Dear Editor,

Infantile vitamin B12 deficiency often affects children born to mothers whose nutritional intake is inadequate. We describe a 7-month-old boy with a 2-month history of recurrent vomiting, neurodevelopmental regression, failure to thrive (FTT) and macrocytic anaemia, who was diagnosed to have vitamin B12 deficiency.

Introduction

Vitamin B12 deficiency in infants can result in profound and permanent health consequences. Prevention, early diagnosis and early treatment are crucial to ensure a better outcome for those affected. However, the symptoms of vitamin B12 deficiency in infants can be non-specific, leading to delayed or missed diagnosis.

Vitamin B12 (cobalamin) is a water-soluble vitamin found naturally only in animal products. It is a cofactor for the reaction that converts methylmalonyl-CoA to succinyl-CoA. It is also a cofactor for the enzyme methionine synthase which catalyses the methylation of homocysteine to methionine, an essential amino acid. Additionally, cobalamin is involved in the reaction that demethylates methyl-tetrahydrofolate (CH3-THF) to THF, a substrate essential in DNA synthesis.

In infants, vitamin B12 deficiency is associated with a wide spectrum of clinical manifestations. These include macrocytic anaemia, failure to thrive, irritability, lethargy, hypotonia, developmental delay, psychomotor delay, regression, tremor, convulsions and coma. Less specific manifestations include pallor, vomiting, diarrhoea, oedema and apathy. Cerebral atrophy is usually also seen on magnetic resonance imaging (MRI). Biochemically, vitamin B12 deficiency is associated with elevated methylmalonate acid (MMA) blood and urine levels, elevated blood folate (due to the folate trap) and elevated plasma homocysteine level. Unfortunately, the vast array of non-specific signs and symptoms pose a challenge for diagnosis of vitamin B12 deficiency.

Patient Case Presentation

A 7-month-old boy was referred for persistent vomiting and FTT. He was the second child of non-consanguineous Caucasian parents. He was born full term after a normal pregnancy. His birth weight was 3.2 kg (25th percentile), length 54 cm (50th percentile) and head circumference was 35 cm (50th percentile). Guthrie test done at birth was normal. He had neonatal jaundice which required phototherapy. His health and growth were normal up to 4 months of age, with weight, length and head circumferences at the 50th centiles.

At 5 months old, he developed coughing and vomiting. This was diagnosed to be due to a viral illness. Initially, his vomiting was post-tussive but this persisted despite resolution of his cough. The vomitus was non-bloody and non-bilious. The child also appeared to be more “floppy” and was babbling less than usual. He had been exclusively breastfed since birth. Attempts to wean to solids at 6 months were unsuccessful as he would refuse any solid that was offered. The child was still exclusively breastfed at the time of presentation.

On physical examination, the child was thin and had the following growth parameters; 5.6 kg (<3rd percentile), height 66 cm (10th percentile) and head circumference 42 cm (10th percentile). He was pale and apathetic. There was hypotonia, but he had normal power and reflexes. He was observed to have isolated gross motor delay consistent with a developmental age of 5 months. The rest of the examination was unremarkable.

Investigations showed that he had macrocytic anaemia (haemoglobin 8.7 g/dL, mean corpuscular volume (MCV) 92.5 fl). His other cell lines were not suppressed, white cell count was normal (8.07 x 10⁹/L) and platelet count was slightly elevated (557 x 10⁹/L). As such, there was no indication of pancytopenia. Vitamin B12 level was low at 57 pmol/L (179 pmol/L to 660 pmol/L). Folate level was increased at 92.9 nmol/L (7 pmol/L to 39.7 nmol/L). Plasma homocysteine was also increased at 93.9 umol/L (5 pmol/L to 15 umol/L). Urine organic acid revealed an elevated MMA of 0.6043 mmol/mmol creatinine (normal <0.008 mmol/mmol creatinine). Plasma acylcarnitine profile showed raised propionylcarnitine (C3) of 2.86 umol/L (0.11 pmol/L to 1.02 umol/L). MRI brain revealed myelination pattern that was appropriate for his age but there was mild diffuse cerebral atrophy. These findings were consistent with significant, prolonged vitamin B12 deficiency.

His mother had a past history of vitamin B12 deficiency.
Fifteen years ago, she was diagnosed to have vitamin B12 deficiency after she was symptomatic from it. The cause was thought to be dietary as she was a vegan then. She was treated and her symptoms resolved. After her diagnosis, she stopped being a vegan and was taking a normal diet that included meat and dairy products. Her current dietary intake appeared to be adequate. Her vitamin B12 status had not been checked in the last decade. In the last decade, she was not taking any B12 supplement and she did not have any symptoms suggestive of B12 deficiency. On examination, she was not pale. Investigations showed that her haemoglobin and MCV were normal at 13.1 g/dL and 93.3 fL respectively. Her vitamin B12 level was, however, low at 97 pmol/L. Anti-intrinsic factor antibodies and anti-parietal cell antibodies were absent.

