Primary carnitine deficiency cardiomyopathy

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Primary carnitine deficiency (PCD) is an autosomal recessive disorder of fatty-acid oxidation caused by deficiency in the plasma membrane carnitine transporter. Carnitine plays an essential part in the transfer of long-chain fatty acids across the inner mitochondrial membrane. Carnitine deficiency blocks the mitochondrial oxidation of fatty acids to carbon dioxide, and can result in acute metabolic decompensation with hepatic encephalopathy, hypoketotic hypoglycemia or, in a more insidious presentation, cardiomyopathy [1]. Cardiomyopathy associated with PCD often presents with life-threatening heart failure. Early recognition of this disorder and treatment with carnitine can save lives. Here, we discuss the clinical features, echocardiographic features, and treatment of PCD cardiomyopathy.

Six patients with PCD cardiomyopathy were diagnosed in our hospital between January 2012 and December 2013 (Table 1, Figs. 1 and 2). In these 6 patients, there were no episodes of hypoketotic hypoglycemia. The main manifestations were cardiac dilatation and cardiac insufficiency. Case 3 had no obvious symptoms and was diagnosed by screening because she was the sister of Patient 2.

Blood levels of glucose, creatinine, blood urea nitrogen, alanine transaminase, aspartate aminotransferase, hemobilirubin, lactic acid, amino acids, creatine kinase (CK), CK-MB, and CK-MM were normal, as was the level of urinary ketones. Chest radiography revealed cardiomegaly. Electrocardiography (ECG) in 2 patients showed high and sharp T waves. In the 6 patients, echocardiography demonstrated enlargement of the left ventricle that was coexistent with myocardial thickening as well as with thickening of the trabecular and mitral valve papillary muscles (Table 2). Left ventricular ejection fraction (LVEF) was strikingly reduced in all cases except for Patient 3. The mean value of the serum carnitine level of the 6 patients was 1.37 ± 0.66 μmol/L (reference range, 10–60 μmol/L) at the time of the diagnosis. High-throughput sequencing revealed that all cases had mutations in the *SLC22A5* gene.

After confirmation of the diagnosis, all patients underwent treatment with L-carnitine supplements (200–300 mg/day, p.o.) plus digoxin, diuretics, and vasodilators. A follow-up study was available in all 6 patients at a median of 11 months (range, 4 months to 2 years).

This treatment resulted in the disappearance of symptoms. Left ventricular (LV) function returned to normal <1 month after carnitine supplementation. Also, the heart size decreased to normal within a few months of therapy.

A considerably broad phenotypic range is associated with PCD, ranging from early infantile decompensation to adults who are asymptomatic. The most common presentation of the disease is progressive cardiomyopathy with or without weakness in skeletal muscles [2]. The average age for the presentation of cardiomyopathy is 2–4 years. More than half of the reported cases of PCD first present between 12 months to 7 years of age with progressive heart failure. This finding suggests that the manifestations of severe carnitine deficiency in the heart and skeletal muscles take a long time to appear [2,3].

Studies have shown that the echocardiographic findings of PCD cardiomyopathy are usually non-specific. Some patients have the characteristics of dilated cardiomyopathy and some have the features of hypertrophic cardiomyopathy [4–7]. However, the present study revealed that the echocardiographic characteristics of PCD cardiomyopathy are different to dilated cardiomyopathy or hypertrophic cardiomyopathy. LV enlargement with decreased LVEF, coexistent with myocardial thickening as well as with thickening of the trabecular and mitral valve papillary muscles, are special characteristics of PCD cardiomyopathy. Interventricular septal and ventricular walls were clearly hypertrophic, but the degree of thickening was less than that for cases with hypertrophic cardiomyopathy, and obstruction of the LV outflow tract was not observed. Papillary muscles and the tendinous cords of the mitral valve and trabeculae were also hypertrophic. Actually, based on the diagnostic experience of the first 4 patients in this study, Patient 5 and Patient 6 were suspected of having PCD solely on their echocardiographic characteristics, and subsequent tests confirmed our initial suspicion. Patient 3 was asymptomatic and echocardiography showed slight LV enlargement with normal LV function, but Patient 3 presented with obvious ventricular hypertrophy. This finding may suggest that, because of carnitine deficiency and defective oxidation of fatty acids, fats accumulate in heart muscle, resulting in ventricular hypertrophy in the initial phase. Then, as the disease progresses, the left ventricle becomes impaired and dilated.

The key to the diagnosis is measurement of plasma carnitine levels, which are extremely reduced (free carnitine <5 μmol/L; controls 10–60 μmol/L) [1,5]. In the present study, plasma levels of free carnitine were <5 μmol/L for all patients. PCD can be confirmed by mutation analyses of the *SLC22A5* gene. PCD has been proven to be an autosomal recessive disorder, and DNA studies have found heterogeneous mutations in different patients [8]. Our patients displayed homozygosity or compound heterozygosity for *SLC22A5* gene mutations. Until now, the association between genotype and phenotype in PCD was not clear.

