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Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte

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ABSTRACT

Introduction: Combined methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type, is an inherited disorder of vitamin B_{12} metabolism caused by mutations in *MMACHC*. CblC typically presents in the neonatal period with neurological deterioration, failure to thrive, cytopenias, and multisystem pathology including renal and hepatic dysfunction. Rarely, affected individuals present in adulthood with gait ataxia and cognitive decline. Treatment with hydroxocobalamin may ameliorate the clinical features of early-onset disease and prevent clinical late-onset disease. Propionic acidemia (PA), methylmalonic acidemia (MMA), and various disorders of cobalamin metabolism are characterized by elevated propionylcarnitine (C3) on newborn screening (NBS). Distinctions can be made between these disorders with secondary analyte testing. Elevated methionine is already routinely used as a NBS marker for cystathionine β-synthase deficiency. We propose that low methionine may be useful as a secondary analyte for specific detection of cbl disorders among a larger pool of infants with elevated C3 on NBS.
Methods: Retrospective analysis of dried blood spot (DBS) data in patients with molecularly confirmed cblC disease.
Results: Nine out of ten patients with confirmed cblC born in New York between 2005 and 2008 had methionine below 13.4 μmol/L on NBS. Elevated C3, elevated C3:C2 ratio, and low methionine were incorporated into a simple screening algorithm that can be used to improve the specificity of newborn screening programs and provide a specific and novel method of distinguishing cblC from other disorders of propionate metabolism prior to recall for confirmatory testing.
Conclusions: It is anticipated that this algorithm will aid in early and specific detection of cobalamin C, D, and F diseases, with no additional expense to NBS laboratories screening for organic acidemias and classical homocystinuria.

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Introduction

Background

Combined methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type, is the most common inherited disorder of vitamin B_{12} metabolism, and has been ascribed to mutations in the *MMACHC* gene, located at 1p34.1 [1]. The biochemical defect in cblC (as well as that observed in cblD and cblF diseases) results in impaired conversion of dietary vitamin B_{12} (cobalamin, cbl) to methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl), essential cofactors necessary for normal functioning of the cytoplasmic enzyme methionine synthase and the mitochondrial enzyme methylmalonyl-CoA mutase, respectively. Methionine synthase catalyzes remethylation of homocysteine to methionine, while methylmalonyl-CoA mutase is responsible for conversion of methylmalonyl-CoA to succinyl-CoA. Untreated cobalamin C, D, and F diseases are therefore characterized biochemically by hyperhomocysteinemia, hypomethioninemia, methylmalonic acidemia, and methylmalonic aciduria. The key steps of intracellular cobalamin metabolism are illustrated in Fig. 1.

Although variable, clinical manifestations of cblC are unlike those of either isolated homocystinuria or isolated methylmalonic

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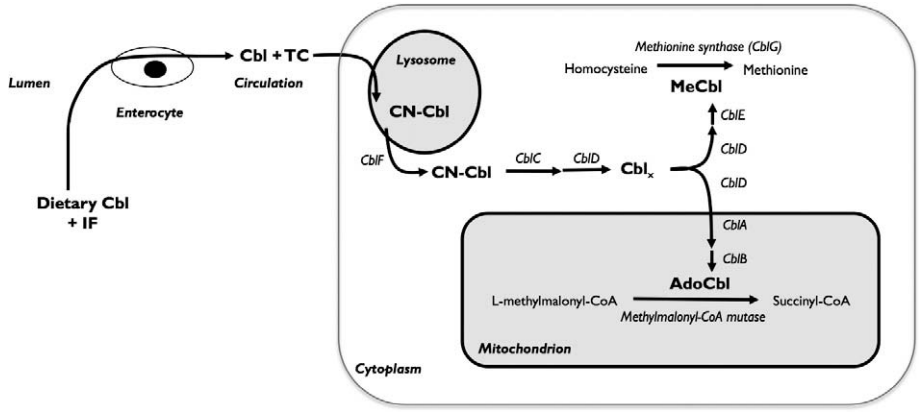

Fig. 1. Extracellular and intracellular cobalamin metabolism. Cobalamin is absorbed in the terminal ileum facilitated by gastric intrinsic factor (IF). Cobalamin enters the cell bound to transcobalamin (TC) by means of lysosome-mediated endocytosis. It is then hypothesized that the MMACHC protein accepts the cofactor from the lysosomal compartment, and catalyzes the reductive elimination of cyanocobalamin (CN-Cbl) [2]. The steps in the cytosol after lysosomal release are unclear but are defined by the complementation groups cblC and cblD [3]. In addition, the exact forms of cobalamin at this stage remain unclear and are indicated by Cblx. In the cytoplasm, cobalamin is reductively methylated by methionine synthase reductase (cblE) to methylcobalamin (MeCbl), the cofactor for methionine synthase (cblG). After its transport into the mitochondrion, cobalamin is converted to adenosylcobalamin (AdoCbl), the cofactor for methylmalonyl-CoA mutase (mut), by cobalamin adenosyltransferase (cblB).

