Milder childhood form of very long-chain acyl-CoA dehydrogenase deficiency in a 6-year-old Japanese boy

Received: 17 April 2000 / Accepted: 5 July 2000

Abstract We investigated the clinical and biochemical characteristics of a 6-year-old Japanese boy with very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. He had hypoketotic hypoglycaemia, exercise- and fasting-induced lethargy, hepatomegaly and cardiomegaly. Significant laboratory findings included elevated plasma levels of creatine phosphokinase and acyl-carnitine and a fatty liver at biopsy suggesting a diagnosis of VLCAD deficiency.

Conclusion The diagnosis of very long-chain acyl-CoA dehydrogenase deficiency was supported by the results of acyl-CoA dehydrogenase activity for C₈ and C₁₆ fatty acids in skin fibroblasts from the patient. Treatment with medium chain triglycerides and L-carnitine in the diet improved his hepatomegaly and cardiomegaly.

Key words Cardiomegaly · Fatty liver · Hepatomegaly · Hypoglycaemia · Very long-chain acyl-CoA dehydrogenase

Abbreviation VLCAD very-long-chain acyl-CoA dehydrogenase

Introduction

Soon after very long-chain acyl-CoA dehydrogenase (VLCAD) was first identified in 1992 [10], several patients were diagnosed as having VLCAD deficiency [3, 6, 25]. Some patients who previously had been diagnosed as having long-chain acyl-CoA dehydrogenase deficiency were found to have VLCAD deficiency [16, 25].

The main clinical symptoms of VLCAD deficiency include muscle weakness, hepatomegaly, cardiomegaly and episodes of hypoketotic hypoglycaemia. Three groups of patients with VLCAD deficiency have been described [2]. In the severe childhood form, characterised by early onset of symptoms with cardiomyopathy, some patients died in circumstances resembling sudden infant death syndrome [4, 5, 6, 25]. In the milder childhood form, characterised by a later onset of symptoms, the main features are hypoketotic hypoglycaemia and rarely cardiomyopathy [5, 15, 23]. Recently, Roe et al. [18] reported sudden unexpected death of a child with unrecognised VLCAD deficiency who required a restorative dental procedure. In the adult form, the main symptoms are exercise- or fasting-induced muscle weakness, rhabdomyolysis and myoglobinuria [14, 19, 21].

In this report, we describe a 6-year-old Japanese boy with VLCAD deficiency whose symptoms and signs appeared at the age of 1 year. Although he had exercise-induced and fasting lethargy, symptoms mainly resembling the milder childhood form, he also had a fatty liver and congestive heart failure.
Case report

Our patient was a 6-year-old Japanese boy, who was born weighing 2450 g to unrelated healthy parents, after 38 weeks of gestation without delivery complications. His history revealed five previous admissions because of lethargy and elevated serum levels of AST, ALT and CK. On the first admission, when he was 13 months old, he had wheezing and dyspnoea and serum transaminase levels were elevated (ALT 150 IU/l, AST 110 IU/l). On the second admission, when he was 4 years and 9 months old, he presented with dehydration due to vomiting, poor appetite and influenza-like symptoms. On this occasion, the laboratory findings showed elevations of AST, ALT and CK to 97 IU/l, 98 IU/l and 886 IU/l, respectively. Urinalysis revealed no specific findings. On the third admission, when he was 5 years and 10 months old, he presented with an acute attack of asthma with a productive cough and wheezing lasting 5 days. He was lethargic with frequent vomiting and serum levels of AST, ALT and CK were markedly elevated at 116 IU/l, 76 IU/l and 1607 IU/l, respectively. Urinalysis revealed no ketonuria or any other specific findings. One month later, he was admitted again with frequent vomiting and mild wheezing. On each admission, he was treated with an intravenous infusion of glucose and recovered dramatically within a few days.

At the age of 6 years and 10 months, he was again admitted to this hospital with a high fever, vomiting, and stupor, and subsequently became lethargic. With neck stiffness and a raised CSF cell count of 38/mm3, a diagnosis of aseptic meningitis was made. He had mild hepatomegaly (Fig. 1a), and a liver biopsy showed a fatty liver (Fig. 1b). The laboratory investigation showed an elevated serum AST level of 83 IU/l, an ALT level of 58 IU/l and a CK level of 1388 IU/l with a CK-MB level of 10.2%. Ketonuria was not detected. Echocardiography showed a dilated left ventricle and poor left ventricular contractility, with an ejection fraction of 40%.

Methods and results

Plasma levels of free carnitine and acylcarnitine were analysed in an assay using mass spectrometry [12].

Skin fibroblasts obtained from the patient were cultured in minimum essential medium with 10% fetal calf serum. Fibroblast pellets were sustained in 50 mM sodium phosphate (pH 8.0), 0.1% Triton X-100, and 0.2 M sodium chloride. After sonication and incubation for 30 min on ice, the supernatant was obtained by centrifugation at 10,000 x g for 10 min. Assay for acyl-CoA dehydrogenase activity was done by the dye-reduction method described by Verity and Turnbull [22], but with some modification [24].

The levels of free carnitine and acylcarnitine in plasma were decreased. C14:1 acylcarnitine was detected. Acyl-CoA dehydrogenase activity in the fibroblast homogenate of the patient, measured using substrates of chain length C24:0 was 13.0% of the control value; its activity with the medium chain length substrate was normal (Table 1).

Treatment with MCT milk and L-carnitine

Once the diagnosis of VLCAD deficiency had been established, our patient was treated with diuretics for heart failure and with a dietary supplementation of L-carnitine (45 mg/kg per day). One month later, after school sports, he suffered muscle weakness, pain in the feet and lethargy. Laboratory investigations showed an elevated serum AST level of 570 IU/l, an ALT level of 230 IU/l and a CK level of 16,430 IU/l with a CK-MB level of 35.4%. His blood glucose level was low at 47 mg/dl. Ketonuria was not detected. He improved soon after treatment with an intravenous infusion of glucose. Dietary supplementation with MCT milk in addition to L-carnitine was then initiated.

With 1.5 g/kg per day of MCT milk and 45 mg/kg per day of L-carnitine supplements, the patient improved clinically as demonstrated by the normal transaminase and slightly elevated CK