Cardiomyopathy in children with mitochondrial disease

Clinical course and cardiological findings


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Aims To determine the frequency of cardiomyopathy in children with mitochondrial disease and describe their clinical course, prognosis and cardiological manifestations.

Methods and results Of 301 children with CNS and neuromuscular disease referred to our institution in 1984 to 1999, 101 had mitochondrial disease. Seventeen patients had cardiomyopathy, diagnosed by echo-Doppler investigations, all of the hypertrophic, non-obstructive type. The onset of symptomatic mitochondrial disease ranged from birth to 10 years of age. Eight children had cytochrome-c oxidase deficiency, while the remaining nine had various defects. Cardiomyopathy was diagnosed from birth to 27 years. Left ventricular posterior wall and septal thickness were both increased: z-scores +4.6±2.6 and +4.3±1.6 (mean±SD), respectively. The left ventricular diastolic diameter z-score, +1.3±3.4, and fractional shortening, 24±13%, displayed marked variations. Nine patients developed heart failure. Eleven patients with cardiomyopathy died, including all eight with cytochrome-c oxidase deficiency, and one patient underwent a heart transplantation. Mortality in children with mitochondrial disease was higher in those with cardiomyopathy (71%) than those without (26%) ($P<0.001$).

Conclusions In children with mitochondrial disease, cardiomyopathy was common (17%) and was associated with increased mortality. The prognosis for children with cytochrome-c oxidase deficiency and cardiomyopathy appeared to be particularly unfavorable.

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KEYWORDS Cardiomyopathy; Children; Mitochondrial disease; Clinical study

Introduction

During the last decade, disorders of the respiratory chain, so-called mitochondrial disorders, have emerged as a major clinical entity. The respiratory chain, embedded within the inner mitochondrial membrane, is made up of five enzyme complexes and the energy that is generated is used to produce ATP via oxidative phosphorylation. Mitochondrial respiratory chain proteins are under the genetic control of both nuclear and mitochondrial genes. Mutations within these genes may cause defects in oxidative phosphorylation. Organs
such as the brain, heart and skeletal muscle are markedly energy dependent and particularly vulnerable to defects in energy metabolism. Mitochondrial encephalomyopathies and cardiomyopathies are therefore common manifestations of mitochondrial disease.

Pathogenic mutations causing mitochondrial disease have been identified in both mitochondrial and nuclear genes. The diagnosis is straightforward when pathogenetic mutations are obvious. However, in many cases, the diagnosis rests on morphologic and biochemical investigations of different organs, mainly skeletal muscle. Morphologic findings of ragged red fibers and ultrastructurally abnormal mitochondria in skeletal muscle suggest mitochondrial disease. Oxidative phosphorylation defects may be due to a defect in any of the five complexes of the respiratory chain, although the most frequent biochemical abnormalities are deficiencies in complex I (NADH-CoQ reductase) and complex IV, (cytochrome-c oxidase).

Reports on mitochondrial cardiomyopathies in infants and children are sparse. Guenthard et al. reviewed the literature in 1995 and found 22 reported cases, mainly with hypertrophic cardiomyopathy. All 22 children had encephalopathy or myopathy.

The aim of the present study was to assess the frequency of cardiomyopathy in a hospital-based population of infants and children with mitochondrial disease and to describe the molecular criteria for the diagnosis, the clinical course and prognosis and specific cardiologic findings in these patients.

Methods

Patients

Three-hundred-and-one children with CNS and neuromuscular disease were referred to our institution between 1984 and 1999 for investigation of mitochondrial disease. According to the following criteria, a total of 101 were found to have mitochondrial disease.

Criteria for the diagnosis of mitochondrial disease

The diagnosis of mitochondrial disease was based on (1) the presence of a known pathogenic mutation of mitochondrial DNA or nuclear DNA, together with compatible clinical findings, or (2) at least two of four criteria:

(a) oximetry with respiratory rates below the control range in the presence of the NADH-linked substrates pyruvate and glutamate but with normal rates in the presence of succinate and ascorbate plus TMPD, indicating a deficiency in NADH-CoQ reductase (complex I), respiratory rates below the control range in the presence of pyruvate, glutamate and succinate but with normal rates in the presence of ascorbate plus TMPD, indicating a deficiency in CoQ-cytochrome-c reductase (complex III), or decreased respiratory rates in the presence of all the tested substrates, indicating a deficiency in cytochrome-c oxidase (complex IV),
(b) spectrophotometry with enzyme activities below the control range of NADH ferricyanide reductase (complex I), succinate cytochrome-c reductase (complex II and/or III) or cytochrome-c oxidase (complex IV),
(c) enzyme histochemical evidence of cytochrome-c oxidase deficiency and
(d) abundant ultrastructurally abnormal mitochondria.

