Heredity in primary endocardial fibroelastosis

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Twenty-six cases of endocardial fibroelastosis were collected from three hospitals in Manchester over a ten-year period. Nine cases occurred in 4 families and these are discussed in detail. X-linked recessive inheritance seems likely in one family in which two probable female carriers had subarachnoid haemorrhages. In a second family an apparently normal man produced two children with endocardial fibroelastosis by different mothers suggesting autosomal dominant inheritance with incomplete penetrance. Autosomal recessive inheritance may be involved in the remaining two families but this was not associated with consanguinity. Genetic heterogeneity is evident in endocardial fibroelastosis and the majority of cases occur sporadically. An accurate family history is therefore necessary but it is difficult to give precise recurrence risks in sporadic cases.

Primary endocardial fibroelastosis in more than one child in a family has been reported previously (Kelly and Andersen, 1956; Nielsen, 1965; Chen, Thompson, and Rose, 1971) though the exact mode of inheritance is not always clear. Various patterns of inheritance have been described, including autosomal recessive (Rosahn, 1955; Nielsen, 1965; Keith, Rowe, and Vlad, 1967), autosomal dominant (Hunter and Keary, 1973), and X-linked recessive (Fixler et al., 1970; Lindenbaum, Andrews, and Khan, 1973).

We have studied 26 patients with endocardial fibroelastosis and in this paper we describe 4 families including 9 patients with primary endocardial fibrosis with special reference to the mode of inheritance. The sporadic cases will not be discussed in detail here. All but one case was seen at one of the 3 main paediatric hospitals in Manchester between 1963 and 1973, but this series cannot be used to determine the incidence of endocardial fibroelastosis or the true proportions of familial and sporadic cases.

Case reports

The clinical and pathological data are seen in the Table.

Family 1 (Fig. 1)
Three members of this family are affected. They are all male, and include the proband and two of his maternal uncles.

Mrs. W. (I. 8) had 2 affected sons (II. 17 and 18), 2 unaffected daughters (II. 13 and 15), and 2 spontaneous abortions (II. 14 and 16).

Case 1 (II.17) Mrs. W.'s first son and fifth pregnancy at the age of 29 was a full-term normal delivery weighing 3.06 kg. The infant had exfoliative dermatitis and a urinary infection in the first week of life and was readmitted to hospital at 3 weeks with a history of cough, lethargy, cyanotic attacks, diarrhoea, and vomiting. Respirations were rapid and the pulse was 200/minute. He died 5 hours after admission.

Necropsy findings The infant weighed 3.4 kg. The heart weighed 56 g (normal 23 g) and both ventricles were strikingly dilated and hypertrophied. The endocardium of the left ventricle was opaque and histologically was thickened by fibrous and elastic tissue typical of endocardial fibroelastosis. The only other cardiac anomaly was the presence of several small bullae on the free margin of the cusps of the mitral valve. The lungs, liver, and spleen showed venous congestive changes and there was also evidence of bronchopneumonia.

Case 2 (II.18) Mrs. W.'s second son was born when she was 39 and was a full-term normal delivery at home weighing 3.48 kg. The infant was referred to the hospital at two weeks of age because of slight cyanosis and a heart murmur and was found to be in mild cardiac failure. He was cyanosed and had a loud third heart sound but no murmur was heard in hospital. Chest x-ray showed a large heart with pulmonary plethora though the electrocardiogram was within normal limits. He failed to respond to digitalis and diuretics and died 2 days after admission.

Necropsy findings The baby weighed 3.5 kg. The heart weighed 52 g (normal 23 g) and was enlarged predominantly by dilatation of the left ventricle. The left ventricular endocardium was thickened and possessed the histological characteristics of endocardial fibroelastosis
TABLE

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EFE = endocardial fibroelastosis; LV = left ventricle.

(Fig. 5). The foramen ovale was widely patent and the ductus arteriosus closed. There were also bilateral pleural effusions and pulmonary venous congestion. There were no other congenital malformations.

No virological or chromosomal studies were done in Cases 1 and 2. The mother (I.8) of Cases 1 and 2 died suddenly of a subarachnoid haemorrhage at the age of 41 years, two years after Case 2 was born. She was not hypertensive. Necropsy showed a large posterior fossa subarachnoid haemorrhage. There was no macroscopic intracerebral haemorrhage and no cerebral aneurysm was demonstrated.

