Cobalamin supplements for infants: a shot in the cradle?\textsuperscript{1,2}

Ralph Green

The elderly have long been considered the primary target group for improved cobalamin nutrition. Cobalamin insufficiency has been associated with a variety of neurodegenerative conditions in this demographic group (1). However, there is mounting evidence that cobalamin deficiency is also associated with neurodevelopmental morbidity during infancy (2). In a simple, well-designed, randomized double-blind interventional trial reported in this issue of the Journal, Torsvik et al (3) provide plausible evidence that some of the vexing feeding problems related to neuromuscular coordination that are encountered in fussy infants are amenable to correction by a single intramuscular injection of hydroxycobalamin.

The findings presented by the authors are significant in that they provide convincing evidence of functional motor impairment in infants with biochemical marker profiles indicative of cobalamin deficiency in whom there was objective improvement after administration of a cobalamin injection. There is continuing debate and uncertainty as to whether evidence of biochemical impairment of cobalamin-dependent pathways (elevated homocysteine or methylmalonic acid) has any functional significance or reflects any underlying clinical condition. Torsvik et al provide plausible evidence to support a connection between pathobiochemistry and clinical consequence.

In their simple, well-designed, randomized double-blind study, the authors show that states of suboptimal cobalamin nutritional status in infants as judged by elevated concentrations of homocysteine are associated with functional motor impairment (feeding difficulties). They studied infants with mild to moderate elevations in plasma homocysteine (defined as between 6.5 and 18.0 μmol/L). After repletion with a one-time injection of 400 μg hydroxycobalamin, the authors reported short-term improvement, both with respect to feeding problems and more globally in gross motor development, compared with infants receiving a placebo. On the basis of these findings, and considering that there is no safe upper limit defined for cobalamin (4), should all infants receive a shot of cobalamin, or should only infants with feeding difficulties or motor problems receive such treatment? Should a plasma homocysteine measurement be carried out as a selection criterion? The authors do not say.

The authors chose their 400-μg dose on the basis of the calculations that this would suffice to provide double the amount of cobalamin required for the first year of life based on Adequate Intake data (4). The observations by Torsvik et al should be confirmed by others and extended beyond their 1-month period of observation. There are also some caveats regarding dosage schedule, form of cobalamin, and the setting in which this prevention or treatment strategy might be applied. Whereas the most commonly used form of injectable cobalamin in Europe is hydroxycobalamin, in the United States cyanocobalamin is the preferred form. Although either form ultimately provides usable cobalamin in otherwise normal infants, there are differences in the pharmacokinetics of these forms, and particularly in their retention. For equivalent doses of the 2 forms, the retention of a dose of cyanocobalamin is only approximately one-half as much as hydroxycobalamin (5). As a rough approximation, to attain a bolus delivery of cobalamin equal to what Torsvik et al achieved, it would therefore be necessary to administer 800 μg cyanocobalamin.

Another consideration relates to differences in national nutritional policies and the geographical practice setting. Unlike in North America and many other countries around the world, mandatory folic acid fortification of the food supply is not practiced in Norway or elsewhere in Europe. It is well known that low folate status can be a cause of raised homocysteine, even though it is also the case that during infancy folate concentrations are high and plasma homocysteine shows weak or absent correlation with serum folate but strong correlation with serum cobalamin (6, 7). Still, there may be other confounders that might bedevil the relation between cobalamin status and plasma homocysteine. Recent studies in adults from folic acid–fortified and somewhat heavily supplemented populations have shown that in individuals with comparably low plasma cobalamin, those with particularly high plasma folate have higher plasma homocysteine and methylmalonic acid concentrations than do individuals whose plasma folate is not high (8, 9). Because maternal folate status is known to affect infant folate concentrations (10), it may not be possible to extrapolate directly from the findings reported in a non–folic acid–fortified population to a folic acid–fortified one. This caveat would apply if the decision whether or not to inject with a cobalamin supplement was contingent on the measured homocysteine concentration.

One of the interesting findings in Torsvik et al’s study is that in both cobalamin and placebo trial groups (with plasma homocysteine

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\textsuperscript{1}From the Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA.

\textsuperscript{2}Address correspondence to R Green, Department of Pathology and Laboratory Medicine, University of California, Davis, 4400 V Street, Sacramento, CA 95817. E-mail: ralph.green@ucdmc.ucdavis.edu.

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of 6.5–18.0 μmol/L, ~50% of infants were exclusively breastfed, contrasted with only 10% in their low-homocysteine comparison group (plasma homocysteine <6.5 μmol/L). This is consistent with the observations that breastfed infants have lower cobalamin status than do formula-fed infants (11) and that there is good bioavailability of cobalamin from dairy products (12). Moreover, the cobalamin content of breast milk appears to be lowest at 4 mo after birth, and this coincides with a nadir in infant cobalamin status (13). The apparent beneficial effect of ingestion of dairy products on cobalamin status and its underlying mechanism deserve further investigation.

An intriguing aspect of the salutary effect of a cobalamin supplement on amelioration of functional neurologic deficits observed in this study is the relative rapidity with which such improvement occurred; mothers reported improvements in regurgitations after the cobalamin injection. The myeloneuropathy associated with cobalamin deficiency is generally attributed to a defect in the synthesis and repair of myelin (1). There are only 2 known reactions that require cobalamin as a cofactor in humans. One is the methionine synthase reaction in which homocysteine is converted to methionine in a methyl transfer reaction that requires methylcobalamin. Methionine is the required precursor for the formation of S-adenosylmethionine, critical for the synthesis of several methylated membrane phospholipids. The other reaction is the mitochondrial conversion of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase. Some evidence has linked the accumulation of methylmalonate to succinyl-CoA by the enzyme methylmalonyl-CoA mutase. Some evidence has linked the accumulation of methylmalonate to the neurologic sequelae of cobalamin deficiency through misincorporation of these substrates into abnormal fatty acids, which then become incorporated into myelin lipids. Myelin repair is a slow process. The administration of cobalamin to an individual deficient in the nutrient is often associated with an immediate, although partial, trajectory of recovery—a subjective feeling of well-being more consistent with a biochemical rather than a structural anatomic repair. Could it be the case that improving the methylmalonate conversion to succinate, which feeds into the energy-producing tricarboxylic acid cycle, results in enhanced substrate supply for oxidative phosphorylation and energy production?

All of this points to the possibility that relative cobalamin deficiency in the neonatal period (like iron and perhaps other micronutrient deficiencies) can result in detrimental or suboptimal neurologic outcome and that supplementation with this vitamin may prove beneficial.

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REFERENCES

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