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Successful reversal of propionic acidaemia associated cardiomyopathy: Evidence for low myocardial coenzyme Q_{10} status and secondary mitochondrial dysfunction as an underlying pathophysiological mechanism

J. Baruteau [a,*], I. Hargreaves [b], S. Krywawych [c], A. Chalasani [b], J.M. Land [b], J.E. Davison [a], M.K. Kwok [a], G. Christov [d], A. Karimova [d], M. Ashworth [e], G. Anderson [e], H. Prunty [c], S. Rahman [a,f], S. Grünewald [a,f]

[a] Metabolic Medicine Department, Great Ormond Street Hospital, London, UK
[b] Neurometabolic Laboratory, National Hospital for Neurology and Neurosurgery, London, UK
[c] Chemical Pathology, Great Ormond Street Hospital, London, UK
[d] Cardiothoracic Unit, Great Ormond Street Hospital, London, UK
[e] Pathology Laboratory, Great Ormond Street Hospital, London, UK
[f] Clinical and Molecular Genetics Unit, UCL Institute of Child Health, London, UK

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ABSTRACT

Dilated cardiomyopathy is a rare complication in propionic acidaemia (PA). Underlying pathophysiological mechanisms are poorly understood.

We present a child of Pakistani consanguineous parents, diagnosed with late-onset PA at 18 months of age. He presented a mild phenotype, showed no severe further decompensations, normal growth and psychomotor development on a low protein diet and carnitine supplementation. At 15 years, a mildly dilated left ventricle was noticed. At 17 years he presented after a 2–3 month history of lethargy and weight loss with severe decompensated dilated cardiomyopathy. He was stabilised on inotropic support and continuous haemofiltration; a Berlin Heart biventricular assist device was implanted. He received D,L-hydroxybutyrate 200 mg/kg/day, riboflavin and thiamine 200 mg/day each and coenzyme Q_{10} (CoQ_{10}). Myocardial biopsy showed endocardial fibrosis, enlarged mitochondria, with atypical cristae and slightly low respiratory chain (RC) complex IV activity relative to citrate synthase (0.012, reference range 0.014–0.034). Myocardial CoQ_{10} was markedly decreased (224 pmol/mg, reference range 942–2738), with a marginally decreased white blood cell level (34 pmol/mg reference range 37–133). The dose of CoQ_{10} was increased from 1.5 to 25 mg/kg/day. Cardiomyopathy slowly improved allowing removal of the external mechanical cardiac support after 67 days.

We demonstrate for the first time low myocardial CoQ_{10} in cardiomyopathy in PA, highlighting secondary mitochondrial impairment as a relevant causative mechanism. According to these findings, a high-dose CoQ_{10} supplementation could be a potential adjuvant therapeutic to be considered in PA-related cardiomyopathy.

1. Introduction

Propionic acidaemia (PA) (OMIM 606054) is an autosomal recessive disease resulting from propionyl-CoA carboxylase (PCC) deficiency with an incidence of 1:200 000 (Deodato et al., 2006). PCC is a biotin-dependent enzyme located in the mitochondrial matrix involved in the metabolism of propionate, an intermediary metabolite from the breakdown of 4 essential aminoacids (methionine, threonine, valine, isoleucine), odd-chain fatty acids and the side chain of cholesterol. Two types of presentations occur: 1) neonatal-onset with early life-threatening decompensation including vomiting, ketoacidosis, hyperammonaemic coma, pancytopaenia with frequent neurological sequelae including mental retardation, epilepsy and spasticity; 2) late-onset disease with recurrent episodes of ketoacidotic coma or Reye-like syndromes triggered by catabolic state. Dilated cardiomyopathy is a rare life-threatening complication in PA. Despite an increasing number of reported cases during recent years, understanding of pathophysiological mechanisms remains poor. Several publications suggested a possible link with secondary RC impairment, however there has been little evidence to support this. Most of the reported cases were associated with an ultimately fatal outcome, hence regular monitoring

* Corresponding author at: Metabolic Medicine Department, Great Ormond Street Hospital for Children, Great Ormond Street, WC1N 3JH, London, UK. Tel.: +44 2078138331; fax: +44 2078138258.
E-mail address: jbaruteau@yahoo.fr (J. Baruteau).

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is recommended (Sutton et al., 2012). Currently there are no prognostic biomarkers, nor any clear therapeutic guidelines regarding how to monitor and manage this potential lethal complication. We report a case with myocardial CoQ_{10} deficiency with progressive therapeutic response to a supplementation of carnitine, thiamine, riboflavin, L-arginine, and CoQ_{10} associated with transient Berlin Heart biventricular assistance.

