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CASE REPORT

Reversal of cardiomyopathy in propionic acidemia after liver transplantation: a 10-year follow-up

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Summary

Cardiomyopathy is a frequent complication in propionic acidemia. It is mostly rapidly fatal and independent of the metabolic control or medical intervention. Here, we present the reversal of a severe cardiomyopathy after liver transplantation in a patient with propionic acidemia and the long-term stability after ten years. Liver transplantation in patients with propionic acidemia may be considered a valid and long-lasting treatment when cardiomyopathy is progressive and unresponsive to medical therapy.

Introduction

Propionic acidemia (PA) is an autosomal recessive inborn error of metabolism caused by the deficiency of propionyl-CoA carboxylase (PCC) leading to the accumulation of toxic compounds. PA may occur at any age, displaying severe metabolic decompensations with acidosis, hyperammonemia, and encephalopathy, with a wide variety of neurological symptoms. The main treatment of PA consists of a protein-restricted diet, carnitine supplementation, and anticatabolic therapy in fasting situations. However, despite improved clinical management, the outcome of PA is still poor. Developmental delay occurs in 59–100% of those patients [1,2].

Cardiomyopathy and long-QT syndrome are frequent complications in patients with PA [1] and associated with a high mortality. Their development is independent of the metabolic control [3], and the pathomechanisms are not yet well understood. Neither dietary interventions nor carnitine supplementation seem to positively affect the cardiac outcome [4]. Orthotopic liver transplantation (OLT) has been described as therapeutic option in PA patients with early onset and repeated decompensations. OLT has been shown to improve the quality of life and the course of the

disease [5]. There are only three patients reported in the literature, who successfully underwent OLT to treat cardiac complications of PA [6,7] and all showed a complete reversal of cardiomyopathy after the procedure. We present here the case of an additional patient with late onset PA and progressive severe cardiomyopathy, who normalized his cardiac function after liver transplantation and remains stable after more than 10 years of follow-up.

Case report

The patient, a male from nonconsanguineous parents, was diagnosed with PA at 26 months of age (Table 1), in the context of a gastroenteritis, associated with ketoacidosis and a severe developmental delay (Developmental Quotient = 55). He was previously known for recurrent vomiting, unclear somnolence, and mild acidosis. Diagnosis was confirmed by deficient PCC activity in fibroblasts (6.5 pmol/min/mgprot, Ref. range 229–2660; 2.8% residual activity) and 2 heterozygous mutations in exon 12 of the PCCA-gene, c.937C>T (p.Arg313Ter) and c.1060C>T (p.Leu354Phe), also found in one asymptomatic sister. Carnitine supplementation, metronidazole therapy for 1 week monthly and a protein-restricted diet according to minimal protein requirements [8] were started (ranging from 1.4 to 0.8 g/kg/day between 26 months and 22 years of age), initially with amino acid supplementation, later using only natural proteins. The clinical course of the index patient was very mild with only one severe metabolic decompensation at 5 years of age (Table 1), showing meantime a substantial cognitive improvement (IQ at 7 years old = 78).

At 18 years, a long-QT interval and a moderately impaired systolic function were documented for the first time, while clinically asymptomatic (Table 2). Within four years, despite increasing dosages of enalapril, metoprolol, digoxin, and torasemide, he progressively developed a severe dilated cardiomyopathy (Table 2) with mitral valve regurgitation and pulmonary hypertension (average pulmonary artery pressure = 60–65 mmHg), classified into NYHA II.

At the age of 21 years, he manifested a cerebrovascular insult in the supply area of the cerebri media artery, with a transitory left hemiparesis, probably consistent with the finding of a left ventricular thrombus, likely generated by the severe compromised cardiac mechanics. An oral anticoagulant therapy (acenocoumarol) was started.

One year later, an OLT was performed using the "piggy-back" technique, with temporary portocaval shunt. An intra-operative cardiac bypass was used preventively to avoid cardiac failure, considering the severely impaired pre-operative left ventricular function (Table 2). High glucose infusion avoided catabolism, and carnitine supplementation supported detoxification. Dialysis was not used, and perioperative glomerular filtration rate was normal. Post-transplant follow-up was uneventful, and initial immunosuppression was achieved with cyclosporine, azathioprine, and prednisone.

Shortly after transplantation, a significant recovery of cardiac function was observed (Table 2), showing no more QT elongation, paralleled by a gradual reduction in plasma and urinary toxic metabolite levels (Table 1).

Currently, the patient is 33 years old, in good health, works in a social cooperative, and lives in a partnership with his girlfriend. He presents a normal cardiac function (Table 2) and had no more metabolic decompensations or cerebrovascular events. He is on an unrestricted diet,

Table 2. Progressive changes in myocardial structure and function before and after orthotopic liver transplantation (OLT) documented by ultrasound.

	LV E-DD (mm)	LV EF (%)
Age before OLT (years)		
18 8/12	57	35
18 11/12	60	35
19 7/12	69	31
21	72	25
22 3/12 (pre-operative)	72	15-17
Age after OLT (years)		
22 4/12	67	35
22 10/12	69	35
23 10/12	61	40
24 10/12	57	45
25 4/12	58	55
32	57	55

LV E-DD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction.

