Short Communication

Fatal Cardiomyopathy Associated with 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

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3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency (HMG-CoA lyase; EC 4.1.3.4; McKusick 246450) is an inborn error of ketogenesis and L-leucine catabolism. HMG-CoA lyase catalyses the final step in leucine degradation, converting HMG-CoA to acetyl-CoA and acetoacetic acid. Clinical manifestations include hepatomegaly, lethargy and apnoea. Biochemically there is a characteristic absence of ketonuria with hypoglycaemia, acidosis and variable hyperammonaemia (Gibson et al 1988). The urinary organic acid profile includes elevated concentrations of 3-hydroxyisovaleric (3-HIV), cis- and trans-3-methylglutaconic (3-MGC), 3-methylglutaric (3-MGR), and 3-hydroxy-3-methylglutaric (HMG) acids. Confirmatory enzyme diagnosis is made in cultured fibroblasts or leukocytes. In this report we describe a patient with HMG-CoA lyase deficiency who manifested a fatal arrhythmia associated with dilated cardiomyopathy, a clinical feature previously unreported in HMG-CoA lyase deficiency.

CASE REPORT AND FINDINGS

A.J., a male born to non-consanguineous parents, presented at 4 months of age (during an intercurrent illness and otitis media) with vomiting, lethargy, apnoea, respiratory arrest, hypoglycaemia (0–6 mg/dl), hyperammonaemia (647 μmol/l) and

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291
acidaemia (venous blood pH 7.34, bicarbonate 8–13 mmol/L). Blood glucose and ammonia levels normalized with administration of normal saline and 10% dextrose solution. Cardiac and abdominal examinations were normal, and there were no dysmorphic features. Subsequently he was generally well with normal growth and development, although by age 5 months he had experienced two additional episodes of hypoglycaemia and hyperammonaemia associated with minor illnesses requiring brief hospitalization for intravenous fluids. He was placed on a low-protein diet and 4 ml of carnitine twice daily, and did well until 7 months of age when he was again hospitalized with a febrile upper respiratory illness and metabolic decompensation. He did not respond rapidly to metabolic correction as he had previously and was still persistently acidotic on day 3 of hospitalization. He was noted to have tachyarrhythmia (heart rate 168) with idioventricular rhythm that progressed to ventricular fibrillation. Emergency echocardiogram revealed poor left ventricular function, suggesting a marked cardiomyopathy. Cardiomegaly was noted on chest radiography. Despite intubation, ventilation, and vigorous pharmacological resuscitation, he died 50 hours after admission.

Enzyme and metabolite findings: Urinary organic acids were analysed by gas chromatography–mass spectrometry as the trimethylsilyl derivatives following ethyl acetate extraction of acidified urine using liquid–liquid columns (Varian CE 1005). Approximate quantitation is given relative to the area of an internal standard, undecanedioic acid. HMG-CoA lyase activity was determined in fibroblast extracts by radiochemical and fluorimetric methods (Gibson et al 1990; Wanders et al 1988). Urinary organic acids at presentation were approximately (mmol/mol creatinine): 3-HIV, 2230 (control 0–46); 3-MGR, 380 (control 0–7); 3-MGC (both isomers combined), 4542 (control 0–9); HMG, 5350 (control 11–36); glutaric acid, 280 (control 0–2); control ranges taken from Sweetman (1991). HMG-CoA lyase activities in extracts of fibroblasts from patient and controls were (nmol/min per mg protein): control (n = 4), 8.2–28.2; patient 0–0.9 (each cell line assayed 1–3 times on separate occasions). The activities of control enzymes assayed in parallel, propionyl-CoA carboxylase and glutamate dehydrogenase, were comparable between patient and controls.

Pathological examination: At autopsy, the heart had a normal mass but exhibited four-chamber dilatation. Atrial and ventricular sections exhibited zonal, very fine vacuolar cytoplasmic changes (Figure 1). There was no evidence of myocarditis. Skeletal and diaphragmatic muscle sections were free of these degenerative vacuolar features. There was congestion of the viscera with mild pulmonary oedema, pleural effusions, and ascites. The enlarged liver (440 g; expected 267 ± 54 g) was pale tan and mildly congested, with fine to moderate-sized vacuolar lipid degenerative changes involving every cell. Fine vacuolar degenerative changes were also seen in central nervous system with generalized oedema, as well as some foamy changes in renal tubular epithelium. The lymph nodes were enlarged and oedematous with lymphocyte depletion, and acute duodenitis was noted. Pre- and post-mortem viral cultures and serologies were negative.