2. Patients and methods

2.1. Patient 1

A first child born to Pakistani consanguineous parents was diagnosed with late-onset PA at 18 months of age after recurrent episodes of ketoacidosis and severe dehydration during intercurrent illnesses. A diagnosis of propionic acidaemia was confirmed by urinary excretion of propionylglycine, 3-hydroxypropionate, methylcitrate and tiglylglycine with elevated plasma propionylcarnitine. He presented a mild phenotype, and showed no further decompensations on conventional treatment including low protein diet and carnitine supplementation. Growth and psychomotor development were normal. At 15 years, on monitoring, a mild dilated left ventricle was noticed, with no haemodynamic relevance in this asymptomatic adolescent. At 17 years, he presented after a 6-week history of increasing lethargy and poor feeding with a severe decompensated dilated cardiomyopathy and mild metabolic decompensation with hyperammonaemia at 161 μmol/L. A septic screen including viral PCRs in blood and nasopharyngeal secretions did not elicit any infectious cause for this decompensation.

2.2. Patient 2

His asymptomatic one-year younger brother was screened and diagnosed at the time of the initial decompensation of his brother. He has experienced a disease course similar to his brother's with normal intellectual development, normal growth and no metabolic decompensation other than one severe episode: whilst on holiday overseas, triggered by an intercurrent vomiting illness and delayed initiation of treatment he acquired substantial neurological sequelae. He was also noted to have mild left ventricular dilatation at 15 years. One year later, this dilatation worsened with impaired systolic function and an ejection fraction of 23% requiring angiotensin conversion enzyme inhibitor therapy and close cardiac monitoring. Ammonia and pro-brain natriuretic peptide (proBNP), a heart failure biomarker, were normal.

3. Methods

3.1. Investigations on cardiac biopsy

Cardiac biopsy in Patient 1 was collected at the time of ventricular assist implantation (Berlin Heart EXCOR, Berlin Heart AG, Germany) 8 days after admission, after informed consent.

3.2. Light and electron microscopy

Samples of cardiac tissue were fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer followed by secondary fixation in 1.0% osmium tetroxide. Tissues were dehydrated in graded ethanol, transferred to propylene oxide and then infiltrated and embedded in Agar 100 epoxy resin. Polymerization was at 60 °C for 48 h. 90 nm ultrathin sections were then cut using a Diatome diamond knife on a Leica Ultracut UCT ultramicrotome. Sections were picked up on copper grids and stained with alcoholic uranyl acetate and Reynold's lead citrate. The samples were examined in a JEOL 1400 transmission electron microscope.

3.3. Tissue homogenisation

The cardiac muscle biopsy was obtained from the patient, frozen at the bedside, stored at −70 °C and couriered to the biochemistry laboratory in liquid nitrogen. The muscle biopsy was homogenised on ice, using a pre-chilled glass hand-held homogeniser as previously described (Hargreaves et al., 1999). Briefly, the skeletal muscle biopsy (50–100 mg) was homogenised 1: 9 (w/v) in: 320 mmol/L sucrose, 1 mmol/L ethylenediamine tetra acetic acid dipotassium salt, 10 mmol/L Trizma-base, pH 7.4.

3.4. Mitochondrial RC enzyme activity assessment

Activities of the RC enzymes were assessed in cardiac muscle homogenates by spectrophotometric methods described previously; complex I (Ragan et al., 1987), complex II + III (King, 1967) and complex IV (Wharton and Tzagoloff, 1967). Citrate synthase activity was measured by the method of Shepherd and Garland (1969). All RC enzyme activities were expressed as a ratio to citrate synthase to correct for mitochondrial enrichment of the samples (Selak et al., 2000). Reference ranges were obtained from 8 human myocardial samples used as controls with ethical consent.

3.5. Coenzyme Q_{10} determination

Cardiac muscle homogenates and blood mononuclear cells were prepared for HPLC analysis of the total coenzyme Q_{10} (CoQ_{10}) concentration from human skeletal muscle, blood mononuclear cells using UV detection at 275 nm by the method of Duncan et al. (2005). Protein concentration of cardiac homogenates and blood mononuclear cells was determined according to the method of Lowry et al. (1951).

3.6. Carnitine measurement

Free carnitine and acylcarnitines were measured in dried blood spots by electrospray tandem mass spectrometry of the butylated derivatives (Applied Biosystems API 4000 LC/MS/MS analyser). Cardiac muscle total and acylated carnitine levels were assessed by electrospray tandem mass spectrometry as described previously (Reuter et al., 2005).

4. Results

4.1. Mitochondrial function

In Patient 1, myocardial biopsy revealed endocardial fibrosis (Fig. 1A), and enlarged mitochondria with atypical cristae on ultrastructural examination (Fig. 1B). RC enzyme assays demonstrated normal complex I (0.161, reference range 0.064–0.267) and II–III (0.063, reference range 0.053–0.201) activities but slightly low myocardial complex IV activity relative to citrate synthase (0.012, reference range 0.013–0.037). Myocardial CoQ_{10} was markedly decreased (224 pmol/mg, reference range 942–2738), with a marginally decreased peripheral blood mononuclear cell level (34 pmol/mg, reference range 37–133).