Cardiac function responds poorly to treatment with diuretics and digoxin in PCD patients. Continued therapy with L-carnitine supplements can lead to dramatic resolution of severe congestive heart failure within a short period, thereby altering the natural history of the disease and reducing (or eliminating) the signs of cardiomyopathy [2]. The Food and Drug Administration in the USA first approved L-carnitine in 1985 for the treatment of PCD. Intravenous therapy with carnitine at 100–400 mg/kg per day is recommended during life-threatening events, whereas carnitine at 100–300 mg/kg per day given *via* the oral route is recommended for chronic cases [3].

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Table 1
Clinical characteristics, free carnitine levels, and *SLC22A5* gene-sequencing results.

Case no.	Sex	Age (y)	Main symptom	Deceased sibling	Free carnitine level (μmol/L)	*SLC22A5* gene sequencing	
						Allele 1	Allele 2
1	F	1.5	Dyspnea, pale complexion	+	0.69	c.760C>T, p.R254X	c.865C>T, p.R289C
2	M	6	Apocleisis, dyspnea	−	0.50	c.338G>A, p.C113Y	c.760C>T, p.R254X
3	F	0.5	Asymptomatic	−	0.55	c.338G>A, p.C113Y	c.760C>T, p.R254X
4	M	1	Dyspnea, hyperhidrosis	+	4.58	c.760C>T, p.R254X	c.760C>T, p.R254X
5	M	14	Dyspnea, weakness	−	1.40	c.338G>A, p.C113Y	c.760C>T, p.R254X
6	M	1	Dyspnea, growth retardation	−	0.49	c.338G>A, p.C113Y	c.338G>A, p.C113Y

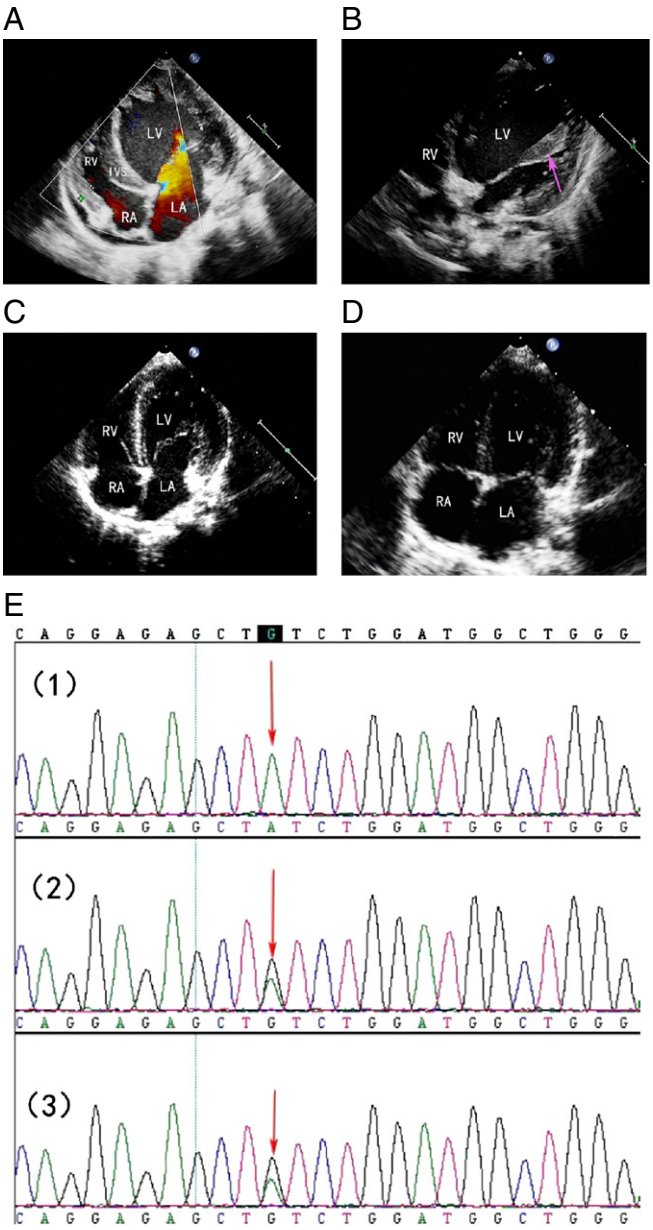

Fig. 1. Images for Patient 4. A: Transthoracic echocardiogram before carnitine supplementation showing myocardial thickening, left ventricular enlargement and pericardial effusion. B: Echocardiogram before carnitine supplementation. Arrow shows thickened papillary muscle. C: Two weeks after carnitine therapy. The left ventricle has decreased in size and pericardial effusion has disappeared. D: One month after therapy. Heart size has reduced to normal with mild myocardial hypertrophy. E: *SLC22A5* high-throughput sequencing of the blood of the family. Gene sequences of Patient (1) show that he has a homozygote of the c.338G>A mutation. Gene sequences of the patient's father (2) and mother (3) show a heterozygote of the c.338G>A mutation. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; and IVS, interventricular septum.

