

Dramatic improvement in mitochondrial cardiomyopathy following treatment with idebenone

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MS received 4.07.00 Accepted 20.09.00

Summary: Idebenone, a synthetic analogue of coenzyme Q₁₀, has been shown to improve cardiac function in patients with Friedreich ataxia and a deficiency of respiratory chain complexes I–III. We describe a woman with severe combined right and left heart failure due to a mitochondrial cardiomyopathy. The patient underwent an endomyocardial biopsy as part of an evaluation for cardiac transplantation. It showed severely decreased respiratory complex activities dependent on CoQ, pointing to CoQ depletion. Following idebenone treatment there was a dramatic improvement in her clinical status with resolution of the heart failure.

Cardiomyopathy is frequently observed in patients with mitochondrial respiratory chain disorders (Marin-Garcia and Goldenthal 1997). In young patients, abnormal oxidative phosphorylation essentially leads to a hypertrophic cardiomyopathy (Marin-Garcia et al 1999), which eventually turns into a dilated form in the course of the disease, a form more frequently reported in adults suffering from this condition (Arbustini et al 1998). Similarly, Friedreich ataxia (McKusick 229300), recently shown to result from respiratory chain dysfunction, is frequently associated with a hypertrophic cardiomyopathy (Rustin et al 1999).

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxy)decyl-1,4-benzoquinone) is a synthetic analogue of coenzyme Q₁₀ (CoQ₁₀). It is a short-chain quinone that crosses cell membranes readily, including the blood–brain barrier. Idebenone can function similarly to CoQ₁₀ as an electron carrier in the respiratory chain of mitochondria

and as a potent free-radical scavenger (Mordente et al 1998). Based on *in vitro* experiments carried out on human heart homogenates showing the ability of idebenone to protect against iron-induced free radical damage, it was given to a limited number of patients with Friedreich ataxia and was found to improve their cardiac function (Rustin et al 1999).

We describe a woman with end-stage mitochondrial cardiomyopathy whose endomyocardial biopsy showed a severe deficiency of complexes I–III of the respiratory chain, which was reversible *in vitro* after addition of quinones. Following idebenone treatment there was a dramatic improvement in her heart failure.

CASE REPORT

A 36-year-old woman presented with progressive combined right and left heart failure with pulmonary congestion at rest, ascites and peripheral oedema (NYHA functional class IV). The patient's mother died at the age of 48 years from a cardiomyopathy after a 10-year illness. Her son suffers from a congenital dilated cardiomyopathy, mental retardation and failure to thrive. At the age of 5 years, he is microcephalic, hyperactive and aphasic. His muscle biopsy shows ragged red fibres but normal respiratory chain complexes. Evaluation of mtDNA did not disclose mutations in the nucleotides described in maternally inherited myopathy and cardiomyopathy (4317A, 3303C, 3260A, 4266A, 15889T>C, 15902A>G, 9997T>C) or in the mitochondrial tRNAs for leucine, isoleucine and glycine.

The patient's cardiomyopathy had been diagnosed at the age of 24 years and had been stable until the birth of her only child, five years ago. Following the diagnosis of mitochondrial myopathy in her son, she was started on treatment with coenzyme Q and antioxidants. Despite this treatment there was a slow deterioration in her ability to function in everyday activities.

In June 1999 she was hospitalized owing to shortness of breath, haemoptysis, peripheral oedema and generalized weakness. On examination, her general condition was poor and she was pale with multiple petechiae. There were signs of biventricular heart failure: marked congestion of the cervical veins, scattered rales over the lungs, enlarged abdomen with ascites, hepatomegaly and peripheral oedema. An echocardiogram showed a mildly dilated left ventricle with moderate to severe left ventricular dysfunction but no hypertrophy. There was also moderate mitral regurgitation, mildly dilated right ventricle (anterior–posterior diameter of 3.3 cm on parasternal long axis view) with severe dysfunction and moderate-to-severe tricuspid regurgitation (Table 1). ECG showed atrial fibrillation and left bundle branch block. A trial of chemical and electrical cardioversion failed. Despite treatment with diuretics, afterload reduction, beta-blockers (carvedilol) and inotropic drugs, her condition did not improve and she was transferred to the cardiac intensive-care unit for pre-cardiac-transplantation evaluation. She underwent cardiac catheterization and an endomyocardial biopsy. The biopsy showed endocardial fibroelastosis.