In Patient 2, the white blood cell CoQ_{10} level was low normal at 37 pmol/mg.

4.2. Carnitine status

In Patient 1, dried blood spot free carnitine and acylcarnitines were mildly raised (104 μmol/L, reference range 23–75 and 43.1 μmol/L, reference range 10.1–43.5 respectively) at admission. Heart total carnitine was 17 (reference range 6.9–30.8 nmol/mg) and free carnitine was 4.1 nmol/mg (reference range 4.8–22 nmol/mg) respectively. Acylcarnitines level was mildly raised (12.9 nmol/mg, reference range 1–10.7). Propionylcarnitine was markedly increased (9.177 nmol/mg,

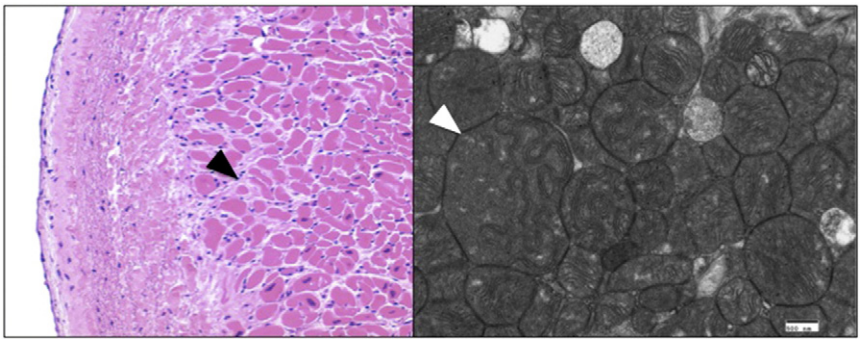

Fig. 1. A: Microscopy of left ventricle biopsy showing non specific endocardial fibrosis (black arrow). B: Electron microscopy of the myocardium highlighting numerous abnormal mitochondria, variable in size up to 6 μm of diameter, with atypical cristae (white arrow) suggestive of a mitochondrial impairment.

reference range 0.021–0.203). These levels were compared to skeletal muscle reference ranges (Verity, 1991).

In Patient 2, total and free L-carnitine levels were normal in dried blood spots.

4.3. Treatment and progress

In Patient 1, ammonia scavengers were used for 72 h and protein intake was restarted 5 days after admission. From admission onwards, a metabolic cocktail was commenced initially composed of D,L-hydroxybutyrate 200 mg/kg/day, riboflavin and thiamine 200 mg/day each, L-carnitine 200 mg/kg/day, metronidazole 10 mg/kg/day and CoQ_{10} 1.5 mg/kg/day. Despite intensive inotropic, diuretic and ventilatory support, haemodynamics deteriorated and continuous veno-venous haemofiltration (CVVH) was needed from days 7 to 18. A ventricular assist device (Berlin Heart EXCOR, Berlin Heart AG, Germany) was implanted at day 8. The dose of CoQ_{10} was increased from 1.5 to 25 mg/kg/day (Fig. 2A) when the low level of myocardial CoQ_{10} was determined. Mononuclear cells levels corrected rapidly with supplementation. Glutathione levels were normal at admission (Fig. 2C). Low plasma arginine and vitamin D levels were corrected by supplementation with L-arginine (50 mg/kg/day) and cholecalciferol respectively (Fig. 2D). Heart failure assessed by proBNP slowly improved (Fig. 2B) allowing removal of the external mechanical cardiac support after 67 days. At the time of discharge – after 95 days – echocardiography showed an improvement of the bilateral ventricular dysfunction with a shortening fraction increasing from <10% at admission to 32% at discharge (Fig. 3). Six months after discharge, the patient has fully recovered: he is able to walk for more than 2 km or to play 90 min football without any fatigue. He continues to be on carnitine,

