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# Two cases of endocardial fibroelastosis—possible X-linked determination

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*Two related male infants succumbed to the primary dilated type of endocardial fibroelastosis; 4 other male relatives had died in infancy. The pedigree is compatible with segregation of an X-linked recessive gene.*

This report concerns a family whose pedigree is shown in the Figure.

## The family: case histories

i) On account of severe iron-deficiency anaemia, the mother of the propositus was transfused in the mid-trimester; her son (IV.8) was born at term, weighing 2730 g. He suffered transient neonatal hypoglycaemia, but was otherwise well, till at 6 weeks he refused feeds and started coughing. On hospital admission he was breathless, with a large heart and liver, and an electrocardiogram showed left ventricular hypertrophy; no murmur was heard. Despite treatment, he died in heart failure three days later.

Necropsy showed a large heart (60 g); in particular, the left ventricle was dilated, with a grossly thickened wall (16 mm); this was lined by dense white endocardium which, microscopy showed, extended at places into the adjacent muscle; the muscle cells were hypertrophied and oedematous – the changes of endocardial fibroelastosis. The liver was intensely green and swollen, and sections showed subacute hepatitis, intrahepatic cholestasis, and chronic venous congestion; the biliary tree was patent. No abnormalities were observed elsewhere.

ii) It was learned that a male first cousin of the mother's had died in similar circumstances. This child (III.9) had weighed only 2260 g at birth at term, after a normal pregnancy. He was well until at 14 weeks he began coughing and vomiting; he was later admitted to hospital in heart failure and died, despite treatment, aged 15 weeks.

Necropsy (Dr. H. J. Voss) showed left ventricular dilatation, and thickened endocardium extending into the myocardium, with muscle cell hypertrophy in this area (left ventricle wall thickness 15 mm). The left kidney was hypoplastic; no other abnormalities were noted.

iii) Other family members – the great-grandmother of the propositus had borne 4 daughters, all presently well, and 4 sons, all of whom had died in the first two years of life. Only fragmentary information was available on the deceased infants, from the General Register Office, Somerset House, and from parish records. No necropsies had been performed, and all available information is given below.

- II.3 Born out of wedlock; half-brother to the other males. Died in 1911, aged 2 years. Death certificate 'Acute bronchitis', 'duration of illness 8 days'.
- II.7 Died in 1927, aged 15 days. Death certificate 'Bronchopneumonia'.
- II.8 Died in 1929, aged 6 months. Death certificate 'Bronchopneumonia'.
- II.10 Died in 1933, aged 4 days. Death certificate 'Natural causes. Convulsions'.

Other deaths in childhood –

- III.6 A female and a non-identical twin died aged 3 years, after encephalitis.

iv) Chest *x*-rays and electrocardiograms were performed on the mother (19 years), father (20 years), and sister (22 months) of the propositus; no abnormality was found, except for a slight left ventricular hypertrophy in the father (S in V2+R in V6=42 mm).

## Discussion

J. E. Edwards (1960) classifies endocardial fibroelastosis into primary and secondary types – the latter associated with obstructions to left ventricular outflow, septal defects, and anomalies of the left coronary artery; independent of this classification is a recognition of dilated and contracted types, based on left ventricular size at necropsy. Endocardial fibroelastosis is usually clearly differentiated from the cardiomyopathies, which are often inherited as autosomal dominants (Paré *et al.*, 1961; Boyd *et al.*, 1965; Horlick, Petkovich, and Bolton, 1966), and occasionally as autosomal recessives (Battersby and Glenner, 1961); sometimes considerable endocardial

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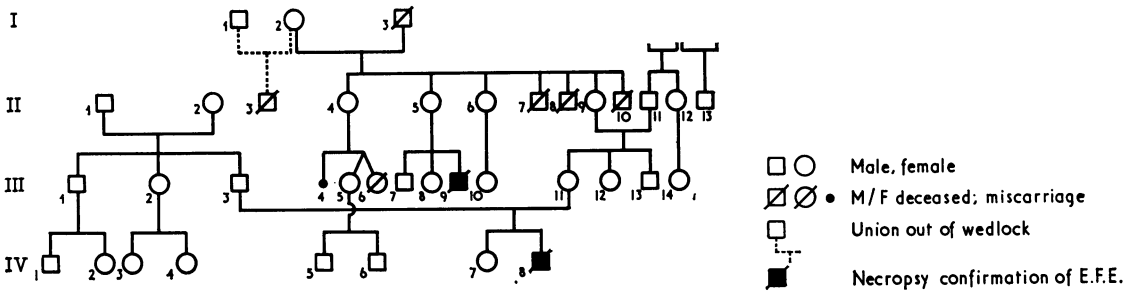


