

Megaloblastic anemia due to combined deficiency of Vitamin B12 and folic acid in an 8-month-old male child: A case report

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ABSTRACT

A combined deficiency of vitamin B12 and folic acid is a rare condition that can cause megaloblastic anemia, pancytopenia, and neurological manifestations in infants. It can result from maternal dietary deficiency or malabsorption of these vitamins during pregnancy or lactation. We report the case of an 8-month-old male infant who presented with features of a combined deficiency of vitamin B12 and folic acid. His serum vitamin B12 and folate levels were low while serum ferritin, fibrinogen, triglycerides, lactate, ammonia, pyruvate, intrinsic factor antibody assay, and autoimmune workup were normal. He was treated with vitamin B12, oral iron, and folic acid supplementation and showed a prompt improvement in clinical picture and blood parameters within 7 days of therapy. This case highlights the importance of early diagnosis and treatment of a combined deficiency of vitamin B12 and folic acid in infants to prevent irreversible neurological damage and improve the outcome.

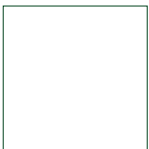
Key words: Vitamin B12 deficiency, Folic acid deficiency, Megaloblastic anemia, Pancytopenia

Megaloblastic anemia is characterized by the presence of enlarged red blood cells (macrocytes) with abnormal nuclear maturation in both peripheral blood and bone marrow. This condition arises due to impaired DNA synthesis stemming from deficiencies or malfunctions in either vitamin B12 or folic acid. These vitamins serve as crucial cofactors for the production of thymidine monophosphate, which is necessary for DNA replication. In addition, vitamin B12 plays a role in converting methylmalonyl-CoA to succinyl-CoA, which is vital for fatty acid metabolism. Insufficient levels of either vitamin can result in the accumulation of toxic metabolites such as homocysteine and methylmalonic acid (MMA), leading to potential neurological damage. The clinical presentation of megaloblastic anemia varies in severity based on the extent of deficiency and duration of exposure. Common symptoms encompass fatigue, weakness, pallor, glossitis, anorexia, nausea, vomiting, diarrhea, weight loss, abdominal pain, jaundice, hepatosplenomegaly, paresthesias, ataxia, dementia, depression, psychosis, seizures, and coma [1-3]. Laboratory findings typically reveal macrocytosis, elevated mean corpuscular volume (MCV), low reticulocyte count (<1%), pancytopenia, hypersegmented neutrophils, ovalocytes, Howell-Jolly bodies, basophilic stippling, and cabot rings [1,2,4]. Bone marrow

aspiration demonstrates erythroid hyperplasia with normoblastic to megaloblastic maturation, dyserythropoiesis (nuclear-cytoplasmic asynchrony, multinucleation, karyorrhexis), and granulocytic abnormalities (left shift, increased azurophilic granules, nuclear hypersegmentation, ringed nuclei). Serum levels of vitamin B12 and folate are diminished, while serum ferritin, fibrinogen, and triglycerides remain normal or elevated [1,2,4]. In cases of vitamin B12 deficiency, serum homocysteine and MMA levels are elevated, whereas only homocysteine shows elevation in cases of folic acid deficiency [4,5]. While megaloblastic anemia seldom presents clinically in infancy, timely assessment, early detection, and treatment are imperative to avert lasting neurological impairment and improve the prognosis.

CASE REPORT

An 8-month-old male infant presented with low-grade intermittent fever, irritability, multiple episodes of non-bilious, non-projectile vomiting, poor oral intake for 2 weeks, (after 7 months). He was the first child of a non-consanguineous marriage, born at 39 weeks with an uneventful antenatal and perinatal period. He received immunizations up to 6 months of age and was exclusively breastfed until then, supplemented with a cereal-based diet afterward. His anthropometric measurements and developmental assessment were appropriate for his age.

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Physical examination showed stable vitals, pallor, graying of hair, hyperpigmentation in the neck, axilla, groin, palms and hepatomegaly (3 cm below the costal margin), graying of hair, and hyperpigmentation in the neck, axilla, groin, and palms.

