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CASE REPORT

# Propionic acidemia in a previously healthy adolescent with acute onset of dilated cardiomyopathy

**Alexander Laemmle · Christian Balmer · Carsten Doell · Jörn Oliver Sass · Johannes Häberle · Matthias R. Baumgartner**

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**Abstract** Propionic acidemia (PA) is a rare autosomal recessive organic aciduria resulting from defects in propionyl-CoA-carboxylase (PCC), a key enzyme of intermediate energy metabolism. PA mostly manifests during the neonatal period, when affected newborns develop severe metabolic acidosis and hyperammonemia. We present a previously healthy teenager, who suffered from acute fatigue and breathlessness. The patient was tachycardic, displayed a precordial heave and a systolic murmur. Cardiac investigations revealed severe dilated cardiomyopathy (DCM). Biochemical work up led to the diagnosis of PA. Remarkably, this patient of consanguineous Hispanic origin was in a good general health condition before the acute onset of DCM. Diagnosis of PA was confirmed by enzymatic and molecular genetic analysis, the latter revealing a novel homozygous mutation in the *PCCB* gene (c.1229G>A; p.R410Q). Residual PCC enzyme activity of approximately 14 % of normal was detected in patient's lymphocytes and fibroblasts, thereby providing a possible explanation for the hitherto asymptomatic phenotype. *Conclusion*: Isolated DCM, although rare, can be the leading and/or sole symptom of late-onset PA. Therefore, patients with DCM should receive a comprehensive diagnostic evaluation including selective screening for inborn errors of metabolism.

**Keywords** Propionic acidemia · Dilated cardiomyopathy · Propionyl-CoA carboxylase · Organic aciduria

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A. Laemmle (✉) · J. Häberle · M. R. Baumgartner
Division of Metabolic Diseases, University Children`s Hospital, Zurich, Switzerland
e-mail: alexander.laemmle@kispi.uzh.ch

J. Häberle
e-mail: Johannes.Haeberle@kispi.uzh.ch

M. R. Baumgartner
e-mail: Matthias.Baumgartner@kispi.uzh.ch

C. Balmer
Division of Cardiology, University Children`s Hospital, Zurich, Switzerland
e-mail: Christian.Balmer@kispi.uzh.ch

C. Doell
Division of Neonatology and Paediatric Intensive Care, University Children`s Hospital, Zurich, Switzerland
e-mail: Carsten.Doell@kispi.uzh.ch

J. O. Sass
Division of Clinical Chemistry & Biochemistry, University Children`s Hospital, Zurich, Switzerland
e-mail: Joern.Oliver.Sass@kispi.uzh.ch

A. Laemmle · C. Balmer · J. O. Sass · J. Häberle · M. R. Baumgartner
Children's Research Center, University Children`s Hospital, Zurich, Switzerland

**Abbreviations**

| | |
|---|---|
| ADHS | Attention deficit and hyperactivity syndrome |
| DCM | Dilated cardiomyopathy |
| ECG | Electrocardiography |
| PA | Propionic acidemia |
| PCCA and PCCB | Propionyl-CoA carboxylase subunits A and B |

## Introduction

Propionyl-CoA-Carboxylase (PCC; EC 6.4.1.3) is a mitochondrial biotin-dependent enzyme that catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA, which is further metabolized to succinyl-CoA, a substrate of the citric acid

cycle. PCC is a dodecameric enzyme complex, consisting of 6α- and 6β-subunits, which are encoded by the *PCCA* and *PCCB* genes, respectively. Mutations in either of the two genes result in propionic acidemia (PA; OMIM #606054), a rare autosomal recessive disease.

Propionyl-CoA is generated by breakdown of the amino acids valine, leucine, methionine, and threonine as well as by the degradation of odd chain fatty acids and cholesterol side chains. An additional source of propionyl-CoA derives from colonic anaerobic bacterial fermentation of carbohydrates. In PA, the impaired conversion of propionyl-CoA to methylmalonyl-CoA leads not only to intracellular accumulation of propionyl-CoA but also to metabolites such as 3-hydroxypropionate, propionylglycine, and 2-methylcitrate, which can be detected by analysis of urinary organic acids [2].

PA mostly presents in the neonatal period with severe metabolic crisis characterized by metabolic acidosis and hyperammonemia. Affected newborns suffer from nonspecific signs such as vomiting, feeding difficulties, and somnolence. Late-onset forms of PA have been described in only few patients, most of whom were suffering from various neurological deficits including mental retardation, ataxia, or metabolic stroke-like episodes [4].

Cardiac involvement such as prolonged QTc-time and dilated cardiomyopathy (DCM) are frequent complications of PA [7]. Prolonged QTc-time, potentially favoring cardiac arrhythmias, is found in up to 70 % of PA patients beyond infancy [1]. Up to 23 % of patients with PA are reported to develop cardiomyopathy during disease course [9]. Acute onset of disease with cardiomyopathy as the first or only clinical sign has only been described in three other patients so far (Table 1) [5, 7].

Here, we present a 16 year old previously healthy patient who suffered from acute cardiac failure due to DCM as the first manifesting sign of late-onset PA.

