Infantile mitochondrial DNA depletion syndrome associated with methylmalonic aciduria and 3-methylcrotonyl-CoA and propionyl-CoA carboxylase deficiencies in two unrelated patients: A new phenotype of mtDNA depletion syndrome

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Summary: Mitochondrial DNA (mtDNA) depletion refers to a quantitative defect in mtDNA and is heterogeneous with regard to causal genotypes and the associated clinical phenotypes. We report two unrelated infants with mtDNA depletion. A diagnosis of methylmalonic aciduria was initially raised in both on the basis of high urine methylmalonic acid and related organic acids and elevated propionylcarnitine and methylmalonylcarnitine. Carboxylase assay with skin fibroblasts revealed low propionyl-CoA and 3-methylcrotonyl-CoA carboxylase and normal pyruvate carboxylase activities. Quantitative Southern blot analysis of mitochondrial and nuclear DNA with muscle tissues revealed the patients’ mtDNA to be depleted to 24% and 39% of normal controls. Our two patients showed multiple mitochondrial dysfunction including respiratory chain defects and deficiencies in the two nuclear DNA encoded carboxylases resulting in abnormal urine organic acids. To our knowledge, there is no obvious connection between the defective pathways other than their mitochondrial locations. These two cases may represent a new entity of mitochondrial disease that might be
due to a defective common mechanism, such as assembly, maintenance and transport, affecting various mitochondrial enzymes and functions. Mitochondrial depletion should be considered in infants with atypical organic aciduria that may resemble methylmalonic aciduria, propionic acidemia, or 3-methylcrotonyl-CoA carboxylase deficiency.

Mitochondrial DNA (mtDNA) depletion syndrome (McKusick 251880) was first described by Moraes and colleagues (1991) as a new class of mitochondrial disease characterized by a quantitative rather than a qualitative abnormality of mtDNA. It refers to a low mtDNA copy number and is highly heterogeneous in terms of associated clinical phenotype and causal genotype. Known clinical phenotypes include Leigh disease (Absalon et al. 2001; Filiano et al. 2002), Alpers syndrome (Naviaux et al. 1999), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE; Papadimitriou et al. 1998), Kearns–Sayre syndrome (Barthélémy et al. 2001), hypertrophic cardiomyopathy (Marin-Garcia et al. 1998), infantile cholestasis and progressive liver fibrosis (Ducluzeau et al. 1999; Mandel et al. 2001a), and nonspecific symptoms such as developmental delay, failure to thrive, muscle weakness and lactic acidosis (Barthélémy et al. 2001; Moraes et al. 1991). Several enzymes have been reported as being causal for mtDNA depletion: mitochondrial deoxyguanosine kinase (EC 2.7.1.113) for hepatocerebral form (Mandel et al. 2001b), thymidine kinase (TK2: EC 2.7.1.21) for myopathic form (Saada et al. 2001), thymidine phosphorylase (EC 2.4.2.4) for MNGIE (Nishino et al. 2001) and mitochondrial gamma polymerase (EC 2.7.7.7) for Alpers syndrome (Naviaux et al. 1999). Most children affected with mtDNA depletion syndrome present in infancy or early childhood with a variety of symptoms depending on the affected tissues. Liver, kidney and skeletal muscle abnormalities are most frequently observed.

Biochemical studies in patients with mtDNA depletion have shown decreased activity of the respiratory chain complexes (I, II/III, IV and V) in the affected tissue. A patient with mtDNA depletion associated with 3-methylglutaconic aciduria with normal hydratase has recently been reported (Scaglia et al. 2001). We report two unrelated patients diagnosed with mtDNA depletion syndrome who showed distinctive clinical presentation in which methylmalonic aciduria (MMA) was initially raised as determined by urine organic acid analysis and plasma acylcarnitine analysis by tandem mass spectrometry. Although multiple mitochondrial respiratory chain enzymes have been reported deficient in mtDNA depletion syndrome, deficiencies of specific nuclear-encoded mitochondrial enzymes involving organic acid metabolism have not been reported. Our cases showed deficient 3-methylcrotonyl-CoA carboxylase (MCC, EC 6.4.1.4) and propiony-CoA carboxylase (PCC, EC 6.4.1.3) activities and abnormal urine organic acids that were atypical for any known organic acidemias. Mitochondrial depletion syndrome should be considered in infants with atypical organic aciduria with elevated TCA cycle intermediates and elevated organic acids associated with propionic acidemia, MMA or MCC deficiency. These two cases may represent a new entity of mitochondrial disease, wherein pathology results from a defective mechanism that may be central to mitochondrial function.