Routine laboratory investigations revealed pancytopenia, macrocytosis, elevated MCV, hypoalbuminemia, and a low reticulocyte count (Table 1). A peripheral blood smear showed dimorphic anemia, severe leukopenia, thrombocytopenia, and >5% hypersegmented neutrophils. Bone marrow aspirate revealed erythroid hyperplasia with normoblastic to megaloblastic maturation, dyserythropoiesis in 20–25% of erythroid cells (nuclear-cytoplasmic asynchrony, multinucleation, karyorrhexis), and granulocytic abnormalities (left shift, increased azurophilic granules, nuclear hypersegmentation, ringed nuclei). Serum vitamin B12 and folate levels were low while serum ferritin, fibrinogen, triglycerides, lactate, ammonia, pyruvate, intrinsic factor antibody assays, and autoimmune workups were normal.

He developed febrile neutropenia during the hospital stay and was treated with intravenous antibiotics and a blood transfusion, diagnosed as a combined vitamin B12 and folic acid deficiency, and treated with intramuscular methylcobalamin (500 mcg/day), oral iron (3 mg/kg/day), and folic acid (15 mcg/kg/day). Rapid improvement occurred within 7 days of therapy. The child's activity and oral intake improved, attributed to nutritional deficiency. Discharged after seven doses of intramuscular methylcobalamin and continued oral vitamin B12 supplementation.

DISCUSSION

This case depicts a rare occurrence of combined vitamin B12 and folic acid deficiency in an infant presenting with megaloblastic anemia and pancytopenia. The infant, exclusively breastfed for 6 months and later on a cereal-based diet, developed symptoms at 8 months, consistent with reported onset in similar cases [6-8]. The mother, a vegetarian, had presumed a low dietary intake of these vitamins. No vitamin supplements were given to the baby in the first 6 months. He exhibited typical features of combined vitamin B12 and folic acid deficiency, including pallor, hepatomegaly, graying of the hair, hyperpigmentation of the skin, macrocytosis, high MCV, low reticulocyte count, pancytopenia, hypersegmented neutrophils, erythroid hyperplasia, dyserythropoiesis, and granulocytic abnormalities. He presented with low serum levels of vitamin B12 and folate, while other parameters including ferritin, fibrinogen, triglycerides, lactate, ammonia, pyruvate, an intrinsic factor antibody assay, and an autoimmune workup were normal. Treatment with vitamin B12 and folic acid supplementation, along with supportive measures, led to a positive response.

Diagnosing combined vitamin B12 and folic acid deficiency in infants is challenging due to its rarity and similarity to other conditions such as Fanconi anemia, Diamond-Blackfan anemia, congenital dyserythropoietic anemia, congenital sideroblastic anemia, congenital infections, hemophagocytic lymphohistiocytosis, or leukemia. A thorough assessment, including history, physical examination, laboratory investigations,

Table 1: Laboratory investigations of the patient

Laboratory Parameter	Value at	Value at	Normal range
	admission	D7	
Hemoglobin (g/dL)	7.3	9.5	10.0–14
WBC count (cells/mcL)	990	11,690	6000–17,000
Platelet count (cells/mcL)	42,000	178,000	150,000–450,000
Mean corpuscular volume (fL)	98.1	96.7	72–84
Mean corpuscular hemoglobin (pg)	32.9	31.7	25–29
Serum albumin (g/dL)	2.3		3.5–5
Reticulocyte count (%)	0.8	2.8	0.5–2.5
Serum vitamin B12 (pg/mL)	135	201	211–946
Serum folic acid (ng/mL)	0.78	4.2	7.1–23
Serum ferritin (ng/mL)	242	321	30–400
S. Iron (µg/dL)	26		49–181
Iron binding capacity (µg/dL)	300		261–462
Transferin Saturation (%)	8.67		
Serum fibrinogen (mg/dL)	317		200–400
Serum triglycerides (mg/dL)	80		<150
Serum lactate (mmol/L)	1		<2.2
Serum ammonia (mcg/dL)	35		<50
Serum pyruvate (mg/dL)	0.6		<1.2

and response to therapy, is crucial for narrowing down the differential diagnosis. Confirmation typically involves measuring serum homocysteine and MMA levels, although these tests may not be widely available in resource-limited settings [1].

