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Methylmalonic aciduria, hyperhomocysteinemia, hematologic and/or neurologic abnormalities in 3 infants born to mothers with asymptomatic B₁₂ deficiency. S.M. Nikke¹, A. Mhanni¹, L. Dilling¹, L. Seargeant¹, K. Stobart¹, D. Rosenblatt², J.B. Gorlin³, M.S. Korson⁴, C.R. Greenberg¹, C. Prasad¹. ¹University of Manitoba, Winnipeg, Manitoba, Canada; ²McGill University, Montreal, Quebec, Canada; ³Memorial Blood Centers of Minnesota, Minneapolis, MN; ⁴Harvard Medical School, Boston, MA.

We describe three unrelated patients who were the offspring of mothers on unrestricted diets and presented with signs and symptoms consistent with either an acquired or inborn error of B₁₂ metabolism. All were solely breast-fed.

Presentations:

Family 1: F: 1y Developmental delay, feeding difficulties, and hypotonia
26y G₂P₂ Term, prenatal vitamins

Family 2: M: 6 wks Emesis and anemia
35y G₁P₀ Term, no prenatal vitamins

Family 3: F: 16 wks Emesis, hypotonia, and anemia
34y G₂P₂ Term, prenatal vitamins

Laboratory Values At Presentation	Family 1		Family 2		Family 3	
	Infant	Mother	Infant	Mother	Infant	Mother
Hemoglobin (Hgb) (g/L) N: 115-135/120-160	126	115	47	131	52	Normal
Mean corpuscular volume (fL) N: 73-87/80-98	109.9	86.2	91.4	100.3	96.6	Normal
Serum Cobalamin (B ₁₂) (pmol/L) N: 140-600	50	96	<74	71	70	70
Urine Methylmalonic acid (μmol/mmol creat) N<10	9100	<10	>1000	74	Elevated	N/A
Blood Homocysteine (μmol/L) N: 4.6-13	48.3	14.3	133	101	245	N/A
RBC-Folate (nmol/L RBC) N: 430-1250	951	1158	384	241	755	N/A
Complementation Studies In Fibroblasts	N/A	N/A	Normal	N/A	Normal	N/A
Schilling Test	N/A	Normal	N/A	Pernicious Anemia	N/A	Pernicious anemia

All three children showed good recovery after B₁₂ replacement, although mild hypotonia still persists in the 3rd patient. These patients demonstrate that mothers without overt signs of pernicious anemia or B₁₂ deficiency can have children with B₁₂ deficiency with anemia and neurologic abnormalities. Acquired infant B₁₂ deficiency must be considered despite a maternal dietary history that includes animal proteins.

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Vitamin B₁₂-responsive methylmalonic aciduria due to a new inborn error of adenosylcobalamin synthesis, *cbIH*. D.S. Rosenblatt, D. Watkins and N. Matiaszuk McGill University Health Centre, Montreal, Quebec Canada

Vitamin B₁₂-responsive methylmalonic aciduria is characterized by deficient synthesis of adenosylcobalamin (AdoCbl) and decreased activity of the AdoCbl-dependent mitochondrial enzyme, methylmalonylCoA mutase. Two distinct disorders of AdoCbl synthesized have been characterized (*cbIA* and *cbIB*) and they can be distinguished on the basis of somatic cell complementation analysis. Such studies have clinical usefulness because in general *cbIA* patients have a better prognosis than do *cbIB* patients. We reported a patient whose fibroblasts had the clinical and biochemical features of the *cbIA* class but complemented cells from all known inborn errors of cobalamin metabolism that cause methylmalonic aciduria, including *cbIA*. The disorder in this patient was designated as *cbIA* variant. Cells from this patient were tested against a panel of 29 cell lines from *cbIA* patients and complemented all members of this panel. These studies strongly suggest that this patient represents a novel complementation class which we have called *cbIH*. Detailed complementation analysis of a panel of 10 *cbIA* lines provided evidence of interallelic complementation. The presence of this interallelic complementation indicates that care must be taken in the use of complementation analysis to identify *cbIA* patients. These studies suggest that additional biochemical steps are required for the reduction and adenosylation of cobalamin. The full clinical spectrum of the new *cbIH* class and its implications remains to be defined.