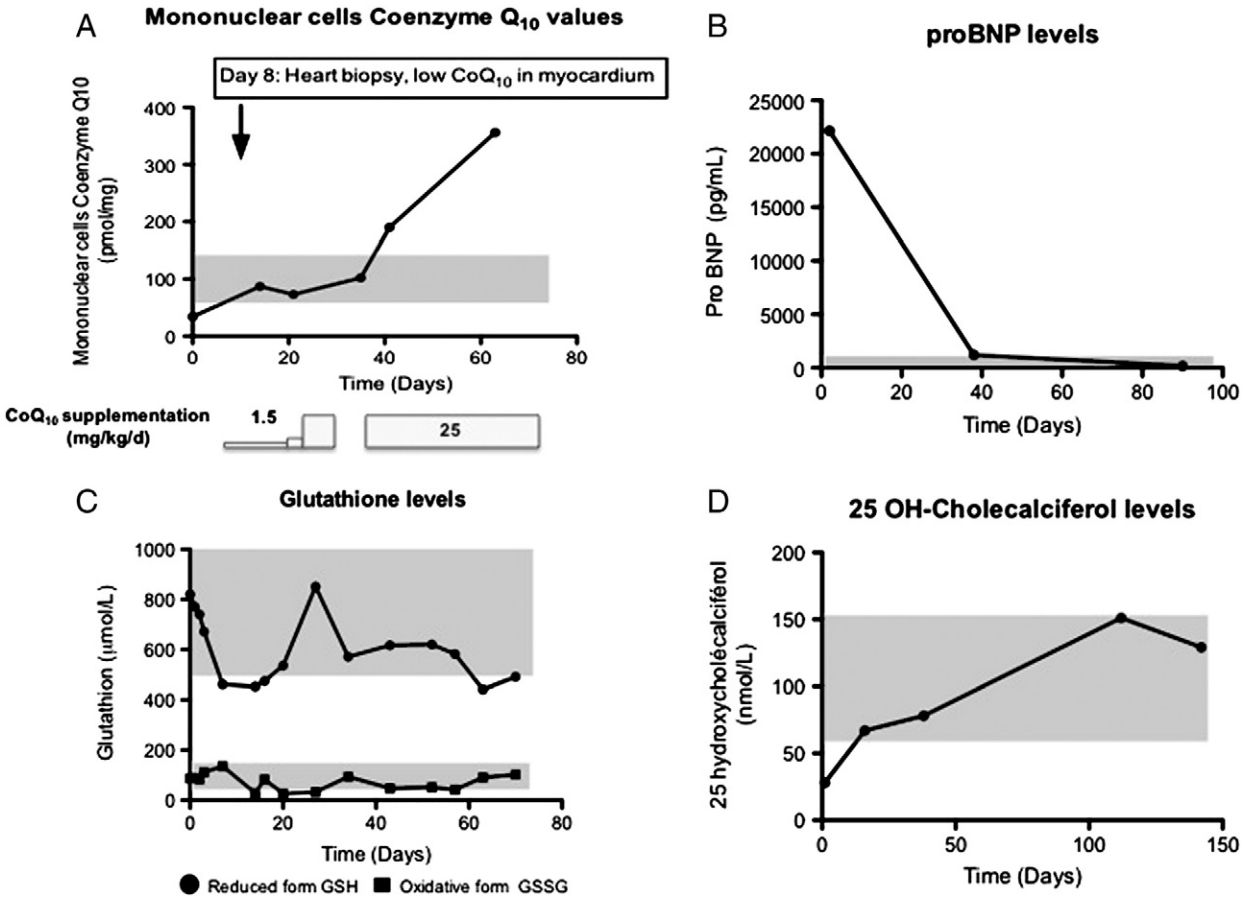

Fig. 2. Evolution of CoQ_{10} in mononuclear cells (A), Brain Natriuretic peptide (proBNP) (B), glutathione (C) and vitamin D (D) levels.

