Pediatr Cardiol 24:295–297, 2003
DOI: 10.1007/s00246-002-0277-2

Pediatric Cardiology

Cardiomyopathy and Pericardial Effusion in Infancy Point to a Fatty Acid β-Oxidation Defect After Exclusion of an Underlying Infection

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Abstract. Pericardial effusion and cardiomyopathy in the first year of life point to a fatty acid β-oxidation defect as underlying disease after exclusion of infectious causes. We report two patients with the early-onset, cardiac phenotype of very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency; in one patient, severe pericardial effusion was the predominating symptom. Because specific noninvasive treatment is available in fatty acid β-oxidation defects that reverses cardiomyopathy and pericardial effusion, early diagnosis is essential to adjust therapy accordingly.

Key words: Fatty acid β-oxidation — Pericardial effusion — Cardiomyopathy

Pericardial effusion in infancy is a rare condition and mostly occurs in this age group secondary to viral or bacterial infections. Fatty acid β-oxidation defects present with pericardial effusion and cardiomyopathy as leading symptoms and should be considered when searching for an underlying diagnosis in the age group of 2 months to 1 year [1, 12].

Very long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the first step in the β-oxidation spiral of fatty acid metabolism, the crucial pathway for cardiac energy production. Three major phenotypes of VLCAD deficiency secondary to heterogeneous VLCAD mutations are apparent [3]: a severe, early-onset presentation with predominating cardiomyopathy with or without pericardial effusion; an infancy-onset, hepatic phenotype with recurrent hypoketotic hypoglycemia; and a milder, later-onset, myopathic form with muscle weakness, myalgia, and episodic myoglobinuria. Infantile cardiomyopathy with arrhythmia is the most common early clinical presentation [7].

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Defects affecting the mitochondrial trifunctional protein (TFP), comprising the next three steps of the β-oxidation spiral, result in either isolated long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency or complete TFP deficiency. In this heterogeneous group of disorders, cardiomyopathy is a recognized clinical feature of early-onset forms as well [6, 10], while pericardial effusion has not been described.

Case Reports

Patient A presented at 4 months of age with lethargy, muscular hypotonia, hypoglycemia, and hepatopathy following an upper respiratory tract infection and decreased food intake. Echocardiography demonstrated concentric hypertrophic cardiomyopathy (interventricular septal thickness of 12.5 mm, norm: 4.1 ± 1.5; posterior wall thickness of 11 mm, norm: 4.2 ± 1.3) with no impairment of cardiac function. A large pericardial effusion (12 mm) was present (Fig. 1). ECG excluded ventricular arrhythmias. Elevated serum long-chain acylcarnitines (C14–C18) of 20 μmol/L together with a low free carnitine of 6 μmol/L were consistent with a VLCAD deficiency. Reduced VLCAD enzyme activity of 0.3 nmol/min/g (norm: 4.7 ± 1.7) in fibroblasts confirmed the diagnosis. Molecular genetic analysis of the VLCAD gene revealed a homozygous one base pair insertion in exon 7, introducing a stop codon (602Ains, Y201ter). The mutation was confirmed in both parents, who declared being consanguineous. Pericardiocentesis yielded 110 mL of transudative fluid. Under a diet with medium-chain triglycerides (MCT, Monogen formula, SHS Germany) and regular feeding every 4 hours, the pericardial effusion resolved nearly completely within 2 weeks (Fig. 2). After 2 months, cardiomyopathy, hepatomegaly, and muscular hypotonia were completely reversed.

Patient B had a similar history with muscular hypotonia since the age of 3 months and hypertrophic cardiomyopathy since 5 months. The diagnosis was not established until the patient was 7 months old, when gastroenteritis resulted in metabolic derangement with cardiorespiratory failure requiring artificial ventilation. Echocardiography revealed severe, hypertrophic cardiomyopathy (interventricular septal thickness of 10.4 mm, posterior wall thickness of 9.5 mm) with diastolic dysfunction. ECG documented ventricular arrhythmias. Pericardial effusion was not observed.

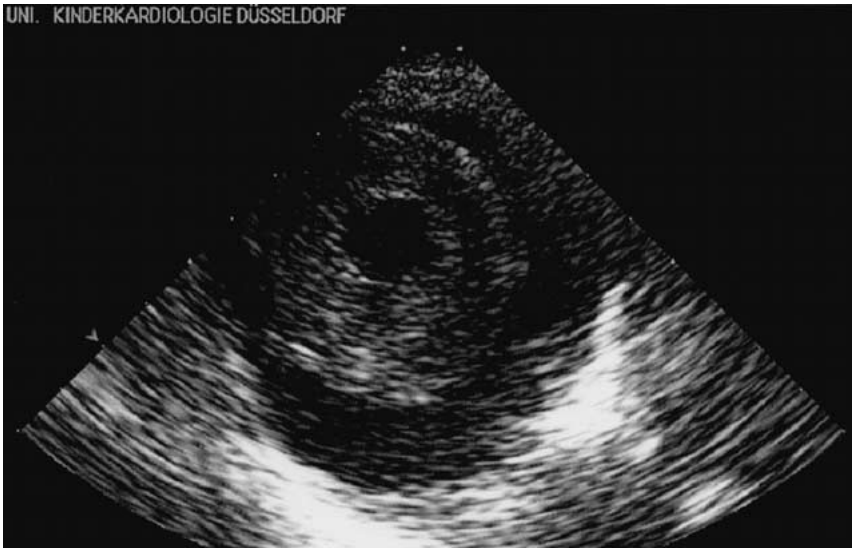

Fig. 1. Parasternal short axis view showing severe pericardial effusion and cardiomyopathy before therapy.