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RadioHPLC profiles of acyl-carnitines improve detection of mild Glutaric Acidemia type II and Short Chain Acyl-CoA Dehydrogenase deficiency WJ Rhead and D Lambert University of Iowa, Iowa City, IA

Detection and diagnostic confirmation of the mild variants of glutaric acidemia, type II (GAI), also termed ethylmalonic-adipic aciduria, and short chain acyl-CoA dehydrogenase deficiency (SCAD) and its variants are problematic and challenging at both the clinical, biochemical and molecular levels. The mild variants of GAI result from partial deficiencies of either electron transfer flavoprotein or its dehydrogenase and have highly variable clinical presentations and often ephemeral metabolite excretion. Direct assay of these latter two enzymes is difficult and performed at only a few laboratories worldwide. The clinical, biochemical, enzymatic, and molecular variation in SCAD is great and complicated by the presence of two common allelic variants, 625G/A and 511C/T, whose effects on enzymatic activities are not fully understood. Quantitation of urine organic acids, plasma acyl-carnitines and urinary acyl-glycines may not suffice to clearly identify patients with these disorders due to variations in clinical status, substrate flux into the partially impaired pathways, and genetic heterogeneity. Therefore, we have modified an existing radioHPLC method for analysis of acyl-³H-carnitine esters in skin fibroblasts to optimize detection of these disorders (Schmidt-Sommerfeld, et al. *Pediatr Res*, 44:210, 1998). Incubating fibroblasts with the branched-chain amino acids, leucine, isoleucine and valine, as well as palmitate, improves detection of the mild GAI variants; the propionyl-carnitine to isovaleryl- α -methyl butyryl-carnitine ratio is a very sensitive index of impaired dehydrogenation of the branched chain acyl-CoAs. For SCAD and its variants, butyryl-carnitine content is a very sensitive measure of SCAD-mediated butyryl-CoA dehydrogenation in intact cells. In normal cells, butyryl-carnitine content is less than 2% of total cellular acyl-carnitine content, while it ranges from 10 to 25% in well defined SCAD cases lacking enzyme activity, antigen and harboring two pathogenetic mutations. In addition, we are routinely identifying patients who have clearly impaired SCAD activity, as judged by fibroblast butyryl-carnitine accumulations of 4 to 8%, who probably represent genetic compounds for the 625A/G and 511C/T variant alleles and/or other pathogenetic mutations. RadioHPLC analysis of fibroblast acyl-carnitines permits uniform, optimal challenging of the metabolic pathways in question, while minimizing the metabolite variation seen in plasma and urine analyses from patients with varying clinical, metabolic and molecular conditions. It is an important adjunct to the laboratory diagnosis of the fatty acid oxidation disorders.

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The detection of carbohydrate deficient glycoprotein syndrome by capillary electrophoresis. H. A. Taylor. Greenwood Genetic Center, Greenwood, SC.

Carbohydrate deficient glycoprotein syndrome (CDGS), which was first reported by Jaeken et al. in 1980, is a disorder in which many glycoproteins are deficient or have reduced carbohydrate side chains. Many subtypes of CDGS have been described based on the isoelectrophoretic patterns of transferrin and on clinical features. Different enzyme deficiencies have been reported in at least four of the subtypes.

Transferrin is a major serum glycoprotein utilized in the diagnosis of CDGS. It has two carbohydrate side chains each ending with two sialic acids. CDGS patients lack portions of these side chains causing different transferrin isoforms. These isoforms can be separated by isoelectric focusing which has been the method of choice for diagnosing these disorders. Capillary electrophoresis can also be used for detecting the aberrant transferrin isoforms in CDGS.

Serum of patients previously diagnosed with CDGS (types Ia, Ib, and IV) was separated by capillary electrophoresis. The transferrin pattern in CDGS patients is easily distinguished from controls in that tetrasialotransferrin is the predominant isoform in normal serum, while in the patient samples both tetra- and disialotransferrin are detected.

Capillary electrophoresis, which takes considerably less time and costs much less than the current methods, is a good choice for detecting patients with CDGS.