

CLINICAL VIGNETTE

Maternal B12 Deficiency Diagnosed after Presentation of Neonatal B12 Deficiency in Exclusively Breast-fed Infant

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Early recognition of vitamin B12 deficiency allows medical interventions before profound and permanent neurologic defects occur. Because Vitamin B12 is critical in the metabolic pathways of bone marrow, spinal column, brain, and peripheral nerve endings, B12 deficiency classically manifests with anemia, peripheral neuropathy, gait imbalance, and memory loss. While B12-associated bone marrow changes are known to be readily reversible, neurologic deficits are not as pliant and prolonged. B12 deficiency can result in permanent nerve damage. Initial laboratory clues reflect defective hematopoiesis resulting in macrocytosis, hyperlobulated neutrophils, and anemia. However, neurologic symptoms can often precede hematologic changes by weeks to years.¹ Neurologic changes are variable and inconsistent and can include peripheral neuropathy and subacute combined degeneration of the posterior and lateral spinal columns, seen on exam as an abnormal Romberg, loss of vibration sense, and impaired proprioception; in addition, B12 deficiency is also linked with nonspecific cognitive impairments though the exact mechanism is unclear. Presented here is a case of maternal B12 deficiency that remained undiagnosed throughout pregnancy and did not manifest as any obvious laboratory or physical anomalies in the mother until neonatal neurologic and developmental deficits became evident.

The patient was a healthy 34-year-old prima gravida who reported the recent diagnosis of severe B12 deficiency in her newborn. The male infant was the product of a normal, uneventful pregnancy and a normal spontaneous vaginal delivery. The baby initially was described as being healthy with normal Apgar scores and neonatal examination. Both mother and son were discharged to home after a routine, uneventful hospital stay. The baby was exclusively breast fed for the first 4 months and the mother reported normal feeding behavior as she introduced solids, primarily strained fruits. Neonatal visits remained normal until 6 months postpartum when the baby gradually developed persistent diarrhea, along with increasing irritability and delay in reaching developmental milestones. After symptoms worsened and weight loss ensued, the baby was diagnosed with failure to thrive and admitted for an extensive inpatient work up. The infant eventually was diagnosed with severe B12 deficiency (approximately 30 pmol/L) and successfully treated with parenteral vitamin B12 with subsequent resolution of diarrhea, increased weight, and

gradual improvement of neurologic status. No evidence of metabolic defect or malabsorption was found in the infant and attention turned toward a maternal B12-deficiency affecting the breastmilk.

On review, the mother had a normal prenatal examination and her prenatal labs included CBC, ferritin, and metabolic panel that were all within normal limits. Because her ferritin was on the “low end of normal” (10 ng/mL), the mother had been prescribed over the counter iron supplements, but she admitted to being inconsistent due to side effects of constipation and stomach upset. After identification of her child’s B12 deficit, she was subsequently tested and found to have a normocytic anemia, severe B12 deficiency (50 pmol/L), normal folic acid level, and elevated homocysteine and methylmalonic acid levels. The mother presented to her internist for additional work up. She initially denied relevant symptoms other than fatigue, which she had associated as being normal for her postpartum status, as well due to stress from her child’s recent illness. Detailed review of systems, however, revealed subjective complaints of imbalance; dizziness without vertigo (worse at night); persistent, mild burning of bilateral plantar feet; and intermittent tingling and numbness of her fingertips. The patient vaguely remembered these symptoms developing and then accelerating during her pregnancy. Her hand symptoms were briefly mentioned during one prenatal visit and had been diagnosed as a mild carpal tunnel syndrome. The patient was prescribed wrist braces but chose not to use them. Attributing these and the remaining symptoms to her pregnancy, she did not bring any additional symptoms to the attention of either her PMD or her gynecologist. During the current evaluation, she denied any medication use other than over-the-counter prenatal vitamins; she specifically denied the use of any antacids or metformin. All her adult vaccinations were up to date. Her past medical history was significant only for a history of iron deficiency anemia. She described an unrestricted diet with daily intake of animal products such as dairy, poultry, fish, and whole eggs. She had no pertinent surgical history, specifically no gastric or small intestinal surgeries. Her family history was significant for hypothyroidism and pernicious anemia in her mother. Her physical exam was normal except for an abnormal neurologic examination. Strength was symmetric in all four extremities and deep tendon reflexes were brisk and symmetric at the patellar tendon but absent at bilateral Achilles tendon.

Sensation was decreased to pinprick on the plantar surfaces of her feet, and she demonstrated an abnormal Romberg exam.