Case 3 (III.3) This boy was the son of the sister of Cases 1 and 2. He was born by forceps delivery at 42 weeks gestation weighing 2.9 kg. His mother (aged 24) had her first pregnancy (twins) terminated by abdominal hysterotomy at 5 months after a subarachnoid haemorrhage. We have no information about these twins. The mother's carotid angiograms at the time of the haemorrhage showed left internal carotid and right middle cerebral aneurysms but at the time of the birth of Case 3, 28 months later, she had fully recovered from her haemorrhage without surgical treatment. The infant (III.3) had rapid respiration from birth and began to have cyanotic attacks on day eight when he was found to be in congestive cardiac failure with poor peripheral pulses but no murmurs were heard. However, at the
age of 6 weeks a grade 2/6 systolic ejection murmur was audible over the whole praecordium and x-ray showed a very large heart. Electrocardiography showed biventricular hypertrophy with gross ST depression in leads V1–3 and tall P waves in standard lead II. Cardiac catheterization and angiography showed an enlarged left ventricle with very poor function. A presumptive diagnosis of primary endocardial fibroelastosis was made. He was discharged on digoxin but remained in mild cardiac failure. He died suddenly at the age of 10 weeks.

Adenovirus type 1 was grown from his stools and the same virus was grown at necropsy from specimens of lung. Heart muscle was not cultured. No virus studies on the mother were carried out.

Necropsy findings The infant weighed 2.8 kg. The heart was very enlarged, globular in shape, and weighed 60.5 g (normal 19 g). The pericardial sac contained a small sanguineous effusion. The cardiomegaly was due mainly to dilatation of the left ventricle which was also mildly hypertrophied. The endocardium of both ventricles, but particularly the left, showed gross and histological changes typical of endocardial fibroelastosis (Fig. 6 and 7). There was no obstruction to the left ventricular outflow. The foramen ovale and the ductus arteriosus were both minimally patent. Both adrenal glands were small, weighing together 3 g (normal 10 g). Apart from some evidence of venous congestion the other organs were unremarkable.

Shortly after the death of Case 3 his mother became pregnant again. At her request she was terminated and sterilized at about 18 weeks partly on genetic grounds and partly in view of the risk of a further subarachnoid haemorrhage. The foetus was male and pathological examination of the heart showed no gross or histological evidence of endocardial fibroelastosis or any other disorder.

Family 2 (Fig. 2) These binovular twins (both girls) were their mother’s fourth pregnancy at age 33 and her first pregnancy by her second husband. She has 3 other children, all healthy boys, by her first husband. There is no family history of heart disease in infancy.

Twin 1 She was a full-term breech delivery weighing 2.78 kg. There was a history from the first few weeks of dyspnoea and cyanosis on feeding and slow weight gain. She was admitted to hospital at the age of 3 months and was found to be in congestive cardiac failure with a widely heard, grade 3/6, systolic murmur maximal at the apex and a soft apical mid-diastolic murmur. X-ray showed a very large heart and an electrocardiogram showed gross left ventricular and left atrial hypertrophy with a QRS axis of +30°. A diagnosis of endocardial fibroelastosis with mitral valve involvement was made.

Reasonable progress was made over the next few years on digoxin and she was able to go to school, her only symptom being mild dyspnoea on effort. She died suddenly at the age of 81 years after being admitted in congestive cardiac failure with right lower lobe collapse, pneumonia, and anaemia. Necropsy showed endocardial fibroelastosis involving the left ventricle and mitral valve. There were no other cardiac abnormalities. She also had right lower lobe collapse and pneumonia with early cardiac cirrhosis.

Twin 2 She was a full-term breech delivery weighing 2.8 kg. The clinical features were very similar to those of her sister when she was admitted to hospital in congestive cardiac failure a week after twin 1 at the age of 3 months.

X-ray demonstrated a very large heart and the electrocardiogram showed gross left ventricular hypertrophy with a QRS axis of +30°. A diagnosis of endocardial fibroelastosis was made.

Like her sister she progressed well on digoxin therapy and for a number of years was asymptomatic. She was admitted to hospital at the age of 64 years in severe cardiac failure with oliguria and anaemia. She failed to respond to treatment and died.

At necropsy she was found to have endocardial fibroelastosis. There was no other cardiac abnormality. No more specific details are available.

Family 3 (Fig. 3) In this family two children (a boy and a girl) with the same father and different mothers were both affected. Both mothers had a normal female child by a previous marriage. The father had no other children and there was no history of cardiovascular disease in the families of the husband or the wives.