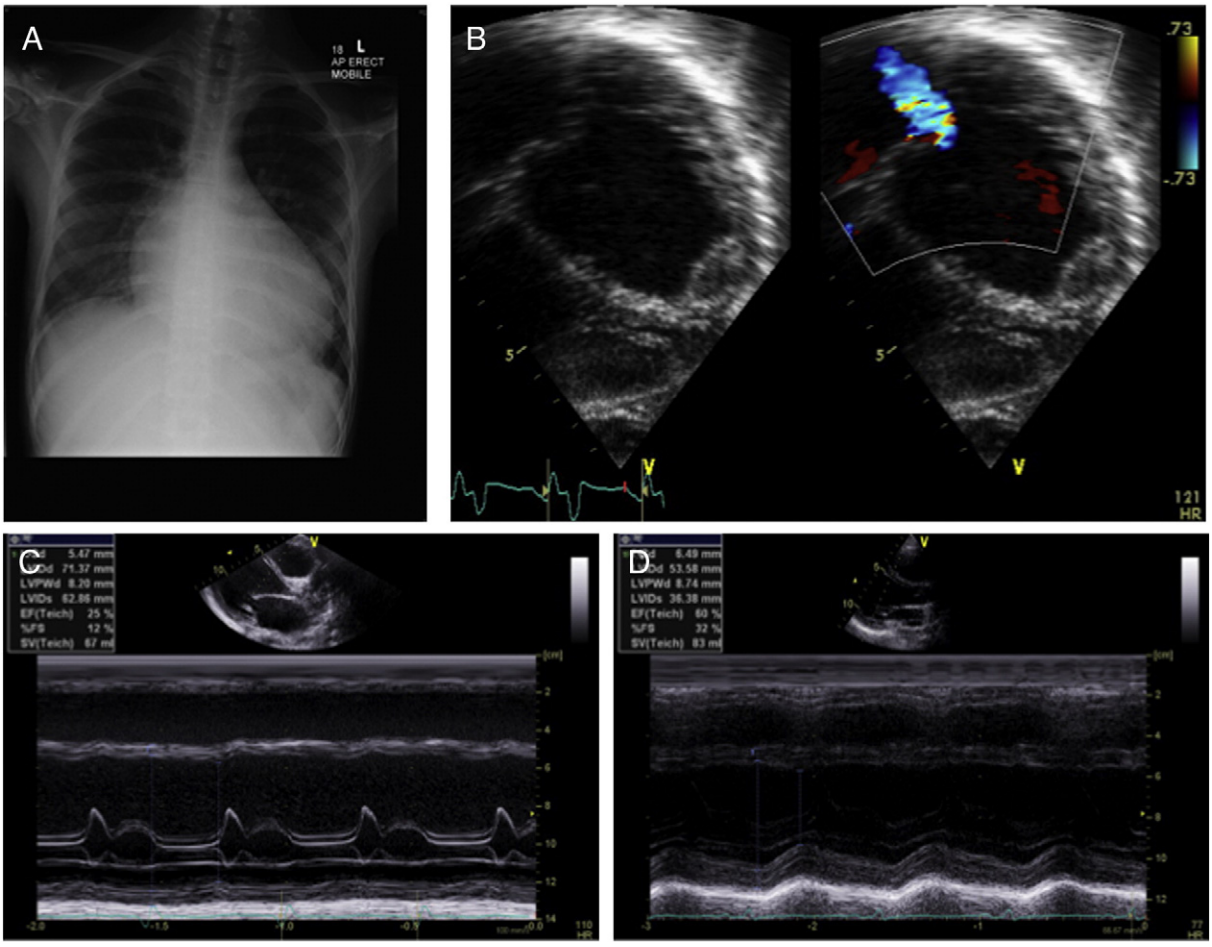

Fig. 3. A: Chest X-ray at admission: cardiomegaly. B: Echocardiography mode 2D (left)/colour Doppler (right): Left ventricle dilation, mitral regurgitation and apical thrombus before Berlin Heart implantation. C: Echocardiography M-mode: At admission, shortening fraction 12%, diastolic left ventricle internal diameter 7.2 cm (Z score +10.1). D: Echocardiography mode TM: At discharge, shortening fraction 32%, diastolic left ventricle internal diameter 5.3 cm (Z score +3.2).

thiamine, riboflavin, L-arginine, and CoQ_{10} supplements and a mildly protein restricted diet (1 g natural protein/kg/day).

In Patient 2, mildly low vitamin D level was treated with 25 hydroxycholecalciferol supplementation. L-arginine level was in the low normal range. Because of low blood white cell CoQ_{10} level (37 pmol/mg, reference range 37–133), CoQ_{10} supplementation (7.5 mg/kg/day) was commenced and regular and cardiac monitoring are ongoing.

5. Discussion

Cardiomyopathy has been recognised as a complication of PA since 1993 (Massoud and Leonard, 1993) with 26 cases reported (Ameloot et al., 2011; de Keyzer et al., 2009; Fragaki et al., 2011; Lee et al., 2009; Mardach et al., 2005; Perez-Cerda et al., 2000; Romano et al., 2010; Sato et al., 2009). Development of cardiomyopathy does not appear to be related to severity of propionic acidaemia; it has been reported in both early- (Perez-Cerda et al., 2000; Romano et al., 2010) and late-onset patients (Ameloot et al., 2011; Lee et al., 2009; Sato et al., 2009) with onset between 3 weeks (Massoud and Leonard, 1993) and 16 years (Ameloot et al., 2011). Cardiomyopathy is more often dilated (Ameloot et al., 2011; de Keyzer et al., 2009; Fragaki et al., 2011; Romano et al., 2010) but can be hypertrophic (Lee et al., 2009; Mardach et al., 2005) with an aspect of non-compaction (Lee et al., 2009). Microscopy shows nonspecific interstitial myocardial fibrosis (Lee et al., 2009; Romano et al., 2010). The prognosis is unfavourable with a fatal outcome reported in 9/24 patients (Table 1), with no statistical difference regarding the age of onset of cardiomyopathy between early- and late-onset groups of patients (Student's *t*-test, $p = 0.65$).

Uncertainty remains regarding the underlying pathophysiology of PA related cardiomyopathy and it might be multifactorial (Fig. 4).