Following the results, idebenone 225 mg/day was started. Other cardiac medications were not changed. There was a gradual improvement in the patient's

Table 1 Echocardiographic measurements before and after idebenone treatment

<i>Variable</i> ^a	<i>Before treatment</i>	<i>After treatment</i>
LA size (mm)	46	41
Septal wall thickness (mm)	10	10
Posterior wall thickness (mm)	10	10
LV end diastolic diameter (mm)	51	51
LV end systolic diameter (mm)	41	37
Ejection fraction (%)	22	50
Fractional shortening (%)	20%	27%
Tricuspid regurgitation	Moderate to severe	Mild
Mitral regurgitation	Moderate	Mild to moderate
Estimated PA pressure (mmHg)	40	34
RV dysfunction	Severe	Mild

^a LA, left atrium; LV, left ventricle; RV, right ventricle; PA, pulmonary pressure

condition, and all signs of right heart failure disappeared. Three months later there was a dramatic change in her clinical status; she was able to take care of her son and to resume normal activities (functional class II). Physical examination revealed a thin woman with no oedema or other significant findings. The neurological examination was also normal. Echocardiography showed a significant increase in LV and RV systolic function (EF = 50%), and mild to moderate mitral and mild tricuspid regurgitation (Table 1). A year later she continues to feel well and there is no deterioration in her cardiac function.

METHODS

The endomyocardial biopsy sample was immediately placed in a sterile vial and was freeze dried in liquid nitrogen. Enzyme activities were measured spectrophotometrically according to previously described methods (Rustin et al 1994a,b).

RESULTS

Enzyme investigation carried out on the patient's endomyocardial biopsy revealed normal activities of respiratory chain (RC) complexes I–V when individually measured, and normal activity ratios. However, a severe decrease of CoQ-dependent respiratory succinate cytochrome-*c* reductase (SCCR: CII+CIII activities) was observed despite normal CII and CIII activities, pointing to CoQ depletion (Table 2). This resulted in abnormal CIV/CII+CIII or citrate synthase/CII+CIII ratios. Most interestingly, as shown in Figure 1, the addition of decylubiquinone, a short-chain analogue of CoQ₁₀, restored normal SCCR activity, which again supported CoQ depletion. A similar restoration was observed when coenzyme Q₄ or idebenone was substituted for decylubiquinone.

Table 2 Respiratory chain enzyme activities^a in endomyocardial biopsy of patient and controls

	<i>Activity (nmol/min per mg protein)</i>	
	<i>Patient</i>	<i>Controls (n = 23)</i>
Complex I	79	44–92
Complex II	152	66–155
Complex III	541	293–793
Complex IV	716	331–1222
Complex V	328	109–374
Citrate synthase	445	229–597
Complex II+complex III	95	100–349
	<i>Activity ratios</i>	
Complex IV/complex I	9.1	8.4 ± 1.3
Complex IV/complex II	4.7	5.4 ± 0.5
Complex IV/complex III	1.3	1.1 ± 0.2
Complex IV/complex V	2.2	2.7 ± 0.7
Complex IV/citrate synthase	1.6	1.7 ± 0.3
Citrate synthase/complex II+complex III	4.7	2.0 ± 0.3
Complex IV/complex II+complex III	7.5	3.5 ± 0.2

^a Both absolute activities and ratios are indicated. The absence of a normal distribution of absolute control values precluded the use of standard deviations. As control activity ratios follow a Gaussian distribution (Chretien et al 1997), these values are presented as mean ± 1 SD. Experimental conditions as described by Rustin et al (1994a,b).

DISCUSSION

Only a few cases of quinone-deficient mitochondrial encephalomyopathies have been described (Boitier et al 1998; Ogasahara et al 1989; Sobreira et al 1997). Rötig et al (2000) described the first defect in CoQ₁₀ biosynthesis in two siblings with encephalomyopathy and renal failure. CoQ₁₀ administration resulted in a major clinical improvement. HPLC analysis suggested that the deficient step in the quinone biosynthesis pathway was located at the level of *trans*-prenyltransferase.

In all these cases the quinone deficiency presented as a mitochondrial encephalomyopathy. A mitochondrial cardiomyopathy resulting from quinone deficiency has not been previously described. However, Folkers and colleagues (1992) found that CoQ₁₀ therapy in patients in severe heart failure prior to cardiac transplantation resulted in significant improvement in cardiac function. Since this report, CoQ₁₀ has been used in cardiology to augment myocardial kinetics, increase cardiac output, elevate the ischaemic threshold and enhance functional capacity in patients with congestive heart failure (Sacher et al 1997). Mortensen (1993) described decreased myocardial tissue levels of CoQ₁₀ determined by high-performance liquid chromatography in patients with advanced heart failure compared with those with milder disease. Furthermore, he claimed that the CoQ₁₀ deficiency might be restored significantly by oral supplementation in selected cases.

