J Inherit Metab Dis (2014) 37:223–230
DOI 10.1007/s10545-013-9640-0

ORIGINAL ARTICLE

Primary Carnitine deficiency in the Faroe Islands: health and cardiac status in 76 adult patients diagnosed by screening

Jan Rasmussen · Lars Køber · Allan M. Lund · Olav W. Nielsen

Received: 27 May 2013 / Revised: 5 July 2013 / Accepted: 12 July 2013 / Published online: 21 August 2013

Abstract
Background Carnitine deficiency can cause cardiomyopathy and cardiac arrhythmia. The prevalence in the Faroe Islands is the highest reported in the world (1:300). A nationwide screening program identified 76 Faroese adult patients (15–80 years) with Primary Carnitine Deficiency (PCD). We describe prior and current health status and symptoms in these patients, especially focusing on cardiac characteristics.
Methods Upon identification, patients were immediately admitted for physical examination, ECG, blood tests and initiation of L-carnitine supplementation. Medical records were reviewed and patients were interviewed. Echocardiography and blood tests were performed in 35 patients before and after L-carnitine supplementation.
Results All patients were either asymptomatic or had minor symptoms when diagnosed. Echocardiography including LVEF, global longitudinal strain and dimensions were normal apart from left ventricular hypertrophy with normal systolic function in one young male. Symptoms, e.g. fatigue, were reported in 43 % with a reduction to 12 % ($p<0.01$) following initiation of L-carnitine supplementation. Eighty two % reported participation in sports of which 52 % were on a competitive level. ECGs showed limited changes and blood tests were normal. Mean plasma free carnitine increased from 6.1 μmol/L to 15.1 μmol/L ($p<0.01$) within 50 days of L-carnitine supplementation.
Conclusion PCD in adults can cause serious symptoms, but adult Faroese patients identified through a screening program were predominantly asymptomatic with a normal cardiac structure and function.

Communicated by: Georg Hoffmann

Electronic supplementary material The online version of this article (doi:10.1007/s10545-013-9640-0) contains supplementary material, which is available to authorized users.

J. Rasmussen (✉)
Department of Internal Medicine, National Hospital,
FO-100 Thorshavn, the Faroe Islands
e-mail: lsjanra@ls.fo

L. Køber
Department of Cardiology, Copenhagen University Hospital,
Rigshospitalet, Copenhagen, Denmark

A. M. Lund
Centre for Inherited Metabolic Diseases, Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet,
Copenhagen, Denmark

O. W. Nielsen
Department of Cardiology, Bispebjerg University Hospital,
Copenhagen, Denmark

Introduction

The frequency of primary carnitine deficiency (PCD), also known as carnitine transporter deficiency, in the Faroe Islands, an isolated archipelago in the North Atlantic, is by far the highest reported in a population worldwide (Lund et al 2007; Rasmussen et al 2012; Rasmussen et al 2013). PCD is a relatively rare genetic disorder with the reported frequencies worldwide at 1 in 20,000–70,000 individuals, and the reported number of untreated adults with PCD is quite low—only 42 adult cases until recently (De Biase et al 2012). A series of sudden deaths attributed to PCD among the small Faroese population of only approximately 50,000 inhabitants lead to the initiation of a voluntary screening program—as a consequence a large number of individuals were identified with low carnitine levels and mutations suggestive of PCD (Rasmussen et al 2012, 2013).

PCD is an autosomal recessive disorder caused by mutations in the *SLC22A5* gene encoding for the high affinity carnitine transporter OCTN2 (organic cation transporter 2) (Nezu et al 1999; Longo et al 2006). Carnitine is essential in the transfer of long-chain fatty acids across the inner mitochondrial membrane for β-oxidation and is involved in other

important cellular processes as well (Mitchell 1978; Rebouche 2004; Steiber et al 2004). The lack of functional OCTN2 carnitine transporters leads to low tissue carnitine levels and an impaired fatty acid oxidation in patients suffering from PCD (Scaglia et al 1998; Longo et al 2006). Reported symptoms range from hypoketotic hypoglycaemia, fatigue and myopathy to neurological and cardiac symptoms (Longo et al 2006; Magoulas and El-Hattab 2012; Rasmussen et al 2012). Children with untreated PCD are especially thought to be at risk of developing potentially fatal metabolic disturbances and cardiomyopathies (Stanley 2004; Magoulas and El-Hattab 2012). However, adult patients can also develop serious and even fatal adverse effects when not on L-carnitine supplementation—as well as be asymptomatic (Longo et al 2006; De Biase et al 2012; Magoulas and El-Hattab 2012; Rasmussen et al 2012). The low number of reported adult PCD patients in the literature has made it difficult to assess the risks and susceptibility to complications in patients suffering from PCD.