Siblings with a similar clinical course were considered to have the same diagnosis as their affected and investigated sibling.

Seventeen of the patients with mitochondrial myopathy were considered to have cardiomyopathy and were studied further, retrospectively.

Clinical definitions

Infantile mitochondrial myopathy with cytochrome-c oxidase deficiency was considered to be present in children with infantile onset of muscle weakness and hypotonia, breathing and feeding difficulties and lactic acidosis, in whom muscle mitochondrial investigations revealed cytochrome-c oxidase deficiency.

Sengers syndrome was considered to be present in children with congenital cataracts, hypertrophic cardiomyopathy, mitochondrial myopathy and hyperlactatemia.

Kearns–Sayre syndrome was considered to be present in patients with the invariant triad of childhood onset of progressive external ophthalmoplegia and pigmentary degeneration of the retina, combined with short stature, cerebellar syndrome, dementia and possible complete heart block.

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome was considered to be present in children with stroke-like episodes with radiologic evidence of focal brain abnormalities, combined with lactic acidosis, ragged red fibers, focal or generalized seizures, dementia, recurrent headache and vomiting.
Myoclonus epilepsy and ragged red fibers syndrome was considered to be present in children with myoclonic seizures, balance problems and muscle weakness, hyperlactatemia and ragged red fibers.

Alpers syndrome was considered to be present in children with infantile onset of a progressive neurologic disease with psychomotor deterioration, infantile myoclonic seizures, combined with EEG changes such as focal or multifocal spikes, mixed with irregular high-voltage, low-frequency activity, radiologic evidence of cortical atrophy and/or typical neuropathologic findings at post-mortem.

Leigh syndrome was considered to be present in children with progressive neurologic disease with motor and/or intellectual developmental delay, signs and symptoms of brain stem and/or basal ganglia disease, combined with radiologic evidence of changes in the basal ganglia and/or typical neuropathologic findings at post-mortem.

Diagnosis of cardiomyopathy

The diagnosis of cardiomyopathy was based on echo-Doppler investigations. The patients were considered to have hypertrophic cardiomyopathy when the myocardium of the left ventricle appeared 'generally or regionally hypertrophic' as judged by two-dimensional echo, and the dimension of the left ventricle posterior wall in diastole and/or the intra-ventricular septum in diastole measured by M-mode was ≥2 SDS (standard deviation scores) according to the normal values. The left ventricle was considered to be dilated when the left ventricle inner diameter in diastole was ≥2 SDS. Potential obstruction of the left ventricular outflow tract was assessed by Doppler measurements and a maximum flow velocity of ≥2 m s⁻¹ in the region of interest was considered to be obstructive. Left ventricular systolic function was evaluated by M-mode measurements using fractional shortening and, when appropriate, by two-dimensional echo using ejection fractions according to Simpson.

Possible hypertrophy of the right ventricle was assessed from two-dimensional echo only, by the 'generally hypertrophic appearance' of the myocardium. Mitral valve and tricuspid valve insufficiencies were revealed by echo-Doppler investigations, and pulmonary hypertension was assessed by maximum flow velocity where there was possible tricuspid valve insufficiency. The occurrence of pericardial effusion was assessed by two-dimensional echo and given as the largest space between the epicardium and serous portion of the pericardium, behind the left ventricle in systole. The heart was considered to be enlarged if this was shown on any chest X-ray examination.

Standard ECG was performed and heart rate, QTc and PR interval were evaluated according to normal values. The QRS axis was considered to be normally oriented when the QRS complex was positive in leads I and III, left oriented when positive in I and negative in III and right oriented when negative in lead I and positive in lead III.

Laboratory investigations

Biochemical and morphologic investigations of skeletal muscle

The isolation of mitochondria, oximetric measurements on fresh mitochondria and spectrophotometric enzyme analyses, as well as muscle biopsy for ultrastructural and enzyme histochemical analyses, were performed as described previously.

DNA investigations

All cases were investigated for mitochondrial DNA mutations by Southern blotting to detect large-scale rearrangements. Investigations for the point mutations A3243G associated with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes, T8993C/G associated with encephalopathy, ataxia and retinitis pigmentosa and A8344G associated with myoclonus epilepsy and ragged red fibers syndrome were performed in selected patients. Investigations for mutations in the SURF1 gene in the nuclear genome were performed in patients with encephalopathy and cytochrome-c oxidase deficiency, according to Tiranti et al. 1999.

