Clin Chem Lab Med 2003; 41(11):1418–1426 © 2003 by Walter de Gruyter · Berlin · New York

Review

Hyperhomocysteinemia and B-Vitamin Deficiencies in Infants and Children

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Measurement of total homocysteine (tHcy) in healthy and diseased children has documented the utility of this marker in pediatric research and diagnostics. This article focuses on novel data obtained in infants, children and adolescents, with emphasis on cobalamin status in infants. In children, determinants of plasma tHcy are similar to those established in adults, and include age, gender, nutrition, B-vitamin status, and some drugs interfering with B-vitamin function. In infants (age <1 year), tHcy is moderately elevated and related to serum cobalamin, whereas in older children and throughout childhood, plasma tHcy is low (about 60% of adult levels), and folate status becomes a strong tHcy determinant. As in adults, hyperhomocysteinemia in childhood is a risk factor for stroke, and folate-responsive hyperhomocysteinemia has been detected in children with renal failure. tHcy seems to be a sensitive indicator of folate deficiency in children on a poor diet, in HIV-infected children, and in children treated with anti-folate drugs. In children at increased risk of cobalamin deficiency, which includes children born to vegetarian mothers or children in developing countries on a poor diet, tHcy and methylmalonic acid are responsive indicators of a deficiency state. In newborns and infants born to mothers with an adequate nutrition, there are consistent observations of low cobalamin, elevated tHcy and methylmalonic acid, and reduction of both metabolites by cobalamin supplementation. These data have raised the question whether cobalamin deficiency may be widespread and undetected in babies born to non-vegetarian women on a Westernized diet. Clin Chem Lab Med 2003; 41(11):1418–1426

Key words: Homocysteine; Folate; Cobalamin; Methylmalonic acid; Children; Infants.

Abbreviations: CVD, cardiovascular disease; MMA, methylmalonic acid; MTHFR, methylenetetrahydrofolate reductase; MTRR, methionine synthase reductase; NTD, neural tube defects; PML, post-methionine load; SCD, sickle cell disease; tHcy, total homocysteine.

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Introduction

The diagnostic utility of total homocysteine (tHcy) determination in adults is well established. Elevated tHcy is a risk factor for occlusive arterial and venous disease (1–3), adverse pregnancy outcomes (4, 5) and impaired cognitive function (6, 7), and tHcy is increased in folate and cobalamin deficiencies, and serves as a useful test for the diagnosis and follow-up of these deficiency states (8). Major determinants of tHcy are folate and vitamin deficiency and renal function, but tHcy is also related to a variety of lifestyle factors, medications and medical disorders, particularly in those associated with renal dysfunction (9, 10). Major tHcy determinants are summarized in Table 1.

Table 1 Main determinants of plasma total homocysteine, as documented in adults or children.

	Adults and elderly	Infants and children
Physiological factors		
Age	+	+*
Gender (male)	+	(+)
Renal function	+	NI
Creatinine	+	(+)
Ethnicity and genetics		
Blacks *vs.* whites	+	+
MTHFR 677C>T	+	(+)
Down syndrome		–
Lifestyle factors		
B-vitamin intake	–	–
Smoking	+	+
Coffee	+	NI
Alcohol	+/–	NI
Physical activity	–	NI
Drugs		
Methotrexate	++	++
Nitrous oxide	++	NI
Anticonvulsants	++	++
Cyclosporin A	++	NI
Medical conditions		
Folate deficiency	+++	++
Cobalamin deficiency	+++	++
Renal failure	+++	++(+)
Diabetes, early	–	–
Diabetes, late	++	++
Malignant disease	++	++
Hypothyroidism	++	NI

+, slight increase within the normal reference range; ++, moderate increase above the reference range (15–30 μmol/l); +++, marked increase (30–100 μmol/l); –, reduction. *Higher tHcy observed in infants (<1 year of age); NI, not investigated.

During the last 5 years, several research groups have published reference levels for tHcy from birth until puberty. Data are also accumulating on plasma tHcy in children with various diseases and on the role of tHcy in risk assessment and laboratory diagnostics. For the diagnosis and follow-up of cobalamin and folate deficiencies in particular, determination of tHcy alone, or in combination with complementary metabolic markers like methylmalonic acid (MMA), may become valuable assets in pediatric medicine. In this Review, we briefly summarize published data on tHcy in healthy and diseased infants and children, with emphasis on B-vitamin deficiencies. Diagnosis of inborn errors of homocysteine (11) or cobalamin metabolism (12, 13) and methylmalonic acidurias (14) by measurement of tHcy or MMA have been comprehensively reviewed elsewhere and will not be dealt with in this article.

