Ebstein's anomaly

Genetic study of 26 families

Richard Emanuel,¹ Kay O'Brien, and Richard Ng

From National Heart Hospital, The Middlesex Hospital, and Cardiothoracic Institute

The families of 26 patients with Ebstein's anomaly were examined. There were 120 first-degree relatives, 100 of whom were living, and 93 of these were examined. Information was available on 14 of the 20 who had died. No case of Ebstein's anomaly was found among the first-degree relatives, but 2 had ventricular septal defects and another, who died at 7 months, was said to have had congenital heart disease. In more distant relatives there were 6 with congenital heart disease, including 2 with ventricular septal defects and 2 with Fallot's tetralogy.

The tendency for congenital heart disease to occur in more than one member of a family has been recognized for many years (Polani and Campbell, 1955; Lamy, de Grouchy, and Schweisguth, 1957; Carleton, Abelman, and Hancock, 1958).

Family studies have been undertaken in many of the common forms of isolated congenital heart disease. These include cardiomyopathy (Evans, 1949; Paré *et al.*, 1961; Barry and Hall, 1962; Emanuel, Withers, and O'Brien, 1971), persistent ductus arteriosus (Polani and Campbell, 1960; Wilkins, 1969), coarctation of the aorta (Campbell and Polani, 1961a), secundum atrial septal defect (Campbell and Polani, 1961b; Zuckerman *et al.*, 1962; Nora, McNamara, and Fraser, 1967; Williamson, 1969; Emanuel *et al.*, 1975), pulmonary stenosis (Campbell, 1962), situs inversus (Campbell, 1963), congenital aortic stenosis (Zoethout, Bonham-Carter, and Carter, 1964), ventricular septal defect (Campbell and Goodwin, 1965), atrioventricular defects (Emanuel *et al.*, 1968), transposition of great vessels and pulmonary atresia (Fuhrmann, 1968), and Fallot's tetralogy (Boon, Farmer, and Roberts, 1972), and it has been possible to quantitate genetic factors in both secundum atrial septal defects and atrioventricular defects.

The familial incidence of Ebstein's anomaly has not been studied though more than one case in a single family has been reported on several occasions. Gueron *et al.* (1966) reported a 20-year-old man with Ebstein's anomaly who died of cardiac failure,

and a 12-year-old sister similarly affected. Both diagnoses were confirmed at necropsy. Donegan *et al.* (1968) reported a 6-year-old boy with a 29-year-old maternal uncle with Ebstein's anomaly, in both of whom the diagnosis was confirmed by cardiac catheterization without angiography. Simcha and Bonham-Carter (1971) noted 2 families: in one a father and daughter, and in the other 2 brothers were affected, but no investigations were reported; and Watson (1974), in his assembled series of 505 cases, found another family in which 2 sisters were diagnosed clinically as having Ebstein's anomaly.

The present study was undertaken to assess the familial incidence of Ebstein's anomaly and to determine the frequency of other congenital cardiac defects in the first-degree relatives. In view of the frequent association of Ebstein's anomaly and secundum atrial septal defect in individual cases, the presence or absence of atrial septal defects in the first degree relatives was of particular interest.

Subjects and methods

Data on the probandi and first-degree relatives were collected as in previous studies (Emanuel *et al.*, 1968, 1971, 1975). There were 26 probandi from the National Heart Hospital, The Middlesex Hospital, and The Hospital for Sick Children. Clinically, all had the classical features of Ebstein's anomaly. In 9 the diagnosis was confirmed by cardiac catheterization and angiocardiology and in 2 by cardiac catheterization alone. In a further 11 the anatomy was examined at either operation (5) or necropsy (6). The remaining 4 probandi were not investigated, but accepted on clinical

Received 26 June 1975.

¹In receipt of a grant from the British Heart Foundation.

grounds. The age range was 5 to 65 years, with a mean of 17.6 years.

There were 65 siblings, 51 of whom were living and 14 dead. Forty-six of the living siblings were examined and this included a chest radiograph and an electrocardiogram. Diagnostic information was available on 10 of the 14 who had died. Of the 52 parents, 46 were living and of these 44 were similarly examined. Six had died and diagnostic information was available on 4. There were 3 children, and all were examined. Diagnostic information was, therefore, available on 107 (89%) of the 120 first-degree relatives.