Statistical methods

Z-scores for echocardiographic M-mode parameters were calculated from equations given by Lester et al. Fisher's exact test was used for comparisons between unpaired data. The overall survival was calculated and presented as Kaplan–Meier curves. All the calculations were made using Systat 7.0 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A summary of the results of the clinical, morphologic, biochemical and cardiologic findings in the 17 patients with cardiomyopathy is given in Table 1. There were two sibling pairs, patients 2 and 3 and
Table 1  Clinical, morphologic, biochemical and cardiologic findings in 17 children with mitochondrial disease and cardiomyopathy

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<td>Age at diagnosis of mitochondrial disease (y)</td>
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<td>Height (at latest heart examination, cm) (SDS)</td>
<td>50</td>
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<td>76</td>
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<td>(50)</td>
<td>105</td>
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<td>(50)</td>
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<td>Weight (at latest heart examination, kg) (SDS)</td>
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<td>67</td>
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<td>Cause of death or present age (y)</td>
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<td>9</td>
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<td>9</td>
<td>17</td>
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<td>27</td>
<td>23</td>
<td>HF, RI</td>
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<td>9</td>
<td>27</td>
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<td>Mitochondrial or nuclear, DNA mutation</td>
<td>Surf 1</td>
<td>8344</td>
<td>3243</td>
<td>Del</td>
<td>COX</td>
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<td>Alpers</td>
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<td>Sengers</td>
<td>MM</td>
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<td>MERRF</td>
<td>MELAS</td>
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<td>Chest X-ray normal (N), enlarged (E) heart</td>
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<td>Supraventricular (SV) ventricular (V) arrhythmia</td>
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<td>Hypertrophy of left (L), right (R) ventricle</td>
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<td>T-wave in lead V6</td>
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<td>Echocardiogram (latest examination)</td>
<td>LVPWd (mm) (SDS)*</td>
<td>5.5 (2.5)</td>
<td>8.5 (5.6)</td>
<td>12 (5.6)</td>
<td>9 (5.2)</td>
<td>9 (9.1)</td>
<td>5.2 (2.0)</td>
<td>7.5 (5.0)</td>
<td>11 (7.0)</td>
<td>12 (3.7)</td>
<td>9 (8.4)</td>
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<td>6 (−0.8)</td>
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<td>10 (3.1)</td>
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<td>IVSd (mm) (SDS)*</td>
<td>6.5 (5.3)</td>
<td>7.4 (4.1)</td>
<td>17 (7.9)</td>
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<td>7 (5.2)</td>
<td>11 (4.7)</td>
<td>5.5 (−0.2)</td>
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<td>LVHd (mm) (SDS)*</td>
<td>21 (3.6)</td>
<td>38 (4.3)</td>
<td>50 (3.1)</td>
<td>27 (2.9)</td>
<td>16 (3.3)</td>
<td>22 (2.7)</td>
<td>28 (4.0)</td>
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<td>70 (4.8)</td>
<td>18 (4.0)</td>
<td>54 (4.3)</td>
<td>42 (0.3)</td>
<td>46 (4.1)</td>
<td>39 (1.9)</td>
<td>51 (2.0)</td>
<td>56 (9.1)</td>
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<td>FS (normal ≥26%)</td>
<td>14 (7)</td>
<td>25 (11)</td>
<td>47 (31)</td>
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<td>44 (10)</td>
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<td>Mitral (MI) and tricuspid valve (TI) insufficiency</td>
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<td>Pulmonary hypertension (mmlg)</td>
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<td>Pericardial effusion (mm)</td>
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<td>Ca-channel blocker</td>
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<td>Heart transplantation (possible candidate) No*</td>
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<td>No*</td>
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<td>Yes</td>
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<td>No*</td>
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**B, birth; d, days; w, weeks; m, months; y, years; Htx, heart transplantation; HF, heart failure; RI, respiratory insufficiency; SD, sudden death; COX, cytochrome-c oxidase; IMM, infantile mitochondrial myopathy with COX deficiency; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonus epilepsy and ragged red fibers; MEM, mitochondrial encephalomyopathy; MM, mitochondrial myopathy; KSS, Kearns-Sayre syndrome; CI-CV, complex I-complex V; N, not investigated; LVPWd, left ventricle posterior wall in diastole; IVSd, intra-ventricular septum in diastole; LVHd, left ventricle inner diameter in diastole; LVOT, left ventricle outflow tract; F5, fractional shortening; EF, ejection fraction; Htx(12 y), heart transplanted at the age of 12 y; SDS, standard deviation scores. *for reference values, see text.

