

Megaloblastic anemia with pancytopenia in infancy: a rare entity

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Abstract

Megaloblastic anemia in infants present with generalized weakness, failure to thrive, or irritability. Diagnosis is usually centered on complete blood count and peripheral smear, which may show macrocytes, hyper segmented neutrophils, reticulocytopenia and a raised mean corpuscular volume (MCV >100 fl). Pancytopenia has also been noted. We report an exclusively breast fed six months old female child who presented with irritability, poor feeding and developmental delay. Her initial blood picture revealed pancytopenia, with normal MCV. Vitamin B12 levels were found to be reduced. Maternal levels of Vitamin B12 were also found to be borderline low. The child was treated as per protocols and improvement was evidenced with return of hematological parameters to normal and gradual advancement of milestones. The authors wish to underscore the importance of Megaloblastic anemia as an important and rare cause of anemia in infancy. Early recognition and treatment are imperative to prevent catastrophic sequelae.

Keywords- Infants, Megaloblastic anemia, Pancytopenia

Introduction

Vitamin B12 is an important component of body metabolism. Nutritional deficiency of the same may seem trivial and is a known causative factor, but in developing countries, where maternal deficiency of Vitamin B12 invariably spells deficiency in the

infant as well, the consequences may be catastrophic. We report one such case of megaloblastic anemia with sequelae in infancy, due to maternal deficiency of Vitamin B12.

Case Presentation

We present the case of a 6 months 20-day old female child, who presented to the Pediatric Outpatient Department with complaints of irritability, reduced feeding and multiple episodes of vomiting per day for 3 months prior to the presentation. Clinical examination revealed pallor and hepatomegaly.

Developmental assessment revealed that the child had Global Developmental Delay. Anthropometric parameters (weight, length and head circumference) were below third centile for age. Laboratory examination revealed Hemoglobin-5.5g/dL, White Blood Cell count-3500/mm³, Platelet-87000/mm³, MCV-97 fL(normal level 72-88 fL), MCH-32.2 pg (normal level 24-30 pg), Reticulocyte count-1.2% and LDH-2825 U/L. The peripheral blood examination reported that red blood cells were macrocytic and neutrophils were hyper segmented with pancytopenia (Fig. 1,2).

Bone marrow aspiration revealed hypercellular marrow with M:E ratio of 0.5:1, erythroid hyperplasia with megalonormoblastic reaction (Fig. 3). Serum Vitamin B12 level was found to be 65 pg/mL (normal level 211-911pg/mL). The maternal Serum Vitamin B12 level was found to be 213.7pg/mL (normal level 211-911pg/mL).

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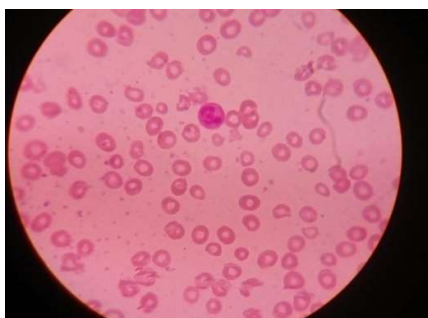


Fig-1: Depiction of microcytosis and pancytopenia



Fig-2: Hypersegmented neutrophils in blood film



Fig-3: Hypercellular marrow and erythroid hyperplasia

The child was treated with 250mcg Vitamin B12 intramuscularly once a week for 4 weeks followed by oral Vitamin B12 supplementation. Following treatment, hemoglobin levels and other relevant hematological parameters rapidly improved, preceding a gradual clinical improvement. Further follow up revealed improvement in all domains of development, although milestones were still delayed, compared for age.

Discussion

Vitamin B12 (Cobalamin) has been attributed to play a huge role in human intermediary metabolism. It is paramount, for the conversion of methyl-malonyl-CoA to succinyl-CoA (a compound metabolized by the Krebs cycle to produce energy) and also to ensure the optimal activity of an enzyme called methionine synthase, that catalyzes the methylation of homocysteine, culminating in the formation of the essential amino acid methionine [1]. Vitamin B12 deficiency, therefore, leads to the accumulation of methylmalonic acid and homocysteine, and these heralds the beginning of various clinical, hematological, neurological and psychiatric manifestations in the child [2].

Cobalamin also functions as a cofactor for methylmalonyl CoA mutase, the enzyme that plays a major role in the conversion of methylmalonyl CoA to succinyl CoA, which is a prerequisite for the metabolism of various odd-chain fatty acids and also for purine and pyrimidine synthesis. Methylmalonic aciduria and defective amino acid synthesis results from the lack of this essential cofactor, manifesting as pancytopenia, metabolic acidosis as well as hypotonia [3]. Various factors such as inborn errors of metabolism

and nutritional problems can result in deficient levels of Vitamin B12 in infancy. The most frequent inborn error, that has been described, is cobalamin C disorder, which has been attributed to a mutation of the *MMACHC* gene [4]. Nutritional causes are however more common and most infants found to have B12 deficiency have been noted to be born to mothers with low vitamin B12 levels and who have been exclusively breastfed.