The objective of this study was to examine and characterize adult Faroese PCD patients, who had not received any prior treatment—especially focusing on their cardiac status. The findings presented are relevant to the management of newly diagnosed adult patients elsewhere, especially considering the internationally increased neonatal screening effort for PCD which has lead to an increased identification of previously undiagnosed mothers with PCD through their newborns (El-Hattab et al 2010).

Methods and materials

Subjects

More than 55 % of the population participated in the voluntary nationwide screening program between 2009–2011. All adult PCD patients (>15 years) identified through the screening program and admitted acutely for examinations and initiation of L-carnitine supplementation were included in this study (Rasmussen et al 2013). All patients were interviewed about their previous and current health status and underwent physical examination when admitted. 24-h cardiac telemetry was performed during hospitalisation. Blood tests were taken and a 12-lead electrocardiogram was obtained. Initial echocardiography was performed either during the admittance when possible or later in an out-patient setting when on L-carnitine supplementation. Patients who had echocardiography performed within 8 days of initiation of L-carnitine supplementation (n=39) were requested to have a follow-up echocardiography performed. All patients were offered an out-patient consultation with a clinical geneticist (AML) to monitor their health status. An online survey was also conducted among all the patients with specific questions regarding, e.g. symptoms, effects of L-carnitine supplementation and physical ability. The patients initially received a total of 3 g of L-carnitine daily either in the form of tablets (333 mg) or solution (100 mg/mL) and administered in the morning, afternoon and evening. Changes in the dosage were recommended according to the level of plasma free carnitine measured in serial follow-up blood samples with an aim of keeping through plasma free carnitine at 20 μmol/L±5 μmol/L (Lund et al 2007). The patients' medical records in the National Hospital were reviewed for previous contacts to the hospital. The local ethics committee approved this study.

Echocardiography

Standard echocardiography was performed in the left decubitus position using a GE Medical Vivid s6 ultrasound system. Image analysis was performed on GE Echopac software. Six experienced physicians performed the primary echocardiographic examinations while the main investigator (JR) performed the follow-up examinations and all measurements on recorded echocardiograms. Measurements were obtained in the parasternal and apical views according to accepted standards and techniques (Lang et al 2005). All reported measures are the average of two separate measurements. The main investigator (JR) and an experienced second observer (OWN) performed measurements on 35 patients picked at random to determine the intra-observer and inter-observer variability. LV mass was calculated by the formula of Devereaux, and body surface area by the formula of Du Bois (Devereux et al 1986; Du Bois and Du Bois 1989). LV hypertrophy was defined as >116 g/m^2 for men and >104 g/m^2 for women (Devereux et al 1996).

2D speckle tracking, an advanced echocardiographic technique to analyse tissue deformation and motion, was performed in the group examined within 8 days of initiation of treatment. The 2D strain analysis was performed on apical four-, two- and three-chamber views optimized for speckle tracking (Mondillo et al 2011).

Inter-observer variability expressed in CV% regarding left ventricular mass, left atrial volume, TAPSE (Tricuspid Annular Plane Systolic Excursion) and e' was 14 %, 13 %, 13 % and 17 %, respectively. Bland-Altman plots showed equally distributed variances within 95 % limits of agreement. Intra-observer CV% for the same parameters was 8 %, 10 %, 8 % and 7 %, respectively.

Blood sample and electrocardiographic analysis

Blood was analysed using standard procedures in the National Hospital laboratory for routine parameters including haemoglobin, glucose, ALAT, urea, urate and creatine kinase. Furthermore blood was sent to the Centre for Inherited Metabolic Diseases in Rigshospitalet, Copenhagen, for DNA analysis to confirm the diagnosis of PCD and to determine plasma acylcarnitines (Rasmussen et al 2013).

All available electrocardiograms taken at primary admission were analysed manually using the Minnesota ECG criteria (Prineas and Blackburn 1982).