FIGURE

fibroelastosis is found together with other signs of cardiomyopathy. Ninety-five per cent of cases of primary endocardial fibroelastosis are of the dilated type (Fixler *et al.*, 1970). McKusick (1971) considers it uncertain that the genetics of the dilated and contracted forms differ, but most of the genetic studies to date have been of the former type. This was the type found in the infants described here; they were free of other congenital anomalies, except for one with a hypoplastic left kidney.

As part of the U.S. National Perinatal Study, Mitchell *et al.* (1966) found 7 cases of primary fibroelastosis (dilated type) among 41,078 live births, or approximately 1 in 6000. Though many cases are sporadic, Chen, Thompson, and Rose (1971) found that 17 out of 128 cases studied came from sibships with 2 or 3 affected infants, i.e. fibroelastosis occurred between 600 and 1000 times as often among the sibs of affected children, as in the general population. They found no satisfactory single explanation of such sibship associations: sibship analysis did not support a recessive gene hypothesis, and in only 2 of 119 familes were the parents consanguineous; neither did the data fit a multifactorial model, by the tests of J. H. Edwards (1960) and of Carter (1965). Though mumps virus can produce fibroelastosis in chicks (St. Geme *et al.*, 1971), Chen *et al.* found no epidemiological evidence favouring a viral aetiology, and further evidence against a viral origin is presented in Mitchell's paper. The only report suggesting X-linked inheritance of primary fibroelastosis concerns a family with the 'contracted' type (Fixler *et al.*, 1970). Moller *et al.* (1966) reported an affected mother and son.

From the family described in our paper, two affected infants were certainly identified; they were both male, and linked by a chain of normal female relatives (III.11, II.9, and II.5). Such a pedigree is consistent with transmission of an X-linked recessive gene from a carrier I.2. Had I.2 been such a carrier, each of her 4 sons ran a 50 per cent chance of being affected. All 4 died young; the deaths of some could be attributed to fibroelastosis, since respiratory symptoms (in II.3, II.7, and II.8?) are the commonest presenting feature of the condition. Had proof been available that any of these males had fibroelastosis, the evidence for X-linkage in this family would be extremely strong. In the absence of such evidence, other arguments can be adduced, in which the existence of the sons of I.2 is assumed to be non-contributory (data from Chen *et al.*, 1971).

i) Given that a pair of affected 4th-degree relatives are found in a family, the probability that they are both male, and linked by normal females, is $(5/13)^2 . (1/2)^3$, which $\approx 1/54$ (where the sex ratio among affected is 5 male:8 female).

ii) The probability of obtaining exactly the observed distribution of affected and non-affected, male and female, within the pedigree, can be calculated for given modes of inheritance, or given a random distribution of affected infants.

A) X-linked recessive (assumes I.2 a carrier) (probability of observed pedigree: $P_{ped}$)
$P_{ped} = 1/13, 828, 096.$

B) Autosomal dominant, with diminished and sex-influenced penetrance (I.1 or I.2 a carrier)
$P_{ped} = 1/644, 380, 256.$

C) Autosomal recessive (I.1 or I.2 a carrier)
$P_{ped} = 1/15, 907, 497, 940.$

D) Random basis (fits viral origin, or multifactorial model with 4th-degree relatives affected)
$P_{ped} = 1/166, 458, 240, 000.$

i.e. P (A) is about 50 times P (B), 1000 times P (C), and 10,000 times P (D).

From the data of Chen *et al.*, the recurrence risk is 1 in 6 per pregnancy; with X-linked transmission, the risk is 1 in 4, but only males will be affected. Furthermore, X-linked transmission would put some other family members at fairly high risk of having affected infants.

The origins of endocardial fibroelastosis are diverse; this is implied by the present failure to find a simple hypothesis satisfying all the data on familial aggregation. A small proportion of cases may be determined by X-linked genes.

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