Neuroregression in an infant: A rare cause

P Subramani, MD; **C Gomathi Saranya**, MBBS; **G M Chand**, MBBS; **R Sowmiya Narayani**, MBBS; **S James**, MD; **P N Vinoth**, MD, MRCPCH

Department of Pediatrics, Sri Ramachandra Medical College, Chennai, India

Corresponding author: *P N Vinoth (vindoc1977@gmail.com)*

Neuroregression in infants has diverse aetiologies, and vitamin B_{12} deficiency is a rare one. Infantile vitamin B_{12} deficiency is usually secondary to maternal pernicious anaemia or maternal vegetarian diet. We report a 10-month-old infant with developmental regression secondary to vitamin B_{12} deficiency. Her mother was a strict vegetarian and the patient was exclusively breastfed. Clinical symptoms normalised after vitamin B_{12} supplementation.

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Dietary sources of vitamin B_{12} include foods of animal origin. Vegans with aversion to milk and eggs have inadequate amounts of vitamin B_{12}. Adults can tolerate a vitamin B_{12}-deficient diet for many years without clinical symptoms, owing to their endogenous pool, whereas infants become symptomatic within a few months owing to limited hepatic reserves. Maternal vitamin B_{12} deficiency is usually secondary to maternal pernicious anaemia or strict vegetarian diet, and can cause ineffective haematopoiesis and severe neurological abnormalities among exclusively breastfed infants.[1] Here, we present a 10-month-old infant with developmental regression associated with vitamin B_{12} deficiency; the child showed marked clinical improvement after vitamin B_{12} supplementation.

Case report

A 10-month-old female child, firstborn to non-consanguineous parents, presented with a history of regression of milestones, namely inability to sit with support, roll over or hold her neck. The mother also complained of the child having abnormal movements, especially in the upper limbs. She attained milestones appropriate for her age until 6 months of age. Birth history was normal, and the child was exclusively breastfed for 6 months. On examination, the patient looked apathetic and exhibited lassitude. She could neither hold her neck up nor reach for objects, but recognised her mother's face. There was no pallor or hyperpigmentation of her oral cavity, the dorsum of her hands or feet. Anthropometric measurements were weight 7.2 kg (<10th centile), head circumference 42 cm (<10th centile) and length 68 cm (10th centile). The child had generalised hypotonia with normal deep tendon reflexes. She displayed abnormal movements in the form of tremors and myoclonic jerks involving the upper limbs. There was no other systemic involvement. She was provisionally diagnosed as having a neurodegenerative disorder and investigated.

Investigations revealed a haemoglobin of 10.4 g/dL, total count 7.9×10^9/μL (differential count of polymorphonuclear cells 40%, lymphocytes 48%, eosinophils 2% and monocytes 10%) and platelets 250×10^9/L. Her mean corpuscular volume (MCV) was 105.5 fL with macrocytic red blood cells in the peripheral smear. Liver and renal function tests were within normal limits. In view of the high MCV and macrocytic picture, vitamin B_{12} deficiency was suspected and serum vitamin B_{12}, folate and homocysteine levels were sent to the lab. Vitamin B_{12} and folate levels were <83 pg/mL (reference range 208 - 963 pg/mL) and 3.78 ng/mL (2.7 - 17.0 ng/mL), respectively. Serum homocysteine levels were elevated (>50.0 μmol/L). Electroencephalogram (EEG) and magnetic resonance imaging brain scans were normal. On further questioning, we found that the mother was on a strict vegetarian diet and her vitamin B_{12} level was also low (<90 pg/mL), hence the child was diagnosed as having a vitamin B_{12}-associated neuroregression, and started on vitamin B_{12} injections (1 000 μg). In our centre, for vitamin B_{12} deficiency in children we administer weekly vitamin B_{12} injections (1 000 μg) for 4 weeks, then once monthly for 3 months and finally once every 3 months for 6 months. After 2 weeks of treatment with vitamin B_{12} injections, the patient showed marked improvement in social interaction, with gradual reduction in tremors and myoclonic jerks. At the end of 4 weeks, the child was able to hold her neck up, sit without support and stand with support. Repeat serum vitamin B_{12} level was 936 pg/mL and serum homocysteine level was 10 μmol/L. She is now on a regular follow-up schedule on an outpatient basis.