Statistical analysis

Data analysis was performed using IBM® SPSS® Statistics Version 19 (SPSS Inc., Chicago, Il, USA). All continuous variables were expressed as mean (standard deviation). Student's paired t-test was used to compare echocardiographic parameters and McNemar's test for paired binominal data was used to test for a difference in symptoms before and after treatment. Level of significance was set at $p<0.05$ (two tailed test). Inter- and intra-observer variability was assessed by using Bland-Altmann statistics and calculating the coefficient of variation (CV%).

Results

Patients and morbidity

From August 2009 to January 2011, 26,462 individuals participated in the screening program (Rasmussen et al 2013). There were 76 adult patients between the ages of 15 to 80 years (mean 37.8 years) included in this study (Table 1). Seven different genotype variants were found (see patient table, web).

A review of medical records among the included patients revealed that 37 patients had previously been admitted to the National Hospital in the Faroe Islands before being diagnosed with PCD. A female patient aged 34 (ref.#58, patient table) survived ventricular fibrillation following exposure to antibiotics containing pivalic acid known to lower carnitine levels (Rasmussen et al 2012). A male patient now aged 29 (ref.#21, patient table) had several previous admissions with hypoglycaemia and convulsions and was diagnosed with epilepsy in 1986 and a 28-year-old female (ref.#38, patient table) had a minor myocardial infarction. Other causes of hospital admissions were mostly minor including abdominal symptoms, atrial fibrillation and common infections (patient table, web).

Mean values of haemoglobin, glucose, urate and creatine kinase, were all within reference ranges (Table 1). Decreased stamina when performing physical activity was reported by 25 %. 82 % reported being or having been active in sports—of which 52 % reported participation in sports on a competitive level.

Cardiac examinations

The mean time from initiation of L-carnitine supplementation to primary echocardiography was 1.5 days (2 SD) in the group examined within 8 days of initiation of L-carnitine supplementation ($n=39$)—of whom 35 had a follow-up echocardiography performed a median 638 days later (range 330–1,264 days). The patients not examined within 8 days of treatment start ($n=37$) had primary echocardiography performed a median 124 days (range 14–478 days) following start of L-carnitine supplementation—a follow-up echocardiography was not performed in those patients. All mean echocardiographic measurements were within normal range including left ventricular mass and ejection fraction (Table 2). There was no significant difference between measurements including global longitudinal strain from the primary and the follow-up echocardiographic examinations in the 35 patients (Table 2). One 20-years-old male patient though exhibited signs of left ventricular hypertrophy with a mass of 303 g and a left ventricle mass index of 141 g/m^2, but with normal systolic and diastolic function. Follow-up echocardiography 970 days later showed a marginal decrease in left ventricular mass (264 g, 119 g/m^2). The patient reported improved stamina and physical ability following supplementation with L-carnitine.

Analysis of obtainable electrocardiograms ($n=69$) identified eight patients (12 %) (mean age 59.6 years, SD 15.4) with atrial fibrillation, bundle branch block, T-wave inversion or ST junction depression—the rest had minor or no changes (see patient table, web). The mean duration of the PR, QRS and QTc intervals were normal (Table 1); 24-h cardiac telemetry showed no signs of serious, e.g. ventricular arrhythmia in all patients.

Effect of L-carnitine supplementation

Mean plasma free carnitine measured pre-treatment was 6.1 μmol/L (SD 2.1) which increased significantly to a mean of 15.1 μmol/L (SD 6.0) ($p<0.01$) within 50 days of L-carnitine supplementation and then reached a plateau (Fig. 1). The mean total daily amount of L-carnitine ingested by the patients increased in 2 years from 3 g to 3.8 g, yielding a mean dosage of 46 mg/kg/day. Nearly all patients (98 %) reported taking L-carnitine supplementation as advised.

Symptoms of mostly fatigue and palpitations were reported by 43 % of the patients, declining to 12 % ($p<0.001$) following a mean 351 (141 SD) days of treatment with L-carnitine (see patient table). There was a tendency, although not significant, that the individuals reporting symptoms of fatigue were younger than those who did not report these symptoms ($p=0.075$). Since being diagnosed with PCD, 94 % reported they had not felt restricted in their daily life, although 46 % experienced side effects from the L-carnitine supplementation—primarily fish odour, weight increase and intestinal discomfort.

