Twin studies in hypertrophic cardiomyopathy

W. A. Littler

From the Cardiac Department, The Radcliffe Infirmary, Oxford

The details of three sets of twins, all with hypertrophic cardiomyopathy, are presented. Twins A were monozygotic and concordant and showed haemodynamic evidence of outflow tract obstruction. The lack of family history suggests a recessive mode of inheritance or a single gene mutation with dominant effect as the cause. Twins B were also monozygotic and concordant, but the rate of progression of their condition was different, one remaining well, the other developing atrial fibrillation and congestive cardiac failure. Twins C were dizygotic, the male member had died suddenly from hypertrophic cardiomyopathy as had his two young sons; the female member and her children are symptomless. The family history suggests a strongly penetrant autosomal dominant inheritance. Our observations suggest that hypertrophic cardiomyopathy could sometimes result from a single gene mutation and that the prenatal environment may be important in determining the expression of the gene and the rate of progression of the condition in adult life.

Cardiomyopathy arises in two main forms, primary congestive and primary hypertrophic. Goodwin (1970) has defined the latter as 'an inherited disorder of ventricular muscle growth leading to irregular contraction and abnormal excessive hypertrophy and fibrosis which is characterized by progressively increasing resistance to filling of the left ventricle, and, in most patients, by incidental outflow tract obstruction'.

The disease may exist in familial or sporadic forms (Braunwald *et al.*, 1964), the former comprising approximately one-third of the cases in most large series (Frank and Braunwald, 1968; Goodwin, 1968). In Braunwald's series, patients with the familial disease tended to be younger and less disabled and their outflow tract pressure gradients tended to be lower or were more frequently absent when compared with the sporadic form of the disease. However, other workers have not found such a clear distinction between the familial and sporadic forms (Swan *et al.*, 1971).

In the majority of pedigrees that have been documented the responsible gene appears to behave as an autosomal dominant with strong penetrance; the most remarkable example being a French-Canadian family starting in the seventeenth century and documented by Paré and his colleagues (1961). However, recently Emanuel, Withers, and O'Brien (1971) have produced evidence in favour of

an autosomal recessive mode of inheritance in some cases of 'idiopathic' cardiomyopathy.

Reports of twins with this condition are rare, but this probably only reflects the incidence of twin births in the population. This report records what are believed to be the first documented cases of monozygotic twins with hypertrophic obstructive cardiomyopathy and then reassesses two other sets of twins who have previously been included in a group of patients with hypertrophic cardiomyopathy reported from this centre (Karatzas, Hamill, and Sleight, 1968).

Patients

Twins A There is a probability of 0.007 that they are dizygotic. They have similar facies and eye colour and their heights differ by 3 cm. Their total ridge counts (fingers) differ by 12 and their palmar *atd* angles differ by 1°. They are alike for the following blood groups: A₁; R₁₁; Kell negative; F_{ya} positive; Jk^a negative; NNss; P₁ positive; Le^a negative; Lu^a negative. (The calculation of probabilities is based on the method of Smith and Penrose (1954-55). They were the youngest of four children born to a non-consanguineous marriage; their mother had died at the age of 50 years from a cerebral neoplasm.

The twins were referred to this centre after a cardiac murmur had been noted at a routine school medical examination. They were symptomless, active boys who regularly took part in competitive sports.

The main findings of the physical examination, cardiac catheterization, and angiocardiography

TABLE 1

Twins	Presentation	Symptoms	Main physical findings	Family history	Electrocardiogram	Chest x-ray
A	Routine medical	None	Sinus rhythm, jerky pulse, third heart sound, ejection systolic murmur at left sternal edge	None	LV + (voltage), T flat aVF	LV + (slight), LV irregular shape
					T flat III, aVF	LV + (slight)
B	Routine chest x-ray	None	Sinus rhythm, jugular venous pressure 4 cm, large 'a', RV +, A ₂ P ₂ widely split, ejection systolic murmur at left sternal edge	Probably	RBBB	Cardiomegaly, RV +, LA +
		None initially, now grade 3	Central cyanosis, atrial fibrillation, jugular venous pressure 8 cm, RV +, LV +; A ₂ P ₂ widely split; third heart sound, ejection systolic murmur		RBBB, flat ST, segments I, II, III, aVF, and V ₂ -V ₆	Cardiomegaly +, RV ++, LV +, LA +
	II.4 Sudden death, necropsy showed hypertrophic cardiomyopathy	None	Sinus rhythm, ejection systolic murmur	Yes	LBBB pattern	LV + (slight)
C	II.5 Examined because of family history					

are set out in Tables 1 and 2. As a result of these investigations a diagnosis of hypertrophic obstructive cardiomyopathy was made; treatment with practolol 100 mg twice a day was started.