Discussion

In a paediatric population, vitamin B_{12} deficiency can be associated with haematologic, neurologic and psychiatric symptoms. Infantile vitamin B_{12} deficiency was first reported in six South Indian infants, who presented at 7 - 12 months with megaloblastic anaemia, developmental regression and skin hyperpigmentation.[2]

Infantile vitamin B_{12} deficiency is a rare but treatable cause of developmental delay and regression, affecting exclusively breastfed infants born to vitamin-B_{12}-deficient mothers. Infant cobalamin status is determined by the cobalamin content in the breastmilk and the maternal cobalamin concentration during lactation. Maternal factors such as pernicious anaemia, vegan diet and malabsorption contribute to infant cobalamin deficiency.[3] Humans are unable to synthesise vitamin B_{12}, and their only dietary sources are products of animal origin, such as meat, liver, fish, eggs or milk. The average body store of vitamin B_{12} in healthy adults is ~3 mg, compared with 25 μg in neonates, so adults can tolerate deficient diets for many years without visible symptoms, whereas neonates born to a vitamin-B_{12}-deficient mother can develop symptoms within a few months.[1] In our patient, vitamin B_{12} deficiency was attributed to the maternal vegetarian diet.

Vitamin B_{12} deficiency principally affects the central nervous system (CNS) and those tissues with rapid mitotic activity, such as digestive tract epithelium and haematopoietic cells. CNS symptoms generally appear between 2 and 12 months of age, and include vomiting, lethargy and feeding problems. Hypotonia, optic atrophy, adynamia, developmental regression and abnormal movements such as tremors or myoclonus are other hallmarks of the disease.[4] In contrast to severe neurological findings in infantile vitamin B_{12} deficiency, in adolescents and adults only mild neuropsychiatric

symptoms are observed. Neuroimaging studies may demonstrate cerebral atrophy in infants in comparison with subacute combined degeneration of cord in adults. The molecular basis for these alterations is not well understood.[2,5,6] Neuroimaging studies did not reveal any abnormalities in our patient.

Synthesis of methionine and succinyl-CoA depends on the coenzyme activity of cobalamin. For synthesis of methionine, a methyl group is transferred from methyltetrahydrofolate (THF) to methylcobalamin (Cbl). Methionine is finally generated by the transfer of the methyl group to homocysteine. Methionine and THF thus formed are essential for DNA synthesis. THF becomes formyl-THF and provides C1 units in purine synthesis. The lack of neurological symptoms in folate deficiency indicates that methionine synthesis may not be causally related to Cbl-associated neuropathy. The other Cbl-dependent reaction is the conversion of methylmalonyl-CoA to succinyl-CoA. Cobalamin deficiency results in the accumulation of precursor propionyl-CoA, which in turn leads to odd-chain fatty acid synthesis, resulting in incorporation of large amounts of unusual C15 and C17 fatty acids in nerve sheets with altered nerve functions.[7]

Abnormal movements such as tremors or myoclonus have been described in vitamin-B_{12}-deficient infants before or during treatment with vitamin B_{12}. The reason for these abnormal movements is not well understood.[2] Hyperglycinaemia causing nonspecific interference with glycine cleavage was suggested to be responsible for abnormal movements. However, normal glycine levels in symptomatic patients excluded this hypothesis.[8,9] Grattan-Smith *et al.*[10] reported that the movement disorder that appeared after treatment is due to the swift availability of cobalamin resulting in intense stimulation of cobalamin and folate pathways, producing a short-term imbalance of metabolic pathways, with local deficiencies or excesses occurring. A metabolite yet to be demonstrated may be responsible for the involuntary movements.[10] Our patient had myoclonic jerks that disappeared after 2 months of treatment with vitamin B_{12}.

Vitamin B_{12} supplementation results in rapid clinical improvement with complete resolution of structural and EEG abnormalities; however, there is a concern for long-term prognosis.[1] Pearson and Turner[11] followed up a child with vitamin B_{12} deficiency diagnosed at 32 months and found an IQ of 60 at the age of 6 years. Graham *et al.*[12] identified mild cognitive impairment in 2/4 patients with cobalamin deficiency.[12] Von Schenck *et al.*[1] observed that when a diagnosis is made within 10 months of age, it has been associated with a favourable outcome compared with permanent neurological abnormalities in children whose diagnoses were made after 1 year of age.

Special attention should be given to pregnant and breastfeeding women on vegan diets to prevent vitamin B_{12} deficiency in their infants. Screening for urinary methylmalonic acid can be a useful tool to identify these individuals.[1] It is important to emphasise that vitamin B_{12} supplementation during pregnancy should be provided for strict vegans and mothers with pernicious anaemia to avoid irreversible neurological damage in exclusively breastfed babies.

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