Table 1 Baseline characteristics, blood tests and ECG measurements, mean (SD)

		All subjects (n=76)	Male (n=39)	Female (n=37)
15–30 y		31	13	18
30–45 y		22	16	6
45–60 y		17	6	11
> 60 y		6	4	2
Mean age (years)		37.6 (16.3)	37.5 (15.8)	37.8 (16.9)
Height (cm)		177 (8.6)	170 (15)	182 (7)
Weight (kg)		82 (19)	91 (17)	71 (15)
Body mass index (kg/m^2)		26.2 (4.6)	27.4 (4.2)	24.6 (4.6)
Systolic blood pressure (mmHg)		125 (15)	130 (15)	119 (14)
Diastolic blood pressure (mmHg)		72 (11)	75 (11)	69 (10)
Heart rate (beats/min)		69 (13)	65 (11)	73 (14)
Blood tests & ECG measurements	**Normal range**			
Haemoglobin (mmol/L)	7/8–10	8.4 (0.8)	8.9 (0.6)	7.8 (0.6)
ALAT (U/L)	10–70	32.1 (25.6)	38.9 (26.2)	25.2 (23.4)
Urea (mmol/L)	3.2–8.1	5.3 (1.7)	5.8 (1.4)	4.8 (1.7)
P-urate (mmol/L)	0.23–0.48	0.3 (0.1)	0.4 (0.1)	0.23 (0.1)
P-glucose (mmol/L)	2–10	5.5 (1)	5.6 (0.8)	5.4 (1.1)
CK-MB (μg/L)	<5	2.8 (1.3)	3.1 (1.4)	2.4 (1.2)
Creatine kinase (U/L)	50–400	140 (97)	175.4 (105)	100.1 (68.7)
Free carnitine in blood (μmol/L)	>7	3.3 (1.1)	3.4 (1.2)	3.1 (0.9)
Free p-carnitine (μmol/L)	>10	6.3 (2.4)	6.7 (2.6)	5.9 (2.2)
PR (ms)	120–220	171 (31)	175 (28)	167 (32)
QRS (ms)	<120	100 (21)	105 (20)	95 (20)
QTc (ms)	<440	417 (35)	410 (41)	422 (27)

Discussion

The 76 adult Faroese PCD patients identified through the nationwide screening program did not suffer from serious symptoms at the time of diagnosis.

All mean values of echocardiographic parameters in our study were within normal ranges (Table 2). The contractile properties were normal in all patients without any signs of impaired cardiac function. Except signs of left ventricular hypertrophy in one young male patient, there were no signs of structural abnormalities or cardiac hypertrophy in the patients. Follow-up echocardiographic examinations in 35 patients following L-carnitine supplementation showed no signs of change in measured echocardiographic parameters and cardiac function.

Hypertrophic or dilated cardiomyopathy has mainly been described in children suffering from PCD and only rarely in adult patients (Ino et al 1988; Stanley et al 1991; Zales and Benson 1995; Marques 1998; Pierpont et al 2000; Lamhonwah et al 2002; Lamhonwah et al 2004; Melegh et al 2004; Yamak et al 2007; Cano et al 2008; Lee et al 2010; Rasmussen et al 2012; Agnetti et al 2013). Koizumi et al reported in 1999 marginal left ventricular hypertrophy among middle-aged Japanese PCD heterozygotes (Koizumi et al 1999). But the general lack of left ventricular hypertrophy among the Faroese PCD homozygous patients, with manifest hypertrophy evident in only one patient, indicates, that cardiac hypertrophy might develop sporadically in a patient cohort—but why some patients are more susceptible to cardiac hypertrophy than others with the same genotype is still unclear.

The role of carnitine depletion in cardiomyopathy and heart failure in patients without PCD, as well as the potential of L-carnitine supplementation as an element in the treatment of these disorders, is still investigated and debated (Rizos 2000; Grube et al 2011; Marcovina et al 2012; Omori et al 2012). Echocardiographic screening should be performed when a patient is diagnosed with PCD, but the need for further control echocardiographic examinations in adult patients adhering to L-carnitine supplementation seems limited.

