



Life Threatening Anemia with Hemolysis, Thrombocytopenia and Brain Atrophy due to Vitamin B12 Deficiency

B12 Vitamini Eksikliğine İkincil Hemoliz Bulguları Olan Yaşamı Tehdit Eden Anemi, Trombositopeni ve Beyin Atrofisi

Ebru Yılmaz Keskin¹, Hilal Kabasakal², Hülya İnce³, Mahmut Keskin⁴, Mahir İğde², Banu Gülcan Öksüz²

¹Samsun Education and Research Hospital, Pediatric Hematology and Oncology, ² Pediatrics, ⁴ Pediatric Cardiology, SAMSUN

³Samsun Maternity and Child Health Hospital, Pediatric Neurology, SAMSUN

CukurovaMedicalJournal 2014;39(4):900-904.

ABSTRACT

Megaloblastic anemia due to vitamin B12 deficiency is rare in infancy. It usually occurs in exclusively breast-fed infants born to vitamin B12-deficient mothers. We report a one-year-old female infant with initial diagnosis of leukemia who was found severely vitamin B12-deficient secondary to maternal deficiency. She had marked neurodevelopmental retardation, and presented with life-threatening anemia, findings of hemolysis, thrombocytopenia and cerebral atrophy on magnetic resonance imaging.

Key Words: Vitamin B12 deficiency hemolysis, thrombocytopenia, growth failure, neuromotor retardation

ÖZET

Süt çocukluğu döneminde B12 vitamini eksikliğine bağlı megaloblastik anemi nadirdir. Bu durum genellikle, annesinde B12 depoları yetersiz olan ve sadece anne sütü ile beslenen bebeklerde görülür. Kendisinde başlangıçta lösemi tanısı düşünülen, ancak tetkikler sonrasında, annedeki eksikliğe ikincil ağır B12 eksikliği olduğu bulunan bir yaşındaki olgu sunulmuştur. Olguda belirgin nörogelişimsel gerilik, yaşamı tehdit eden anemi, hemoliz bulguları, trombositopeni ve cranial manyetik rezonans görüntülemeye serebral atrofi mevcuttu.

Anahtar Kelimeler: B12 vitamini eksikliği, hemoliz, trombositopeni, büyüme geriliği, nöromotor gerilik

INTRODUCTION

Vitamin B12 which is present only in foods of animal origin such as meat, egg, fish and milk is essential for the development and myelination of the central nervous system in the early years of life. As it is required for the conversions of methylmalonic acid (MMA) to succinyl CoA and homocysteine (hcy) to methionine, its deficiency leads to the accumulation of MMA and hcy, and

the onset of reversible bone marrow failure and demyelinating central nervous system disorder^{1,2}.

Breast-feeding in infants born to vitamin B12-deficient mothers is the main cause of vitamin B12 deficiency during infancy which may manifest as failure of brain development in addition to overall growth and development, usually between 4 and 6 months of age¹. We report an exclusively breast-

fed vitamin B12-deficient infant presenting with life-threatening anemia with findings of hemolysis, and thrombocytopenia initially thought to have leukemia.

CASE

A one-year-old female infant, born to non-consanguineous parents was referred with the initial diagnosis of leukemia, as she had mild hepatomegaly, was found severely anemic, and had thrombocytopenia. The exclusively breast-fed infant was admitted due to loss of appetite during the last few weeks. She was born spontaneously at term with 3500 g weight as the third child of the mother with low socioeconomic status consuming only rarely food of animal origin. In the physical examination, the infant was pale, hypoactive, her hair looked fine and brittle, and mild icterus in her sclerae and hyperpigmentation in the flexor surfaces of both her upper and lower extremities

were noted. Her weight, length and head circumference were 7200 g (<P3), 69 cm (<P3) and 44 cm (P3-10), respectively, indicating growth retardation and microcephaly. She was tachycardic (heart rate: 160/min), and the liver was 4.5 cm below the costal margin palpable.

The laboratory findings of the patient and her mother are presented in Table 1. Peripheral blood smear displayed marked anisocytosis and poikilocytosis with macrocytes and small, fragmented red cells (schistocytes) and occasional normoblasts mimicking microangiopathic haemolytic anemia in addition to hypersegmentation of the nuclei of the neutrophils. Serum iron parameters were normal, and direct Coombs testing was negative. In the urinary examination, no proteinuria was present, excluding Imlerslund-Grasbeck syndrome. Bone marrow examination was initially not done due to refusal of the mother.