No evidence of systemic carnitine deficiency was present in our patient who had remained on long-term carnitine supplementation since diagnosis. Heart total carnitine and acylcarnitines were respectively normal and mildly raised. It is interesting to note that myocardial free carnitine level was very mildly low. Mardach et al. (2005) described a case with much lower total and acylcarnitines levels (respectively 4.5 and 0.2 nmol/mg) but similar free carnitine level (4.2 nmol/mg). Compared to the skeletal muscle reference range proposed in Mardach et al., our patient's free carnitine level is mildly low and certainly not comparable to severe carnitine depletion observed in carnitine transporter deficiency (Magoulas and El-Hattab, 2012).

Increased intracellular propionylCoA ester levels in heart raise a possible direct acute toxicity of propionylcarnitine leading to a cataplerotic state and a secondary impairment of energy metabolism (Kolker et al., 2013). Levels of plasma propionylcarnitine in our case were similar during the acute cardiac decompensation compared to levels determined during routine monitoring when he was well. This illustrates the discrepancy between plasma and tissue levels. Additionally, we cannot exclude cumulative long-term toxicity. The incidence of cardiomyopathy is comparable in the reported cases of early-onset ($n = 12$) and late-onset ($n = 12$) patient groups (Table 1). This complication is not universal in the natural history of this disease and no specific

Table 1
Summarised review of the literature of PA related cardiomyopathy. BVAD: Biventricular assist device; CHDF: continuous haemodiafiltration; CVVH: Continuous veno-venous haemofiltration; ECMO: Extra corporeal membrane oxygenation; LVAD: Left ventricular assist device; NA: Not available; and OLT: Orthotopic liver transplantation.

Age-Onset	Age at first symptom	Cardiomyopathy		Pathology	Myocardial respiratory chain activity	Treatment (medical cardiac drugs excluded)	Outcome	Publication
		Age at diagnosis	Features					
Early-onset	3 days	NA	NA	NA	NA	NA	Alive	Perez et al.
Early-onset	15 days	NA	NA	NA	NA	NA	Death (4 months)	Perez et al.
Early-onset	3 days	Neonatal	"Congenital cardiopathy"	NA	NA	NA	Death (15 days)	Perez et al.
Late-onset	4 months	NA	NA	NA	NA	NA	Alive	Perez et al.
Late-onset	9 months	8 years	Hypertrophic, no dilatation	Low myocardial total and free carnitine, Increased cardiomyofiber size, Enlarged and hyperchromatic nuclei	Complex I deficiency		Death (8 years)	Mardach et al.
Late-onset	14 years	14 years	Dilated, Left ventricular non compaction	Endocardial thickening, interstitial fibrosis	NA	Cardiac transplantation	Alive	Lee et al.
Late-onset	10 months	6 years	Dilated	NA	Complex III deficiency	OLT	Alive	De Keyser et al.
Late-onset	1 month	8 years	Dilated	Endomyocardial fibrosis	Normal		Alive	De Keyser et al.
Late-onset	46 days	2 years	NA	NA	NA	ECMO + CHDF (recovered in 7 days), OLT 3 months later	Alive	Sato et al.
Late-onset	8 months	6 years	Dilated	Light and electron microscopy normal	NA	LVAD (126 days) + OLT	Alive	Ameloot et al.
Early-onset	14 days	11 years	Dilated	NA	NA		Death (11 years)	Fragaki et al.
Late-onset	1 month	8 years	Dilated	Fibrosis	NA	Antioxidant 6 months	Alive	Romano et al.
Late-onset	10 months	6 years	Dilated	NA	NA	OLT	Alive	Romano et al.
Early-onset	6 days	11 years	Dilated	NA	NA		Death (11 years)	Romano et al.
Early-onset	3 days	9 years	Dilated	NA	NA	OLT	Alive	Romano et al.
Early-onset	20 days	5 years	Dilated	NA	NA		Death (13 years)	Romano et al.
Early-onset	3 days	5 years	Dilated	NA	NA		Alive	Romano et al.
Early-onset	neonate	8 years	NA	NA	NA		Death (8 years)	Massoud et al.
Late-onset	2 years	2 years	Dilated	NA	NA		Alive	Massoud et al.
Late-onset	13 months	13 months	NA	NA	NA		Alive	Massoud et al.
Early-onset	neonate	2 years	Dilated	NA	NA		Death (2 years)	Massoud et al.
Early-onset	3 days	3 weeks	NA	NA	NA		Alive	Massoud et al.
Early-onset	3 days	4 years	NA	NA	NA		Death (4.5 years)	Massoud et al.
Late-onset	18 months	15 years	Dilated	Abnormal mitochondria	Complex IV deficiency	BVAD + CVVH + CoQ10 + metabolic cocktail	Alive	Our report
24 Patients 12 Early-onset 12 Late-onset	Mean value 1.02 years ± 2.88	Mean value 6.56 years ± 4.05	Dilated n = 14/15 Hypertrophic n = 1/15 Non compaction n = 1/15				9 Deaths/24 (37.5%)	

time-course has been observed between disease presentation and development of cardiomyopathy.