*Not a candidate for Htx due to severe myopathy.

**Hepatopathy.

**Encephalopathy.

**Scoliosis.
patients 13 and 14. Patient no. 11 had two older siblings who died of cardiac failure due to Sengers syndrome.12 The onset of symptoms of disease took place during infancy in all cases except in patients 15, 16 and 17 with mitochondrial DNA mutations. Short stature (height≥ 2 SD) was observed in eight patients, one of whom (no. 8) received growth hormone treatment.

Diagnosis

The diagnosis of mitochondrial disease was made before the age of 1 year in eight children but ranged from birth to 27 years of age. The male:female ratio was 2.5:1. Specific diagnoses of different types of respiratory chain deficiency varied, but almost half the patients had cytochrome-c oxidase deficiency.

Cardiomyopathy was diagnosed before the age of 6 years in the majority of children, six of whom were less than 1 year old at the time of diagnosis. In one patient (no. 17), however, the diagnosis of mitochondrial disease was delayed until 27 years of age. This patient was still included in our series as he was symptomatic and had had short stature from the age of 10 years, which resulted in an extensive investigation at our hospital at the age of 12 years. The symptoms were explained as a result of malabsorption at that time and he was considered for growth hormone treatment but failed to appear for medical check-ups. He presented at the age of 27 years with terminal heart failure when the diagnosis of mitochondrial disease was made.

The diagnosis of mitochondrial disease and cardiomyopathy was made at the same time or within a few months in 10 of the patients. In the remaining seven, the time that elapsed between the two diagnoses ranged from 1 to 13 years. The diagnosis of cardiomyopathy preceded the diagnosis of mitochondrial disease in five patients.

Clinical course and survival

Eleven of the 17 patients with cardiomyopathy died and one underwent heart transplantation (71%) during the study period, as compared with 22 deaths in the group of 84 patients (26%) with mitochondrial disease but without cardiomyopathy (P=0.001). The cause of death (including heart transplantation) in patients with cardiomyopathy was cardiac in 10 patients (eight heart failure, two sudden deaths) and respiratory insufficiency in two. The overall survival curve for the patients with mitochondrial cardiomyopathy is shown in Fig. 1. All eight children with cytochrome-c oxidase deficiency died before the age of 13 years. Three patients died as young adults. In all, nine of the patients with cardiomyopathy developed heart failure as judged by echo (left ventricle dilation and decreased fractional shortening). Eight of these patients deteriorated to end-stage heart failure (age 3 days–27 years); at least four of them died and one underwent heart transplantation within about 1 year of the first sign of left ventricle dysfunction on echo. Five of the nine patients with heart failure were regarded as possible candidates for heart transplantation. The remaining four patients were excluded due to severe manifestations of mitochondrial disease from organs other than the heart (nos. 1, 8, 15 and 16) or severe scoliosis (no. 14). Only one patient, a patient with Sengers syndrome (no. 11) previously described elsewhere,12 actually underwent heart transplantation. Three possible candidates for heart transplantation died due to rapid deterioration and one patient (no. 9) is still alive nine years after the diagnosis of left ventricle dysfunction.

Another patient with Sengers syndrome (no. 12) presented with hypertrophy of the myocardium at the age of 2 years with left ventricular posterior wall in diastole and intra-ventricular septum in diastole measurements of 3.5 SDS and 2.0 SDS, respectively. The left ventricular hypertrophy gradually diminished and, since the age of 5 years, the left ventricular inner diameter in diastole, left ventricular posterior wall in diastole and intra-ventricular septum in diastole have been within the normal range, except for some slight asymmetric hypertrophy of the intra-ventricular septum in diastole. In this particular patient, the QTc was normal (0.33 ms) up to the age of 6 years. At the age of 7.8 years, a slight QTc prolongation was observed (0.45 ms). Due to a further progression of the long QTc (0.53 ms), treatment with atenolol was started at the age of 12 years. The patient is doing fairly well with normal cardiac function at the age of 15 years.