Table 1. Changes in plasma and urine organic acids levels before and after orthotopic liver transplantation (OLT).

Parameters	Reference values	At diagnosis (26 months)	Range before OLT	3 months after OLT	9 months after OLT	3 years after OLT
Propionate (plasma) (μmol/l)	<5.1	3048	6.1–72.6	2.4	1.8	0
3OH-Propionate (urin) (mol/mol Cr)	<0.03	0.68	0.01–0.20	0.01	0.01	0.01
Methylcitrate (urin) (mol/mol Cr)	<0.02	n.d.	0.09–0.20	0.13	0	0

carnitine supplementation, and low dosages of enalapril and metoprolol.

The sister never displayed neurological symptoms or metabolic decompensations (5.3% PCC residual activity, plasma propionate range: 1.5–14.5 μmol/l, urinary 3OH-Propionate range: 0.03–0.10 mol/mol creatinine). At the age of 23 years, a mildly prolonged QT interval, without myocardial dysfunction, was documented. She is now 36 years old, works as a secretary, is married, and has a healthy son, and she still follows a protein-restricted diet, carnitine supplementation, and metronidazole.

Discussion

Cardiomyopathy affects 9–23% of patients with PA [2]. It is most frequently dilated [6,7], rarely hypertrophic [4]. Further 70% of patients with PA present long QT, with a high risk of cardiac arrest [9]. The pathomechanisms of the cardiac complications are not yet completely understood. Kölker *et al.* [10] suggested mitochondrial impairment at different levels. Physiological supply of Krebs cycle intermediates from deficient propionate breakdown is hampered. Moreover, toxic metabolites, inhibiting the pyruvate dehydrogenase and the succinyl-CoA ligase, may compromise the Krebs cycle and interfere with ureagenesis inducing hyperammonemia. In addition, increased reactive oxygen species may impair mitochondrial DNA expression. Thus, multiple deficiencies of respiratory chain complexes were found in cardiac cells of patients with PA [4,11]. Baruteau *et al.* [12] found low coenzyme Q10 levels in cardiac muscle in two patients with PA and reported a beneficial effect of high-dose coenzyme Q10 supplementation on cardiomyopathy.

Isolated severe cardiomyopathy was described in two patients [13,14] who both received heart transplantation before PA was diagnosed. The heart transplantation does, however, not prevent metabolic decompensations.

In current guidelines, cardiomyopathy is not an indication for OLT in patients with PA. OLT is restricted to patients with recurrent metabolic decompensations [1,2]. Liver-transplanted patients show metabolic stabilization and an overall improvement in quality of life and do not follow a protein-restricted diet anymore. A survival rate of 72% 1 year after OLT and on unrestricted diet was described in a retrospective study of 12 patients with PA (mean age, 4 years) [5]. Further neurocognitive impairment was prevented, supporting an unrestricted diet after transplantation. However, there are hardly any long-term data about cardiac complications after OLT in the medical literature [5].

Romano *et al.* [6] reported complete normalization of cardiac dysfunction after OLT in two children with PA. In the same publication, two other PA patients with cardiomyopathy are mentioned, but OLT was considered contraindicated because of the severe cardiac situation [6]. But as published by others, severely impaired cardiac function in OLT in PA can be supported by cardiac devices [7].

Despite good adherence to treatment, our patient developed a progressive, severe drug-resistant cardiomyopathy. At the time we performed OLT, only few patients with PA had already experienced liver transplantation [15] and little was known about its effect on PA-related cardiomyopathy. A multidisciplinary consultation set the final decision for OLT, thinking about the potential correction of toxic metabolites. Considering the severely impaired cardiac function, an intra-operative cardiac bypass was used preventively. In liver transplantation in patients with cardiac insufficiency, it is essential to evaluate the need for devices, as extracorporeal bypass to stabilize the haemodynamic conditions [16]. The complete regression of both cardiomyopathy and long-QT syndrome may suggest a similar underlying mechanism. This is an important finding as both complications may contribute significantly to the mortality, independently of metabolic decompensations [3,4]. Treatment of choice of long QT are beta-blockers [17,18], and special care has to be taken not prescribing long QT-inducing drugs such as antipsychotics or antibiotics [19]. The overall stability 10 years after OLT is an additional positive effect of the control of the disease. Liver transplantation definitely corrects the hepatic detoxification, but as PCC is also expressed in the brain [20] and metabolic strokes have been described independent of diet and metabolic decompensations, there is concern about possible strokes post-OLT [21]. Further studies are needed to assess the effect of OLT or other options such as hepatocyte transplantation or auxiliary liver transplantation [22,23] on metabolic strokes and on the long-term benefit for patients with PA.

In summary, the age of onset of cardiomyopathy in PA is variable but often rapidly progressive and fatal. Currently available data from our experience and literature are limited, but suggest that liver transplantation may have a positive and lasting effect on PA-related cardiomyopathy, otherwise life-threatening. The possibility to use an extracorporeal bypass device to safely drive the patient through the operation is a relevant key point to increase eligibility to the intervention.

Authorship

J-MN, ADeG and EF: participated in patient management. CA and J-MN: participated in case report and manuscript design. ADeG, EF and MG: participated in critical review of the manuscript. MB: participated in enzymatic and molecular analysis. All co-authors approved the final manuscript.

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