Increased C3 Acylcarnitine Concentration in a Newborn

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CLINICAL HISTORY AND BACKGROUND

A 2-week-old (term) female was brought to the emergency room following newborn screening results showing increased C3 acylcarnitine, (16.7 μmol/L; reference interval, <4.5 μmol/L). She was admitted for further evaluation. Acylcarnitine profile in plasma, repeated using tandem mass spectrometry (MS/MS),2 confirmed the high C3 result (10.6 μmol/L; reference interval, <0.87 μmol/L). The child was asymptomatic and was growing and developing normally with no concerns. A urine sample was collected for organic acids analysis by GC-MS (Fig. 1).

DIAGNOSIS AND SUMMARY

This child has methylmalonic acidemia (MMA), a term used to describe a group of metabolic disorders biochemically characterized by the accumulation of methylmalonic acid in body fluids. In addition to the production of methylmalonic acid, these disorders are further subclassified based on enzymatic and genetic complementation analysis (1). MMA is caused by a defect in the conversion of L-methylmalonyl-CoA to succinyl-CoA, catalyzed by the enzyme methylmalonyl-CoA mutase (EC.5.4.99.2), which requires 5-deoxyadenosylcobalamin (AdoCbl) as a cofactor. This patient has MMA cblA type, caused by a defect in the intramitochondrial processing of vitamin B12 (in the form of hydroxocobalamin), the precursor of the active cofactor AdoCbl. Deficiency of AdoCbl results in decreased MMCoA mutase activity, accumulation of methylmalonyl-CoA, and subsequent production of methylmalonic acid. The methylmalonic acidemias include disorders in which the MMCoA mutase itself is defective (mut0 or mut− types), defects in the production of AdoCbl (cblA, or cblB types) or combined disorders of cobalamin and homocysteine metabolism (cblC, cblD, or cblF types).

The diagnosis was made in this child by newborn screening using MS/MS to confirm an increased C3 (propionylcarnitine) concentration. Since the propionyl-CoA carboxylase enzyme reaction is reversible, propionyl-CoA accumulates and conjugates to free carnitine to produce propionylcarnitine (Fig. 2). However, since increased propionylcarnitine may be observed in both propionic and methylmalonic acidemias, further testing with organic acid analysis is necessary. Subsequent second-line organic acid analysis by GC-MS revealed the presence of methylmalonic acid (723 mg/g creatinine; reference interval: <10 mg/g creatinine), in addition to 2-methylcitric acid, a metabolic byproduct of propionyl-CoA.

One of the most common causes of MMA in newborns is deficiency of vitamin B12, particularly if the mother follows a strict diet (e.g., vegan) or has subclinical pernicious anemia. In this case, the child’s plasma vitamin B12 was within the reference interval at 254 pg/mL (reference interval, 126–717 pg/mL), effectively excluding dietary deficiency as a cause of the MMA. Plasma amino acids were also within reference intervals, excluding a combined disorder of cobalamin and homocysteine metabolism, such as cblC, cblD, or cblF types. Although the concentrations of methylmalonic acid in cblA patients are generally less than those observed in cases of MMCoA mutase deficiency (mut0 or mut− types), the concentration per se is of limited value in discriminating between different groups of MMA, requiring enzyme studies or molecular analysis. In this case, sequencing of the methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) gene, which encodes the cblA

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Received April 22, 2016; accepted May 23, 2016.
DOI:10.1373/clinchem.2016.259705
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1 Nonstandard abbreviations: MS/MS, tandem mass spectrometry; MMA, methylmalonic acidemia; MMCoA, methylmalonyl-CoA; cbl, cobalamin.
protein, revealed 2 compound heterozygous mutations, C433C>T and c.450_451InsG.

Unless detected by newborn screening, cblA type patients typically present in the first year of life with recurrent vomiting, dehydration, hepatomegaly, respiratory distress, hypotonia, and various degrees of encephalopathy. Severe keto- and lactic acidosis, neutropenia, and hyperammonemia are important laboratory features. Many mild cblA cases...
detected by newborn screening remain asymptomatic throughout life. In cblA patients who do present clinically, their presentation is generally later than in the mut types, and their clinical outcomes are more favorable. Also, in contrast to the mut types, a substantial number of cblA type patients respond to treatment with vitamin B₁₂ (hydroxocobalamin). In this case, the child responded biochemically to hydroxocobalamin (1 mg daily) in combination with protein restriction with no further complications, remaining asymptomatic.

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What Is Your Guess?

Three Patients with an Unusual Pattern on Urine Immunofixation

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CASE DESCRIPTION

Three unrelated urine immunofixations, ordered for diagnostic purposes of monoclonal gammopathy of renal significance (MGRS) (1, 2), exhibited several abnormal fractions in the protein electrophoresis lane (Fig. 1, A–C). Corresponding monoclonal fractions were undetectable in the immunofixation lane against γ/κ/μ heavy chains and κ or λ (free) light chains. All patients had a medical history of type 1 diabetes mellitus and a combined kidney and pancreas transplant. Total urinary protein concentrations were 0.84, 0.78, and 0.26 g/L, respectively.

Fig. 1. (A–C), immunofixation on urine concentrated 20 to 25 times; samples from 3 different patients (Sebia, Lisses, France). ELP, protein electrophoresis lane; GAM, immunofixation lane against γ/κ/μ heavy chains; K, immunofixation lane against all κ light chains; L, immunofixation lane against all λ light chains; Kf, immunofixation lane against free κ light chains; Lf, immunofixation lane against free λ light chains.

QUESTIONS

• What is the purpose of the pancreas transplant?
• How can the presence of abnormal fractions in the protein electrophoresis lane of the urine immunofixation be explained?
• What additional laboratory studies could be used to support the diagnosis of MGRS?