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CASE REPORT

Neonatal lethal mitochondrial trifunctional protein deficiency mimicking a respiratory chain defect

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We report the third (a girl; A) and the fourth (a boy; B) children of an unrelated healthy Turkish couple with two other healthy girls. They were born after uneventful pregnancies and deliveries. In both neonates, an identical disorder occurred leading to death at the ages of 4 days and 2 days, respectively. At the age of 24 h, both presented with neurological distress, severe metabolic acidosis and impaired perfusion. Within the next 24 h both developed dilated cardiomyopathy and had cardiac arrhythmia and cardiac arrest leading to death in patient B. Child A was resuscitated. Renal failure occurred and peritoneal dialysis was initiated. This child died at 4 days of age owing to cardiorespiratory failure. Special laboratory evaluations revealed a tendency for hypoglycaemia, increased plasma ammonia concentrations (165 $\mu\text{mol/L}$ and 100 $\mu\text{mol/L}$ for patients A and B respectively), greatly increased blood lactate levels (20.5 mmol/L and 14.5 mmol/L), and elevated plasma creatine kinase (1130 U/L, measured only in child A). At the second day of life, child A showed greatly increased urinary lactic acid excretion with an otherwise normal organic acid pattern; she was on intravenous glucose at this time. The urine of child B contained excessive amounts of lactic acid and substantial amounts of ketones (3-hydroxybutyric acid 500 $\mu\text{mol/mmol}$ creatinine, normal <80) and $\text{C}_6\text{--C}_{10}$ dicarboxylic acids. In particular, adipic acid was greatly increased (1860 $\mu\text{mol/mmol}$ creatinine, normal <20) and to a lesser degree suberic acid (57 $\mu\text{mol/mmol}$ creatinine, normal <10). In addition, the urine contained increased amounts of unsaturated adipic and suberic acids, 3-hydroxyadipic, 3-hydroxysuberic and 3-hydroxysebacic acids as well as 3-oxoadipic acid.

In both children, autopsy produced no results indicative of a specific disorder. The tissue analyses of child A (liver, skin fibroblasts) for respiratory chain complexes including pyruvate dehydrogenase and pyruvate carboxylase (W. Ruitenbeek, Nijmegen) gave normal results. Later, fatty acid oxidation studies in cultured skin fibroblasts demonstrated decreased rates for myristic and palmitic acids as substrates. After it had been established that the patient's defect in fatty acid oxidation was not due to a deficiency of any of the acyl-CoA dehydrogenases, strikingly reduced activities were demonstrated for the enoyl-CoA hydratase measured with 2-laureoyl-CoA ($\text{C}_{12:1}$) as a substrate (23 nmol/min per mg protein, normal 79 ± 26 ($n = 50$)) and for the 3-hydroxyacyl-CoA dehydrogenase measured in the reverse

direction with 3-ketohexadecanoyl-CoA (16 nmol/min per mg protein, normal 81.3 ± 22.7 ($n = 91$)). Undetectable activity (normal 20.9 ± 7.9 nmol/min per mg protein ($n = 38$)) was found for the thiolase using 3-ketohexadecanoyl-CoA. The 3-hydroxyacyl-CoA dehydrogenase measured with acetoacetyl-CoA was normal. These results establish a mitochondrial trifunctional protein (MTP) deficiency in this family which so far has been described in its early lethal and a later-manifesting form in 4 patients (Jackson et al 1992; Wanders et al 1992; Dionisi-Vici et al 1996).

Degradation of long-chain fatty acids by mitochondrial β -oxidation involves the sequential action of very-long-chain acyl-CoA dehydrogenase followed by the mitochondrial trifunctional protein, which is an octamer of 4 α and 4 β subunits. Whereas the α subunit contains both the enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase activity, the β subunit catalyses the thiolase step. The clue to the suspicion of a β -oxidation defect in our family was the impressive dicarboxylic aciduria in patient B. However, the MTP deficiency was established in fibroblasts of child A, who showed an organic acid pattern in urine that was much more indicative of a pyruvate degradation defect.

The clinical course of MTP deficiency in our family, including signs of dilated cardiomyopathy, is very similar to that of a neonatal lethal form of isolated long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (Duran et al 1991). Our patients had metabolic acidosis with high blood lactate concentration which could not directly be attributed to an extremely distressed state. Contrasting with normal lactate levels in patients with other defects of β -oxidation, lactic acidosis appears to be a frequent feature in LCHAD deficiency (Sewell et al 1994). This has been shown to occur owing to an inhibitory effect on the system of oxidative phosphorylation by intermediates of fatty acid oxidation in this particular disorder, leading to an inhibition of pyruvate oxidation and to a shift to lactate formation (Ventura et al 1996).

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