Our study revealed that oral treatment with L-carnitine was quite effective against PCD cardiomyopathy. One study in patients with PCD cardiomyopathy suggested that long-term carnitine supplementation can normalize cardiac function for >30 years, showing that supplementation therapy can allow PCD patients to lead a normal life [6].

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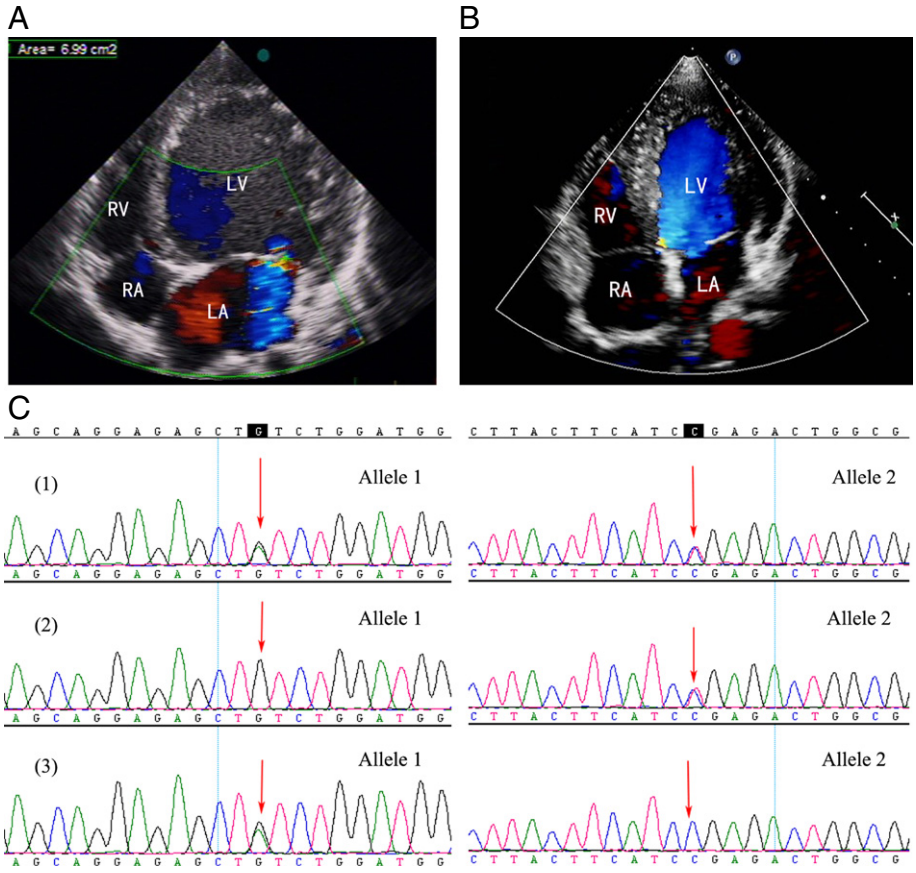

Fig. 2. Images for Patient 5. A: Echocardiogram before therapy. Myocardial thickening, left ventricular enlargement and mitral regurgitation is observed. B: Echocardiogram 3 months after L-carnitine treatment shows a left ventricle reduced in size and no mitral regurgitation. C: *SLC22A5* gene sequences of the blood of the family. Gene sequences of Patient (1) show that compound heterozygosity for c.338G>A and c.760C>T mutations. His father (2) has a heterozygote of the c.760C>T mutation and his mother (3) has a heterozygote of the c.338G>A mutation. LV, left ventricle; RV, right ventricle; LA, left atrium; and RA, right atrium.

Table 2
Echocardiographic parameters before and after L-carnitine supplementation*.

Case no.	LVDd (mm)		LVEF (%)		IVSd (mm)		LVPWd (mm)		RVAWd (mm)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	46.70	28.00	37	64	6.50	6.20	6.70	6.90	6.0	5.8
2	51.00	39.00	24	74	10.60	8.70	11.5	7.20	6.90	6.20
3	32.00	28.00	62	73	8.20	7.20	7.60	6.40	7.10	5.80
4	45.20	33.00	39	75	11.70	11.00	8.80	8.50	8.10	7.50
5	60.40	45.00	33	64	17.50	15.00	16.60	12.00	11.00	8.6
6	40.80	31.00	32	66	8.30	6.30	9.30	7.60	7.50	6.30

* LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; IVSd, interventricular septum diameter; LVPWd, left ventricular posterior wall diameter; RVAWd, right ventricular anterior wall diameter.

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