A detailed review of her post-partum labs showed a co-existing normocytic anemia with decreased ferritin levels (5 mcg/L) and B12 levels. It is likely that the combined deficiencies of B12 and iron masked any expected changes in red blood cell volume (MCV) such as macrocytosis. This was consistent with studies showing that MCV alone cannot be relied upon successfully to diagnose B12 deficiency.² Subsequent labs detected the presence of both intrinsic factor antibody and parietal cell antibody, consistent with a diagnosis of pernicious anemia. The patient was started on daily oral iron supplements and intramuscular vitamin B12 1000 mcg weekly for 4 weeks and then was instructed on self-administration of intramuscular B12. The patient declined a trial of oral B12 supplements. At last evaluation, the patient's labs showed normalization of ferritin, B12 levels, methylmalonic acid, as well as CBC. Her Romberg exam one-year post-treatment has improved, and her subjective feelings of fatigue and imbalance have improved as well.

While pernicious anemia remains a leading cause, Vitamin B12 deficiency is an increasingly common finding, especially in light of popular trends such as veganism, bariatric surgeries, the increasing use of metformin for diabetes mellitus type 2, PCOS and pre-diabetes, and the ready availability of proton-pump inhibitors, both over the counter and by prescription. B12 is stored in the liver and inadequate absorption or intake can take as long as 3-5 years to manifest as lowered laboratory B12 levels. In this particular case, the accelerated metabolic demands of pregnancy along with continued losses from breastfeeding likely accelerated the onset of her neurologic and hematologic symptoms over the space of a year.

Vitamin B12 is naturally obtained in most subjects from a diet containing animal products—in particular shellfish as well as meat, egg yolk, dairy, and fish products. Although B12 is available immediately upon consumption, B12 is believed to have only a 50% bioavailability.³ Beginning in the mouth, free B12 is bound to salivary R-protein, whereas protein-bound B12 must be cleaved free by hydrochloric acid in the stomach. Hydrochloric, released by parietal cells in the stomach, plays an additional role and activates the digestive enzyme pepsin. After pepsin dissociates B12 from its R-protein, stomach-derived intrinsic factor (IF) binds to the now free cobalamin in the lower acidity environment of the duodenum. The complex of IF-B12 binds to a receptor in the ileum (“cubilin”) and from there B12 is absorbed into the bloodstream. Pernicious anemia is distinguished by the presence of IF antibodies or anti-parietal cell antibodies. In this case, the patient tested positive for both types.

This patient's case illustrates the subtleties of diagnosing B12 deficiency early on, before hematologic and permanent neurologic effects manifest on examination. Her situation was complicated by several factors, not least of which was her pregnancy, and resulted in serious complications with her infant. First, normal hematologic markers are not sufficient to exclude B12 deficiency, both because neurologic damage can precede hematologic changes by weeks to months but also because common iron deficiencies can effectively mask classic

changes in MCV. Second, this patient had neurologic signs that were easily overlooked as common complications of pregnancy. While carpal tunnel syndrome can have similar neuropathic signs on presentation, it would be expected that the patient's examination would exclude such a diagnosis. Although simple tests such as Phalen's and Tinel's sign would be expected to be normal, neither are reliable diagnostic measures. Failure to respond to routine measures such as a wrist brace might have suggested an alternative diagnosis. In this case, the patient's lack of compliance and failure to follow up when symptoms did not resolve likely hindered the diagnosis. Third, although dizziness or unsteadiness can be reported in pregnancy, the patient had concomitant complaints of lower extremity neuropathy that are atypical of pregnancy. Reasonable evaluation for this should include B12 and methylmalonic acid levels. Last, the severity and persistence of the infant's B12 deficiency brought to light his mother's underlying pernicious anemia. The baby was exclusively breastfed for 3 months, and, when the baby transitioned from breastmilk to solids, the baby was fed a diet of fruits and veggies, all lacking in natural or enriched B12 (such as cereal grains). Presumably, if the baby had started solids with animal products and enriched cereals, the baby may have corrected naturally for any B12 deficiency. Then, his mother's B12 deficiency may in fact have been diagnosed much later, increasing her risk of neurologic damage.

Outside of pernicious anemia, clinicians should also be aware of B12 deficiency occurring in other unique populations. Increasingly, the crisis of obesity has led to a rise in bariatric surgeries such as gastric bypasses that effectively isolate the ileum and its absorptive surfaces.⁴ Patients who follow a vegan or limited vegetarian diet are also at risk. More recently, recommendations on the use of metformin advise the routine monitoring of B12 levels along with HgbA1c in diabetics, pre-diabetics, and PCOS patients.⁵ Just as parietal cell antibodies cause achlorhydria so can the chronic and indiscriminate use of proton pump inhibitors, thus effectively restricting accessibility of protein-bound B12. These patients, if properly instructed, should maintain regular supplementation of vitamins including B12 and should also be screened even in the absence of symptoms.

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