Analysis of ECGs from primary admission did not show signs of abnormalities, which can be attributed to PCD. Prolonged QT interval with syncope has been described previously in two young women with PCD, but PCD patients without prior ECG changes can also suffer from sudden severe and lethal cardiac arrhythmia

Table 2 Echocardiographic results. *LV* left ventricle; *LA* left atrium; *BSA* body surface area; *TAPSE* tricuspid annular plane systolic excursion; *GLS* Global Longitudinal Strain. Mean (SD)

Group 1 (<8 days from start of treatment to primary echo)			
Echocardiographic variables	Primary echo (n=39)	Follow-up echo* (n=35)	Significance** p
LV mass (g)	156.5 (42.4)	149.4 (52)	0.19
LV mass/BSA (g/m^2)	80.6 (14)	79.4 (18)	0.5
LA volume (mL)	47.4 (12)	48.8 (15.5)	0.74
LA volume/BSA (mL/m^2)	24.7 (5.1)	24.9 (6.4)	0.95
LV ejection fraction (%)	59 (3.9)	58.7 (4)	0.7
TAPSE (mm)	26.3 (3.7)	26.4 (3.4)	0.74
E/A	1.6 (0.5)	1.6 (0.7)	0.93
e′ (cm/s)	0.15 (0.04)	0.2 (0.03)	0.3
s′ (cm/s)	0.09 (0.03)	0.13 (0.08)	0.05
GLS (%)	20.9 (2.3)	20.6 (2.1)	0.95
Group 2 (>8 days from start of treatment to primary echo)			
Echocardiographic variables	Primary echo (n=37)		Significance*** p
LV mass (g)	165.8 (49)		0.39
LV mass/BSA (g/m^2)	81.6 (20.9)		0.82
LA volume (mL)	55.9 (18.2)		0.06
LA volume/BSA (mL/m^2)	27.3 (7.2)		0.15
LV ejection fraction (%)	59 (3.8)		0.99
TAPSE (mm)	26.9 (3.9)		0.51
E/A	1.6 (0.6)		0.83
e′ (cm/s)	0.15 (0.05)		0.78
s′ (cm/s)	0.08 (0.02)		0.23

*Follow-up echo performed a median 638 days later. **Paired samples T-test. ***Independent samples t-test used to compare Group 1 primary echo and Group 2 primary echo

(Rijlaarsdam et al 2004; Schimmenti et al 2007; Tadros and Klein 2009; De Biase et al 2012; Rasmussen et al 2012). Unless finding obvious predisposing signs of cardiac arrhythmia, which might be attributed to PCD, one should be wary of

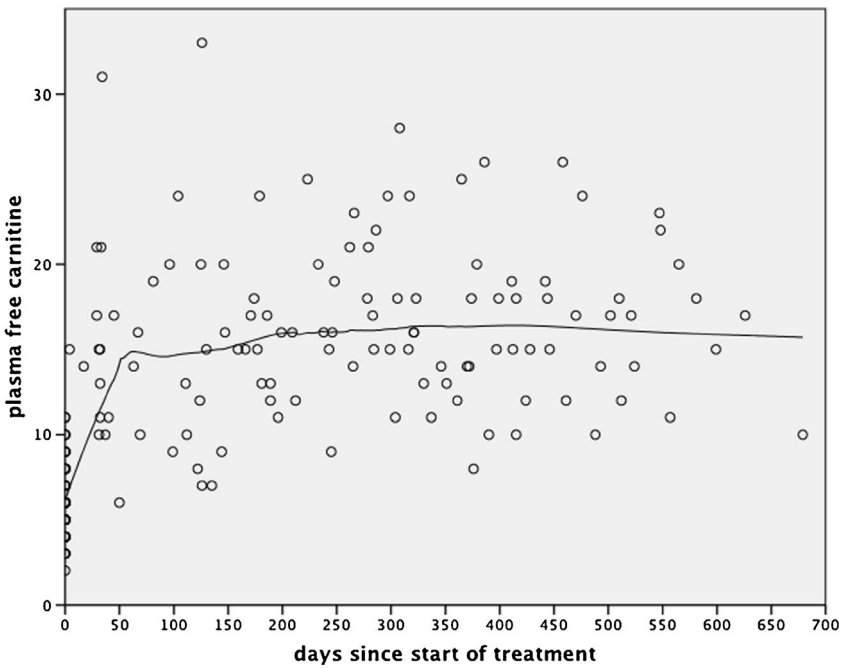

Fig. 1 Mean plasma free carnitine levels in the patients before and after L-carnitine supplementation

using ECG analysis in asymptomatic PCD patients to predict their risk of future cardiac events.

Mean through plasma free carnitine rose quickly from 6.1 μmol/L to 15.1 μmol/L when the patients received L-carnitine supplementation. Although the initial increase in mean plasma free carnitine was rapid, the subsequent increase proved slow even though the dosage of L-carnitine was increased (Fig. 1).

