Cardiomyopathy in respiratory chain disorders

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Abstract

Disorders of mitochondrial oxidative phosphorylation may disturb cardiac energy metabolism and cause cardiomyopathy. Twenty one cases from the literature and one further patient with cardiomyopathy due to biochemically defined respiratory chain defects were reviewed for clinical course, morphology, and pathophysiological mechanisms of the cardiomyopathy.

All cases showed concentric hypertrophy of the myocardium without an outflow tract obstruction. In most patients the cardiomyopathy was diagnosed early in infancy and showed rapid deterioration with death before the age of 2 years. Hypertrophy of the myocardium appears to result from swelling of the cardiomyocytes caused by accumulation of mitochondria and by morphologically abnormal megamitochondria.

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Infantile cardiomyopathy has been described in several genetic metabolic diseases such as lysosomal storage, mitochondrial, amino acid, organic acid, and carnitine disorders.¹ Recently, increasing interest has been focused on the manifestations of respiratory chain defects.^{2,3} In general they present either as isolated myopathy or as a multisystemic disorder with encephalomyopathy, nephropathy, hepatic involvement, and cardiomyopathy.^{4–6}

We have attempted to define and explain the cardiomyopathy in respiratory chain disorders based on the observations in our patient as well as on the reports in the literature. Emphasis has been placed on the clinical course, pathophysiological mechanisms, and morphological abnormalities.

Methods

The case history of a 2 year old child with cardiomyopathy and encephalomyopathy due to a defect of the respiratory chain was compared with previous reports of patients with respiratory chain disorders and cardiac involvement. Since 1975, 54 patients have been reported with evidence of mitochondrial disease with cardiomyopathy. In 21 of these, the cardiomyopathy was confirmed by echocardiography or postmortem examination and the biochemical diagnosis was established by quantitative assay of enzymes of the respiratory chain. The clinical course, the echocardiographic and

morphological nature of the cardiomyopathy, as well as the type of biochemical defect were evaluated in these 21 cases and in our own patient.

Results

CASE REPORT

A boy was the first born to healthy non-consanguineous parents after an uneventful pregnancy and delivery. His birth weight was 3090 g, length 50 cm, head circumference 34 cm, and the Apgar score 8/10/10.

At the age of 2 months the child was referred to our cardiac unit because of supraventricular tachycardia. On admission he was in poor condition with tachypnoea, mottled skin, hepatomegaly, and oedema indicating congestive heart failure. He showed several dysmorphic features with hypertrichosis of the face, dysplastic ears, and a small forehead. Cardiac examination revealed a precordial impulse without murmur. Electrocardiography (ECG) showed pre-excitation and echocardiography revealed concentric hypertrophic cardiomyopathy with a septal and posterior wall thickness of 7.5 mm (normal 3.5–4.2 mm). There was no left or right ventricular outflow tract gradient. Treatment with digoxin and propranolol was introduced and there was no recurrence of the tachycardia.

At the age of 10 months the boy showed failure to thrive with a weight of 7 kg (<3rd centile), length of 70.5 cm (10th centile), and microcephaly with a head circumference of 41.5 cm (<3rd centile). Furthermore nystagmus, prominent muscular weakness, and psychomotor retardation were evident. Screening for metabolic disorders revealed a slight acidosis with a pH of 7.34, carbon dioxide tension of 5.87 kPa, and increased lactate of 6.9 mmol/l in plasma and of 4.3 mmol/l in cerebrospinal fluid. The lactate/pyruvate and β -hydroxybutyric acid/acetoacetate ratio in plasma were raised to 45 (normal <20) and 5.4 (normal <1) respectively; plasma carnitine was normal.

Microscopic examination of striated muscle obtained by biopsy of quadriceps muscle showed mainly small fibres with augmented and enlarged fuchsinophilic drops in several enlarged fibres. Electromicroscopic examination revealed sparse myofibrils and focal accumulation of enlarged mitochondria that were morphologically abnormal. Biochemical analysis of this muscle biopsy specimen was performed as previously described⁷ and showed a reduced activity of complex I (3.2 mU/mg protein; controls 8.9–27 mU/mg protein) and complex IV (28 mU/mg protein; controls 52–186 mU/mg protein) of the respiratory chain. Total and

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Details of 22 patients reviewed