Table 1. Hematological data of the patient (at admission and during follow-up) and her mother.

	At admission	4 th day	5 th day	7 th day	2 nd week	4 th week	Mother (At admission)
Hb, g/dl	2.6*	9.4	8.9	9.6	11.9	11.1	13.3
MCV, fl	101.1	79.5	80.7	85.8	89.0	86.0	90.7
MCHC, g/dl	29.5	31.9	31.8	31.3	31.1	31.8	32.4
RDW, %	38.2	21.8	23.7	25.4	17.2	15.0	13.3
WBC /mm ³	15,370	13,770	11,160	12,920	19,700	14,200	11,650
Plt /mm ³	118,000	27,000	20,000	263,000	982,000	299,000	445,000
IB, mg/dl	2.46	1.69	n.a.	n.a.	0.25	0.23	n.a.
LDH, U/l	1,233	1,002	n.a.	n.a.	726	531	n.a.
VitB12, pg/ml (192-982)	<150	>1,000	n.a.	n.a.	n.a.	n.a.	258
Folate, ng/ml (3-17)	12,8	n.a.	n.a.	n.a.	n.a.	n.a.	6.53
Hcy, µmol/l (<12)	>50.0	17.7	n.a.	3.2	n.a.	n.a.	15.8

Hb: hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; WBC: white blood cells; Plt: platelets; IB: indirect bilirubin; n.a.: not available; LDH: lactate dehydrogenase; VitB12: vitamin B12; Hcy: homocysteine.

*The patient received packed erythrocyte transfusions at admission.

Echocardiography ordered due to chronic anemia was normal. In Denver II developmental testing, the infant showed delayed developmental milestones in each category assessed, the overall retardation rate being 32%. Cranial magnetic

resonance imaging (MRI) displayed prominence of the extra-axial cerebrospinal fluid space in the frontal and temporal regions and deepening of the cortical sulci consistent with cerebral atrophy (Fig.).



Fig.: Cranial MRI of the infant showing frontal and frontoparietal cerebral atrophy

In the diagnosis, nutritional vitamin B12 deficiency secondary to maternal deficiency was thought. The infant received packed erythrocyte transfusions, and intramuscular vitamin B12 (100 mcg cyanocobalamin daily for two days, followed by 1 mg daily for ten days, and then once monthly until 2 years of age) was begun. Additionally, formula was introduced into her diet due to malnutrition, and oral iron was started at the second week of B12 administration due to the expected increase in iron utilization. At the 5th day of vitamin B12 treatment, the platelet count dropped to 20,000/mm³, upon which bone marrow aspiration was performed after informed consent of the mother was obtained. The examination excluded leukemia. At the 7th day of treatment, platelet count increased to normal range (263,000/mm³), and the patient was discharged.

The follow-up hematological data of the patient are shown in Table 1. After treatment, she showed marked acceleration in neurological and

growth development, displaying interest toward her surroundings, increase in appetite with subsequent weight gain and improvement in motor activities, although she was still falling behind the normal milestones in Denver II testing at 16 months of age. She is still being followed-up regularly.

DISCUSSION

The infant presented here was initially thought to have leukemia due to marked anemia, thrombocytopenia and hepatomegaly. Further investigation revealed severe vitamin B12 deficiency to be the underlying cause, however. Indeed, severe B12 deficiency is well known to cause thrombocytopenia or leukopenia in addition to megaloblastic anemia³⁻⁶. Notably, our case presented with life-threatening anemia, having an initial Hb value of 2.6 g/dl.

In the peripheric smear of the patient, findings mimicking microangiopathic hemolytic anemia were seen. In accordance with this, she had elevated

lactate dehydrogenase (LDH) and indirect bilirubin levels which decreased significantly after vitamin B12 treatment (Table 1). Findings of hemolysis in our patient probably occurred due to intramedullary destruction of erythrocytes (ineffective erythropoiesis)^{2,7}. Besides, high levels of hcy secondary to B12 deficiency may have contributed to hemolysis by causing microangiopathic changes⁷. In our case, findings in the peripheric smear associated with hemolysis resolved completely, and hcy levels decreased to normal after B12 treatment. Although hemolytic anemia with thrombocytopenia and schistocytosis is often suggestive of hemolytic uremic syndrome (HUS) in children, physicians should be aware of the possible occurrence of these features in the context of B12 deficiency. As our patient's clinical (cardiovascular) status was relatively well considering her very low Hb level, we did not think initially an acute disorder like HUS as the probable underlying disorder.

