

## Endocardial fibroelastosis: possible X linked inheritance

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**SUMMARY** We report a pedigree in which six males died of cardiac failure within the first eight months of life. These males were related through healthy females, as with X linked recessive inheritance. There was no consanguinity. None of the affected boys had an anatomical cardiac abnormality. In two affected brothers, histological evidence for endomyocardial fibroelastosis was documented, and in one of these electron microscopy demonstrated abnormalities of the mitochondria as found in mitochondrial cytopathy. A review of published reports revealed five similar X linked pedigrees, and in two of these mitochondrial abnormalities were found. We suggest that these families may show an X linked recessive cardiomyopathy with mitochondrial abnormalities.

We present a family in which six males died of heart failure in infancy. Two of the infants, who were brothers, were found to have endomyocardial fibroelastosis (EMFE) at necropsy and abnormal mitochondria were found in one of these. Other male relatives who died of heart failure as infants had similar clinical courses, but were not given this specific diagnosis. The pedigree was compatible with X linked recessive inheritance of mitochondrial cardiomyopathy. Female presumptive carriers were healthy.

### Case reports

A young woman (III.6, fig 1) sought advice regarding the possibility that she might bear sons

who would die of heart failure in infancy, as her mother (II.3) had given birth to two daughters, both well, and to three sons who had all died in infancy.

The first son (III.3) was stillborn at eight and a half months' gestation, with a malformation of the head. Birthweight was 1134 g. No necropsy was carried out.

The second son (III.4) was born at term, birthweight 2835 g. He was admitted to hospital at two days of age suffering from hypothermia. On examination, he had pink skin, with pitting oedema of the hands and feet, and a rectal temperature of 28.6°C. He was warmed to 35°C and developed oliguria and apnoeic attacks which led to death 36 hours after admission. At necropsy, oedematous lungs were found, with

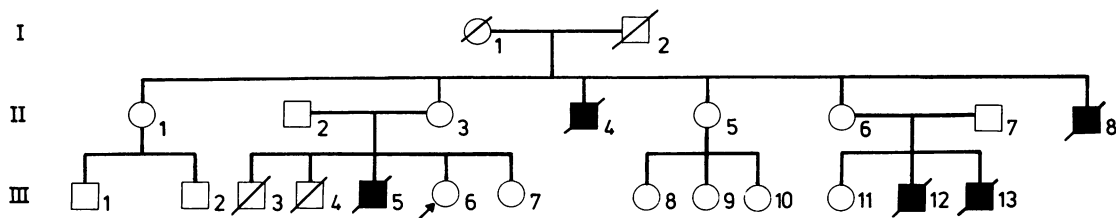


FIG 1 Pedigree showing probable X linked recessive inheritance.

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small areas of lobular haemorrhage. There was marked dilatation of the heart, especially of the right atrium and ventricle, but the valves, myocardium, and aorta were said to be normal. There was peripheral oedema and ascites and the brain was swollen. A diagnosis of neonatal cold injury was made.

The third son (III.5) was born by normal delivery following an uneventful pregnancy (birthweight 2835 g). He was apparently well until three months of age when he developed signs of heart failure, with shortness of breath and difficulty feeding. He died at three and a half months of age. No necropsy was performed, but the death certificate read: "(a) Heart failure and pulmonary oedema, (b) congenital heart disease". The paediatrician wrote that the baby had died of a cardiomyopathy with heart failure.

The consultand had two uncles who had also died in infancy. The first (II.4) was born at term, birthweight 3969 g. His mother stated that he always had difficulty with feeding and could not lift his head or kick normally. He died at four months of age in heart failure. His death certificate read: "(a) Lobar pneumonia and heart failure, (b) congenital malformation of the heart. PM". This infant's brother (II.8) was born at term, birthweight 3856 g. He too had feeding difficulties and resembled his brother clinically. His mother said that, on *x* ray, "his heart filled his little body". He died at eight months of age. His death certificate read: "Heart failure due to

congenital maldeveloped heart". There was no necropsy.

