Cardiomyopathy in the Kearns-Sayre syndrome

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SUMMARY The Kearns-Sayre syndrome is a mitochondrial myopathy characterised by ptosis, chronic progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects. A unique case is reported in which there was rapid development of progressive congestive cardiac failure that required cardiac transplantation.

A review of published reports of mitochondrial myopathy shows that a minority of cases (< 20%) have cardiac involvement. This had previously been limited to abnormalities of cardiac conduction with progressive heart block. Myocardial biopsy has, however, shown ultrastructural evidence of a generalised mitochondrial disorder which hitherto has not been associated with a functional deficit.

The association of external ophthalmoplegia, abnormal retinal pigmentation, and complete heart block was first reported by Kearns and Sayre in 1958,¹ although Sandifer had already described a case of bundle branch block in association with external ophthalmoplegia.² The high risk of sudden death from the cardiac conduction defect in this syndrome has become less important with the development of implantable pacemakers, and prolonged survival has been reported.³ The aetiology of the condition is unknown but the pathology has only recently been elucidated.

Several early necropsy studies did not show any specific abnormality of the myocardium.^{1,4} Endomyocardial biopsy also showed non-specific changes—for example, interstitial fibrosis and hypertrophy⁵ on light microscopy. Only on electron microscopy has any specific abnormality been detected, namely glycogen accumulation and proliferation of abnormal mitochondria.^{3,5} It is now recognised that the Kearns-Sayre syndrome forms part of a heterogeneous group of mitochondrial cytopathies.^{6,7}

Although abnormalities of myocardial ultrastructure have been found in the Kearns-Sayre syndrome these have not been associated with myocardial dysfunction. We report a patient with Kearns-Sayre syndrome who presented with congestive cardiac failure caused by dilated cardiomyopathy which was so severe that heart transplantation was required.

Case report

INITIAL PRESENTATION

A 21 year old man presented with a two month history of dry cough and progressive dyspnoea. At the time of admission he became breathless when he climbed a single flight of stairs and he was orthopnoeic. He did not have chest pain. There was no history of a preceding influenza-like illness. In the past he had had bilateral ptosis surgically corrected when he was 16 years old and had been investigated for abnormal retinal pigmentation (visual evoked responses and electroretinograms were normal).

He smoked 20 cigarettes a day and drank about 20 pints of beer a week. He had two siblings who were well and there was no family history of note.

He was plump and normally developed. The pulse rate was 100 beats/minute with frequent extrasystoles, and the blood pressure was 110/80 mm Hg. The jugular venous pressure was grossly elevated to the level of his pinna and did not fall on inspiration. The apex was readily palpable in the 6th intercostal space in the anterior axillary line, and auscultation showed normal heart sounds. There was palpable hepatomegaly. Chest and neurological examination appeared normal. Fundal examination showed abnormal pigmentation around the macula (fig 1).

INVESTIGATIONS

Full blood count, blood sugar, thyroid function tests, and concentrations of fasting lipids, serum urea, and electrolytes were all normal. Antinuclear factor and rheumatoid factor were negative. The concentration of serum bilirubin was increased at 27 mmol/l (normal < 17 mmol/l), as was aspartate aminotrans-

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Fig 1 Retinal photograph showing the typical "salt and pepper" retinal pigmentation of mitochondrial myopathy.

ferase activity at 41 units/l (normal 6–35 units/l). Alkaline phosphatase activity was normal. Chest x ray showed pulmonary oedema with cardiomegaly (cardiothoracic ratio 17.8/30.6). The electrocardiogram showed sinus tachycardia with ventricular extrasystoles and left axis deviation. Echocardiogra-

phy showed biventricular dilatation and generalised poor function, but all the valves appeared to be normal. The isotope ventriculogram gave a calculated ejection fraction for the right ventricle of 15% and 17% for the left ventricle. Twenty four hour ambulatory electrocardiography showed frequent ventricular extrasystoles and technical ventricular tachycardia (runs of three consecutive extrasystoles).

COURSE

A diagnosis of dilated cardiomyopathy was made and he was treated with diuretics, enalapril, warfarin, and amiodarone. On this regimen the pulmonary oedema cleared and he became less breathless. Two months later, however, he deteriorated and was readmitted with increasing dyspnoea, cough productive of pink frothy sputum, and lethargy. He had four pillow orthopnoea. On examination he was in severe congestive cardiac failure with bilateral pitting ankle oedema, high venous pressure, sinus tachycardia, and gallop rhythm.