We could not perform bone marrow aspiration initially due to the refusal of the mother. However, platelet count decreased to as low as 20,000/mm³ at the 5th day of treatment, upon which the mother agreed with the procedure. As megaloblastic changes disappear rapidly following B12 therapy, we did not see any megaloblastic changes, however, leukemia could be excluded. At the 7th day of therapy, platelet count was found normal, whereas in the laboratory examination done 2 weeks after therapy, thrombocytosis (982,000/mm³) was evident. Reactive thrombocytosis may occur in vitamin B12-deficient individuals following B12 therapy⁸.

Growth and neurodevelopmental retardation, hyperpigmentation, weakness, irritability, lethargy, hypotonia, hyporeflexia, convulsions and coma are among the most common findings of infantile B12 deficiency^{1-3,9,10}. Replacement with vitamin B12 usually reverts the related neurological symptoms, and many infants recover fully. However, in cases with severe and prolonged duration of deficiency, irreversible neurological deficits may occur despite

therapy highlighting the importance of early diagnosis and treatment. In our patient, replacement with vitamin B12 enabled rapid improvement in her neurodevelopmental status, although the Denver II testing was not completely appropriate for her age 4 months after B12 administration.

Most infantile cases of B12 deficiency are exclusively breast-fed babies born to mothers with deficient B12 stores. Maternal vitamin B12 deficiency usually develops secondary to pernicious anemia or a strict vegetarian diet. In our one-year-old case, insufficient consumption of animal origin products by the mother with low socioeconomic status and being exclusively breast-fed were thought as the cause of B12 deficiency in the infant. Notably, her mother had only mild B12 deficiency, as evidenced by slightly increased plasma hcy level. The absence of any specific hematological and neurological findings in the mothers of exclusively breast-fed, B12-deficient infants who themselves may in fact be severely affected may contribute to the underrecognition of this condition in infancy.

CONCLUSION

Neonates born to families with low income are particularly at high risk of developing vitamin B12 deficiency. The infant presented here is in fact one in the visible part of the iceberg. We believe that many mild, moderate (or even severe) cases are not recognized, and (almost) normal serum B12 levels after the beginning of weaning may contribute to the escape of the diagnosis. To prevent this disorder with potentially irreversible neurological sequelae, pregnant women should be supplemented with adequate doses of vitamin B12, and the supplementation be continued throughout the period of lactation.

REFERENCES

1. Honzik T, Adamovicova M, Smolka V et al.. Clinical presentation and metabolic consequences in 40

- breastfed infants with nutritional vitamin B12 deficiency--what have we learned? Eur J PaediatrNeurol 2010;14:488-95.
2. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med 2013;368:149-60.
 3. Demir N, Koc A, Ustyol L, et al.. Clinical and neurological findings of severe vitamin B12 deficiency in infancy and importance of early diagnosis and treatment. J Paediatr Child Health 2013;49:820-4.
 4. Sekhar J, Stabler SP. Life-threatening megaloblastic pancytopenia with normal mean cell volume: Case series. Eur J Intern Med 2007;18:548-50.
 5. Yenicesu I. Pancytopenia due to vitamin B12 deficiency in a breast-fed infant. PediatrHematolOncol 2008;25:365-7.
 6. Citak FE, Citak EC. Severe vitamin B12 deficiency in a breast fed infant with pancytopenia. J Trop Pediatr 2011;57:69-70.
 7. Acharya U, Gau JT, Horvath W et al..Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: three case reports and review of the literature. J HematolOncol 2008;1:26.
 8. Chandra J, Jain V, Narayan S et al.. Tremors and thrombocytosis during treatment of megaloblastic anaemia. Ann Trop Paediatr 2006;26:101-5.
 9. Demir N, Dogan M, Koc A et al.. Dermatological findings of vitamin B12 deficiency and resolving time of these symptoms. CutanOculToxicol 2013.Doi:10.3109/15569527.2013.861477.
 10. Quentin C, Huybrechts S, Rozen L et al.. Vitamin B12 deficiency in a 9-month-old boy. Eur J Pediatr 2012;171:193-5.

YazışmaAdresi / Address for Correspondence:

Dr.Ebru Yılmaz Keskin
Samsun Education and Research Hospital
Department of Pediatric Hematologyand Oncology
55100 İlkadım, SAMSUN
E-mail: ebruyilmaz81@hotmail.com

Geliştarihi/Received on : 05.03.2014

Kabul tarihi/Accepted on: 14.04.2014