At presentation of cardiomyopathy in PA, other potential treatable associated causes (vitamin D, carnitine deficiencies) need to be excluded. Vitamin D deficiency was noted in our patient and was proactively treated as this has been associated with cardiomyopathy (Maiya et al., 2008) and could have been an additional factor contributing to the cardiac decompensation.

Previous reports have observed RC dysfunction in PA-related cardiomyopathy. Reported mitochondrial abnormalities in PA include low myocardial free carnitine (Mardach et al., 2005) and low myocardial complex I (Mardach et al., 2005) or complex III (de Keyzer et al., 2009). We report various lines of evidence demonstrating mitochondrial dysfunction in our patient: electronic microscopy showed abnormal enlarged mitochondria with atypical cristae, whilst myocardial RC activities revealed low complex IV activity providing evidence of functional impairment. We sought to further understand the contribution of mitochondrial pathology to cardiomyopathy in PA, and performed white blood cell and myocardial CoQ_{10} measurements. Our report assesses CoQ_{10} status in PA for the first time and shows a mildly low white blood cell level and severe myocardial CoQ_{10} depletion. Toxicity of propionate metabolites in tricarboxylic acid cycle leads to secondary RC impairment (de Keyzer et al., 2009). However reactive oxidative species (ROS) have been reported either decreased (de Keyzer et al., 2009) or increased in organic acidurias (Richard et al., 2007). Consumption of antioxidants used to combat this oxidative stress that has been described in methylmalonic aciduria (Haas et al., 2009; Richard et al., 2007; Treacy et al., 1996). Different organs can be variably affected, reflecting their relative energy requirements; thus, high-requiring energy organs such as the muscle, liver and heart are preferentially affected. PA-associated RC dysfunction has been reported in several organs such as the liver (de Keyzer et al., 2009; Fragaki et al., 2011) or muscle (Fragaki et al., 2011; Mardach et al., 2005; Schwab et al., 2006). Interference of propionate metabolites with tricarboxylic acid cycle function

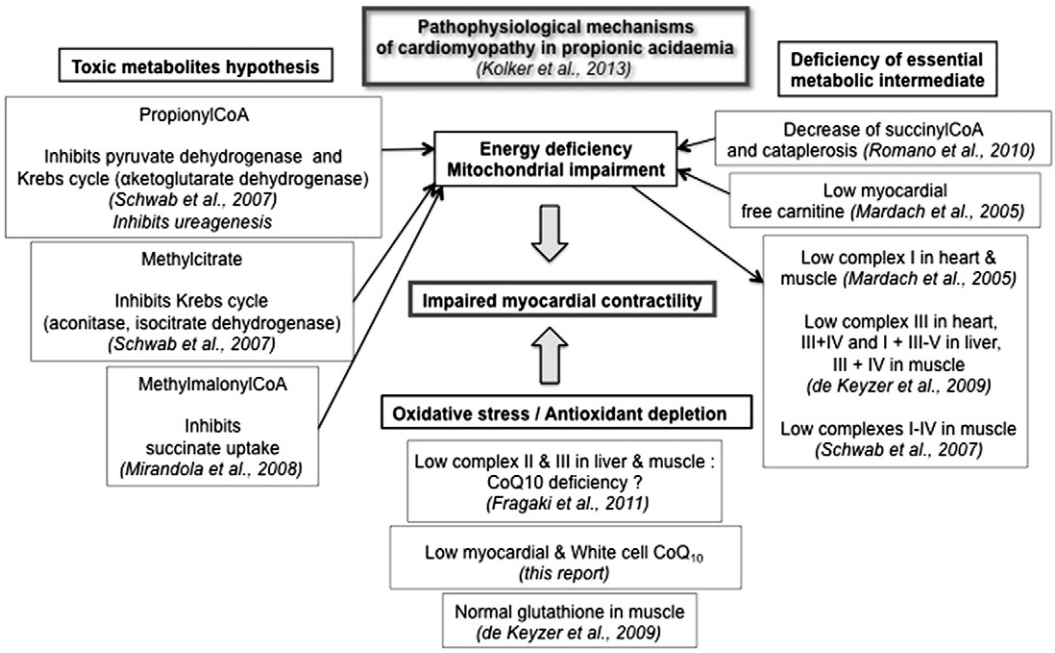

Fig. 4. CoQ_{10} in pathophysiological mechanisms involved in secondary respiratory chain deficiencies in propionic acidaemia.

has been discussed as one of the main explanations (Kolker et al., 2013; Mirandola et al., 2008; Pettenuzzo et al., 2006; Schwab et al., 2006). Furthermore, a report of fatal cardiomyopathy in PA showed low complexes I + II and I + III in liver, raising the possibility of secondary CoQ_{10} deficiency, although this was not measured in that patient (Fragaki et al., 2011). Pathophysiological mechanisms and previously published mitochondrial investigations in PA are summarised in Fig. 4. Taken together, all of these findings strongly support a secondary RC impairment in the myocardium as one of the main pathophysiological explanations for PA-associated cardiomyopathy.