Cardiac catheterisation at this time showed raised right heart pressures with mean right atrial pressure of 24 mm Hg. Right ventricular pressure was 60/30 and pulmonary artery pressure was 60/40 (mean of 45 mm Hg). Pulmonary wedge pressure was 38 mm Hg and left ventricular pressure was 78/30. Cardiac output was 2.9 l/min. During the catheterisation a 2:1

Fig 2 Limitation in the extent of eye movements by external ophthalmoplegia.

atrioventricular block developed. During this second admission his voice weakened and a bovine cough developed. Indirect laryngoscopy showed a paralysed left vocal cord which raised the possibility of Ortner's syndrome.

He was transferred to Harefield Hospital where an urgent heart transplantation was performed. He had a postoperative course complicated by a cardiac arrest, status epilepticus, and he required artificial ventilation for about 10 days. He gradually recovered and ten weeks after the transplantation he was transferred back to Bristol for rehabilitation.

On readmission there was considerable distal wasting of the hands, forearms, and legs with contractures of both achilles tendons. He had ophthalmoplegia and weak sternomastoids. His cardiovascular state was satisfactory with no signs of heart failure.

The history of corrected ptosis and finding of abnormal retinal pigmentation with the development of ophthalmoplegia and skeletal myopathy led to the diagnosis of the Kearns-Sayre syndrome.

NEUROLOGICAL INVESTIGATIONS

Electroencephalography was abnormal with a generalised excess of very slow wave activity particularly over the left hemisphere. There were occasional sharp wave discharges suggestive of a liability to seizures. Computed axial tomography of the brain showed no midline shift and no focal changes. The ventricular system showed mild dilatation. Nerve conduction studies showed normal motor and sensory velocities and normal amplitudes of evoked motor potentials apart from those muscles which had atrophied completely. Electromyographic sampling showed generalised and diffuse non-specific abnormalities with loss of interference patterns related to the number of units that had atrophied within the muscles.

On review 12 months after cardiac transplantation he was fully independent without dyspnoea on exertion. He had a persistent right foot drop and weakness of dorsiflexion of the left foot. There was persistent wasting of calf muscles bilaterally. There

Fig 3 Electron photomicrograph of myocardial biopsy specimen showing large numbers of abnormal mitochondria. The mitochondria are large, vacuolated, and contain electron densities.

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was weakness and wasting of the intrinsic hand muscles and wasting of the forearm muscles but no clinical weakness. Eye movements were markedly impaired (fig 2). All the reflexes were present.

HISTOPATHOLOGY

The excised heart weighed 500 g without the upper atria. The ventricular cavities were dilated and there was adherent thrombus at the apices. The specimen was fixed routinely in formol saline and processed for both histological and ultrastructural examination. Light microscopy of the myocardium showed degeneration of myocardial fibres with perinuclear vacuolation and nuclear pleomorphism and enlargement. There was diffuse and focal interstitial fibrosis that was particularly noticeable in the sub-endocardial region. Although these features were present in both ventricles the left ventricle showed the most severe changes. Foci of myofibrillar degeneration were also noted as demonstrated by trichrome staining. There were no features of an active myocarditis. Electron microscopy showed no significant abnormality of the myofibrils but showed various mitochondrial abnormalities. Mitochondria were increased in number but in addition were of varying size and shape, with giant mitochondria measuring up to 1.8 μ m in diameter. Within the mitochondria there were electron dense areas and vacuoles (fig 3). In many the cristae were disrupted.

Discussion

The Kearns-Sayre syndrome is characterised by the triad of chronic progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects and is part of a heterogeneous group of mitochondrial myopathies. The first of these myopathies was described by Luft *et al* in 1962⁸ and they are all characterised by abnormal muscle mitochondrial morphology on electron microscopy. Recently attempts have been made to separate different clinical syndromes, for example myoclonus epilepsy with ragged red fibres (MERRF) and mitochondrial myopathy/encephalopathy, lactic acidosis, and stroke-like episodes (MELAS),^{6,9} but there is no association with either specific morphological changes or mitochondrial enzyme abnormalities.⁷