Treating combined vitamin B12 and folic acid deficiency in infants involves administering both vitamins orally or through injection, along with supportive therapies. The recommended Vitamin B12 regimen consists of 500 mcg intramuscularly daily for a week, followed by 100 mcg weekly for 4 weeks, then 100 mcg monthly for life or until oral supplementation is feasible. For folic acid, the recommended oral dose is 15 mcg/kg/day for 4 months, then 5 mcg/kg/day for life or until oral supplementation is viable. Iron supplementation at 3 mg/kg/day orally for 3 months or until iron stores are replenished is also advised. Treatment should commence promptly, regardless of diagnostic confirmation, and should be monitored through clinical and blood parameter assessments, continuing indefinitely or until the underlying cause is addressed [1].

Early diagnosis and prompt treatment offer a favorable prognosis for megaloblastic anemia in infants. Delayed intervention, however, can lead to irreversible neurological damage and adverse outcomes, including developmental delay,

hypotonia, seizures, coma, cerebral atrophy, demyelination, axonal degeneration, and neuropathy [9-11]. These complications stem from the accumulation of toxic metabolites, such as homocysteine and MMA, impairing neuron and myelin function [10,11]. Despite treatment, these neurological complications may persist. Therefore, preventing deficiency through sufficient maternal intake during pregnancy and lactation, along with providing vitamin supplements to infants until complementary feeding begins, is essential [1,6,7].

Megaloblastic anemia primarily arises from nutritional deficiency, vitamin B12, or folic acid malabsorption [4,5]. Vitamin B12 is abundant in animal products, while folic acid is found in green leafy vegetables, fruits, nuts, beans, and fortified cereals. Adult daily requirements are 2.4 mcg for B12 and 400 mcg for folic acid, with infants needing 0.4 mcg and 65 mcg, respectively. B12 absorption occurs in the terminal ileum with intrinsic factor secretion, while folate absorption happens in the jejunum after conversion to tetrahydrofolate. Malabsorption of B12 can occur due to pernicious anemia, gastrectomy, ileal resection, Crohn's disease, bacterial overgrowth, fish tapeworm infection, or specific medications. Folate malabsorption may result from conditions such as celiac disease, tropical sprue, inflammatory bowel disease, or medications inhibiting DHFR or folate absorption.

A combined deficiency of vitamin B12 and folic acid can lead to megaloblastic anemia, posing severe hematological and neurological risks for infants. Stemming from maternal dietary deficiency or malabsorption during pregnancy or lactation, this rare condition depletes maternal stores crucial for fetal growth and development. With increased secretion into breast milk, infants rely on maternal vitamin supplies for their first 6 months. If maternal levels are insufficient, infants may experience symptoms such as failure to thrive, irritability, poor feeding, vomiting, diarrhea, pallor, hepatosplenomegaly, graying of the hair, hyperpigmentation of the skin, developmental delay, hypotonia, seizures, and coma [6-8].

Diagnosing a combined deficiency of vitamin B12 and folic acid in infants relies on clinical presentation, laboratory findings, and therapeutic response. Treatment involves parenteral or oral administration of both vitamins, supplemented by supportive measures such as blood transfusions and antibiotics [6-8]. Prognosis is favorable with early diagnosis and prompt treatment, but delayed intervention can result in irreversible neurological damage and poor outcomes [9-11].

CONCLUSION

Combined deficiency of vitamin B12 and folic acid in infants, while rare, presents as a treatable cause of megaloblastic anemia

and pancytopenia. It often stems from maternal dietary deficiency or malabsorption during pregnancy or lactation, with clinical severity varying based on deficiency degree and duration of exposure. Diagnosis relies on clinical presentation, laboratory findings, and treatment response. Therapy involves parenteral or oral administration of vitamin B12 and folic acid, supplemented by measures such as blood transfusions and antibiotics. Prognosis is generally favorable with prompt diagnosis and treatment, yet delayed intervention can lead to irreversible neurological damage and poor outcomes.

KEY MESSAGE

In cases of megaloblastic anemia and pancytopenia in infants, it is imperative to entertain the prospect of combined Vitamin B12 and folic acid deficiency. Swift diagnosis and intervention are paramount to forestall irreversible neurological harm and improve outcomes.

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