Results

None of the first-degree relatives had Ebstein's anomaly, but ventricular septal defects were present in one sibling and one child. Another sibling, who died in infancy, was said to have had congenital heart disease, but no further information was available.

In more distant relatives, a ventricular septal defect was present in 2, in one of whom the diagnosis was confirmed at necropsy and in the other by cardiac catheterization and angiocardiography. A further 2 relatives had Fallot's tetralogy which was surgically corrected in both. Two other relatives may also have had congenital heart disease but neither was investigated (Table).

There was no incidence of consanguinity between the parents. Information relating to pregnancy was obtained from all 26 mothers; 108 pregnancies were reported, 15 (13.8%) of which ended in miscar-

riages. In addition there were 2 stillbirths. These figures are well within the accepted range quoted by Logan (1959).

Conclusion

There was no evidence of a familial incidence of Ebstein's anomaly in these 26 families, and no relative with an isolated secundum atrial septal defect. The frequency of congenital heart disease in first-degree relatives was considerably higher at 2.8 per cent (3 out of 107) than in the general population, 0.05–0.07 per cent (Carlgren, 1959; McKeown and Record, 1960; Mustacchi, Sherins, and Miller, 1963; Smithells, 1968). This finding was in keeping with the results from other family studies of isolated congenital heart disease.

The frequency of ventricular septal defects in these families, either as a simple lesion (4 cases) or as part of Fallot's tetralogy (2 cases) was noted, but no embryological explanation for this association could be found.

We are grateful to Dr. R. E. Bonham-Carter for access to a number of patients who were originally seen at The Hospital for Sick Children, Great Ormond Street, London.

References

- Barry, M., and Hall, M. (1962). Familial cardiomyopathy. *British Heart Journal*, **24**, 613.

TABLE Congenital heart disease in 9 affected relatives

Relationship and sex	Diagnosis	Method or source of diagnosis
<i>First degree</i>		
1. Sibling (M)	Ventricular septal defect	Clinical*
2. Sibling (F)	'Congenital heart disease'	Death certificate (died at 7 months)
3. Child (M)	Ventricular septal defect	Cardiac catheterization and angiocardiography
<i>Second degree</i>		
4. Niece	Ventricular septal defect	Cardiac catheterization and angiocardiography
5. Maternal uncle	'Congenital heart disease'	Death certificate (died at 6 months)
<i>Third degree</i>		
6. First cousin (M)	Ventricular septal defect	Necropsy
7. First cousin (M)	Pulmonary valve stenosis	Clinical*
<i>Others</i>		
8. (M)	Fallot's tetralogy	Surgery
9. (M)	Fallot's tetralogy	Surgery

*Clinical investigations = physical examination, electrocardiography, and a chest radiograph but excludes haemodynamic investigations.