This sibship contains four healthy females, one of whom (II.1) had two normal sons, while another (II.5) had three normal daughters. The fourth sister of the sibship (II.6) is well. She has a normal daughter (III.11) who is also well. Her next child, a son (III.12), was born at term, birthweight 3118 g. He fed poorly and had laboured breathing. His mother noted mild muscle weakness. He was admitted to hospital at three months of age because of breathlessness. On examination he was pale and cold, with tachypnoea, tachycardia with ventricular gallop, and an enlarged liver. He died of heart failure soon after admission. Necropsy showed chronic pulmonary oedema and congestion of the brain and meninges. The pericardium was healthy, but the heart was enlarged with a thickening of the left ventricular wall by a combination of fibrous tissue and endocardial thickening, characteristic of endomyocardial fibroelastosis (EMFE). The cause of death was given as "Acute LVF due to EMFE".

His brother (III.13) was a normal term delivery, birthweight 3090 g, with an Apgar score of 10. He remained well until six weeks of age when he developed breathlessness and feeding difficulties. He was treated with digoxin but deteriorated, and died of heart failure at 11 weeks. Necropsy showed chronic pulmonary congestion, hepatic and splenic

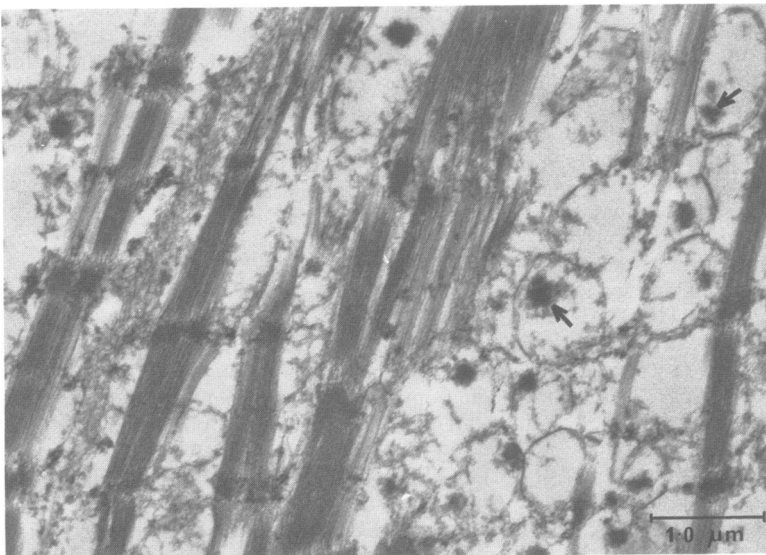


FIG 2 Part of a cardiac muscle fibre showing an accumulation of distorted mitochondria, some of which (arrowed) contain dense bodies.

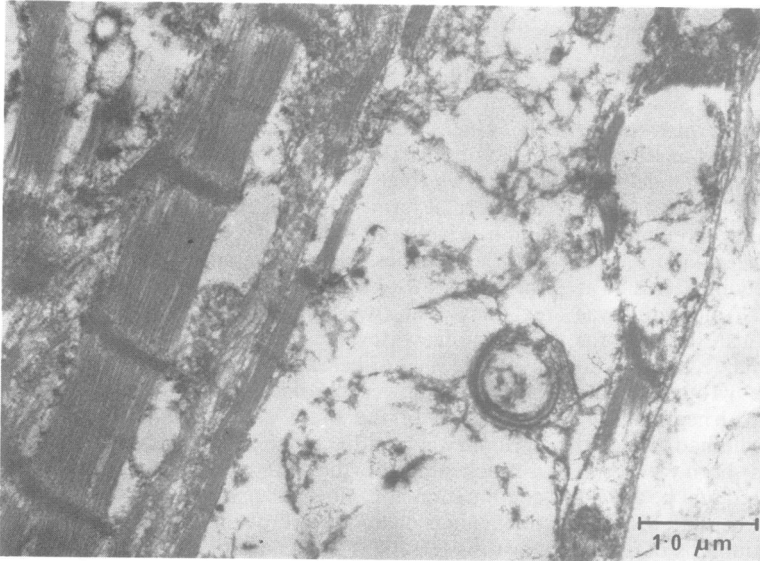


FIG 3 Subsarcolemmal region of a cardiac muscle fibre showing an abnormal mitochondrion with circularly arranged cristae.

enlargement, and cardiomegaly. The pericardium was normal, but there was fibroelastosis affecting the left ventricle in particular. There were no other abnormalities in the heart or great vessels. Histology confirmed EMFE.