Hypoketotic hypoglycaemia, anaemia, elevated transaminases and creatine kinase have previously been reported in children rather than adults suffering from PCD (Stanley et al 1991; Tein 2003; Longo et al 2006; Cano et al 2008). All mean blood test parameters were within normal ranges in our study, and it is unlikely that asymptomatic adult patients with PCD suffer derangement of important blood parameters. Fig. 2

It seems clear that most patients with PCD are capable of performing high intensity physical activities without risk of complications as 82 % of the patients reported having been active in sports, of which 52 % had participated in competitive endurance sports *before* receiving L-carnitine supplementation. It is not clear if untreated PCD patients are able to maintain normal fatty acid oxidation during physical activities even with very low levels of carnitine or if there is a shift towards increased glucose oxidation in these patients (Paulson 1998; Calvani et al 2000).

Reported symptoms of mainly fatigue and decreased stamina while at rest improved significantly following initiation of L-carnitine supplementation.

We have previously reported five sudden deaths associated with PCD and are currently in the process of systematically investigating how many more might have died previously in the Faroe Islands (Rasmussen et al 2012). Although PCD can potentially cause lethal encephalopathy and cardiac arrhythmia in untreated adult patients, we also identified many seemingly asymptomatic patients who had not previously suffered serious symptoms, indicating that serious events might be relatively uncommon, at least in Faroese PCD patients, and often influenced by secondary, modulating factors, e.g. pivalic acid exposure (Spiekerkoetter et al 2003; Melegh et al 2004; Rijlaarsdam et al 2004; Vijay et al 2006; Lund et al 2007; Schimmenti et al 2007; Tadros and Klein 2009; El-Hattab et al 2010; Lee et al 2010; Li et al 2010; Rasmussen et al 2012). At present we are most concerned about the patients homozygous for the c.95A>G genotype, because all previously reported Faroese individuals who suffered severe symptoms had this genotype (Rasmussen et al 2012). These patients also exhibit the lowest free carnitine levels in the cohort—but although severe symptoms in the Faroese patients seems to be genotype dependant, this does not seem to be the case regarding less serious symptoms of, e.g. fatigue (patient table). Accurately predicting which patients are at most risk seems at present impossible. Thus, all patients are currently recommended to continue supplementation with L-carnitine and avoid carnitine lowering drugs—thereby likely evading an increased risk of suffering from, e.g. cardiac arrhythmia when compared to persons without PCD.

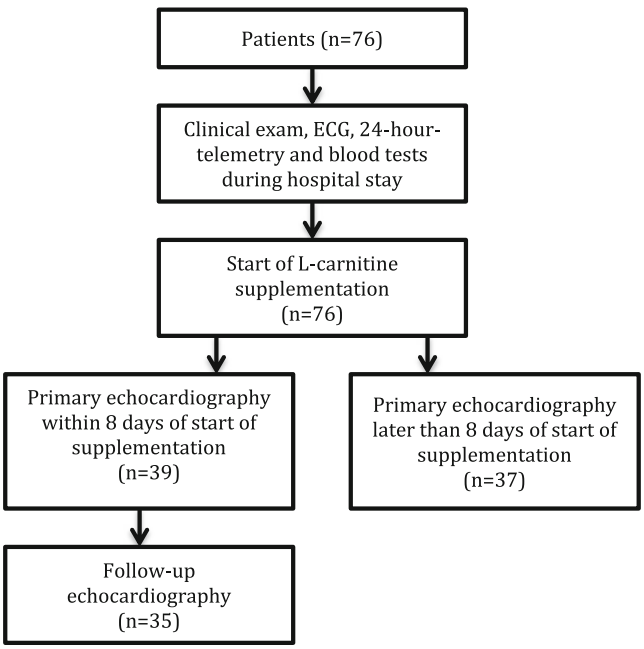

Fig. 2 Flow chart

Strengths and limitations

This is the largest reported study of a cohort of adult PCD patients. Because the patients were identified through a screening program, we could examine them before treatment and then monitor the effect of L-carnitine supplementation. The generalizability of the findings may not be absolute, since there are three common mutations involved in this particular population, which may differ in other populations.

It is not ethically possible to randomize patients to treatment with either L-carnitine or placebo in order to uncover a possible placebo effect of L-carnitine supplementation in symptomatic patients.