In view of the near fatal cardiac presentation of the patient, several therapeutics were started simultaneously: thiamine, riboflavin and CoQ_{10} to support mitochondrial function; β-hydroxybutyrate as an alternative energy substrate; 25 hydroxycholecalciferol and L-arginine to correct levels. Berlin Heart biventricular assist device was required for haemodynamic support combined with continuous veno-venous haemofiltration potentially removing toxic substances. It is impossible to determine retrospectively which of these treatments was the most beneficial.

CoQ_{10} primary deficiency was ruled out as these patients did not present usual described clinical phenotypes (Quinzii and Hirano, 2010), they had a primary metabolic inherited disease accounting for the clinical and biochemical findings, and the cardiac biopsy from Patient 1 had a normal complexes II–III ratio in cardiac biopsy for Patient 1. Only complexes II–III activity was measured as this parameter has been suggested as a more sensitive marker of decreased CoQ_{10} status compared to complexes I–III (Montero et al., 2008). CoQ_{10} has been described in an increasing number of conditions (Quinzii and Hirano, 2011) and this has been suggested in PA (Fragaki et al., 2011). Consistent with our report, normal complexes II–III activity has been observed with low CoQ_{10} status in tissue suggesting a partial CoQ_{10} deficiency associated with an inconsistent electron transfer to complex III (Lamperti et al., 2003).

CoQ_{10} has been considered as a potential treatment in heart failure whatever the underlying causes and was used in several clinical trials with controversial results (Pepe et al., 2007) or more recently with mild benefits (Kocharian et al., 2009) with high doses (2 to 10 mg/kg/day). CoQ_{10} therapy has been proposed in Friedreich's ataxia but a randomised phase III clinical trial did not support this suggestion (Lagedrost et al., 2011). Animal studies in rodents have demonstrated improvement in myocardial fibrosis, hypertrophy and decrease of ROS production in the *db/db* mouse model of type 2 diabetes (Huynh et al., 2012) and improvement of cardiac hypertrophy and diastolic function in association with propionylcarnitine administration and omega 3 fatty acids in cardiomyopathic Syrian hamsters (Mancinelli et al., 2005). Our observation highlights the importance of measuring CoQ_{10} levels in PA patients with cardiomyopathy. Although white blood cell levels are the easiest to measure, they may not represent intracellular levels, as demonstrated in our patient. High-dose CoQ_{10} supplementation is thought to be beneficial by its antioxidant effect and was used to increase intracellular cardiac levels. A second cardiac biopsy was not performed, and therefore we were unable to directly assess the efficacy of high-dose CoQ_{10} supplementation in restoring myocardial CoQ_{10} levels. However considering this life-threatening complication, our findings combined with published results in the literature, and the safety of the drug, CoQ_{10} supplementation should be considered. Further clinical trials will be required to confirm the hypothesis that long-term CoQ_{10} therapy in PA reduces the incidence of cardiomyopathy.

PA related cardiomyopathy has been reported to be reversible after orthotopic liver transplantation (Hansson et al., 1999) with normalisation of echocardiography in addition to metabolic improvement within 70 days (Ameloot et al., 2011), 3 or 12 months (Romano et al., 2010). Sato et al. suggested performing orthotopic liver transplantation after recovery of the cardiac decompensation, in order to prevent any further relapse (Sato et al., 2009). This high-risk procedure particularly in PA patients would need careful planning with close preoperative cardiac monitoring (Collins and Kelly, 1994). In our patient, liver transplantation is being considered.

6. Conclusion

This report demonstrates for the first time low myocardial CoQ_{10} in cardiomyopathy in PA, highlighting secondary mitochondrial impairment as the relevant causative mechanism. As in our patient with a life-threatening scenario such as decompensated cardiomyopathy, several therapeutics are often started immediately and in tandem in order to stabilise the patient as quickly as possible. This creates enormous challenges when trying to retrospectively attribute efficacy to individual medications. Considering the severity of myocardial CoQ_{10} depletion and the increasing evidence of secondary mitochondrial

impairment as one of the main pathophysiological explanations for cardiomyopathy in PA, we do think that CoQ_{10} supplementation should be considered as an adjuvant therapeutic in PA-related cardiomyopathy. We would recommend adding high-dose CoQ_{10} supplementation in this situation especially in case of cardiac decompensation. Supplementation should be started even in the case of normal or borderline white cell CoQ_{10} levels, as this cannot exclude severe CoQ_{10} depletion in tissues.

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