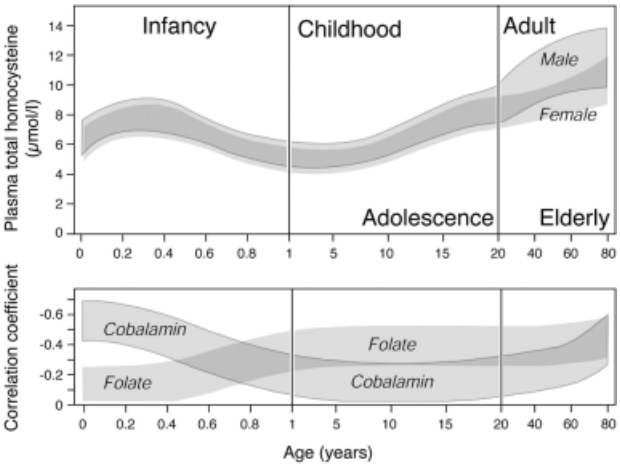

Figure 1 Schematic presentation of variations in, and effect of B-vitamins on, total homocysteine (tHcy) from birth to senescence. The upper panels depict the high tHcy during the first year of life, and low level in early childhood, which approaches the adult sex-related level in late adolescence. In the panel (upper right) for adults and elderly, the upper curve represents the level in males, the lower curve the level in females. The lower panels indicate the age-related effects of B-vitamins in terms of univariate correlation coefficients for serum folate and serum cobalamin. The graph is an overall impression of the authors, based on data of tHcy in healthy infants (29–32, 34–36) and children (16, 19–22, 25–28, 33, 37–43).

Total Homocysteine according to Age and Gender

In adults, median tHcy concentration is about 6–8 μmol/l in young women, higher and about 10 μmol/l in young men, and increases after age of 40 years by 0.5–1 μmol/l for each decade in both genders (15, 16). In children between 1 and 15 years of age, the mean tHcy concentration is low and about 4–7 μM (17–20). tHcy increases as a function of age (20, 21). Some (16, 22, 23), but not all (19, 20, 24–27), studies demonstrate a slightly higher tHcy level in boys than in girls, and this gender effect is enhanced during and after puberty (> 15 years) (25, 28).

In newborns and infants (< 1 year of age), mean tHcy concentrations of 6–9 μmol/l have consistently been reported (29–32), which is higher than the levels (20, 21, 25, 26, 33) often encountered in children of 1–10 years of age. The tHcy concentration according to age and gender is depicted in the upper panel of Figure 1.

Lifestyle Factors, Nutrition and Genetics

In addition to age, folate and cobalamin status are the most important determinants of plasma tHcy in infants and children. But the variability in tHcy explained by folate or cobalamin status seems to be critically dependent on age. In children aged 2–19 years, there are consistent reports of a strong relation (coefficients often in the range 0.2–0.6) between tHcy and serum folate (Figure 1). The relations to serum cobalamin are generally weaker (19, 21, 22, 25, 28), whereas B_6 among the B-vitamins has the weakest (20, 22) or no effect (44). In contrast, the elevated tHcy concentration often observed in newborns and infants (< 1 year) shows a stronger association with cobalamin than with folate (29–32), suggesting that during the first year of life, homocysteine status is critically dependent on cobalamin. The tHcy in various age groups, according to folate and cobalamin status, is depicted in the lower panel of Figure 1.

As in adults (45), tHcy shows a positive relation to serum creatinine in healthy children without renal dysfunction (19, 27). This could be explained by formation of homocysteine during creatinine synthesis (46) rather than the effect of renal function on creatinine and homocysteine clearance.

tHcy levels vary according to ethnicity, and are higher in black than in white (41) or Hispanic children (22). Notably, the effect of the methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism on tHcy and folate status reported in adults, characterized by a 25% higher tHcy and lower serum folate in homozygous TT than in CC subjects (47), was demonstrated in 92 children with familial hypercholesterolemia aged 6–11 years (48), in 64 healthy children aged ≥ 10 years, but not in 63 younger children (21). Likewise, there are consistent reports on no effects from the MTHFR C677T and A1298C polymorphisms on plasma tHcy in newborns (31, 36).