Author	Sex	Age at diagnosis	Outcome	Echocardiography		Heart at necropsy		Histology: enlarged muscle fibres	Electron microscopy		Defect of respiratory chain enzyme	Other comments
				Septum/LV wall hypertrophy	Reduced fractional shortening	Increased weight	Septum/LV wall hypertrophy		Reduced myofibrils	Increased mitochondria		
Oldfors <i>et al</i> ⁹	F	Birth	Died 3 days*	ND	ND	ND	+	ND	+	+	Co IV	Pre-excitation on ECG
Papadimitriou <i>et al</i> ¹⁰	F	3 Months	Died 3 months*	+	+	+	ND	+	+	+	Co III	
Müller-Höcker <i>et al</i> ¹¹	M	3 Months	Died 5 months*	ND	ND	+	+	ND	+	+	Co I+IV	Pericardial effusion
Zheng <i>et al</i> ¹²	M	3.5 Months	Died 4 months*	+	ND	+	+	ND	+	+	Co I+IV	
Zeviani <i>et al</i> ¹³	F	4.5 Months	Died 8 months*	+	+	ND	ND	ND	ND	ND	Co I+IV	Leigh's syndrome
Sieverding <i>et al</i> ¹⁴	F	4.5 Months	Died 6 months	+	+	ND	ND	ND	ND	ND	Co IV	
Di Mauro <i>et al</i> ¹⁵	M	7 Months	Died 7.5 months*	+	+	+	ND	ND	ND	ND	Co IV	Conduction anomaly on ECG
Hoppel <i>et al</i> ¹⁶	—	7 Months	Died 7 months*	ND	ND	+	+	ND	ND	—	Co I	
Böhles <i>et al</i> ¹⁷	F	10 Months	Died 10 months *	+	ND	ND	ND	+	+	+	Co I–IV	Fibre disarray
Tulinus <i>et al</i> ¹⁸	M	13 Months	Died 2.5 years*	+	+	+	+	ND	ND	+	Co I+IV	
Rustin <i>et al</i> ¹⁹	F	3 Months	Alive	+	+	ND	ND	ND	ND	ND	Co I	Pericardial effusion
	M	10 Days	Died 3 months*	+	+	ND	ND	ND	ND	ND	Co I	
	M	10 Months	Died 4 months*	+	+	ND	ND	ND	ND	ND	Co I–IV	Fibre disarray
	—	<2 Years	Died 2 years	+	ND	ND	ND	ND	ND	ND	Co II	
Müller-Höcker <i>et al</i> ²⁰	F	13 Years	Died 13 years	ND	ND	+	+	ND	+	+	Co I+IV	MELAS syndrome
Kobayashi <i>et al</i> ²¹	M	14 Years	Alive	+	+	ND	ND	ND	ND	ND	Co I	
Yoneda <i>et al</i> ²²	M	14 Years	Died 14 years	+	—	+	+	ND	ND	ND	Co I, III, IV	Pre-excitation on ECG, MELAS syndrome
Nishizawa <i>et al</i> ²³	F	16 Years	Died 16 years*	+	ND	ND	ND	+(RRF)	+	+	Co I	MELAS syndrome
Angelini <i>et al</i> ²⁴	M	19 Years	Alive	+	ND	ND	ND	ND	ND	+	Co II	
	M	25 Years	Alive	+	ND	ND	ND	ND	ND	+	Co II	Leigh's syndrome
Schwartzkopff <i>et al</i> ²⁵	F	30 Years	Alive	+	—	ND	ND	+	+	+	Co IV	Atrial flutter, asymmetrical septal hypertrophy
Index patient	M	2 Months	Alive	+	+	ND	ND	ND	ND	ND	Co I+IV	Ventricular tachycardia, neuropathy
												Pre-excitation on ECG

*Death from heart failure. Yes (+); no (—); ND=not done/mentioned; LV=left ventricular; RRF=ragged red fibres.

free carnitine concentrations were normal in muscle. Analysis of mitochondrial DNA, isolated from peripheral blood thrombocytes, did not reveal major deletions. More detailed examinations are in progress to exclude small deletions or a point mutation.

A therapeutic trial with vitamin K3 (between 20 and 80 mg/day), coenzyme Q10 (50 mg/day), riboflavin (100 mg/day), vitamin E and vitamin C (between 100 and 500 mg/day) for seven months had no effect either on biochemical or on cardiological findings.

At 24 months of age the patient's weight was 9 kg (<3rd centile) and the head circumference was 44.5 cm (<3rd centile). At this time he was able to sit and to take a few steps alone. Hearing and vision were present but there were poor reactions to noises and only a rudimentary interest in playing with objects. Speech was limited to a few single words. Echocardiographic examination showed a marked progression of cardiomyopathy with a septal and left ventricular wall thickness of 12 mm (normal 4.8–6.0 mm). Left ventricular function was diminished with a fractional shortening of 10–15% (normal 28–44%). Diastolic filling was also impaired with a mitral valve E/A ratio of 1 (normal 1.5)⁸ revealed by Doppler examination.