It follows then, that the breast milk of vegan mothers is frequently poor in vitamin B12, and their newborn infants run the possibility of having low vitamin stores [1]. Rarer causes of deficiency include the surgical removal of the stomach and /or distal ileum, autoimmune gastritis, Crohn disease, exocrine pancreatic insufficiency and Whipple disease[5].

Vitamin B12 deficiency has now been recognized as an important cause of infant morbidity and mortality throughout the world, and this is more so in the Indian subcontinent, Mexico, Central America and certain regions of Africa [6]. Infantile Vitamin B12 deficiency is important to recognize because early recognition and

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treatment can prevent potentially fatal neurological sequelae [7]. A positive co-relation has been found between maternal and breastfed infant vitamin B₁₂ deficiency linked to deficient B₁₂ levels in breast milk. Specker and colleagues did postulate that vitamin B₁₂ milk concentrations less than 360 pmol/L, approximately corresponding to a maternal serum B₁₂ of less than 300 pmol/L, could potentially result in vitamin B₁₂ deficiency in infancy [5]. It has been stated previously that the offspring of women with low vitamin B₁₂ levels during the period of pregnancy and lactation may have reduced stores of the vitamin at birth [8]. Such children run the risk of developing signs of vitamin B₁₂ deficiency during infancy, generally not prior to the fourth month of life, although neonatal cases have been reported[9].

Childhood vitamin B₁₂ deficiency appears to be more significant than previously thought, and has been considered a rarity, especially in infancy [10]. It has been stated previously that approximately one-third of low-income women and children in Guatemala have deficient (<148 pmol/L) or marginal (148–220 pmol/L) levels of plasma vitamin B₁₂, and that the lowest levels bear a stark relation to abject growth and development [11]. In the Indian population, individuals tend to be partial to a vegetarian diet; therein vitamin B₁₂ deficiency during pregnancy is common[12]. It has been reported that the infants of such mothers seem to be affected by a syndrome characterized by mild developmental regression and alterations in skin pigmentation[13].

A significant question at this juncture would be the apparent lack of observable signs and symptoms among deficient pregnant mothers. This may be attributable to the fact that due to the consumption of a diet inclusive of large amounts of vegetables that contain high folate concentrations, the hematological effects of vitamin B₁₂ deficiency may be masked. Moreover, the neuropsychiatric manifestations of vitamin B₁₂ deficiency are usually mild in adolescents and adults, and stand a high chance of being overlooked[1]. On the contrary, breastfed infants born to vegan mothers develop substantial neurological damage. Importantly, these may persist and result in long-term cognitive and developmental delay irrespective of adequate therapy and the complete disappearance of hematological problems[14]. The clinical features of infantile vitamin B₁₂ deficiency depends on the severity of the deficient state. Many children may be asymptomatic, some may present with megaloblastic anemia, diagnosed only via hematological profile[15]. Symptomatic infants usually

present between 2 and 12 months of age, when neonatal stores of vitamin B₁₂ have been depleted and dietary sources prove inadequate. Typical symptoms include poor feeding, weight loss and irritability. Other reported features include glossitis and susceptibility to infections [16]. The neurological manifestations are profound and include irritability, apathy, lethargy and regression of the gross motor developmental milestones. Routine plotting of the head circumference on follow up visits will allow the noting of receding values of the same, indicative of regression of brain growth.

Gradually, children progress to hypotonia with hyperreflexia, and also exhibit choreo-athetoid movements. Demyelination, delayed myelination, impaired methylation and lactate accumulation in the peripheral nerves, spinal cord and cerebrum have all been hypothesized as being responsible for these profound neurological manifestations, although no clear putative factor has been recognized[17].

The diagnosis of vitamin B₁₂ deficiency in infants may be confirmed by determining the serum vitamin B₁₂ concentration, although it is not an absolute requirement for initiating treatment. Bone marrow studies may also confirm the diagnosis [5]. Treatment regimens for Vitamin B₁₂ deficiency include both intramuscular and oral replacement, although oral supplementation in infants is fraught with inherent issues such as regurgitation and vomiting. The British Columbia Guidelines and Protocols Advisory Committee have recommended oral B₁₂ replacement therapy of 1000 µgdaily [5].

As was observed in our patient, treated vitamin B₁₂ and iron deficient infants tend to improve dramatically, the hematological values returning quickly to the normal state, and the neurological signs thereby progressively decrease[1]. That being said, the severe cases described thus far have also identified permanent sequelae[14]. In our case, it was also imperative to address the issue of borderline low maternal levels of Vitamin B₁₂, that required extensive dietary planning.

Conclusion

The authors wish to use this case to highlight the varied signs, symptoms and complications of Vitamin B₁₂ deficiency in infancy, as well as the need to consider vitamin B₁₂ deficiency in infants presenting with severe anemia even if their hematological parameters may not indicate megaloblastic anemia, attributable to the concomitant presence of iron deficiency that may modify the presentation.

Editorial

What this study adds to existing knowledge- Megaloblastic anemia is a well-researched entity. However, megaloblastic anemia in infantile period attributable to deficiency in maternal nutrition is a rare entity and surplus literature is not available for the same. The authors wish to highlight the consequences of said deficiency and enlighten readers with respect to current guidelines for treatment, that may aid in halting progress and improve prognostication.

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