Case 1 (propositus) He was the mother’s second child and the father’s first. He was a normal full-term delivery following an uneventful pregnancy and weighed 3.8 kg. He progressed well until just before admission at 3 months with a history of lethargy and dyspnoea, and cyanosis during feeding. He was in congestive cardiac failure with normal heart sounds and no murmurs. Chest x-ray showed gross cardiac enlargement and increased vascular pulmonary markings. An electrocardiogram showed left ventricular hypertrophy. He improved on...
digitalis therapy but repeated hospital admission for chest infections followed.

His first such admission to hospital was at 3 years of age when he was in severe congestive cardiac failure with gross mitral incompetence. The apical systolic murmur was first noted at 9 months of age.

Left ventriculography showed a dilated and normally contractile left ventricle with a normal aortic arch and outflow tract but with gross mitral regurgitation. He was referred for surgical treatment but died during the induction of the anaesthesia. Necropsy showed a hypertrophied and dilated left ventricle with endocardial fibroelastosis. The valves were normal and there were no other cardiac abnormalities. No viral or chromosomal studies were done and there were no other congenital abnormalities.

Case 2 She was the father's second child and the second child of his second wife, but her first by this marriage. The infant was delivered normally at 41 weeks gestation and weighed 2.4 kg. She fed poorly from birth, was pale, and was admitted to hospital at the age of 5 months with a 24-hour history of fever, vomiting, dyspnoea, and restlessness. On examination she was very dyspnoeic and in congestive cardiac failure. She had a triple rhythm but no murmurs were heard. Chest x-ray showed gross cardiomegaly. She was treated with digitalis, diuretics, and nursed in oxygen but collapsed and died 6 hours after admission.

Necropsy showed endocardial fibroelastosis of the left ventricle but no other cardiac abnormality. There was collapse and consolidation of the right upper lobe and congestion of the lungs, liver, and spleen. No viral or chromosomal studies were done and there were no other congenital abnormalities.

Family 4 (Fig. 4)

Case 1 This family's first child was a boy who died at the age of 9 months after being admitted to hospital with pneumonia. Endocardial fibroelastosis had not been suspected. Necropsy showed a large globular heart with endocardial fibroelastosis of the left ventricle.

A third pregnancy resulted in an unexplained macerated male stillbirth at five months gestation. There was no previous family history of congenital heart disease.

Case 2 (propositus) The second affected child (fifth pregnancy) was a girl who was a full-term normal delivery weighing 3.03 kg and was born 8 years after the first affected child. She was admitted to hospital with a 1-day history of vomiting, feeding difficulty, and an attack of pallor and sweating. On examination she had a pulse of 190, intercostal indrawing, and some basal crepitations but no murmurs. The liver was not enlarged. An electrocardiogram showed a QRS axis of +120° and inverted T waves over the precordial leads but no other evidence of left or right ventricular enlargement. She responded poorly to digoxin and ampicillin and died three weeks after admission. No chromosomal or viral studies were done. Necropsy showed an enlarged heart with endocardial fibroelastosis of the left ventricle also affecting the posterior papillary muscle.

Histologically the right ventricle was normal. The left ventricular myocardium was mildly atrophic and reduced in thickness and covered by endocardium greatly thickened by a proliferation of fibrous and elastic tissue characteristic of congenital endocardial fibroelastosis. No anomaly of the coronary arteries or other defect was noted. The other bodily organs were unremarkable.

The second and fourth pregnancies produced two normal boys.

Comment

We studied 26 patients with primary endocardial fibroelastosis who by definition had no other cardiac abnormalities or whose abnormalities were trivial and unlikely to lead to secondary endocardial fibroelastosis. Necropsies were performed on all 9 patients with a family history and on the 9 out of 17 sporadic cases who had died. In the surviving sporadic cases the diagnosis of endocardial fibroelastosis has been made clinically. Nearly all the patients who had necropsies had endocardial fibroelastosis of the left ventricle only, the exception being Case 3, Family 1, who had fibroelastosis of both ventricles. All cases were of the dilated type.

No other congenital abnormalities were detected with the exception of one girl who died at the age of 8 months with Niemann-Pick's disease and endocardial fibroelastosis of the left ventricle. Endocardial fibroelastosis has not been reported before in association with this lipid storage disorder though it has been seen in glycogen storage disease of the heart (Hudson, 1965-1970).