The effects of lifestyle factors on tHcy have been less documented in children than in adults. As with adults, smoking was associated with elevated tHcy (20, 22, 25), which may partly be attributable to impaired vitamin status (22) and poor nutrition (49) in smokers. The effect of diet on tHcy in children is indicated by the observations of a positive association with sugar intake (19) and high tHcy in obese children (50). In addition to inadequate diet in obese children, elevated tHcy may also be attributed to relative insulin resistance (50).

Other traits linked to overweight, like diastolic blood pressure and cholesterol, do not correlate with tHcy in children (20, 22, 50), which contrasts to observations made in adults (15).

Several drugs interfering with folate metabolism or

function affect plasma tHcy in children, as documented in adults (9). In children treated with high doses of methotrexate as part of anticancer regimens, there is a transient increase in tHcy before rescue therapy with leucovorin is administered (17, 51). The cholesterol-lowering drug cholestyramine increased tHcy in children (48), and prolonged treatment of children with the anticonvulsant drugs carbamazepine or valproate increased both fasting and post-methionine load (PML) tHcy almost 2-fold (52, 53). Treatment with these drugs was also associated with reduction in folate and/or vitamin B_6 (48, 52, 54), and the tHcy elevation was more pronounced in children with the *MTHFR* T-allele (48, 54).

Diseases in Childhood

There are two types of evidence that link tHcy in childhood to cardiovascular disease (CVD). First, elevated tHcy in children shows a positive association with CVD in their parents (33, 55–57) or grandparents (56, 57) or relatives (19). Such associations may reflect environmental or genetic CVD risk factors. Second, tHcy shows a strong relation with stroke (42, 58–60), but also venous thrombosis (61) in newborns and children. These findings are potentially important, since there is serious under-recognition of neonatal and childhood stroke, and risk factors and appropriate treatment strategies are largely unidentified (62). If the role of tHcy as a strong risk factor is confirmed in larger studies, tHcy-lowering therapy with B-vitamins should be investigated.

tHcy is markedly elevated in pediatric patients with chronic renal failure, including patients on hemo- or peritoneal dialysis, but also in pediatric renal transplant recipients (63, 64). Hyperhomocysteinemia is more pronounced in renal patients with the *MTHFR T*-allele than in those with the *CC* genotype (38, 65), and is responsive to high-dose folic acid (63, 65–67). Treatment with folic acid slightly improved flow-mediated dilatation, but not significantly as compared with placebo (68). Thus, it is uncertain whether folic acid supplementation may have beneficial cardiovascular effects on pediatric renal patients.

In children (and adolescents) with early type 1 diabetes, both fasting and PML tHcy are reduced as compared to age-matched controls (39, 69–72). The reduction may be related to glomerular hyperfiltration occurring in early diabetes (73). These young patients may not have developed diabetic complications and nephropathy, which explains high tHcy in children with long-lasting diabetes type I (> 10 years) (72) and in adult diabetics (74).

Low tHcy in children with early diabetes suggests that the diabetic angiopathy is not caused by hyperhomocysteinemia. But high red cell folate in such patients is associated with better endothelial function, as measured by higher flow-mediated dilatation and lower thrombomodulin (75). This observation motivates intervention trials to assess whether folate improves endothelial function in children with diabetes.

Impaired folate status and altered homocysteine metabolism have been reported in congenital anomalies, *i.e.*, neural tube defects (NTD) and Down syndrome (76). A major role of folate metabolism in the etiology of NTD was demonstrated by the prevention of recurrent NTDs by 50–70% with folic acid supplementation. Altered folate status and elevated tHcy have been reported in both mother and child (5). The association of NTD with polymorphisms in enzymes involved in one-carbon metabolism, like MTHFR (77) and methionine synthase reductase (MTRR) (78, 79), brings additional support to an etiological role of dysfunctional folate metabolism.

Low tHcy in children with Down syndrome was demonstrated by Chadefaux and colleagues more than 15 years ago (80). This observation was confirmed and extended in a recent study showing a metabolite profile in Down's patients, suggesting increased homocysteine degradation through the trans-sulfuration pathway (81). Such increased flux may be explained by increased gene dosage and activity of cystathionine β-synthase, which is located on chromosome 21 (80). It has been speculated whether low tHcy contributes to the low frequency of atherosclerosis in Down syndrome (82), but also whether increased homocysteine degradation affects intracellular folate distribution, which in turn may explain increased methotrexate sensitivity (83, 84), increased mean corpuscular volume, gastrointestinal malabsorption (81), and impaired DNA synthesis and thereby a high incidence of leukemia (81).