## Case report

A 16-year-old male patient presented with dyspnoea on exertion and exercise intolerance for 1 week and was hospitalized at the intensive care unit. Echocardiographic investigations revealed a severe DCM with a severely impaired ventricular function (Fig. 1). The previous medical history was unremarkable except for a nonproductive cough and generalized myopathy for 1 month. However, although he was very athletic, playing hockey and soccer regularly, on few occasions he previously complained of nausea and vomiting during endurance sports such as leisure cycling. The patient is the offspring of consanguineous Hispanic parents and was adopted at the age of 2 years when he was taken to Switzerland. No further information with regard to the first 2 years of his life is available. He was treated with methylphenidate for ADHS since the age of 6 years. Due to behavioral problems, he attended special school education. Recent neurocognitive evaluation showed various mild deficits and an IQ of 83.

On the ICU, therapy for congestive heart failure was immediately initiated and paralleled by a broad diagnostic work up of DCM. Besides diuretic therapy with furosemide, spironolactone, and hydrochlorothiazide, continuous infusion of milrinone was added to support circulation. Upon hemodynamic recovery, this therapy was replaced by angiotensin-converting enzyme inhibitors (captopril and then enalapril) and additionally carvedilol. On one occasion, electrocardiography (ECG) revealed a slightly prolonged QTc-time (457 ms; ref. <440). During this short episode, hypomagnesemia (0.71 mmol/L; ref. 0.74–1.03) and hypokalemia (3.2 mmol/L; ref. 3.5–5.0) were noticed and immediately treated. Thereafter, no further ECG abnormalities occurred. Cardiac angiography including cardiac muscle biopsy was performed. Histopathological examination of the affected cardiac muscle showed discrete lymphocyte infiltration but no other pathology. Multiplex PCR investigations for viral genomic material in blood and cardiac muscle were negative. Metabolic work up revealed a markedly elevated concentration of propionylcarnitine (13.5 μmol/L; ref. <3.5) in the acylcarnitine profile of a dried bloodspot, whereas free carnitine level was in the normal range (32.3 μmol/L; ref. <54.8). In addition, increased urinary levels of 3-hydroxypropionate (130 mmol/mol creatinine; ref. <10) and 2-methylcitrate (110 mmol/mol creatinine; ref. <20), but not methylmalonate (<10 mmol/mol creatinine; ref. <10) were detected, thus leading to the diagnosis of PA. In line with these findings, glycine (417 μmol/L; ref. 147–299) was elevated in the plasma amino acid profile. Acid–base status revealed no significant abnormalities, and all lactate levels were in the normal range.

Diagnosis of PA was confirmed by enzyme activity measurements according to an established method [10]. PCC activity assays in the patient's lymphocytes (32.5 pmol/min/mg protein, lower limit of normal 228) and skin fibroblasts (39.7 pmol/min/mg protein, lower limit of normal 287) revealed residual activities of 14.3 and 13.8 % of lower limits of normal, respectively. Activity of methylcrotonyl-CoA carboxylase, another biotin-dependent mitochondrial carboxylase, was in the normal range, thus pointing away from defects or deficiencies in biotin metabolism.

Finally, a homozygous mutation in the *PCCB*-gene (c.1229G>A; p.R410Q) was identified. After the diagnosis of PA was made, the patient received L-carnitine (80 mg/kg bodyweight/day) in addition to treatment for congestive heart failure. His dietary protein intake was 3 g/kg bodyweight/day which was limited to 1.5 g/kg bodyweight/day following the diagnosis. No additional amino acid mixtures were supplied. Therapy with methylphenidate was stopped due to previously reported association of methylphenidate and the development of DCM [8]. After the initiation of the anticongestive therapy,

**Table 1** Patients with cardiomyopathy (CM) leading to diagnosis of late-onset propionic acidaemia (PA)

| Patient, sex | Age at onset of CM | Acute therapy | Clinical course/recovery after diagnosis | PCC activity | Genotype (*PCCB* gene) | Reference[a] |
|---|---|---|---|---|---|---|
| 1, m | 6 years | Diuretics and inotropes | Rapid recovery; asymptomatic 2 months after onset of CM | Unknown | Unknown | [7] |
| 2, f | 13 months | Diuretics and bicarbonate | Rapid recovery within 1 week | Unknown | Unknown | |
| 3, m | 14 years | Cardiac transplantation | Rapid recovery after cardiac transplantation | 19.9 %[b] | IVS7+2 T>G; p.R410Q | [5] |
| 4, m | 16 years | Diuretics and inotropes | Rapid recovery within 2 months | 14.3[b] and 13.8 %[c] | Homozygous for p.R410Q | Present case |

*m* Male, *f* female

[a] Reference search was restricted to PubMed. Search restrictions were: "propionic acidemia or propionic acidaemia and cardiomyopathy"

[b] PCC activity in lymphocytes and [c] fibroblasts: percentage of normal lower limits

his cardiac output improved steadily with the ejection fraction increasing from an initial value of 25 to 40 % within 10 days. Notably, this improvement occurred before PA was diagnosed and treated. Currently, 4 months after acute onset of DCM, the patient's general health condition allows moderate physical exercise again, although he has not yet fully recovered. On echocardiography, left-sided chambers remain dilated, with a mildly to moderately impaired ventricular function (left ventricular ejection fraction stable at 40 %).