The characteristic features of endocardial fibroelastosis will only be discussed briefly, as our cases correspond well with those described in the reviews by Kelly and Andersen (1956), Sellers, Keith, and Manning (1964), and others. Most of our cases presented in the first year of life with respiratory infections, congestive cardiac failure, and failure to thrive. Most died rapidly but a few responded to digoxin and other measures and survived for varying periods up to 8 years. One girl who presented at 3 months and who is now 5 years old no longer requires digoxin and is clinically well with a normal chest x-ray and electrocardiogram. However, most cases died suddenly or developed fatal respiratory infection. Viral studies were not often
done but Case 3 from Family 1 had an adenovirus in his stools at 1 week of age and the same virus was grown from the lungs after his death 9 weeks later. One of the sporadic cases died of pneumonia and a Coxsackie B type 3 was grown from the right upper lobe while another had an adenovirus grown from the throat on the day of death. Chromosomal studies were not always carried out but those that were done were all normal. Twin I of Family 2 had a normal female karyotype with prominent satellite formation on one member of the 13-15 group. Her twin sister did not have chromosomal studies.

Discussion
The normal endocardium is thin and transparent. Endocardial fibroelastosis is characterized by a proliferation of dense collagenous and elastic tissue which gives the endocardial surface a pale, opaque or ‘porcelain’ appearance. The elastic fibrils are arranged in an orderly pattern parallel to the luminal surface and in most areas they predominate over the collagenous component (Fig. 5). The muscular trabeculae are not destroyed by this process but tend to be accentuated by tongue-like extensions of the thickened endocardium into the myocardium (Fig. 6 and 7). When ventricular dilatation is prolonged a smooth muscle component may be present within the endocardium, but this was not observed in any of the cases in the present series. The histological features of congenital fibroelastosis are pathognomonic especially with regard to the regular arrangement of the elastic fibrils, and a clear distinction can be made between this condition and the non-specific, usually focal form of endocardial thickening commoner in adult hearts particularly in relation to myocardial infarction or hypertension.

Aetiology
Current theories on the aetiology of endocardial fibroelastosis have recently been summarized by Harris and Nghiem (1972). Virus infection, particularly mumps, Coxsackie B3, echovirus, and rubella have been implicated. According to this theory, children with viral myocarditis recover from the inflammatory phase of the disease to enter a proliferative stage which leads to endocardial sclerosis (Rowe and Mehrizi, 1968). The role of the mumps virus is particularly controversial, there being widely varying reports on the frequency of positive mumps skin tests in cases of endocardial fibroelastosis, and only one woman with mumps during the first trimester of pregnancy has been known to have had a child who at 22 months developed fibroelastosis (St. Geme et al., 1971). St Geme et al. also produced an endocardial fibroelastosis-like lesion in chickens after inoculating

**FIG. 5** Family 1, Case 2. Section of left ventricular endocardium which is composed of dense elastic fibrils regularly arranged parallel to the luminal surface, on the right together with collagen. Myocardium is just visible on the left. (Elastic van Gieson. × 362.)
eggs with mumps virus. Mumps skin tests were not done in our cases. In one of our sporadic cases Coxsackie B3 was isolated from the lung (probably the cause of pneumonia and unrelated to the endocardial fibroelastosis), and adenovirus type 1 was grown from Case 3 in Family 1, both pre- and post-necropsy. In this latter case hereditary factors appear to be particularly clear and the occurrence of the virus is probably an incidental finding but might represent an environmental trigger in a susceptible genotype.

Familial endocardial fibroelastosis
Primary endocardial fibroelastosis has on several occasions been described in more than one member of a family. Kelly and Andersen (1956) found more than one case in 2 of 14 families (14%), while Chen et al. (1971) in 119 families observed 9 in which 2 or more cases occurred (8%). In our data, 4 of 21 families had 2 or more cases (19%).

It is extremely difficult to obtain an accurate incidence for this disease as many patients die suddenly at home and even at necropsy the lesion, unless suspected, may be missed by an inexperienced examiner. When more than one case occurs in a family, ascertainment is more likely and we feel that the true frequency of familial cases is probably lower than our figure suggests. However, an unknown proportion of single cases in small families may be genetically determined.

