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Neurologic Impairment in Children Associated with Maternal Dietary Deficiency of Cobalamin --- Georgia, 2001

During 2001, neurologic impairment resulting from cobalamin (vitamin B_{12}) deficiency was diagnosed in two children in Georgia. The children were breastfed by mothers who followed vegetarian diets*. This report summarizes the two cases and provides guidance for health-care providers on identifying and preventing cobalamin deficiency among breastfed infants of vegetarian mothers.

Case 1

During August 2001, a girl aged 15 months was hospitalized for lethargy and failure to thrive. She was born after a full-term pregnancy complicated by prolonged nausea and vomiting. She was breastfed for 8 months, but the extent (exclusivity) of breast milk consumed relative to other food was unknown. Her mother reported following a vegan diet during the preceding 7 years and took nutritional and vitamin supplements. The cobalamin content of the supplements was unknown. When the child was aged approximately 8 months, organic whole-grain cereals and fruit shakes were introduced, but she had a poor appetite and vomited regularly. Her parents became concerned about her growth and development, and she was evaluated by a pediatrician at age 15 months. The pediatrician diagnosed failure to thrive, developmental delay, and severe macrocytic anemia. The child was hospitalized, and cobalamin deficiency was diagnosed (marked elevation [not quantified] of urine methylmalonic acid; serum B_{12}:100 pg/mL [normal range: 210--911 pg/mL]) (Table 1).

The child received supplementary food by mouth and by nasogastric tube. She also received 2 mg of cyanocobalamin and 3 mg of hydroxocobalamin intramuscularly (IM) over 3 days. Three days later, she had partial complex seizures, which stopped without anticonvulsants. A brain MRI indicated global cerebral atrophy. The mother was treated with 1 mg of cobalamin IM.

At age 16 months, the child was seen in a genetics clinic to eliminate possible genetic causes of her neurologic deficiency. At age 28 months, her developmental skills ranged from 9 months for fine motor skills to 18 months for gross motor skills. Her expressive language was at 10 months, and her receptive language was at 12 months. At age 32 months, she had made developmental progress but continued to have developmental delays, especially in speech and language. She was prescribed daily sublingual cobalamin supplements.

Case 2

During March 2001, a boy aged 30 months with failure to thrive and mild global developmental delays was taken to a genetics clinic. He was born after a full-term pregnancy and breastfed exclusively until age 9 months. The mother reported following a vegetarian diet during the preceding 20 years, with negligible amounts of meat, fish, and dairy products. She reported intermittent intake of a vitamin supplement (TwinLab® Stress B Complex Caps, containing 250 mcg of "cobalamin concentrate," according to the label). When the boy was age 9 months, the health-care provider and his parents became concerned about the child's growth and development (Table 1). His diet was supplemented with fruit and dry cereals to improve growth. When this was unsuccessful, he underwent a frenectomy at age 11 months to free tongue movements and improve coordination of swallowing and chewing. Despite this intervention, growth was inadequate. His diet was supplemented with soy- and cow's milk--based formulas. He tolerated neither and started a multigrain nondairy formula (Multigrain Milk®) in addition to fruit, vegetables, chicken, an unknown vitamin supplement, and a product called Greens Plus® (no cobalamin content listed on label). Because of poor motor and speech development at age 11 months, the child was evaluated by a developmental pediatrician, who ordered genetic and metabolic studies and prescribed speech, occupational, and physical therapies. The child had persistent elevation of urine methylmalonic acid on three occasions but received no treatment for cobalamin deficiency until after the third measurement, which was ordered for a genetics clinic evaluation.

After diagnosis of cobalamin deficiency was confirmed at the genetics clinic (moderate peak [not quantified] of urine methylmalonic acid; serum B_{12}: 149 pg/mL) (Table 1), the child was treated with 1 mg of hydroxocobalamin IM (2 weeks apart) and 1 mg sublingual doses daily. The mother also was treated with 1 mg of oral cobalamin daily. At the genetics clinic visit, the child had no frank neurologic signs but exhibited delays in speech. He experienced catch-up development in motor skills and completed physical therapy but continued speech, language, and occupational therapies. Approximately 6 months after beginning treatment, the child exhibited slight speech and fine motor skill delays but had age-appropriate gross motor skills. The parents reported that the child was administered a 1 mg cobalamin sublingual preparation every other day.

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Editorial Note:

The most common cause of cobalamin deficiency in infants and young children is maternal dietary deficiency (*2*), which generally manifests in breastfed infants at age 4--8 months (*3*). This deficiency is difficult to diagnose because of nonspecific symptoms (*4*). The two children described in this report had cobalamin deficiency and manifested multiple symptoms of undernutrition, particularly growth failure. After treatment for cobalamin deficiency, both children showed marked improvement in cobalamin status and development. In some cases, irreversible neurologic damage results from prolonged cobalamin deficiency, but the extent and degree of disability depends on the deficiency severity and duration (*4*). Seizures after treatment have been reported previously in children with cobalamin deficiency, although whether these are secondary to the treatment or to the underlying condition is unknown (*5*).

The prevalence of cobalamin deficiency is unknown for children aged <4 years. No clinical practice guidelines exist for diagnosing cobalamin deficiency in young children. Methylmalonic acid is a sensitive and specific indicator of cobalamin deficiency; holotranscobalamin II, total homocysteine, and serum B_{12} also are useful indicators (*2*,*4*,*6*). Macrocytic anemia and other hematologic indices are not appropriate screening tools (*4*).

