementation. The infant presented with neurological symptoms, including paroxysmal events and developmental regression. Laboratory analysis revealed pancytopenia and severe vitamin B12 deficiency. The patient's mother's serum level of vitamin B12 was also low and ant parietal cell antibodies were positive, suggesting maternal autoimmune gastritis. Treatment with hydroxocobalamin led to clinical and analytical improvement. Maternal deficiency is the major cause of cobalamin deficiency in infants. It is paramount to raise awareness to this issue to prevent its avoidable repercussions.

Keywords: Infant, Anemia, Cobalamin, B12, B12 deficiency, Pernicious anemia, Neurocognitive impairment, Pregnancy

INTRODUCTION

Anemia is a common diagnosis in infants, children and adolescents, with a vast spectrum of possible causes, depending on factors such as age, gender and geographical origin.[1]

Nutritional deficits, namely iron deficiency, are one of the most common causes of anemia in children older than six months, with exclusively breastfed infants being at higher risk.[2] Albeit being rarer in children growing up in developed countries, other nutritional deficits are responsible for a significant burden of disease particularly in developing countries.[3] Some authors have hypothesized that combined nutritional deficits may have a higher impact on hemoglobin production in a synergistic fashion.[4,5]

Maternal diseases and nutritional deficits arising during pregnancy can significantly impact the newborn's health, including anemia itself, which can be avoided with adequate screening. While the role of iron and folic acid deficiency in pregnancy and its impact on fetal and newborn health have been thoroughly investigated, other nutritional deficits may play a more obscure part.[6]

In the pediatric population, accurate diagnosis of dietary deficits is crucial to prevent negative health consequences, such as failure to thrive and neurocognitive impairment.[2]

CASE REPORT

We describe the case of a six-month-old female, exclusively breastfed, born of non-consanguineous parents. The mother had pre-existing, unspecified anemia, under sole folic acid supplementation, with no dietary restrictions. Pregnancy was unremarkable with a full-term normal delivery.

The patient presented to the neurology department with a one-month history of daily brief paroxysmal events characterized by unresponsiveness, upward deviation of the eyes and cervical extension, with sudden onset and ending, lasting less than five minutes. The mother also reported developmental regression, with loss of ability to sit up without support and hypotonia.

The physical examination revealed apathy, few movements of the four limbs (though symmetrical and harmonious) and axial hypotonia with poor cephalic control and inability to sit without support. Mild gross tremor of the hands was present when attempting to grasp objects and social smile and good eye contact were present. The neurological examination was otherwise unremarkable.

Laboratory analysis showed pancytopenia including severe normocytic normochromic nonregenerative anemia as well as severe neutropenia (Table 1). Blood smear showed rare hyper-segmented neutrophils and tear drop cells. Capillary blood gas analysis was normal. The patient was admitted and received a red blood cell concentrate.

Further etiological investigation revealed normal iron and folic acid reserves and a severe vitamin B12 deficiency with high levels of homocysteine and lactate dehydrogenase (LDH). Hemoglobin study by high-performance liquid chromatography (HPLC) was normal (HbA of 89,9%, fetal Hb of 7,7% and HbA2 of 2,4%). Infection screening and viral serologies for Epstein-Barr virus, cytomegalovirus and parvovirus B19 were negative. EEG and abdominal ultrasound were normal.

The patient's mother's serum level of vitamin B12 was low and ant parietal cell antibodies were positive, although her hemoglobin levels were normal. Both our patient's anti-parietal and anti-intrinsic factor antibody titers were negative, however.

The infant received a total of 3 daily doses of 1 000 mcg of hydroxocobalamin, subsequently raising vitamin B12 levels with clinical and analytical improvement. From the third day of hospitalization (DOH), she did not present paroxysmal events again.

She was discharged on the eighth DOH, maintaining only mild hypotonia. During follow-up, she remained asymptomatic and progressively improved her psychomotor development. Cerebral magnetic resonance imaging (MRI) showed an enlargement of the frontotemporal subarachnoid space which was interpreted as a non-pathological finding.

At three months of follow-up, most hematological and biochemical markers were normal, such as red cell and platelet count, as well as homocysteine and LDH, with the exception of *de novo* microcytosis and hypochromia, in the absence of iron deficiency. Genetic study diagnosed an heterozygous state for an alpha+ thalassemia.

Complementary food introduction was uneventful and one year later the patient had a diversified diet without restrictions.

Table 1: Laboratory data of the patient.

Variables	1st DOH	4th DOH	7th DOH	3 months follow-up	Reference range
Red cell count, (10^{12}/l)	2.04	3.11	3.31	5.57	3.7-5.3
Hb, (g/dL)	5.5	8.6	8.6	12,3	10.5-13.5
Hematocrit, (%)	16.6	24.7	26.5	37.8	33-39
MGV, (fl)	81.4	79.4	80.1	67.9	70-86
MGH, (pg)	27	27.7	26	22.1	23-31
RDW, (%)	29.1	20.9	20.9	13.8	11.5-15.5
Reticulocytes, (%)	0.65	0.44	9.55	1.03	0.5-2.5
White cell count, (/ul)	4680	5270	6030	7410	6000-16000
Neutrophils, (/ul, %)	180 (3.9)	250 (4.8)	700 (11.6)	2116 (29.1)	1000-7000 (40-75)
Platelet count, (/ul)	121 000	96000	103000	408000	200000-550 0000
Vitamin B12, (pg/ml)	<125	>6000	>6000	520	259-1578
Homocysteine, (µmol/l)	191.1	16.2	5.6	5.9	2.87-9.99
LDH, (U/l)	4998	4120	2176	299	163-452

Siglas, day of hospitalization (DOH), hemoglobin (Hb), lactate dehydrogenase (LDH), mean globular volume (MGV), mean globular Hb (MGH) and red cell distribution width (RDW).