Epidemiological studies indicate that folate deficiency in the mother is associated with Down syndrome (76, 85). Additional evidence of the involvement of folate metabolism is obtained from the observations of increased frequencies of the *MTHFR 677 T* and *MTRR 66 G* alleles in mothers with Down syndrome children (86–88). However, these findings have been contested in studies of Italian (89) and French populations (90), suggesting effect modification by environmental or nutritional factors.

Folate Deficiency

Folate deficiency is seldom observed in newborns (13), probably because of fetal folate stores generated by transplacental transfer of folate from the maternal to the fetal circulation. In the newborn, the folate level in the cord blood and in erythrocytes and plasma is 2–3 times higher than in erythrocytes and plasma of the mother (13, 30).

Moderate folate deficiency has been found in less than 10% of preschool children, but it may be more common in school children (91). This could be related to low dietary folate in a substantial portion of children at this age (92).

In children aged 2–19 years, there is a strong relation between serum folate and plasma tHcy, as summarized in Figure 1. This indicates that tHcy is a marker of folate status in this age group.

Plasma tHcy has been used as a folate indicator in a few studies in children. Elevated tHcy inversely associated with serum folate has been reported in children with anorexia nervosa (93) and children with HIV infection (94). Some (95–97), but not all, studies (98) have demonstrated hyperhomocysteinemia in non-supplemented children with sickle cell disease (SCD), which is a condition believed to increase folate requirements (99). Elevated tHcy may reflect impaired folate status but may also be a risk factor for stroke in SCD patients (95).

Occurrence of Cobalamin Deficiency in Childhood

In infancy, cobalamin deficiency is usually secondary to maternal deficiency, which may be related to malabsorption (including gastric surgery, short gut syndrome) or unrecognized early pernicious anemia. The most common cause is vegetarianism (100). Most cases of cobalamin-deficient infants are breastfed and born to mothers adhering to a strict vegetarian diet. There is probably insufficient cobalamin transfer across the placenta, leading to low newborn cobalamin stores (101). The inadequate cobalamin status in the newborn is further deteriorated by insufficient cobalamin in the breast milk, since cobalamin in milk is closely correlated with the low serum cobalamin in vegetarian mothers (102). These infants may develop deficiency symptoms already within 4–6 months after birth (101).

A high frequency of cobalamin deficiency in pregnant and breastfeeding women and their babies has been demonstrated in several developing countries. A diet low in animal products and intestinal parasite infection, such as Gardia lamblia infection, are common causes (13, 101, 103, 104). Studies in Mexico (104), Venezuela (105) and Kenya (106) have also demonstrated low plasma cobalamin in 33–52% of older children, which may be related to a poor diet, low in animal products.

The view prevails that cobalamin deficiency is rare in children and adolescents on a typical Western diet (107, 108). However, the pediatric reference ranges for cobalamin are poorly defined (109), and in newborns there are marked changes in serum cobalamin during the first weeks after birth (110–112). This complicates the laboratory diagnostics of cobalamin deficiency in infants and children.

Methylmalonic Acid, Homocysteine and Cobalamin Status

Early diagnosis and treatment of cobalamin deficiency in infants and children are paramount, because one possible long-term consequence is impaired cognitive performance (113, 114). In adults, MMA and tHcy in serum/plasma have been established as useful indicators of cobalamin status, and both metabolites increase in cobalamin-deficient subjects (8). tHcy is a less specific indicator of cobalamin function than MMA, because tHcy concentration is influenced by folate status and a diversity of genetic and lifestyle factors and disease states (Table 1) (9).

MMA and tHcy have been used to a limited extent to diagnose cobalamin deficiency in children. Metabolic evidence of cobalamin deficiency, in terms of elevated MMA or tHcy, has been detected in school children or older children in developing countries. The deficiency is attributed to inadequate diet (43, 115).

In newborns and infants (<1 year old), elevated MMA and/or tHcy has been reported in breastfed infants born to cobalamin-deficient vegetarian mothers (18, 116) and breastfed infants of Guatemalan mothers with low intake or malabsorption of cobalamin (117). Increased metabolite levels indicate low cobalamin stores and impaired cobalamin function in tissues in these infants.

It has consistently been observed that in newborns of well nourished mothers, serum cobalamin is high at birth and declines to about 60% during the first months of life (30, 118–120). The decline may be related to physiological redistribution and/or low cobalamin stores relative to the requirement during rapid growth and development. Measurement of the cobalamin markers MMA and tHcy may serve to distinguish between these two possibilities.