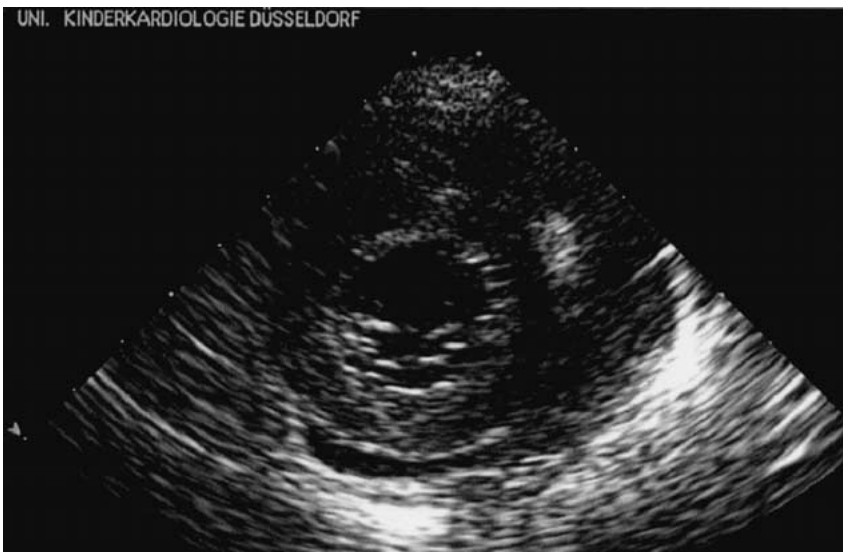

Fig. 2. The same patient 2 weeks after starting treatment. The effusion has nearly completely resolved.

VLCAD deficiency was obvious on acylcarnitine analysis by tandem mass spectrometry with long-chain acylcarnitines (C14–C18) of 30 μmol/L. Enzyme analysis with an activity of 0.3 nmol/min/g protein (versus 10.5 + 3.3) as well as molecular analysis (homozygous change in exon 5 of the VLCAD gene, GT to CC at cDNA positions 327–328) confirmed the diagnosis. The parents denied consanguinity, but they derived from the same small village in Turkey. After initial intensive care treatment, a diet with MCT fat, regular meals, and overnight gastric feeding were implemented. Within 3 weeks, cardiac function normalized, although hypertrophic cardiomyopathy remained initially. This ventricular hypertrophy reversed completely after 4 months. Muscular hypotonia and hepatomegaly had already completely resolved at 2 months. Low values of serum long-chain acylcarnitines (3–5 mmol/L) and normal serum creatine kinase (all isoenzymes) and transaminase concentrations were reached during treatment in both patients. During more than 2 years' follow-up, intermittent short increases of long-chain acylcarnitines of up to 20–30 μmol/L occurred, but arrhythmias, pericardial effusion, or cardiac insufficiency were not observed. Both patients are growing well along the percentiles and their mental and motor development is normal. Carnitine supplementation was not necessary.

Discussion

The early-onset cardiac phenotype of VLCAD deficiency is characterized by hypertrophic cardiomyopathy with or without pericardial effusion. Cardiomyopathy occurs in various metabolic diseases and due to different pathogenetic modes [4, 5]. Abnormal storage products are implicated in glycogen and lysosomal storage diseases; in respiratory chain disorders and mitochondrial β-oxidation defects, the

hypothesis favored for the development of cardiomyopathy is a lack of energy, especially during periods of fasting and illness. Also, a wide variety of conditions may result in pericardial effusion [8, 11]. In infancy, underlying infections, malignancy, autoimmune diseases, congenital heart defects, and metabolic disorders are known causes. Large pericardial effusion may lead to life threatening cardiac tamponade. In fatty acid β-oxidation disorders, as case A illustrates, avoidance of fasting and administration of medium-chain triglycerides (MCT) can result in a complete reversal of pericardial effusion and cardiomyopathy. Early detection of the underlying diagnosis therefore, changes the approach to these symptoms. Reviewing the literature [11], the management of pericardial effusion is heterogeneous, mostly due to uncertainties in underlying diagnoses. While the acute management of pericardial effusion and cardiomyopathy is dependent on their hemodynamic consequences, longer-term therapy must be adjusted to the underlying disease. MCT, as the major source of dietary fat, provides fuel with the potential of full energy production in long-chain fatty acid oxidation defects, that can normalize cardiac function and reverse cardiomyopathy and pericardial effusion [1, 2, 12]. Under this diet, polyunsaturated long-chain fatty acids must be substituted according to the needs [9]. The diagnosis of fatty acid β-oxidation disorders is generally based on the plasma acylcarnitine profile determined by tandem mass spectrometry from blood spots collected on a Guthrie card [10] or urinary organic acid analysis. These methods are especially sensitive during metabolic derangement. Diagnosis can be confirmed by enzymatic and molecular genetic analyses.

We conclude that fatty acid β-oxidation disorders should be considered as causes of pericardial effusion and hypertrophic cardiomyopathy occurring in infancy because early diagnosis is essential to adjust therapy accordingly.

Acknowledgments. We thank Dr. Arnold Strauss for helpful discussions.

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