aciduria [4]. The disorder typically presents in the newborn period with progressive neurological deterioration, manifesting as lethargy, hypotonia, and poor feeding, with seizures and coma appearing later. Affected infants frequently exhibit failure to thrive, anemia and/or pancytopenia, and multisystem pathology including renal and hepatic dysfunction, and cardiomyopathy. The disorder also appears to predispose to microangiopathic disease [5,6]. The most common *MMACHC* mutation, 271dupA, is found in approximately 40% of mutant alleles, is especially common in persons of European ancestry, and presents almost universally with the early-onset phenotype [1]. More rarely, symptomatic onset of cblC occurs later in childhood or in adulthood, in the form of acute or chronic neurological deterioration (neuropsychiatric disturbance, dementia, and gait ataxia) without systemic manifestations [7–9]. The moderate or severe hyperhomocysteinemia inherent to untreated cblC confers high risk of thromboembolic events in all age groups [10]. Following the confirmation of diagnosis, typically by complementation studies on cultured fibroblasts and/or mutational analysis to localize the defect within the cbl pathway, treatment with pharmacologic doses of cobalamin and other adjunctive therapies can be employed.

Routine screening for disorders of propionate metabolism at birth has only been possible with the introduction of tandem mass spectrometry (MS/MS). An increase in propionylcarnitine (C3) on acylcarnitine profile (ACP) may indicate the presence of propionic acidemia (PA, caused by propionyl-CoA carboxylase deficiency), methylmalonic acidemia (MMA, caused by methylmalonyl-CoA mutase deficiency), various cobalamin defects, or dietary deficiency of vitamin B_{12}. A C3 value of 1.65 μmol/L represents the 50th centile in our region. Extremely high concentrations of C3 (>10 μmol/L) generally indicate acute PA, while moderate increases (5–10 μmol/L) may indicate MMA or a cobalamin defect. It is not possible, however, to reliably differentiate between these disorders on the basis of C3 levels alone [11], and organic acid analysis and other confirmatory tests are required for accurate diagnosis [12]. There has been some debate as to the C3 level which best represents the most appropriate cut-off for newborn screening: high cut-offs will miss a proportion of cases of cobalamin disorders (false negatives), while low cut-offs will inevitably result in high numbers of false positives and consequent unnecessary parental anxiety. Some MMA disorders and cbl disorders may not produce significant concentrations of C3 and will therefore defy detection when C3 is used in isolation [13]. Many laboratories now use ratios of C3 to other acylcarnitine species (C2, C0, C16) as primary [14] or secondary [12,15] parameters for screening for disorders of propionate metabolism. When used in conjunction with C3, these metabolite ratios serve to improve the diagnostic capabilities of screening and reduce false-positive rates.

In 2002, a validation study was undertaken by the New York State screening program (Wadsworth Center) in part to establish cut-off values for the majority of analytes (amino acids and acylcarnitines) detectable by MS/MS. The estimate of an appropriate C3 cut-off was calculated as the mean value from a population of normal specimens plus eight standard deviations [16]. The cut-off was set at 7 μmol/L, slightly below the lowest calculated value, in order to accommodate data from the instrument producing the lowest cut-off. An additional cut-off was set at 5 μmol/L [13,16] such that 'borderline' cases could be subjected to additional algorithmic evaluation (C3:C2 ratio) as detailed above and a repeat specimen requested, if appropriate.

Newborn screening for PA/MMA based on C3 and C3:C2 was begun in New York State in November 2004. The screening program identifies those children that may be considered at risk for these disorders. Results are referred to specialty care centers throughout the state. The diagnosis is made by the specialty care centers based on confirmatory results and evaluation by a metabolic specialist. Until 2008, a protocol was used in New York State which referred patients with suspected disorders of cobalamin or propionate metabolism under three categories, for severe or equivocal elevations of C3 (category 1 and 2, respectively). Category 1 referrals required both a C3 value >7 μmol/L and a C3:C2 ratio >0.2. Category 2 and 3 referrals are made in the context of more modest elevations. Category 2 referrals are defined as cases where initial C3 >7 μmol/L with a C3:C2 value less than 0.2, and category 3 referrals are those where initial C3 values are in the 5–7 μmol/L range and a C3:C2 value is elevated to more than 0.2. In both the category 2 and 3 scenarios, a repeat specimen is requested, acylcarnitine profiling is repeated and cases are referred to the relevant specialty care center if repeat specimen is again 'positive' for C3 (C3 greater than 7 μmol/L or C3 in the range 5–7 μmol/L and the C3:C2 ratio greater than 0.2). The algorithm utilized until 2008 is shown in Fig. 2a.

In May 2005, methylmalonylcarnitine (C4DC) was added to the newborn screening panel as a secondary marker for PA/MMA. In some instances, samples were referred to rule out disorders of

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