LITERATURE REVIEW

The table shows the clinical, echocardiographic, postmortem, and biochemical data of the 22 patients who were documented in sufficient detail to be included in the review. In all patients there was, in addition to cardiomyopathy, an encephalopathy and/or peripheral myopathy.

Boys and girls were equally affected. In most of the patients a diagnosis of cardiomyopathy

was made in early infancy; 10 died before 1 year of age, one at 2 years, and another at 2.5 years of age. In seven patients cardiomyopathy was detected much later during adolescence or early adulthood. Three of these died shortly after diagnosis while four remained alive with ages ranging from 14–30 years. Heart failure was the cause of death in 11 of the 15 patients who died.

Hypertrophic cardiomyopathy was found in all patients. Concentric hypertrophy of the septum and posterior wall was reported in 16 of the 18 patients in whom echocardiography was performed, while only two cases showed septal asymmetry. Left ventricular outflow tract obstruction was not observed in any case. Echocardiographic evaluation of systolic function was reported in only 12 patients of whom 10 showed impaired systolic function as measured by fractional shortening.

Histology of the myocardium was reported in four patients and in each case showed enlarged swollen muscle fibres. Examination of heart muscle by electron microscopy was reported in 13 patients. Twelve of them showed an increased number of mitochondria some of which were morphologically abnormal, that is, megamitochondria. In eight of these, myofibrils were reduced in number with concomitant accumulation of mitochondria.

The most common enzyme defects were deficiencies of complex I and complex IV, either isolated or in combination, being found in 17 of the 22 patients.

Pre-excitation was an important finding in our patient, but this and other forms of rhythm disturbance such as atrial flutter, ventricular tachycardia, or a conduction anomaly were only observed in older patients but not in the younger ones.

Discussion

Echocardiography is a well established method for evaluation of different forms of cardiomyopathy, which can be classified as dilated, hypertrophic, or restrictive.²⁶ Hypertrophic cardiomyopathies can present as asymmetric septal hypertrophy or symmetric hypertrophy of the septum and posterior wall with or without obstruction.²⁷ In our study all patients fulfil the same morphological criteria of a hypertrophied left ventricle with involvement of the septum and free wall without an outflow tract gradient. The markedly hypertrophied myocardium leads to impairment of diastolic filling and a reduction of systolic function. A dilated cardiomyopathy has been described in several other patients with a suspected mitochondrial disorder, but in whom the exact biochemical defect was not defined.^{28–32} These patients were therefore excluded from this study.

The clinical course of cardiomyopathy is usually dependent on the severity of impairment of diastolic and systolic cardiac function. As diminished systolic function and death in early childhood was found in the majority of the cases we conclude that the cardiomyopathy associated with a respiratory chain defect is severe with rapid deterioration. Survival to adulthood was reported in only four patients who had mainly neurological symptoms and probably a more benign cardiac involvement.

In the more common familial hypertrophic cardiomyopathy, which may be caused by a mutation of the structural protein β cardiomyosin,³³ tropomyosin and cardiac troponin T, impaired diastolic function is found either with increased or with normal systolic function.³⁴ Histological findings consist of hypertrophic cardiocytes with increased myofibrils.³⁵ An increased number of small mitochondria is thought to enhance energy supply that could lead to increased systolic function.³⁶

In disorders of the respiratory chain, however, cardiomyopathy presents as a concentric distribution of myocardial thickening with impaired diastolic and systolic function. The main histological findings are hypertrophic and swollen cardiocytes with reduced and disrupted myofibrils. Defects of electron transport and energy production, which play a vital part in myocardial energy metabolism may cause structural abnormalities of mitochondria.^{10–37} It has been suggested that mitochondrial proliferation is an attempt by the cardiac muscle cell to compensate for deficient energy production. The increased number of mitochondria leads to cellular swelling and myocardial hypertrophy.¹⁶ Decreased systolic function may therefore be the result of reduced myofibrils and defective mitochondrial function.

During the last decade mutations and deletions of the mitochondrial and nuclear genome have been established as the basic defect in many of the disorders of the respiratory chain.³⁸ The involvement of mitochondrial DNA explains many of the special features of disorders of oxidative phosphoryla-

tion. For example maternal inheritance and the varying degree of organ involvement and clinical severity.

In conclusion, hypertrophic cardiomyopathy without obstruction is the characteristic form of cardiomyopathy encountered in respiratory chain disorders. The clinical course shows rapid deterioration often causing death before the third year of life. The possibility of a disorder of the respiratory chain must be considered in patients with hypertrophic cardiomyopathy, particularly in infancy.

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