## Discussion

We report on a young man with acute onset of DCM at the age of 16 years. Notably, before diagnosis of DCM, the patient was in a good general health condition. The behavioral problems necessitating special school education were tentatively attributed to an ADHS and to the patient's social history. The severe DCM responded rapidly to congestive heart failure treatment and moreover was substantiated by an amelioration of ejection fraction from initially 25 to 40 % within 10 days. Diagnostic work up for DCM including metabolic screening led to a strong suspicion of PA, which prompted us to initiate respective treatment with oral carnitine and dietary protein restriction. Noteworthy, the clinical improvement occurred before treatment for PA was started and thus can be attributed solely to the effects of DCM therapy. This observation is in line with reports from other patients, who recovered rapidly after initiation of DCM treatment (Table 1) [7], although some PA patients have been reported to require liver transplantation for therapy-resistant DCM [9].

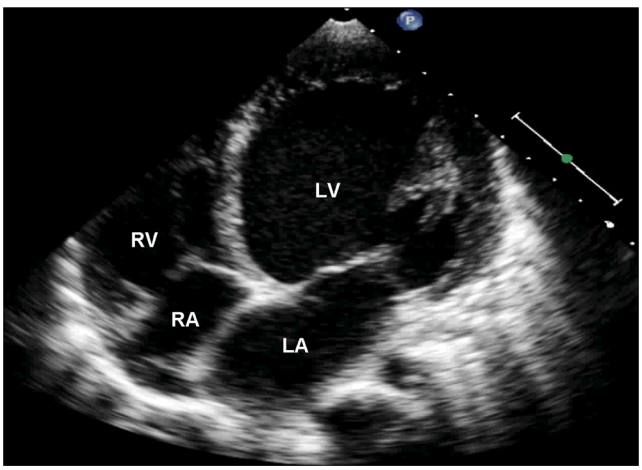


**Fig. 1** Dilated cardiomyopathy on echocardiography. Initial echocardiography of the patient showing severe dilated cardiomyopathy. *LV* left ventricle, *LA* left atrium, *RV* right ventricle, *RA* right atrium

Diagnosis of PA was confirmed by enzyme activity assays in lymphocytes and skin fibroblasts, revealing high residual PCC activities which may explain the hitherto asymptomatic course. Patients with relevant residual PCC activity are likely to live a normal and active life, which may ultimately increase their risk of developing DCM due to recurrent metabolic stress, e.g., during endurance exercise.

More recently, the relationship between genotype and phenotype in PA has been the subject of a limited investigation [3]. While some mutations are associated with late-onset PA reflecting a rather mild phenotype, certain mutations are known to cause a more severe phenotype [3]. Molecular genetic analysis of the patient revealed a novel homozygous mutation in the *PCCB* gene. Interestingly, the same mutation has previously been described in monoallelic form in a 14-year-old male late-onset PA patient with isolated DCM and compound heterozygosity (p.R410Q/IVS7+2 T>G; Table 1) [5]. Theoretically, this specific mutation may predispose towards the development of cardiomyopathy. Therefore, it would be of interest to determine the genotype in additional patients with PA-associated DCM. However, another mutation affecting the same residue (p.R410W), which is one of three frequent *PCCB* gene mutations in Japanese PA patients, is

not associated with an increased risk towards the development of DCM [11].

Pathophysiology underlying the PA-associated cardiomyopathy remains unclear and different hypotheses have been brought up. One aspect is a potential harm to cardiomyocytes through the accumulation of toxic byproducts such as 3-hydroxypropionate and 2-methylcitrate. However, recent studies by Romano et al. [9] did not find a correlation between excretion of propionate metabolites in urine and occurrence of cardiomyopathy. Although we cannot rule out such an effect, cardiac muscle biopsy samples of our patient lacked signs of previous damage such as tissue fibrosis or necrosis. Deficiency in free carnitine [6, 7] as well as biotin deficiency has been suggested as potential risk factors for the development of cardiomyopathy in PA patients. In our patient, normal free carnitine levels in dried blood make carnitine deficiency unlikely. PCC activity did not respond to biotin supplementation in vitro, rendering biotin deficiency unlikely. Although methylphenidate probably did not contribute to DCM, therapy was stopped due to reported cases of methylphenidate-associated DCM [8]. Other hypotheses suggest a more general impairment of energy metabolism by depletion of the anaplerotic metabolite succinyl-CoA or secondary respiratory chain deficiencies as favoring the onset of cardiomyopathy [6]. However, the inconsistent relationship between the development of DCM and the frequency of metabolic decompensations remains unexplained.

While the differential diagnosis of DCM is diverse and most commonly associated with infectious pathogens, it seems prudent to also consider the rare causes such as PA. Therefore, regardless of their age, patients with DCM need to undergo a comprehensive diagnostic evaluation including selective screening for metabolic diseases.

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**Conflict of interest** None.

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