Echo-Doppler and ECG findings

A summary of the echo-Doppler findings at the latest examination is given in Table 2. The cardiomyopathy was of the hypertrophic, non-obstructive type in all the patients. Both the left ventricular posterior wall in diastole and intra-ventricular septum in diastole were increased in all the patients but three, whereas the left ventricular inner diameter in diastole and fractional shortening displayed marked variations.
The ECG revealed sinus tachycardia in 10 patients, long QTc in six, a left-oriented QRS-axis in eight, left ventricular hypertrophy in 12 and negative T-waves in lead V6 in nine patients. Supraventricular arrhythmia was found in four patients.

Morphologic findings

A morphologic examination of myocardial tissue was performed in five cases. The explanted heart of patient no. 11 with Sengers syndrome showed hypertrophy and it was also dilated. Light-microscopic investigation showed marked interstitial fibrosis and hypertrophic cardiomyocytes. Ultrastructural investigation showed a proliferation of mitochondria with abnormal structure, including densely packed cristae (Fig. 2a). An endomyocardial biopsy of patient no. 17 with large-scale mitochondrial DNA deletion showed hypertrophy of cardiomyocytes and a deficiency in cytochrome-c oxidase in a mosaic pattern (Fig. 2b). A post-mortem examination of patient no. 5 (7 weeks) with partial cytochrome-c oxidase deficiency revealed a markedly hypertrophic heart (60 g). The enlarged cardiomyocytes included collections of abnormal, giant mitochondria. A post-mortem examination of patient no. 8 (age 2 years), with Alpers syndrome, revealed a hypertrophic and dilated heart weighing 200 g. There was marked interstitial
fibrosis. Enzyme–histochemical analysis showed cytochrome-c oxidase deficiency in a mosaic pattern. Electron microscopy disclosed collections of abnormal mitochondria with a tubular arrangement of cristae in cardiomyocytes. A post-mortem investigation of patient no. 2 with infantile cytochrome-c oxidase deficiency showed an enlarged heart with huge collections of ultrastructurally abnormal, giant mitochondria.

**Discussion**

**Epidemiology**

Cardiac involvement including hypertrophic and dilated cardiomyopathies has been reported to be frequent in mitochondrial diseases. However, the incidence and prevalence figures for mitochondrial cardiomyopathy in children have not been reported. The present report was based on patients referred to our institution (tertiary referral center for pediatric neuromuscular disorders and cardiology) during a 16-year period. Referral was mainly from our own region (population 1.8 million), but selected patients were also referred from other parts of Sweden (population 8.5 million) and one case each came from Iceland and Finland. The results can therefore not be interpreted in terms of epidemiologic data but represent minimal figures for cardiac involvement in a large cohort of children with mitochondrial disease. All the patients were investigated at least once at our center. Follow-up was mainly carried out at the referring hospital from where continuous reports were sent to us. However, the vast majority of the patients with cardiomyopathy were investigated repeatedly at our institution. As a number of patients without cardiomyopathy were not systematically followed at our institution, some may have developed cardiomyopathy after the first investigation without our knowledge. This may have resulted in an underestimation of the frequency of cardiomyopathy in the present study.

In spite of these reservations, the results in the present paper indicate a frequency of cardiomyopathy in mitochondrial diseases of around 20%. This is in agreement with the truly epidemiologic results published by Darin et al. in 2001. In this report, a frequency of cardiomyopathy of 25% was found in children with mitochondrial encephalomyopathies (8/32 children <16 years of age). The incidence of mitochondrial encephalomyopathy in their population-based study was found to be 1/11 000. Based on these assumptions and the results of the present study, it is possible to speculate that the incidence of mitochondrial cardiomyopathies in children and young adults would be around 1/50 000. The male/female ratio in children with mitochondrial cardiomyopathy was about 2.5:1 in the present study. In the study by Darin et al. in 2001, the male/female ratio was 1:1 for patients with mitochondrial encephalomyopathy, but the ratio for patients with mitochondrial cardiomyopathy was not given.

**Diagnosis**

The diagnosis of mitochondrial disease in the present study was based on investigations of skeletal muscle samples. In those patients for whom myocardium was available for examination (explanted hearts, endomyocardial biopsy or necropsy), the diagnosis of mitochondrial disease was also confirmed in the myocardium. We have been liberal in performing skeletal muscle biopsies in patients with cardiomyopathy at our center, but we have not performed endomyocardial biopsies as a matter of routine. Patients with mitochondrial disease present from the neonatal period to adulthood with a variety of manifestations of symptoms of varying severity. As cardiac involvement is common, patients with mitochondrial diseases should be thoroughly investigated with respect to cardiomyopathy and conduction abnormalities. The results of the present study show that ECG findings such as left ventricular hypertrophy, negative T-waves in lead V6, a left-oriented QRS axis and prolonged QTc should be regarded as
highly indicative of cardiac involvement and possible cardiomyopathy. About half the patients with cardiomyopathy were diagnosed as having a mitochondrial disease during the first year of life. In some of the patients, the cardiomyopathy was detected before the identification of the disorder as a mitochondrial disease. In others, there was a significant delay between the presentation of symptoms and the time of diagnosis.

