Primary Carnitine (OCTN2) Deficiency Without Neonatal Carnitine Deficiency

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Abstract Although the diagnosis of a primary carnitine deficiency is usually based on a very low level of free and total carnitine (free carnitine: 1–5 μM , normal 20–55 μM) (Longo et al. 2006), we detected a patient via newborn screening with a total carnitine level 67 % of the normal value. At the age of 1 year, after interruption of carnitine supplementation for a 4-week period the carnitine profile was assessed and the free carnitine level had dropped to 10.4 $\mu\text{mol/l}$ (normal: 20–55 μM) and total carnitine level had dropped to 12.7 $\mu\text{mol/l}$ (normal: 25–65 μM). Transient carnitine deficiency was not likely anymore and DNA mutation analysis of the OCTN2 (SLC22A5) gene showed a homozygous c.136C>T (p.P46S) mutation, confirming the diagnosis of primary carnitine deficiency. We would like to emphasize that neonates with a primary carnitine deficiency might present with relatively high levels of total carnitine due to placental carnitine transfer, and also draw the attention to the importance of regular follow-up and the significance of genetic diagnostics in patients with a nonclassical presentation.

Introduction

Although the diagnosis of a primary carnitine deficiency is usually based on a very low level of free and total carnitine (free carnitine: 1–5 μM , normal 20–55 μM) (Longo et al. 2006), we detected a patient via newborn screening with a total carnitine level 67 % of the normal value.

Primary carnitine deficiency is an autosomal recessive disease caused by a defect in OCTN2 (OMIM 212140), a carnitine transporter, due to various mutations of the *SLC22A5* gene. OCTN2 is expressed in muscle, heart, kidney, lymphoblasts, and fibroblasts. *SLC22A5* mutations result in impaired fatty acid oxidation in skeletal and heart muscle (Longo et al. 2006). In addition, renal wasting of carnitine results in low serum levels, usually with free carnitine levels between 1 and 5 μM . The disease can present in infancy with acute hypoglycemic episodes or in childhood with cardiomyopathy and muscle weakness. Carnitine supplementation can prevent these episodes. Usually total carnitine levels are < 2.5–10 % of the normal value and in urine elevated levels of free carnitine are detected (Longo et al. 2006).

A male neonate was referred to our hospital with a suspicion on primary carnitine deficiency because of a positive newborn screening (NBS). The free carnitine level (C0) in the NBS bloodspot was 3.9 $\mu\text{mol/l}$ (age: 7 days). The boy, born at term with a birth weight 3,590 g, was in a good clinical condition and showed no signs of muscle weakness. Confirmatory testing at the age of 11 days in our laboratory showed a free carnitine of 12.4 $\mu\text{mol/l}$ (normal 20–55 $\mu\text{mol/l}$) and a total carnitine concentration of 16.8 $\mu\text{mol/l}$ (normal 25–65 $\mu\text{mol/l}$). Plasma carnitine levels in the mother were normal (free: 25.3 μM , total: 29.6 μM). Because of a relatively high carnitine level for the suspected diagnosis of primary carnitine deficiency, the

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possibility of transient carnitine deficiency was also considered in the differential diagnosis, and a carnitine supplementation of 50 mg/kg was initiated. The dose was adjusted to 30 mg/kg upon controlling carnitine levels after 6 months of therapy. On supplementation, total carnitine values remained between 50.3 $\mu\text{mol/l}$ and 63.3 in the first year of life and the child showed no clinical symptoms. At the age of 1 year, after interruption of carnitine supplementation for a 4-week period the carnitine profile was assessed again. Unexpectedly, the free carnitine level had dropped to 10.4 $\mu\text{mol/l}$ (normal: 20–55 μM) and total carnitine level had dropped to 12.7 $\mu\text{mol/l}$ (normal: 25–65 μM). A urine sample showed elevated excretion of free carnitine (50.0 $\mu\text{mol/mmol}$ kreatinine; normal < 35 $\mu\text{mol/mmol}$). Supplementation of L-carnitine was resumed. A cardiac ultrasound showed no abnormalities. DNA mutation analysis of the *OCTN2* (*SLC22A5*) gene showed a homozygous c.136C>T (p.P46S) mutation in the patient and heterozygous state in both the parents, confirming the genetic diagnosis of a primary carnitine deficiency.

The male patient is now 4 years old and on continuous supplementation of L-carnitine, 60 mg/kg; the plasma carnitine levels, both free and total, remain in the normal range. Clinically, the patient showed a transient motor developmental delay with starting to walk at 20 months, but his development is now adequate for his age. He has a mildly decreased muscle strength and has a history of muscle pain, which has resolved spontaneously. Temporarily increasing the carnitine dose to 100 mg/kg had no effect on these complaints. On the contrary, he started to complain about side effects of the carnitine, including diarrhea and intestinal discomfort. At follow-up, his cardiac function has always been normal.

To our knowledge, the *SLC22A5* c. 136 C>T mutation has not been described before in homozygous state. It has been described as a heterozygous mutation in asymptomatic

mothers of patients. Although these carrier individuals showed a decreased carnitine transport, it was higher than symptomatic patients (Rose et al. 2012). It has been also described in a patient with severe decreased carnitine transport in fibroblasts (Schimmenti et al. 2007), in combination with a null mutation, c. 844C>T, p.R282X, identified before as a pathogenic mutation (Wang et al. 1999). In a study on glycosylation of the OCTN2 carnitine transporter (Filippo et al. 2011), it is postulated that the p. P46S mutation retains residual transport activity and might be responsible for a milder or no overt phenotype. This could explain the relatively high carnitine level detected in our patient.

In summary, we would like to emphasize that neonates with a primary carnitine deficiency might present with relatively high levels of total carnitine due to placental carnitine transfer, and also draw the attention to the importance of regular follow-up and the significance of genetic diagnostics in patients with a nonclassical presentation.

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