The family There was no history of cardiac disease or 'sudden death' in this family and no obvious evidence of cardiac disease was found when the surviving members of this kindred were examined (Fig. 1).

Twins B (Cases 1 and 2 of Karatzas *et al.*, 1968). There is a probability of 0.020 that these twins are dizygotic. They have similar facies and eye colour and their heights differ by 1.75 cm. Their 10 finger total ridge count differs by 14 and their palmar *aid* angles differ by 2°. They were identical for 9 blood grouping systems. Briefly, these girls, now aged 28 years, were the product of an uneventful pregnancy and led a normal childhood.

Their mother died from active pulmonary tuberculosis when the twins were 5 years old, and because of this they were reviewed annually, both clinically and radiologically, at a chest clinic. In 1960, when aged 17 years, they were examined by their general practitioner for insurance purposes and found to be perfectly well. However, two years later, a routine chest x-ray revealed cardiomegaly. As a result of the subsequent investigations a diagnosis of hypertrophic cardiomyopathy was made and twin III.1 was considered to be the more severely affected (Table 2).

These twins have now been observed regularly for the past 9 years and their progress has been seen to be widely different.

Twin III.2 This woman is well and disclaims any symptoms whatsoever. She has had two uneventful pregnancies and produced two healthy children aged 8½ and 2½ years, respectively. On

TABLE 2 Haemodynamic data

Case	RV (mmHg)	PA (mmHg)	LA (mmHg)	LV (mmHg)	Aorta (mmHg)	Rest	Peak systolic LV - aortic gradient				
							Post- ectopic	Valsalva manoeuvre	Isoprena- line	Amyl nitrite	CO (l./min)
Twin A (IV.3)	32/2	27/10 (17)	a = 9 v = 14.5 y = 4	140/8	140/70	0	30	25	30	30	13.5
Twin A (IV.4)	40/8	26/9 (16)	a = 11 v = 10 y = 5	135/8	135/70	0	25	23	22	22	10.0
Twin B (III.2)	45/15	45/20 (30)	a = 31 v = 30 y = 19	134/20	134/70	0	0	—	—	—	4.0
Twin B (III.1)	80/32	80/44 (60)	a = 36 v = 45 y = 28	120/36	125/73	0	0	—	—	—	3.5

physical examination the findings were virtually identical to those found nine years earlier and are set out in Table 1.

Twin III.1 This woman's condition deteriorated considerably as compared to her twin, since the onset of atrial fibrillation. She first developed her arrhythmia in June 1967, with associated systemic embolization to the left popliteal artery. DC cardioversion returned her to sinus rhythm on that occasion, but she relapsed into atrial fibrillation within seven months. Since then she has relapsed into this arrhythmia on six occasions, each time being converted back to sinus rhythm, but the intervals between relapses are becoming shorter. These episodes have been associated with a worsening of symptoms and the onset of congestive cardiac failure. Since her first pregnancy in 1963 she has had three spontaneous abortions occurring during the tenth, eighth, and sixteenth week, respectively.

The results of the most recent investigations are set out in Table 1.

The family The maternal grandmother had 'died young from a heart attack'; apart from her, no other member of the family that we were able to examine showed any evidence of cardiac disease (Fig. 2).

Twins C This set of dizygotic twins came to our attention when the son of the female member (II.5) was investigated at this centre (Case 4, Karatzas *et al.*, 1968). This boy was symptomless but the family were worried because of the alarming number of sudden deaths that had occurred among their relatives. The male twin (II.4) had died suddenly at the age of 39 years and necropsy revealed hypertrophic cardiomyopathy. Twin II.5 is alive and symptomless; the physical findings are set out in Table 1. Her son remains well and his physical findings, electrocardiogram, and chest x-ray remain unchanged after four years.

The family Fig. 3 illustrates that the cardiomyopathy seems to be controlled by an autosomal dominant gene in this family. The details

FIG. 1. Family pedigree of Twins A.

of III.1, 2, and 3 have been given by Karatzas *et al.* (1968).

Discussion

There is little doubt that twins A have an obstructive type of hypertrophic cardiomyopathy. Haemodynamically, they resemble the familial type of that disease in having no resting gradients and developing relatively small gradients with provocation (Frank and Braunwald, 1968). The interesting thing here, however, is the apparent lack of family history of cardiac disease or sudden death. We do not deny that clinical and electrocardiographic evidence alone may be insufficient to diagnose this condition; Nasser and his colleagues (1967) emphasized this point in their investigation of a large negro kindred; they catheterized 20 of the 33 patients examined and found evidence of hypertrophic cardiomyopathy in several who had been classed as 'normal' on clinical examination.