There was no other history of congenital heart disease in this family and no consanguinity. The consultand (III.6) and her mother had cardiac ultrasound performed and these were both normal.

Electron microscopy was carried out in subject III.12. A sample of endomyocardium obtained at necropsy, fixed in neutral formalin, and embedded in paraffin wax, was examined. It was decerated in CNP 30 for 72 hours and rehydrated by passage through a graded series of alcohols over a three and a half hour period. The tissue was left in phosphate buffer containing 2 mol/l sucrose (pH 7.4) overnight, post-fixed in osmium tetroxide for 90 minutes, dehydrated, and embedded in TAAB resin. Ultrathin sections were cut with an LKB Ultratome fitted with a diamond knife, stained with uranyl acetate and lead citrate, and examined with a Hitachi HU-12A transmission electron microscope.

The electron microscopic appearance of typical sections is shown in figs 2, 3, and 4. Apart from autolytic changes associated with delay in the fixation of the sample, the endocardial component appeared normal. However, some abnormalities not considered to be entirely associated with fixation artefacts were found in the cardiac muscle fibres. Contraction of the cardiac muscle myofibrils resulted

in accumulation of the mitochondria in groups (fig 2). Many contained dense bodies and some had circularly arranged cristae (figs 3 and 4). No glycogen was found within the mitochondria.

### Discussion

In this pedigree there are two brothers who died of documented EMFE. They had two maternal uncles and a male cousin who died in infancy of heart failure with similar clinical manifestations. Another male cousin, said to have died of 'neonatal cold injury', had signs compatible with heart failure, but the necropsy report stated that the heart was normal. Affected males were linked through healthy females, as found in X linked recessive inheritance. There was no family history of subarachnoid haemorrhage or heart disease in any other family members and there was no consanguinity.

Forfar *et al.*<sup>1</sup> in their review of 433 cases of EMFE, described the symptomatology as respiratory distress, dyspnoeic attacks, failure to thrive, and chronic cardiac failure with tachycardia and intermittent cyanosis. Of their cases, 93% showed cardiomegaly with left ventricular enlargement in 62% of uncomplicated cases. Of their uncomplicated cases, 75% had died by one year of age (31% by three months of age) and the longer the infant survived, the more extensive was the degree of pathological involvement of the heart. EMFE was found to be associated with congenital cardiovascular abnormalities in 78% of

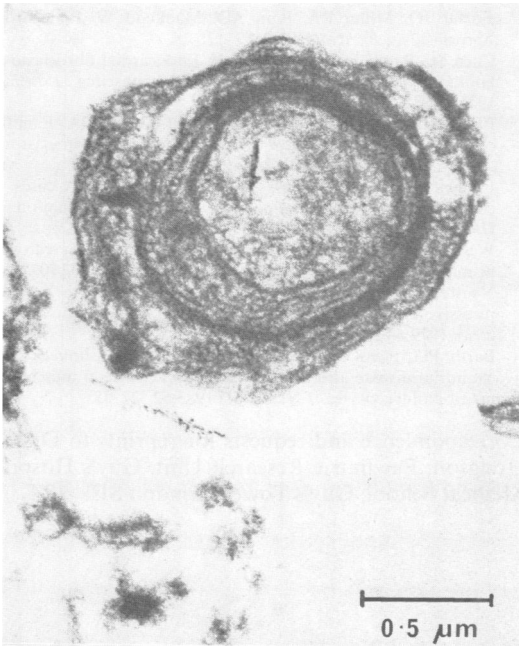


FIG 4 Mitochondrion of a cardiac muscle fibre showing circularly and irregularly arranged cristae.

cases ('complicated EMFE'). Our cases correspond clinically to those described in patients with EMFE uncomplicated by anatomical abnormalities.

