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Short Communication

Mitochondrial complex deficiencies in a male with cardiomyopathy and 3-methylglutaconic aciduria

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Excessive excretion of 3-methylglutaconic acid has been associated with a variety of clinical phenotypes (Gibson et al 1991; Chitayat et al 1992), but only in a few cases has the primary metabolic defect been identified. A deficiency of 3-methylglutaryl-CoA hydratase activity is associated with 3-methylglutaric aciduria (MGA) type 1, a relatively mild condition described in only two families. In other patients, such as those with the X-linked cardiomyopathic type (Barth et al 1983; Kelley et al 1991), or the Iraqi-Jewish optic atrophy (Elpeleg et al 1994) or neuropathic (Chitayat et al 1992) types, defects in mitochondrial function have been found (Holme et al 1992; Bakkeren et al 1992; Ibel et al 1993). Recent reports would suggest that excessive excretion of 3-methylglutaconic acid may be a useful marker for underlying respiratory-chain defects. We report such a patient who died with marked cardiomyopathy.

CASE REPORT

The patient, an 8-year-old male (M.C.), had presented with sweating and tachypnoea. He was found to have a cardiomyopathy with left ventricular hypertrophy and pleural effusion. An enlarged liver (3–4 cm) was noted. He returned home after initial treatment but died suddenly some two weeks later. At post-mortem the heart was enlarged to 96 g (normal 40 g), the right atrium was dilated and the ventricles showed marked hypertrophy consistent with a congenital hypertrophic cardiomyopathy. The liver showed mild fatty change, but large amounts of lipid and glycogen were noted in skeletal and cardiac muscle. Mitochondria were increased in size and number, leading to peripheralization of the myofibrils. No ragged-red fibres were seen.

Table 1 Respiratory chain complex activities[a,b] in muscle

		Controls	
	Patient	*(Mean ± SD)*	*(Range)*
Complex I[b]	12	101 ± 36	40–210
Complex II	245	314 ± 101	150–550
Complex III	0.80	3.9 ± 1.5	1.9–8.5
Complex IV	0.2	6.1 ± 2.6	2.5–12.0
Complex V	23	510 ± 119	300–760
Citrate synthase	920	436 ± 240	120–1160

[a]Activities expressed as a ratio to citrate synthase activity (μmol/min per mg protein)
[b]Complex activities measured as NADH oxidized (I), or DCPIP reduced (II), or ADP formed (V)/per min per mg protein, or first-order rate constants (III and IV)/s per mg protein

BIOCHEMICAL FINDINGS

Urine was collected at presentation, and GC-MS analysis of organic acids revealed a marked increase of 3-methylglutaconic and 3-methylglutaric acid excretion.

Muscle was collected at post-mortem (approximately 12 h) and frozen at −70°C prior to enzyme and DNA assay. The activities of respiratory-chain complexes were assayed on mitochondrial preparations by spectrophotometric methods basically as described (Ragan et al 1987; Birch-Machin et al 1994). Activities were expressed as a ratio to citrate synthase activity. DNA was extracted from muscle preparations and analysed for point mutations using PCR and specific restriction-enzyme digests. Mitochondrial DNA deletions were investigated by Southern blot analysis.

Marked deficiencies were found in the activities of several respiratory-chain complexes (see Table 1). Activities, expressed as percentage of controls, were as follows: complex I (12%), complex II (78%), complex III (21%), complex IV (3%) and complex V (5%). It is significant that those complexes with subunits coded for by mitochondrial DNA showed the most significant reductions, whereas citrate synthase and complex II activities appeared to be normal. The observed deficiencies could not be explained simply as post-mortem changes.

Studies on mitochondrial DNA failed to identify the following point mutations: MELAS (3243), MERRF (8344), NARP (8993) and LHON (11778, 3460), and no significant deletion was found by Southern blot analysis. There was also no evidence for mtDNA depletion (J. Poulton, Oxford).

DISCUSSION

The coexistence of 3-methylglutaconic aciduria with cardiomyopathy appears to be a useful indicator for an underlying defect in mitochondrial function. Several patients have now been described with this combination where the organic acid abnormality seems to be an epiphenomenon associated with respiratory-chain defects. The precise site of the mutation is not always defined, although the pattern of enzyme deficiency, as in this case, would point to mtDNA. However, the locus for Barth syndrome has been found on the X-chromosome at q28 (Christodoulou et al 1994). Nevertheless,

genetic mechanisms regulating the coordinated expression of nuclear and mitochondrial genes are not yet fully understood and mutations here must also be considered.

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