If twins A have inherited their lesion, the picture suggests a recessive condition or a dominant with incomplete penetrance (Emanuel *et al.*, 1971). However, another possible explanation could be a gene mutation for a dominant condition or lesion due to intrauterine abnormalities, but we favour the former. These twins are remarkably concordant in respect of their cardiac lesion, whereas in studies of monozygotic twins with congenital heart disease concordance is surprisingly low (Uchida and Rowe, 1957; Lamy, de Grouchy, and Schweisguth, 1957; Campbell, 1965). Since concordance should be 100 per cent for a strictly monogenic genetic disorder without modification this lack of concordance may indicate polygenic inheritance or other aeti-

LV - angiocardiology

LV shows indentations of floor and lateral wall; substantial mural irregularities developed during systole; no definite outflow obstruction or significant mitral regurgitation

LV wall thickened; ventricular outline irregular during systole; no significant mitral regurgitation or outflow obstruction

Thickening and nodularity on inferior and median aspect of LV; no outflow tract obstruction or mitral regurgitation

LV wall abnormally thin laterally, but thick and nodular inferomedially; no narrowing of outflow obstruction, or mitral regurgitation

ology. An intrauterine origin for certain types of cardiomyopathy has been suggested, and presumably changes in uterine environment such as temperature, blood supply, site of implantation, and infection might possibly be responsible for causing cardiac muscle to grow abnormally. Brachfeld and Gorlin (1961) have suggested that the embryogenic defect is an arrest of the normal evolution of the bulbus cordis. Many of these points have been reviewed recently by Shem-Tov and his colleagues (1971). Hypertrophic cardiomyopathy has been found in a stillborn infant and a neonate (Neufeld, Ongley, and Edwards, 1960), while several authors have noted murmurs in patients during the early years of life (Braunwald *et al.*, 1964; Daoud, Gallaher, and Kaplan, 1961; Cohen *et al.*, 1964). Somerville and McDonald (1968) and Shem-Tov *et al.* (1971), have reviewed cases of congenital heart disease associated with cardiomyopathy and suggest that this is more than coincidence. Haring (1960) added support for a developmental environmental cause by experimental work with pregnant rats. These animals were exposed for 24 hours to an atmosphere which contained 62 per cent CO₂; 25 per cent subsequently developed abnormal hearts, the common finding being diffuse myocardial thickening with narrowing of both right and left ventricular outflow tracts.

However, we feel that the close concordance in twins A is more in favour of a genetic cause. If this were a single gene germinal mutation then it could well manifest itself in the offspring of these two boys in the future.

The second set of twins was also monozygotic and concordant in respect of their cardiac lesion. The family history suggests that their grandmother may have had a similar cardiac lesion. The interesting fact is that these twins were seen annually for 12 years and yet showed no overt signs of cardiac disease. It is perhaps not so surprising then that their own children should appear normal at this time.

These children can be assumed to have had the fundamental fault present from birth but certain factors, such as environment, may be necessary before the gene can find expression. What is of particular interest is the different rate of progress in the two individuals. Twin III.2 has remained remarkably stable over the past 10 years and undertaken two successful pregnancies without deterioration. Swan *et al.* (1971), reviewing the experience of pregnancy and hypertrophic obstructive cardiomyopathy at Hammersmith Hospital, found that though there was a tendency for an increase in symptoms there was no

FIG. 2. Family pedigree of Twins B.

added risk of permanent harm to the mother or child. Twin III.1 on the other hand has deteriorated due in large part to the onset of atrial fibrillation. She has been less successful with her pregnancies, both in the outcome and symptomatic deterioration. This poor obstetrical history may be related to the severe pulmonary arterial hypertension (PAP 64 mmHg in 1965) since such levels are known to increase the risk of foetal death (Wooley *et al.*, 1961). Her general deterioration seems likely to be due to increasing inflow obstruction. The difference between these two twins may possibly have been environmentally induced, the prenatal environment being of particular importance. Though twins share the same uterine environment it is well known that there may be disturbance of the circulation of one of the twins because of the common placenta and chorion in 50 per cent of cases; this

FIG. 3. Family pedigree of Twins C.

may induce abnormal muscle development to a different degree even though they have the same genetic defect.

The dizygotic twins II.4 and II.5 have been included to emphasize how the clinical picture may vary within a family (Nasser *et al.*, 1967). Whereas the female member of the twins and her children undoubtedly have cardiomyopathies, they are completely symptom free. On the other hand her twin and his male children plus a nephew have all died suddenly from hypertrophic cardiomyopathy. Penetration of the gene is obviously high in this family but expression is variable. Again it is possible that an intrauterine factor could be responsible for this difference between these twins. Harley and Orgain (1971) reported a kindred with cardiomyopathy which included a pair of dizygotic female twins who were concordant. Braunwald *et al.* (1964) found the familial form of cardiomyopathy to be commoner in males, though in general the sexes seem to be affected equally (*British Medical Journal*, 1966). It is unlikely that sex difference contributed towards the clinical picture expressed by our third set of twins.