More than 10 years ago, Specker and colleagues (121) noted that the normal range for urinary MMA of infants (0.4–23 μmol/mmol creatinine) was wider and higher than that of adults (122) (0.7–3.2 μmol/mmol creatinine) and older children (123) (2.0–5.1 μmol/mmol creatinine). Plasma MMA concentration (mean (SD) = 0.36 (0.26) μmol/l) is also higher in newborns (30) and infants (40), and plasma MMA returns to adults levels at the age of 6–12 months (40). Both urine (121) and plasma MMA (30, 40) show a strong, inverse correlation with circulating cobalamin.

The infancy period, characterized by declining serum cobalamin and elevated MMA, also exhibits concentrations of serum folate (40) and plasma tHcy exceeding those found in older children (29, 30, 35, 40), and cobalamin (and not folate) is the main tHcy determinant (29–32, 35). Furthermore, there are indications that both MMA (121) and tHcy (29, 35) are reduced in newborns given cobalamin supplementation or formula rich in cobalamin.

Some observations may suggest that an elevated metabolite level in infants is an innocuous phenomenon not related to impaired cobalamin function. There may be enhanced production of MMA or its precursor(s) by intestinal micro-organisms (124, 125), and formation of MMA from odd-chain fatty acids (126) known to be present in human milk (127). Once formed, clearance of MMA may be low due to immaturity of enzyme or organ systems. The observation that plasma MMA is higher in infants than older children over the whole cobalamin distribution (40) may indicate the presence of factors affecting MMA metabolism that are independent of cobalamin status. Also, normal erythrocyte folate inversely related to tHcy (40) is not ex-

Table 2 Observations that are relevant to the question of whether impaired cobalamin status is common in infants of mothers on an omnivorous Westernized diet.

Observations suggesting impaired cobalamin status
The combination of low cobalamin, elevated MMA and elevated tHcy
Inverse and strong correlation between Hcy and cobalamin, but weak correlation between tHcy and serum folate
Relatively high serum folate positively associated with MMA
The vitamin and metabolite profiles suggesting a methylfolate trap mechanism
The metabolite concentrations responsive to cobalamin
MMA elevation predicted by factors related to negative maternal cobalamin balance
Low serum cobalamin
Multiparity
Smoking
Observations in agreement with normal cobalamin status in infants
Plasma MMA higher in infants than older children and adults over the whole cobalamin distribution
Normal erythrocyte folate inversely related to tHcy
Production of MMA precursors by intestinal micro-organisms
Odd-chain fatty acids, precursors of MMA, present in human milk
Immaturity of enzyme and organ systems

pected after a long-lasting methylfolate trap (128) (Table 2).

There are several lines of evidence pointing to commonly occurring cobalamin dysfunction in infants. Most important, in newborns and infants, there is a reduction in cobalamin occurring at a time of increase in both MMA and tHcy, and the concentrations of both metabolites are responsive to cobalamin supplementation. The MMA elevation is provoked by several factors known to cause negative cobalamin balance, such as low maternal cobalamin status (30, 121) and multiparity (30). The observed increase in serum folate, which is inversely associated with serum cobalamin and positively related to plasma MMA (40), may reflect a methyl folate trapping (Table 2). Thus, taken together, the possibility that cobalamin deficiency may be widespread and undetected in babies born to non-vegetarian women on Westernized diets (13) deserves further attention. As a first step to unravel cobalamin status in infants, reference ranges for MMA and tHcy in B-vitamin replete or supplemented subjects must be established.

Conclusion

Determinants of plasma tHcy in children are similar to those established in adults, and include age, gender, nutrition, B-vitamin status, and some drugs interfering with vitamin function. In addition, tHcy is elevated in certain medical conditions, like renal failure, and is associated with childhood stroke, but the role of tHcy in cardiovascular risk assessment has not been established.

High plasma tHcy is a responsive marker of impaired folate or cobalamin function in tissues (8). Recent reports have demonstrated that its measurement, in conjunction with the cobalamin marker MMA or the vitamin concentrations, is an efficient strategy for the diagnosis of these deficiency states in children. Metabolite determination may be particularly useful for the diagnosis of subtle deficiency states that lack the typical clinical signs of anemia and megaloblastosis (8). Deficiencies of cobalamin among infants are probably more common than hitherto recognized (13, 30), and B-vitamin deficiencies are the main indications of metabolite determination in the pediatric setting.

Acknowledgements

This work was supported by grants from the Norwegian Research Council.

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Received 17 April 2003, accepted 19 August 2003

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