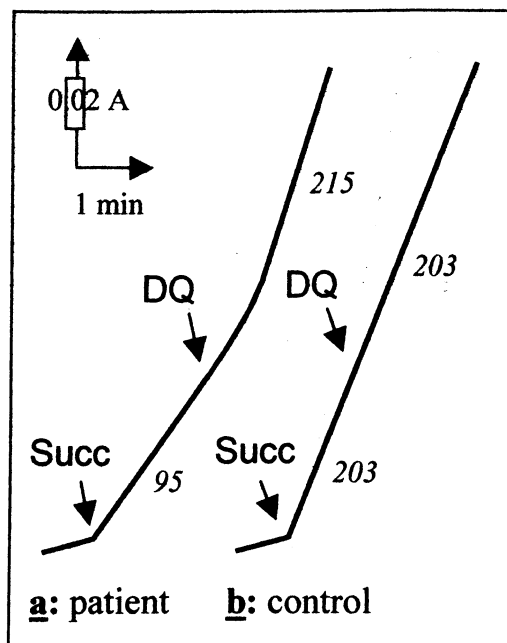


Figure 1 Effect of decylubiquinone on the succinate cytochrome-*c* reductase activity of heart homogenate from patient and control. Measurements were carried out as described by Rustin et al (1994a,b). DQ, decylubiquinone; Succ, succinate. Numbers along the traces are nmol/min per mg protein

Recently, Jarreta and colleagues (2000) found decreased complex III enzyme activity in patients with idiopathic dilated cardiomyopathy. This was considered a secondary phenomenon due to increased free radical production. A secondary deficiency of complex III can be excluded in our patient because the absolute activity of this complex was in the control range and the activity of complex III related to other respiratory chain complexes or citrate synthase was normal. Furthermore, deficient activity of complex III in mitochondria or tissue homogenate from patients with complex III deficiency is not significantly stimulated *in vitro* by quinone analogues, such as decylubiquinone or idebenone, and such a stimulation is only observed in patients in whom an ubiquinone deficiency has been documented (Rotig et al 2000). We therefore assume that we are dealing here with a defect of ubiquinone of unknown origin, either primary, due to a defect in quinone biosynthesis, or secondary to her severe heart failure, that has led to the respiratory chain defect. Unfortunately, owing to lack of available tissue we were not able to measure ubiquinone content directly.

The beneficial effect of idebenone could result both from its effect on the respiratory chain and from its antioxidant activity. However, we know from studying

patients with decreased ubiquinone that there is no evidence of increased peroxidation or superoxide production in these patients.

The inheritance pattern in our family was initially assumed to be maternal, since both the patient's mother and her son were affected and the son's muscle biopsy showed ragged red fibres. However, the patient's endomyocardial biopsy showed deficiency of the quinone-dependent complexes and none of the previously described mtDNA mutations associated with maternally inherited myopathy and cardiomyopathy were detected. Therefore, considering the nature of the defect, i.e. a defective quinone pool function, it is difficult to see how a mitochondrial mutation could be the cause. Nevertheless, a mitochondrial mutant load, variable among tissues and among individuals in a given family, can be problematic when trying to trace the mitochondrial versus nuclear origin of a defect.

Other possibilities are dominant or X-linked inheritance (since the son is more severely involved than his mother or grandmother). The inheritance patterns of defects of the quinone biosynthetic enzymes are not known at present, so this family may represent a deficiency of one of these enzymes transmitted by Mendelian inheritance.

Our patient continued to deteriorate despite treatment with CoQ₁₀ for 4 years. The dramatic improvement in her condition occurred only after idebenone was initiated. The superiority of idebenone as compared to CoQ₁₀ in our patient can be explained by its better pharmacokinetics (Valliant et al 1996). CoQ₁₀ attains high plasma levels but enters tissues rather poorly. Therefore, CoQ₁₀ supplementation might be a good strategy to ameliorate oxidant damage within the plasma milieu but not in intracellular environments. These problems are not observed with idebenone, which distributes throughout the body and readily approaches similar concentrations in tissues and fluids. Idebenone also lacks pro-oxidant activity in hypoxic conditions (Rustin et al 1999).

This case demonstrates the importance of a myocardial biopsy, with assessment of respiratory chain enzymes, in patients with idiopathic cardiomyopathy. The finding of a reduction in complexes I+II and II+III should lead to treatment with idebenone. We suggest that idebenone should also be tried in patients with severe heart failure, where a biopsy is not feasible, since there are no side-effects and it can be life-saving.

ACKNOWLEDGEMENT

We thank Takeda, Italy, for donating the idebenone for treatment of our patient.

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