Familial cases of primary endocardial fibroelastosis have been documented previously, but only in five families has an X linked recessive pattern of inheritance been likely. Indeed, in the survey by Chen *et al*<sup>2</sup> of 141 cases of primary EMFE in 119 families, the incidence was higher in girls than in boys (M:F sex ratio=0.63). However, among their nine families with multiple cases of EMFE (7.56% of EMFE families, where the recurrence risk was estimated at 17.7% in sibs), there were two where only males were affected. When they divided their cases into those who died early and those who survived longer, the sex ratio was 0.91 for those with a poor prognosis (26 males, 32 females), while in the longer term survivors it was 0.52 (15 males, 29 females). This suggests that males are represented more often in the severely affected group. However, these differences in sex ratios did not reach significance. A severe X linked type of EMFE could be one of the heterogeneous causes of EMFE, responsible for a minority of those affected.

Three pedigrees showing primary EMFE with X linked recessive inheritance have been described by

Fixler *et al*,<sup>3</sup> Lindenbaum *et al*,<sup>4</sup> and Westwood *et al*.<sup>5</sup> The cases of Fixler *et al*<sup>3</sup> showed pathological evidence of diffuse endocardial fibroelastosis involving all heart chambers, and affected infants had severe heart failure with generalised oedema and cardiomegaly, leading to death by three years of age. Lindenbaum *et al*<sup>4</sup> found EMFE in two of the affected males in their pedigree, and all six affected males in this family died of heart failure within the first two years of life. Westwood *et al*<sup>5</sup> described a family containing three affected males who died of heart failure before three months of age, and who showed histological evidence of EMFE. In this family, two presumptive carrier females suffered subarachnoid haemorrhages, and one of these had radiological evidence of cerebral aneurysms. The possibility that this was a manifestation of the carrier state was discussed. There is no evidence to support this in the other X linked pedigrees, however, and it is not a feature in our family.

There are two further reports of pedigrees with X linked recessive inheritance of a cardiomyopathy where mitochondrial abnormalities have been demonstrated in the myocardium. In the family reported by Neustein *et al*<sup>6</sup> the proband died of heart failure at 16 months of age, and there was histological evidence of EMFE. Five other males in this family were found to have EMFE and in five out of these six cases electron microscopy demonstrated characteristic abnormalities of the mitochondria, particularly in the myocardium, but also in skeletal muscle, liver, and kidneys. The mitochondria were enlarged with increased numbers of cristae, and glycogen particles and dense bodies were found in the matrix. Histological myopathic change was found in the skeletal muscle of affected subjects.

Barth *et al*<sup>7</sup> described a large pedigree showing X linked inheritance of a mitochondrial disease characterised by dilated cardiomyopathy, neutropenia, and skeletal myopathy. Electron microscopy studies in these cases also showed abnormal mitochondria with concentric, tightly packed cristae and occasional inclusion bodies.

Although our tissue, from case III.12, had to be prepared for examination by electron microscopy in a far from ideal manner, having first been processed for light microscopy, the finding of mitochondrial features similar to those observed by Neustein *et al*<sup>6</sup> and Bath *et al*<sup>7</sup> in more appropriately processed biopsy material suggests that the features we have observed are not artefactual and that they are related to mitochondrial abnormalities present before the death of the patient.

The suggestion that there may have been skeletal muscle weakness in affected males in our pedigree is of interest in the light of the reports of Neustein *et*

*al*<sup>6</sup> and of Barth *et al*<sup>7</sup> suggesting that an X linked form of EMFE could be part of a generalised mitochondrial abnormality primarily involving myocardial function, with some effect on skeletal muscle function.

We suggest that our reported pedigree has enough similarities to those described by Neustein *et al*<sup>6</sup> and Barth *et al*<sup>7</sup> to suggest that the condition of mitochondrial cardiomyopathy found in the three families could be the same.

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