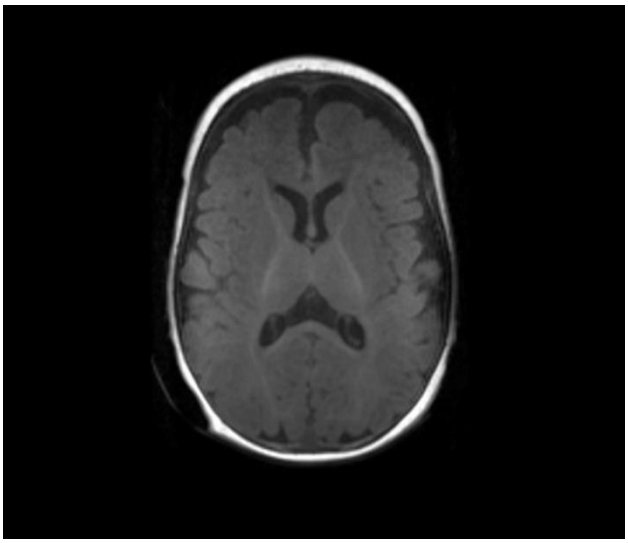

Figure 1: Cerebral magnetic resonance imaging.

DISCUSSION

Vitamin B12 plays a pivotal role in several reactions in the human body. In its absence, the development of megaloblastic anemia and other cytopenias, or even hemolysis, is common.[3]

In our case, despite severe B12 deficiency, the infant did not have macrocytosis. This should trigger an evaluation of concurrent deficiencies, which she did not have. It should be noted that supplementation with iron and folic acid may be necessary during ongoing medullary production recovery. Following treatment, our patient had microcytosis, leading to a diagnosis of alpha thalassemia trait, explaining the absence of macrocytosis at presentation.

Cobalamin also acts as a cofactor in homocysteine methylation to methionine and it participates in the conversion of methylmalonyl-CoA to succinate-CoA. With cobalamin lacking, odd chain fatty acids are synthesized and incorporated into the nerve sheaths, creating abnormal myelination.[7] The more common neurological symptoms of b12 deficiency in infancy appear to be apathy, developmental impairment, involuntary movements, hypotonia, and seizures, which were present in our case.

It is important to note that even in absence of anemia, neurological symptoms can be present.[8] Although data is scarce, it appears that developmental and cognitive delay is a common long-lasting effect of early vitamin B12 deficiency.[9,10]

Several studies on the neurological effects of cobalamin deficiency have reported MRI findings including cerebral atrophy, thinning of the corpus callosum, delayed myelination and ventriculomegaly.[11] In our case, only enlargement of the fronto-temporal subarachnoid space was described, which is typically considered benign, but may also be associated with some extent of cerebral atrophy.

However, throughout follow-up, there were no persistent neurological issues such as developmental delays or behavioral problems. Because of the favorable outcome, regarding neurological and developmental issues and the need for sedation to perform the exam, cranial MRI was not repeated during follow-up.

While there is no gold standard in defining cobalamin deficiency, it appears that even borderline levels (200-300 pg/ml) may be associated with neurological symptoms. Consequently, levels below 300 pg/ml should prompt supplementation.[12]

Maternal deficiency constitutes the major cause of cobalamin deficiency in infants. Vitamin B12 deficiency is a global concern affecting 10% to 50% women of childbearing age and pregnant women, from across diverse populations and ethnicities.[13,14] The risk is particularly high among vegetarians or vegan mothers, since it is exclusively present in animal products. This is of significant concern, especially for exclusively breastfed infants in developing countries where adequate supplementation is lacking. In infants, another leading cause for vitamin B12 deficiency is the impaired absorption of cobalamin from the final segment of the small intestine, caused by pernicious anemia or Biermer's disease in the mother, as seen in our case.

Even in the presence of chronic gastritis, it is not uncommon to come across mothers who are asymptomatic.[15] Cobalamin needs to bind to an intrinsic factor, which is produced by gastric parietal cells, and attacked by anti- intrinsic factor antibodies in this disease.

CONCLUSION

While iron and folate supplementation are widely recognized as integral components of routine care in pregnant women, cobalamin is not usually evaluated and supplementation is often overlooked.

The first step to ensure adequate pediatric care is to secure quality obstetric surveillance. Therefore, it’s imperative to enhance both public and medical professionals' awareness regarding symptoms, even in the absence of hematological findings, in order to prevent severe but avoidable repercussions.

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