- Boon, A. R., Farmer, M. B., and Roberts, D. F. (1972). A family study of Fallot's tetralogy. *Journal of Medical Genetics*, **9**, 179.
- Campbell, M. (1962). Factors in the aetiology of pulmonary stenosis. *British Heart Journal*, **24**, 625.
- Campbell, M. (1963). The mode of inheritance in isolated laevocardia and dextrocardia and situs inversus. *British Heart Journal*, **25**, 803.
- Campbell, M., and Goodwin, J. (1965). Some factors in the etiology of ventricular septal defect. *Progress in Cardiovascular Diseases*, **7**, 417.
- Campbell, M., and Polani, P. E. (1961a). The aetiology of coarctation of the aorta. *Lancet*, **1**, 463.
- Campbell, M., and Polani, P. E. (1961b). Factors in the aetiology of atrial septal defect. *British Heart Journal*, **23**, 477.
- Carleton, R. A., Abelman, W. H., and Hancock, E. W. (1958). Familial occurrence of congenital heart disease. *New England Journal of Medicine*, **259**, 1237.
- Carlgen, L.-E. (1959). The incidence of congenital heart disease in children born in Gothenburg 1941-1950. *British Heart Journal*, **21**, 40.
- Donegan, C. C., Jr., Moore, M. M., Wiley, T. M., Hernandez, F. A., Green, J. R., Jr., and Schiebler, G. L. (1968). Familial Ebstein's anomaly of the tricuspid valve. *American Heart Journal*, **75**, 375.
- Emanuel, R., Nichols, J., Anders, J. M., Moores, E. C., and Somerville, J. (1968). Atrioventricular defects—a study of 92 families. *British Heart Journal*, **30**, 645.
- Emanuel, R., O'Brien, K., Somerville, J., Jefferson, K., and Hegde, M. (1975). Association of secundum atrial septal defect with abnormalities of atrioventricular conduction or left axis deviation. Genetic study of 10 families. *British Heart Journal*, **37**, 1085.
- Emanuel, R., Withers, R., and O'Brien, K. (1971). Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet*, **2**, 1065.
- Evans, W. (1949). Familial cardiomegaly. *British Heart Journal*, **11**, 68.
- Fuhrmann, W. (1968). A family study in transposition of the great vessels and in tricuspid atresia. *Humangenetik*, **6**, 148.
- Gueron, M., Hirsch, M., Stern, J., Cohen, W., and Levy, M. J. (1966). Familial Ebstein's anomaly with emphasis on the surgical treatment. *American Journal of Cardiology*, **18**, 105.
- Lamy, M., de Grouchy, J., and Schweisguth, O. (1957). Genetic and non-genetic factors in the etiology of congenital heart disease: a study of 1188 cases. *American Journal of Human Genetics*, **9**, 17.
- Logan, W. P. D. (1959). Vital statistics of reproduction. In *British Obstetric and Gynaecological Practice*, 2nd ed., Vol. 2, p. 1195. Ed. by E. Holland. Heinemann, London.
- McKeown, T., and Record, R. G. (1960). Malformations in a population observed for five years after birth. In *CIBA Foundation Symposium on Congenital Malformations*, p. 2. Ed. by G. E. W. Wolstenholme and C. M. O'Connor. Churchill, London.
- Mustacchi, P., Sherins, R. S., and Miller, M. J. (1963). Congenital malformations of the heart and the great vessels. *Journal of the American Medical Association*, **183**, 241.
- Nora, J. J., McNamara, D. G., and Fraser, F. C. (1967). Hereditary factors in atrial septal defect. *Circulation*, **35**, 448.
- Paré, J. A. P., Fraser, R. G., Pirozynski, W. J., Shanks, J. A., and Stubington, D. (1961). Hereditary cardiovascular dysplasia. A form of familial cardiomyopathy. *American Journal of Medicine*, **31**, 37.
- Polani, P. E., and Campbell, M. (1955). An aetiological study of congenital heart disease. *Annals of Human Genetics*, **19**, 209.
- Polani, P. E., and Campbell, M. (1960). Factors in the causation of persistent ductus arteriosus. *Annals of Human Genetics*, **24**, 343.
- Simcha, A., and Bonham-Carter, R. E. (1971). Ebstein's anomaly: clinical study of 32 patients in childhood. *British Heart Journal*, **33**, 46.
- Smithells, R. W. (1968). Incidence of congenital abnormalities in Liverpool, 1960-64. *British Journal of Preventive and Social Medicine*, **22**, 36.
- Watson, H. (1974). Natural history of Ebstein's anomaly of tricuspid valve in childhood and adolescence. An international co-operative study of 505 cases. *British Heart Journal*, **36**, 417.
- Wilkins, J. L. (1969). Risks to offspring of patients with patent ductus arteriosus. *Journal of Medical Genetics*, **6**, 1.
- Williamson, E. M. (1969). A family study of atrial septal defect. *Journal of Medical Genetics*, **6**, 255.
- Zoethout, H. E., Bonham Carter, R. E., and Carter, C. O. (1964). A family study of aortic stenosis. *Journal of Medical Genetics*, **1**, 2.
- Zuckerman, H. S., Zuckerman, G. H., Mammen, R. E., and Wassermil, M. (1962). Atrial septal defect: familial occurrence in four generations of one family. *American Journal of Cardiology*, **9**, 515.

Requests for reprints to Dr. R. Emanuel, Cardiothoracic Institute, 2 Beaumont Street, London W1N 2DX.