Conclusions

As a result of observations on three sets of twins (2 monozygotic, 1 dizygotic) the following suggestions have been made: (1) Hypertrophic cardiomyopathy may result from a single gene mutation. (2) The prenatal environment may be important in determining the expression of the gene and possibly the rate of progression of the condition in adult life.

I should like to thank Drs. Peter Sleight and Grant Lee for permission to report these patients, Dr. Lindenbaum of the M.R.C. Population Genetics Unit, Oxford, for the genetic studies, and Dr. J. Hamill for the radiological reports.

References

- Brachfeld, N., and Gorlin, R. (1961). Functional subaortic stenosis. *Annals of Internal Medicine*, **54**, 1.
- Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. G. (1964). Idiopathic hypertrophic subaortic stenosis. *Circulation*, **30**, Suppl. IV, p. 3.
- British Medical Journal* (1966). Leading article. Hypertrophic obstructive cardiomyopathy. **1**, 2.
- Campbell, M. (1965). Causes of malformations of the heart. *British Medical Journal*, **2**, 895.
- Cohen, J., Effat, H., Goodwin, J. F., Oakley, C. M., and Steiner, R. E. (1964). Hypertrophic obstructive cardiomyopathy. *British Heart Journal*, **26**, 16.
- Daoud, G., Gallaher, M. E., and Kaplan, S. (1961). Muscular subaortic stenosis. *American Journal of Cardiology*, **7**, 860.
- Emanuel, R., Withers, R., and O'Brien, K. (1971). Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet*, **2**, 1065.
- Frank, S., and Braunwald, E. (1968). Idiopathic hypertrophic subaortic stenosis. *Circulation*, **37**, 759.
- Goodwin, J. F. (1968). Obstructive cardiomyopathy. *Cardiologia*, **52**, 69.
- Goodwin, J. F. (1970). Congestive and hypertrophic cardiomyopathies. *Lancet*, **1**, 731.
- Haring, O. M. (1960). Cardiac malformations in rats induced by exposure of the mother to carbon dioxide during pregnancy. *Circulation Research*, **8**, 1218.
- Harley, A., and Orgain, E. S. (1971). Hypertrophic cardiomyopathy with unusual features in a family. *British Heart Journal*, **33**, 55.
- Karatzas, N. B., Hamill, J., and Sleight, P. (1968). Hypertrophic cardiomyopathy. *British Heart Journal*, **30**, 826.
- Lamy, M., de Grouchy, J., and Schweisguth, O. (1957). Genetic and non-genetic factors in the etiology of congenital heart disease - a study of 1,188 cases. *American Journal of Human Genetics*, **9**, 17.
- Nasser, W. K., Williams, J. F., Mishkin, M. E., Childress, R. H., Helmen, C., Merritt, A. D., and Genovese, P. D. (1967). Familial myocardial disease with and without obstruction to left ventricular outflow: clinical, haemodynamic and angiographic findings. *Circulation*, **35**, 638.
- Neufeld, H. N., Ongley, P. A., and Edwards, J. E. (1960). Combined congenital subaortic stenosis and infundibular pulmonary stenosis. *British Heart Journal*, **22**, 686.
- Paré, J. A. P., Fraser, R. G., Prizynski, W. J., Shanks, J. A., and Stubington, D. (1961). Hereditary cardiovascular dysplasia. *American Journal of Medicine*, **31**, 37.
- Shem-Tov, A., Deutsch, V., Yahini, J. H., and Neufeld, H. N. (1971). Cardiomyopathy associated with congenital heart disease. *British Heart Journal*, **33**, 782.
- Smith, S. M., and Penrose, L. S. (1954-55). Monozygotic and dizygotic twin diagnosis. *Annals of Human Genetics*, **19**, 273.
- Somerville, J., and McDonald, L. (1968). Congenital anomalies in the heart with hypertrophic cardiomyopathy. *British Heart Journal*, **30**, 713.
- Swan, D. A., Bell, B., Oakley, C. M., and Goodwin, J. (1971). Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy. *British Heart Journal*, **33**, 671.
- Uchida, I. A., and Rowe, R. D. (1957). Discordant heart anomalies in twins. *American Journal of Human Genetics*, **9**, 133.
- Wooley, C. F., Runco, V., Levin, H. S., and Ryan, J. M. (1961). Pregnancy and congenital heart disease (abstract). *Circulation*, **24**, 1075.

Requests for reprints to Dr. W. A. Littler, Cardiac Department, The Radcliffe Infirmary, Oxford, OX2 6HE.