The patient was diagnosed with vitamin B12 deficiency, most likely due to inadequate intake (i.e. her mother’s breast milk was most likely deficient in vitamin B12 given that she was vitamin B12 deficient). The mother was also diagnosed to have vitamin B12 deficiency and treated for it.

The patient was treated with daily 0.1 mg intramuscular (IM) vitamin B12 injections. The clinical improvement in this child was dramatic. After the first vitamin B12 injection, his parents reported that he was more active and less apathetic. The vomiting ceased within a few days and his appetite improved. His parents decided against breastfeeding and switched to formula milk. He also became receptive of solids. There were no side effects from the treatment.

A week after treatment, his weight increased from 5.6 kg to 5.8 kg. His haemoglobin increased from 8.7 g/dL to 9.5 g/dL, vitamin B12 level increased to 1301 pmol/L (179 pmol/L to 660 pmol/L), folate level decreased to normal (due to removal of the folate trap), plasma homocysteine level decreased to normal and urine MMA levels became undetectable. The frequency of IM vitamin B12 injections was adjusted to weekly for 3 weeks then monthly thereafter.

After 2 weeks of treatment, his neurological status improved significantly, including resolution of hypotonia and achievement of new developmental milestones. Brain imaging was not performed post-treatment due to cost consideration. His growth continued to improve. At 8 months, his weight was 7.3 kg (10th percentile), height was 67 cm (10th percentile) and head circumference was 43.2 cm (10th percentile).

Discussion

In a recent study by Demir et al where 41 infants with severe vitamin B12 deficiency were reviewed, all patients had motor retardation, hypotonia and pallor. Seventy-eight percent of patients in the study also had skin hyperpigmentation, apathy and anorexia. Long-term neurological sequelae such as low intelligence quotient (IQ) and developmental delay have been described in patients with delayed diagnosis. Of note, while biochemical and MRI abnormalities often resolve shortly after treatment, their resolution may not predict the child’s long-term outcome. What is important is early diagnosis and early treatment. Schenck et al noted that there was complete neurological recovery when the affected were diagnosed and treated at an earlier age.

Infantile vitamin B12 deficiency is often due to maternal deficiency secondary to pernicious anaemia, strict vegan or vegetarian diet, malabsorption or low socioeconomic status. Infants who are exclusively breastfed are particularly at risk, as they have limited hepatic vitamin B12 reserves and require adequate dietary vitamin B12 intake to maintain good health. Our patient’s mother was vitamin B12 deficient and yet she was asymptomatic, did not have anaemia or macrocytosis. This highlights the importance of testing for vitamin B12 when one is suspicious of it as symptoms and macrocytosis may not occur when the deficiency is mild or in the early stages. Our patient’s mother’s vitamin B12 deficiency is possibly due to inadequate intake of vitamin B12-rich foods coupled with increased requirement during pregnancy and lactation. The possibility of non-immune mediated malabsorption of vitamin B12 is still a possibility in her case.

There are currently no existing guidelines for the treatment of childhood vitamin B12 deficiency. Vitamin B12 intake exceeding the recommended daily allowance is not known to be toxic and has been associated with lower MMA values. IM vitamin B12 injection is the common mode of treatment. High dose oral vitamin B12 is an alternative treatment modality used in adults. Intravenous dosing of vitamin B12 is not recommended as it can result in excessive vitamin loss in the urine as well as trigger an anaphylactic reaction. Vitamin B12 treatment may be associated with the risk of some side effects. In adults with severe B12 deficiency, hypokalaemia has been observed during treatment initiation with vitamin B12. Hence, low initial doses have been recommended. Treatment of vitamin B12 deficiency will result in an increase in red cell production. This increases the demand for iron and it is essential to monitor and correct for iron deficiency. In addition, folate deficiency may also be unmasked by vitamin B12 treatment.

Prevention of infantile vitamin B12 deficiency is possible. Pregnant women should be screened for a history of vegan diet, vegetarian diet or pernicious anaemia. For those at risk, effort should be made to ensure that they have adequate vitamin B12 intake and are not vitamin B12 deficient. If these at-risk women chose to breastfeed, one may consider closely monitoring them and/or supplement the mothers and/or infants with vitamin B12.
Conclusion

Individuals with vitamin B12 deficiency may be asymptomatic or present with non-specific symptoms. Delayed diagnosis or delayed treatment in infants may result in permanent long-term neurological consequences. It is essential to be alert, to diagnose and treat these babies early. The best way to ascertain for vitamin B12 deficiency is to check its level, not by looking for anaemia or macrocytosis. Prevention of vitamin B12 deficiency is possible if care is given to those who are at risk of it.

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REFERENCES


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