In the biggest published series of patients, from one centre, with mitochondrial myopathy defined by muscle biopsy, 40 (61%) of 66 cases presented before age 20 years and the commonest presentation was ptosis in 37 (56%) often with chronic progressive external ophthalmoplegia, which ultimately affected 48 (73%) of cases.⁷ Many cases (47 (71%)) also had proximal limb weakness or easy fatigue, often with absent reflexes but occasionally with extensor plantar

responses. Abnormal retinal pigmentation occurred in 24 (36%) and was usually of a "salt and pepper" appearance and without associated visual defect. Sensorineural deafness occurred in 17 (26%) and important central nervous system disease with cerebellar ataxia or dementia in 18 (27%). Similar frequencies of abnormalities have been reported in cumulative series culled from published reports.^{10,11} Our case is typical in that onset was before the age of 20 years with ptosis and "salt and pepper" retinal pigmentation. Neither external ophthalmoplegia nor skeletal muscle weakness was noticeable before cardiac surgery but these are often mild and ignored by the patient.⁷ After his complicated postoperative course the skeletal abnormalities and ophthalmoplegia became obvious.

Cardiac function in the Kearns-Sayre syndrome as assessed clinically⁷ and by haemodynamic^{3,5} and imaging techniques has always previously been shown to be normal. Indeed, cardiac involvement in mitochondrial myopathies has hitherto been limited almost exclusively to the conducting tissue (though the development of cardiomyopathy has been forecast as a consequence of prolonged longevity resulting from pacing).³ Of the 66 cases from the National Hospital of Nervous Diseases, 11 (17%) had electrocardiographic abnormalities without overt myocardial dysfunction.⁷ These included in 11 cases, non-specific ST segment or T wave abnormalities (often T wave flattening),⁹ and in nine cases conduction defects ranging from pre-excitation syndrome in one, first degree heart block (two cases), non-specific intraventricular conduction defects (two cases), right bundle branch block (three cases), and complete heart block (one case). Two patients had permanent pacemakers. In our case, the electrocardiogram was abnormal before transplantation with left axis deviation indicative of left anterior hemiblock and transient second degree atrioventricular block. Progressive heart block from left anterior hemiblock to symptomatic complete heart block over a seven year period has been documented³ and prophylactic pacing has been advocated for patients with the syndrome and evidence of conduction disturbance short of complete heart block.⁵ Previous cardiac biopsy specimens have shown characteristic mitochondrial abnormalities^{3,5} similar to those seen in skeletal muscle. The morphological hallmark first reported by Luft *et al* is the ragged red fibre, seen with the modified Gomori trichrome stain, which contains peripheral and intermyofibrillary accumulations of abnormal mitochondria.⁸ These mitochondrial abnormalities are seen on electron microscopy. The mitochondria are increased in number and may form large aggregates. They may appear morphologically normal but are often abnormally

large with vacuoles or dense inclusions (made up largely of lipid). The cristae are disrupted and may form concentric whorls or honeycomb patterns.⁶ Excessive accumulation of glycogen particles is also seen. Many of the morphological abnormalities of mitochondria are, however, non-specific and may be seen in other muscle diseases; they probably represent non-specific responses to noxious stimuli.¹²

One other case of cardiac failure in this syndrome has been described.¹³ In this case, a 23 year old man, first presented at the age of 12 with high output cardiac failure and again at the age of 16. At the time of his second presentation a profound lactic acidosis and considerable deterioration in the myopathy developed. He responded to treatment with prednisone and thiamine. Endomyocardial biopsy was not performed, and it was suggested that his cardiac failure resulted from a chronic high output state caused by the disturbances in muscle glycolytic metabolism producing excess lactate and pyruvate (akin to beriberi). Our case presented with severe rapidly progressive congestive cardiac failure and it is possible that this was precipitated by other factors. Abnormal cardiac muscle may be more susceptible to the toxic effects of alcohol, and although the drinking history of our patient would not be expected to produce cardiomyopathy in an otherwise normal heart it may have contributed to the speed and severity of his deterioration. In alcoholic cardiomyopathy^{14,15} and other cardiomyopathies cardiac muscle may show mitochondrial abnormalities,¹⁶ but the clinical features make our case otherwise typical of mitochondrial myopathy.⁷

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Addendum

Since this report was prepared, two other cases of Kearns-Sayre syndrome presenting with heart block and heart failure have been reported.¹

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