Persons who follow vegetarian diets should ensure adequate cobalamin intake. The only reliable unfortified sources are animal products, including meat, dairy products, and eggs. Most naturally occurring plant sources of cobalamin are not bioavailable; however, plant foods fortified with cobalamin, such as some cereals, meat analogs, soy or rice beverages, and nutritional yeast (*7*), can be reliable and regular sources. The content of fortified food is usually listed on the food label and ingredient list. Fortified food and supplements made from cobalamin (e.g., cyanocobalamin) provide cobalamin that is physiologically active in humans (*6*). Products whose labels do not specify cobalamin and list only vitamin B_{12} might include nonbioavailable sources. Vegetarians, particularly women during pregnancy and lactation, should be knowledgeable about the cobalamin content of their food or seek nutritional advice. Few of the common infant-toddler cereals are fortified with cobalamin (*8*). Breast milk from mothers with adequate nutritional status, infant formula, cow's milk, or a cobalamin-fortified soy or rice beverage provide a cobalamin source for infants and children. If it is not possible to acquire the recommended dietary intake of cobalamin through food, a daily supplement should be taken that contains at least the recommended dietary intake of cobalamin from a reliable source (Table 2).

Health-care providers should be vigilant about the potential for cobalamin deficiency in breastfed children of vegetarian mothers. Potential cobalamin deficiency should be included in the differential diagnosis when assessing young children of vegetarian mothers who have symptoms consistent with cobalamin deficiency, including failure to thrive, developmental delay, neurologic/psychiatric manifestations, and hematologic abnormalities (*4*).

Health-care providers who care for mothers in the preconceptional, prenatal, and postpartum periods and their young children should ask pregnant and lactating mothers about their diets to identify those who are vegetarians. Pregnant and lactating women should eat foods rich in cobalamin or take a daily supplement containing at least the recommended dietary intake of cobalamin (Table 2). For those eating no or very limited food of animal origin or a known cobalamin source, a cobalamin assessment is indicated. If lactating mothers are cobalamin deficient, their infants should be evaluated for cobalamin deficiency and treated appropriately.

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* Vegetarian diets vary. For example, vegan diets generally do not include food of animal origin, whereas lacto-ovovegetarian diets include dairy products and eggs. In this report, the term "vegetarian" refers to all diets that limit food of animal origin.

Table 1

TABLE 1. Metabolic studies* and anthropometric measurements† of two children with cobalamin deficiency and the mother of one of the children — Georgia, 2001

Tests/Measurements	Patient 1, female	Patient 2, male	Mother of patient 2§
Metabolic studies			
Age	15 months	30 months	38 years
Urine methylmalonic acid	Marked elevation	Moderate peak	Mildly increased
Urine methylcitrate	Marked elevation	Not detected	—
Plasma homocysteine	8.2 µmol/L (3.3–8.3)	12.4 µmol/L (3.3–8.3)	13.5 µmol/L (7.7–13.3)
Serum B_{12}	100 pg/mL (210–911)	149 pg/mL (210–911)	253 pg/mL (210–911)
Serum folate	30 µg/mL (2.8–40)	12.8 µg/mL (5.4–40)	Normal
Red cell folate	584 ng/mL (145–903)	452 ng/mL (280–903)	Normal
Hematocrit	18.6% (33–39)	32% (33–39)	—
Mean corpuscular volume	115.7 fL (77–86)	103.2 fL (77–86)	—
Brain MRI	Global cerebral atrophy	—	—
Anthropometric measurements¶			
Age at first measurement	15 months	9 months	—
Length-for-age	69 cm (2.5 cm below the 3rd percentile)	72 cm (54th percentile)	—
Weight-for-age	6.34 kg (2.2 kg below the 3rd percentile)	5.95 kg (1.5 kg below the 3rd percentile)	—
Head circumference	43 cm (0.5 cm below the 3rd percentile)	39.5 cm (3.1 cm below the 3rd percentile)	—
Age at second measurement	16 months	30 months	—
Length-for-age	64.6 cm (7.5 cm below the 3rd percentile)	85 cm (3rd percentile)	—
Weight-for-age	6.34 kg (2.4 kg below the 3rd percentile)	12.5 kg (24th percentile)	—
Head circumference	41.7 cm (2 cm below the 3rd percentile)	49.5 cm (56th percentile)	—

* Reported laboratory qualitative or quantitative values and laboratory-specific reference ranges in parentheses.
† First measurement for patient 1 is from the medical chart at the hospital; the second is from the medical chart at the genetics clinic. First measurement for patient 2 is from the medical chart at the pediatrician's office; the second is from the medical chart at the genetics clinic.
§ No metabolic studies performed for mother of patient 1 before treatment.
¶ Derived from CDC growth charts (*1*).

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Table 2

TABLE 2. Recommended intake of vitamin B_{12}, by population subgroup

Population subgroup	µg/day
Infants aged <6 months*	0.4
Infants aged 7–12 months*	0.5
Children aged 1–3 years†	0.9
Children aged 4–8 years†	1.2
Children aged 9–13 years†	1.8
Children aged 14–18 years†	2.4
Adults aged ≥19 years†	2.4
Pregnant women aged 14–50 years†	2.6
Lactating women aged 14–50 years†	2.8

* Adequate intake.
† Recommended dietary allowance.
Source: Institute of Medicine (*9*).

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