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## Muscle carnitine deficiency presenting as familial fatal cardiomyopathy

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**SUMMARY** Three siblings presented with fatal cardiomyopathy confirmed by electron microscopy, and normal serum but low muscle carnitine concentrations. A fourth had similar signs but remained asymptomatic. He was treated with carnitine orally which increased the concentration in muscle, though it remained below normal. Electron microscopic features were unchanged.

Carnitine deficiency was first described by Engel and Angelini in 1973.<sup>1</sup> Carnitine is a carrier in the long chain fatty acid transport system that is essential for the transport of fatty acids across the inner mitochondrial membrane. Deficiency of carnitine affects mitochondrial oxidation of fatty acids



Fig 1 *Electron photomicrograph of muscle biopsy specimen from case 3 showing a myofibril with central nucleus (×16 500).*

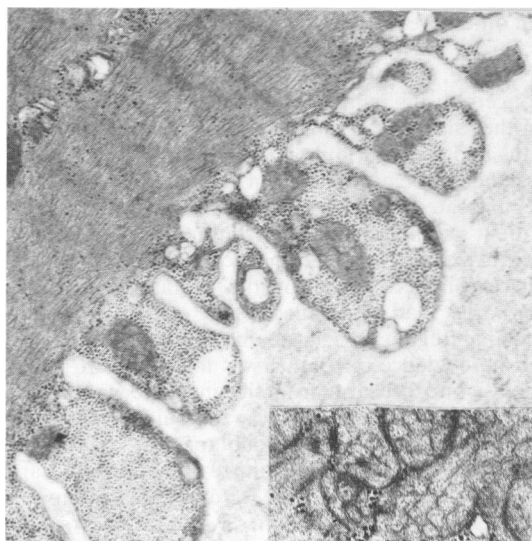


Fig 2 *Electron photomicrograph of muscle biopsy specimen from case 4 showing irregular folds of sarcolemma. Note presence of small lipid droplets under the sarcolemma and between the myofibrils (×22 100). Inset: cluster of mitochondria with tubular cristae (×32 500).*

and results in the accumulation of lipids in the cytoplasm.<sup>2</sup>

We describe a non-consanguineous Sephardic family with two healthy children and three children who presented with fatal cardiomyopathy probably due to muscle carnitine deficiency (fig 1). A sixth and youngest surviving sibling was asymptomatic at

Table Clinical and laboratory details of the siblings

Variable	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Female	Male
Age at presentation	3 years	2 years 4 months	1 year 6 months	10 months
Presenting illness	Wheezing	Wheezing	Wheezing	Wheezing
Age at death	4 years	3 years 2 months	3 years	Alive
Cardiac impairment	Right and left heart failure	Left heart failure, arrhythmia	Right and left heart failure	None
Chest x-ray	Enlarged heart size, decreased pulsations	Enlarged heart size, pulmonary venous congestion	Enlarged heart size, pulmonary venous congestion	Normal
Electrocardiogram	Left axis deviation, left ventricular hypertrophy, Q waves in V <sub>5-6</sub>	Ventricular premature beats, right bundle branch block, Q waves in V <sub>5-6</sub> , ST elevation in V <sub>4-5</sub>	Left and right ventricular hypertrophy, Q waves and ST elevation in I, AVL, V <sub>5-6</sub>	Normal
Echocardiogram	Not done	Dilatation and hypertrophy of left atrium and ventricle, ejection fraction 0.55	Biventricular hypertrophy, decreased contractility, thickening of mitral valve	Normal
Cardiac catheterisation	Not done	Cardiomyopathy and mitral insufficiency	No anatomic abnormality, decreased cardiac output consistent with cardiomyopathy	Not done
Serum glutamic oxaloacetic transaminase activity (normal= $\leq$ 40 U)	$\leq$ 830	Not done	$\leq$ 1100	Normal
Creatine phosphokinase (normal= $\leq$ 30 u)	Not done	Not done	34	Normal
Serum carnitine concentration (nmol/ml) (normal=30-60)	Not done	Not done	51.2	28
Muscle carnitine (micromole/g wet weight) (normal: above 1.5)	Not done	Not done	0.4	0.33
Muscle biopsy: haematoxylin and eosin stain	Not done	Not done	Variation in fibre size, increased number of central nuclei, some fibres undergoing phagocytosis	Variations in fibre size
NADH and myosin stains adenosine triphosphatase	Not done	Not done	Preponderance of type 1 myofibrils and atrophy of type 2 fibres	Preponderance of type 1 fibres
Oil red o stain	Not done	Not done	Enhancement of lipid stain	Increased amount of neutral lipids
Electron microscopy	Not done	Not done	Increased number of myofibres with central nuclei, lipid droplets, sarcolemmal folds	Irregular folds of the sarcolemma, small lipid droplets, tubular cristae in mitochondria

the time of writing but has muscle carnitine deficiency. No clinical muscle weakness was detected in any of the cases.

### Case reports

The table shows the clinical and laboratory details of the four patients. Cases 1–3 died, and case 4 remained asymptomatic. When his muscle carnitine deficiency was diagnosed treatment with oral carnitine (400 mg three times a day) was started. Repeated examination after an interval of four months showed a rise in serum carnitine concentration to 91.2 nmol/ml. Muscle carnitine concentration was 0.9  $\mu$ mol/g wet weight which, though still below normal, was nevertheless more than double the value before treatment. Histological and electron microscopic examination of the second muscle biopsy specimen were unchanged (fig 2). There was no clinical or laboratory evidence of muscle, heart, or liver disease.

### Discussion

There are two forms of primary genetic carnitine deficiency: systemic carnitine deficiency is characterised by low concentrations of carnitine in both serum and muscle, and muscle carnitine deficiency by low concentrations in muscle but normal concentrations in serum.<sup>2</sup> Serum carnitine deficiency presents most commonly as a syndrome similar to Reye's disease,<sup>2,3</sup> but a familial cardiomyopathy has also been described in which carnitine treatment leads to increased serum and muscle carnitine concentrations and improved cardiac function.<sup>4,5</sup>

Muscle carnitine deficiency usually presents with progressive muscle weakness and is often complicated by cardiomyopathy. Because decreased transport of carnitine into the muscle cell is the pathophysiological defect treatment with oral carnitine is not usually effective.<sup>2</sup> We know of one case report, however, in which a successful clinical response to

carnitine was described.<sup>6</sup> Muscle carnitine deficiency presenting as cardiomyopathy without noticeable muscular weakness has not previously been described as far as we know, although respiratory symptoms in children with carnitine deficiency and cardiomyopathy are common.<sup>4,5</sup>

Case 4 had a low muscle carnitine concentration but no clinical evidence of muscle or cardiac disease. This may be due to his being in the preclinical stage of the disease, but heterozygosity as the cause of the benign course cannot be excluded. Another possibility is that he was responding to treatment as the muscle carnitine content increased. The histopathological picture, however, did not improve over four months.

The possibility of congestive cardiomyopathy being the only sign of muscle carnitine deficiency makes estimation of muscle carnitine concentration desirable in all cases of undiagnosed cardiomyopathy. Biochemical studies of muscle specimens obtained by needle biopsy are currently widely used and relatively easy to perform.

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