Genetic heterogeneity
Some cases are almost certainly genetically determined. In our Family 1, X-linked inheritance is likely; the male proband (Case 3 – III.3) having had two affected maternal uncles (Cases 1 and 2 – II. 17 and 18). The mother (I.8) had two abortions and
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FIG. 7 Family 1, Case 3. Section to show how the muscular trabeculae are partially surrounded by tongues of fibroelastic tissue extending from the thickened endocardium. (Elastic van Gieson. × 58.)

her sister (II.11) had 5 abortions suggesting a genetic abnormality though the sex of the abortions was not recorded. Of additional interest in our family I is the fact that both mothers (I.8 and II.13) had possibly coincidental subarachnoid haemorrhages. Though a cerebral aneurysm could not be demonstrated in a post-mortem examination of the grandmother (I.8) of the proband it is not uncommon for a large subarachnoid haemorrhage to disrupt and mask the presence of an aneurysmal sac. Two cerebral aneurysms were detected by a carotid angiography in her daughter (II.13), the mother of the proband.

Two families with probable X-linked inheritance have previously been reported. Fixler et al. (1970) described a boy with two uncles with the contracted type of endocardial fibroelastosis, no other member of the family being affected. Lindenbaum et al. (1973) reported two affected males linked by a chain of normal female relatives with a number of males dying of respiratory symptoms which could have been attributed to endocardial fibroelastosis. Familial cases of cerebral aneurysms have recently been reviewed (Bannerman, Ingall, and Graf, 1970; Kak, Gleadhill, and Bailey, 1970), but only 47 cases could be found. Dominant inheritance is possibly involved in some families (Beumont, 1968), though no instances were included of a mother and daughter with cerebral aneurysms and there was no mention of endocardial fibroelastosis in the families.

In our Family No. 2, binovular twin girls and in Family No. 4 a brother and sister were affected. X-linked recessive inheritance is extremely improbable and in the absence of consanguinity autosomal recessive inheritance can only be suggested as a possibility. However, in Family 3 one man produced a child with endocardial fibroelastosis by two different women with a gap of four years. Since one of these children was a male, X-linked recessive inheritance from the father is impossible though autosomal dominant inheritance involving a gene with wide variation in expression cannot be excluded. In the absence of admitted consanguinity it seems unlikely that he as well as both of his wives are carriers of the same rare autosomal recessive. The parents refused investigation of any kind.

Case 3 from Family 1 was distinct in that both adrenal glands were hypoplastic. The infant had not received steroid therapy and it is reasonable to assume that the adrenal hypoplasia was congenital. Though there is no established association between endocardial fibroelastosis and adrenal hypoplasia, it is interesting that in a recent account of 10 children with idiopathic adrenal hypoplasia (Favara, Franciosi, and Miles, 1972) there were two infants
(Cases 2 and 3) who were shown to have endocardial fibroelastosis at necropsy. One was a boy of 4 months and the other his sister aged 3½ months. Both died suddenly and unexpectedly.

In conclusion, though the majority of cases of endocardial fibroelastosis have no family history we have obtained evidence for X-linked recessive, incompletely penetrant autosomal dominant, and perhaps autosomal recessive inheritance.

**Prognosis**

The prognosis of the familial type appears to be particularly bad. Thus, all the children in our series died early in the first year of life with the exception of Case 1 in Family 3 who died while under a general anaesthetic at 3 years of age and Family 2 where binovular twin girls lived until 6½ and 8½ years, respectively. However, it is possible that endocardial fibroelastosis in these binovular twins resulted from non-genetic causes since there was no other family history.

The prognosis within each family was fairly consistent except in Family 3. Rowe and Mehrizi (1968) have pointed out that the prognosis is very poor in babies presenting with the disease in the first month of life. This occurred in half of our familial cases. There are, however, many recorded instances of infants surviving the initial illness and living up to or beyond puberty and we have already mentioned a 5-year-old girl who is now clinically normal. It is hardly surprising that the prognosis is so variable since endocardial fibroelastosis probably occurs in response to a number of different aetiological factors (see above). Some of the long-term survivors may have had viral myocarditis from which they eventually recovered completely, emphasizing the need for vigorous medical treatment with digitalis and sometimes diuretics. Surgical treatment may occasionally be necessary to correct endocardial deformities resulting from endocardial fibroelastosis and one of our cases (Case 1, Family 3) was submitted for mitral valve replacement but died during induction of anaesthesia. Others have reported a child who first presented with endocardial fibroelastosis at 2 years of age and developed severe mitral incompetence successfully treated by mitral valve replacement at the age of 11 (Harris and Nghiem, 1972).

We would like to thank the many paediatricians in the Manchester area who allowed us to study patients under their care and the pathologists who gave us access to necropsy reports and material. They are too numerous to mention personally. We would particularly like to thank Mrs. Edith Quinn for obtaining the pedigrees in Family 1, and Dr. E. G. Wade for his encouragement.

**References**


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