Conclusion

All 76 Faroese adult PCD patients were either asymptomatic or had minor symptoms, e.g. fatigue when diagnosed, and all echocardiographic parameters were normal except in one young male with signs of left ventricular hypertrophy. Treatment with L-carnitine significantly reduced symptoms in symptomatic patients, but did not affect echocardiographic parameters. Blood tests were normal and only limited ECG changes were found.

Mean plasma free carnitine increased rapidly following initiation of L-carnitine supplementation.

Serious adverse effects of PCD in adult patients seem rare but L-carnitine supplementation is recommended to avoid an increased risk of, e.g. cardiac arrhythmia.

Conflict of interest None.

Compliance with Ethics Guidelines All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Proof that informed consent was obtained is available upon request.

References

Agnetti A, Bitton L, Tchana B et al (2013) Primary carnitine deficiency dilated cardiomyopathy: 28years follow-up. Int J Cardiol 162(2):e34–e35

Calvani M, Reda E, Arrigoni-Martelli E (2000) Regulation by carnitine of myocardial fatty acid and carbohydrate metabolism under normal and pathological conditions. Basic Res Cardiol 95(2):75–83

Cano A, Ovaert C, Vianey-Saban C et al (2008) Carnitine membrane transporter deficiency: a rare treatable cause of cardiomyopathy and anemia. Pediatr Cardiol 29(1):163–165

De Biase I, Schroer R, Pollard LM et al (2012) Primary carnitine deficiency presents atypically with long QT syndrome: a case report. JIMD Rep 2:87–90

Devereux RB, Alonso DR, Lutas EM et al (1986) Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 57(6):450–458

Devereux RB, Dahlof B, Levy D et al (1996) Comparison of enalapril versus nifedipine to decrease left ventricular hypertrophy in systemic hypertension (the PRESERVE trial). Am J Cardiol 78(1):61–65

Du Bois D, Du Bois EF (1989) A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 5(5):303–311, discussion 312–303

El-Hattab AW, Li FY, Shen J et al (2010) Maternal systemic primary carnitine deficiency uncovered by newborn screening: clinical, biochemical, and molecular aspects. Genet Med 12(1):19–24

Grube M, Ameling S, Noutsias M et al (2011) Selective regulation of cardiac organic cation transporter novel type 2 (OCTN2) in dilated cardiomyopathy. Am J Pathol 178(6):2547–2559

Ino T, Sherwood WG, Benson LN et al (1988) Cardiac manifestations in disorders of fat and carnitine metabolism in infancy. J Am Coll Cardiol 11(6):1301–1308

Koizumi A, Nozaki JI, Ohura T et al (1999) Genetic epidemiology of the carnitine transporter OCTN2 gene in a Japanese population and phenotypic characterization in Japanese pedigrees with primary systemic carnitine deficiency. Hum Mol Genet 8(12):2247–2259

Lamhonwah AM, Olpin SE, Pollitt RJ et al (2002) Novel OCTN2 mutations: no genotype-phenotype correlations: early carnitine therapy prevents cardiomyopathy. Am J Med Genet A 111(3):271–284

Lamhonwah AM, Onizuka R, Olpin SE et al (2004) OCTN2 mutation (R254X) found in Saudi Arabian kindred: recurrent mutation or ancient founder mutation? J Inherit Metab Dis 27(4):473–476

Lang RM, Bierig M, Devereux RB et al (2005) Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. J Am Soc Echocardiogr 18(12):1440–1463

Lee NC, Tang NL, Chien YH et al (2010) Diagnoses of newborns and mothers with carnitine uptake defects through newborn screening. Mol Genet Metab 100(1):46–50

Li FY, El-Hattab AW, Bawle EV et al (2010) Molecular spectrum of SLC22A5 (OCTN2) gene mutations detected in 143 subjects evaluated for systemic carnitine deficiency. Hum Mutat 31(8):E1632–E1651

Longo N, di San A, Filippo C, Pasquali M (2006) Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin Med Genet 142C(2):77–85

Lund AM, Joensen F, Hougaard DM et al (2007) Carnitine transporter and holocarboxylase synthetase deficiencies in The Faroe Islands. J Inherit Metab Dis 30(3):341–349

Magoulas PL, El-Hattab AW (2012) Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis 7(1):68

