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SHORT REPORT

Silent and symptomatic primary carnitine deficiency within the same family due to identical mutations in the organic cation/carnitine transporter OCTN2

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Summary: A family of Turkish origin with primary systemic carnitine deficiency in the father and his two sons is described. In all three individuals, the same homozygous mutation in the OCTN2 gene (R471H) was present and carnitine uptake in fibroblasts was deficient. Whereas one boy became symptomatic with a Reye-syndrome-like picture of hepatopathy and encephalopathy in infancy, the other affected family members remained asymptomatic up to their current ages of 28 and 5 years, respectively.

Primary systemic carnitine deficiency (McKusick 212140) is an autosomal recessive disorder of mitochondrial β-oxidation resulting from defective carnitine transport. This disorder is caused by heterogeneous mutations in the organic cation/carnitine transporter (OCTN2, McKusick 603377) gene *SLC22A5* located on human chromosome 5q31 (Nezu et al 1999). Carnitine is essential for the transfer of long-chain fatty acids from cytosol into mitochondria for subsequent β-oxidation. A lack of carnitine results in impaired energy production from long-chain fatty acids, especially during periods of fasting or stress. Disease phenotypes are heterogeneous, comprising early-onset hypoketotic hypoglycaemia, Reye syndrome and sudden infant death, as well as later-onset skeletal myopathy and/or cardiomyopathy. Phenotypic variability has been observed in affected siblings with identical mutations (Wang et al 2000). In addition, heterozygous individuals have been reported with a predisposition to late-onset benign cardiac hypertrophy (Koizumi et al 1999).

We report a family of Turkish origin with primary carnitine deficiency in two brothers and the father. Clinically, this disorder became manifest with a Reye-syndrome-like picture of hepatopathy and encephalopathy induced by fever and gastroenteritis in one of the boys at 11 months of age. Cardiomyopathy

was excluded. The acylcarnitine profile by tandem mass spectrometry demonstrated systemic carnitine deficiency, with a free serum carnitine of 1 μmol/L. Family screening revealed free serum carnitine concentrations of 2 μmol/L in the father and 3 μmol/L in the brother. Carnitine uptake in fibroblasts was deficient in both boys and the father (<0.05 pmol/min per mg protein) and confirmed the OCTN2 transporter defect. In all three individuals, the same homozygous mutation in the OCTN2 gene (R471H) was delineated, which has not been reported before. The mother was heterozygous for this mutation.

OCTN2 exhibits about 30% similarity with the organic anion transporter (OAT) and organic cation (OCT) transporter families and arginine at position 471 is conserved in the different species of OAT and OCTN families, suggesting functional and structural importance. For the rOAT3 gene, it has been shown that the residue corresponding to R471 is essential for recognition and transport of organic anions (Feng et al 2001). For the rOCT1 gene, the otherwise polyspecific transporter has been more selective due to a mutation at the residue corresponding to R471 (Gourboulev et al 1999), suggesting that a mutation at the R471 position in human OCTN2 is likely disease-causing.

Clinical investigations in the father at 28 years and the brother at 5 years excluded any carnitine deficiency-associated symptoms. Neither recalled any known stressors such as severe illnesses. In fact, the father regularly performed high-intensity exercise. The index patient remained asymptomatic during follow-up until 5 years of age, but mildly elevated serum creatine kinase and transaminase concentrations were observed during infectious illnesses.

Carnitine was supplemented in all three individuals (80–100 mg/kg per day), but the father did not comply with regular treatment. With carnitine supplementation, plasma free carnitine was 28.6 μmol/L (controls >23) in the index patient and 19.0 μmol/L in the elder brother. The father presented with a low plasma free carnitine of 7.0 μmol/L during follow-up. Under treatment, urinary excretion of carnitine was strongly increased in both boys, with free carnitine concentrations of 211.3 μmol/mmol creeatine (controls 3–51) in the patient and 340.6 μmol/mmol creatinine in the asymptomatic brother. Concentrations of total carnitine were 310.5 and 452.8 μmol/mmol creatinine (controls 15–70), respectively, in urine collected over a period of 24 h. These data clearly demonstrate the loss of carnitine due to deficient uptake in the kidney.

We here present the first case of asymptomatic primary carnitine deficiency through adulthood diagnosed because of disease manifestation in the son. The lack of correlation between residual carnitine uptake and the severity of clinical presentation suggests that disease manifestation is due to exogenous stressors (Lamhonwah et al 2002), as known from other β-oxidation defects.

Expanded newborn screening by tandem mass spectrometry may identify asymptomatic individuals with primary carnitine deficiency, raising the question whether carnitine supplementation should be implemented on a regular basis. Our data demonstrate that low free serum carnitine concentrations do not result in a specific phenotype under normal conditions, supporting the fact that

environmental modifiers as well as the supply of carnitine in the diet affect onset and type of phenotypic expression.

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