As has been reported previously, cardiomyopathy may occur in different types of mitochondrial disease. In contrast to what has been reported in other studies, the cardiomyopathy was classified as hypertrophic, non-obstructive in all the patients in our series. The majority of the patients with cardiomyopathy had a normal left ventricular inner diameter in diastole and fractional shortening at the time of diagnosis. The hypertrophic appearance of the myocardium thus made the diagnosis fairly obvious. On the other hand, if the first echo investigation had been performed at the stage when the left ventricle was dilated and poorly functioning, the diagnosis might have been confused with dilated cardiomyopathy. At this stage, the hypertrophy of the myocardium in terms of increased wall thickness is diminished in a dilated ventricle, while the hypertrophy in terms of left ventricle mass is preserved or even exaggerated.

Prognosis

The difference in prognosis between patients with and without cardiomyopathy, with mortality rates of 71 and 26%, respectively, indicates that patients with cardiomyopathy follow a different and more severe clinical course. Since the underlying mitochondrial abnormality was variable with, for example, only 1/9 patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes and 1/8 patients with myoclonus epilepsy and ragged red fibers presenting with cardiomyopathy, it is not possible to speculate on the prognosis of cardiomyopathy in a particular mitochondrial disease. However, it is worth noting that, in infantile mitochondrial myopathy with cytochrome-c oxidase deficiency, 8/16 children in the total material had cardiomyopathy and in those with cardiomyopathy the outcome was particularly poor with 100% mortality during the study period and ‘cardiac death’ in 75% of the patients. Patient no. 3 in our series illustrates that cardiac function may deteriorate rapidly. She had normal fractional shortening on echo 6 months before she developed terminal heart failure. In spite of treatment at the intensive care unit with i.v. inotropics such as milrinon and dobutamin, she died within 2 weeks. Only one of five possible candidates for heart transplantation in our series was actually transplanted. This patient is doing well 5 years after heart transplantation, although she has some persistent muscle weakness. This illustrates that heart transplantation may be a reasonable option for those patients without severe symptoms from other organ systems. Of the remaining four possible candidates for heart transplantation, one patient died before heart transplantation was an established form of treatment at our center and two died due to a rapid deterioration in cardiac function. On the other hand, one possible candidate for heart transplantation (patient no. 9) is still alive almost one decade after the first signs of left ventricle dysfunction, which illustrates that cardiac function may not always deteriorate rapidly. Furthermore, it is interesting to note that one of the patients with Sengers syndrome developed terminal heart failure (no. 11), whereas the other patient (no. 12) improved with an almost complete remission of the left ventricular hypertrophy. The reason for the difference in prognosis is unclear.

Cardiomyopathy has previously been reported in Kearns–Sayre syndrome, but conduction disturbances appear to occur more frequently. Of a total of 10 patients with Kearns–Sayre syndrome referred to our hospital, patient no. 17 was the only one to develop cardiomyopathy. Of the remaining nine patients, three received a pacemaker at the age of 13, 14 and 25 years due to bradycardia, complete atrioventricular block and syncope, respectively.

Morphology

In all the cases in which the heart was available for examination, there were obvious mitochondrial alterations, not only with respect to the number of mitochondria but also with respect to their ultrastructure and size. In two cases in which enzyme–histochemical analysis was performed, there was also evidence of a respiratory chain defect. These observations indicate that a diagnosis of mitochondrial cardiomyopathy may be obtained by endomyocardial biopsy. Paracrystalline inclusions that are found in skeletal muscle mitochondria in various mitochondrial myopathies were not present in the hearts of the investigated cases and appear to be a skeletal muscle-specific alteration.

Summary

Hypertrophic non-obstructive cardiomyopathy may occur in about 20% of children with mitochondrial...
disease. About half the patients with cardiomyopathy developed heart failure, with a poor overall prognosis and a mortality rate of around 70% before the age of 30 years. Cardiac function may deteriorate rapidly. About half those who develop heart failure may be candidates for heart transplantation.

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