Marcovina SM, Sirtori C, Peracino A et al (2012) Translating the basic knowledge of mitochondrial functions to metabolic therapy: role of L-carnitine. Transl Res 161(2):73–84

Marques JS (1998) Dilated cardiomyopathy caused by plasma membrane carnitine transport defect. J Inherit Metab Dis 21(4):428–429

Melegh B, Bene J, Mogyorosy G et al (2004) Phenotypic manifestations of the OCTN2 V295X mutation: sudden infant death and carnitine-responsive cardiomyopathy in Roma families. Am J Med Genet A 131(2):121–126

Mitchell ME (1978) Carnitine metabolism in human subjects. I. Normal metabolism. Am J Clin Nutr 31(2):293–306

Mondillo S, Galderisi M, Mele D et al (2011) Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med 30(1):71–83

Nezu J, Tamai I, Oku A et al (1999) Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter. Nat Genet 21(1):91–94

Omori Y, Ohtani T, Sakata Y et al (2012) L-Carnitine prevents the development of ventricular fibrosis and heart failure with preserved ejection fraction in hypertensive heart disease. J Hypertens 30(9):1834–1844

Paulson DJ (1998) Carnitine deficiency-induced cardiomyopathy. Mol Cell Biochem 180(1–2):33–41

Pierpont ME, Breningstall GN, Stanley CA et al (2000) Familial carnitine transporter defect: a treatable cause of cardiomyopathy in children. Am Heart J 139(2 Pt 3):96–106

Prineas R, Blackburn H (1982) The Minnesota code manual of electrocardiographic findings: Standards and procedures for measurements. John Wright-PSG Inc, Littleton

Rasmussen J, Nielsen OW, Lund AM et al (2012) Primary carnitine deficiency and pivalic acid exposure causing encephalopathy and fatal cardiac events. J Inherit Metab Dis 36(1):35–41

Rasmussen J, Nielsen OW, Janzen N et al (2013) Carnitine levels in 26,462 individuals from the nationwide screening program for primary carnitine deficiency in the Faroe Islands. J Inherit Metab Dis (May 8 Epub ahead of print)

Rebouche CJ (2004) Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci 1033:30–41

Rijlaarsdam RS, van Spronsen FJ, Bink-Boelkens MT et al (2004) Ventricular fibrillation without overt cardiomyopathy as first presentation of organic cation transporter 2-deficiency in adolescence. Pacing Clin Electrophysiol 27(5):675–676

Rizos I (2000) Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 139(2 Pt 3):S120–S123

Scaglia F, Wang Y, Singh RH et al (1998) Defective urinary carnitine transport in heterozygotes for primary carnitine deficiency. Genet Med 1(1):34–39

Schimmenti LA, Crombez EA, Schwahn BC et al (2007) Expanded newborn screening identifies maternal primary carnitine deficiency. Mol Genet Metab 90(4):441–445

Spiekerkoetter U, Huener G, Baykal T et al (2003) Silent and symptomatic primary carnitine deficiency within the same family due to identical mutations in the organic cation/carnitine transporter OCTN2. J Inherit Metab Dis 26(6):613–615

Stanley CA (2004) Carnitine deficiency disorders in children. Ann N Y Acad Sci 1033:42–51

Stanley CA, DeLeeuw S, Coates PM et al (1991) Chronic cardiomyopathy and weakness or acute coma in children with a defect in carnitine uptake. Ann Neurol 30(5):709–716

Steiber A, Kerner J, Hoppel CL (2004) Carnitine: a nutritional, biosynthetic, and functional perspective. Mol Aspects Med 25(5–6):455–473

Tadros T, Klein M (2009) Cardiac arrest in a 22 year old postpartum female with carnitine deficiency. Circulation 120:S720

Tein I (2003) Carnitine transport: pathophysiology and metabolism of known molecular defects. J Inherit Metab Dis 26(2–3):147–169

Vijay S, Patterson A, Olpin S et al (2006) Carnitine transporter defect: diagnosis in asymptomatic adult women following analysis of acylcarnitines in their newborn infants. J Inherit Metab Dis 29(5):627–630

Yamak A, Bitar F, Karam P et al (2007) Exclusive cardiac dysfunction in familial primary carnitine deficiency cases: a genotype-phenotype correlation. Clin Genet 72(1):59–62

Zales VR, Benson DW Jr (1995) Reversible cardiomyopathy due to carnitine deficiency from renal tubular wasting. Pediatr Cardiol 16(2):76–78