Congenitally bicuspid aortic valves

Clinicogenetic study of 41 families

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SUMMARY The families of 41 patients with surgically proved isolated bicuspid aortic valves were examined. There were 275 first degree relatives of whom 220 were living, and 188 (85.5%) of these were examined. Seven first degree relatives were found to have aortic valve disease, and in a further 11 there was 'doubtful' evidence of bicuspid aortic valves. In 6 families there was more than 1 affected member and in an additional 7 families there was 1 or more 'doubtful' first degree relative. The minimum family incidence was therefore 14.6 per cent, or 31.7 per cent if 'doubtful' cases were included. The inheritance is most probably multifactorial, but occasionally the condition may occur as an autosomal dominant.

The difficulties of diagnosing bicuspid aortic valves before the development of obstruction of left ventricular outflow were encountered and are discussed. The association of a bicuspid aortic valve with asymmetric septal hypertrophy, hypertrophic cardiomyopathy, and Marfan's syndrome was also noted.

Peacock (1866) was the first to recognise the role of congenitally bicuspid aortic valves in the development of aortic stenosis, but he neither appreciated the frequency of this lesion nor realised that most cases of isolated aortic stenosis were congenital. The delay in recognition of the prevalence of bicuspid aortic valves has been partly caused by difficulty in diagnosis before the development of stenosis with the clinical signs of obstruction to left ventricular outflow; this may not occur until the third or fourth decade or even later, by which time the bicuspid nature of the valve has often become obscured by calcification. Koletsky (1941) reported a frequency of 0.54 per cent from 3300 consecutive necropsies and Roberts (1970) 0.9 per cent from 1440 necropsies. These figures, if representative, suggest that the incidence for all types of congenital heart disease in the population usually quoted as between 0.7 and 1.0 per cent may be an underestimate

(Mitchell *et al.*, 1971; Bound and Logan, 1977). The importance of bicuspid valves in the development of isolated aortic stenosis is evident from Roberts' (1970) postmortem findings where over 50 per cent of all cases were considered to be the result of congenital bicuspid valves, which is in keeping with current surgical experience.

The present study was undertaken to examine the frequency of family aggregates and the inheritance of bicuspid aortic valves.

Subjects and methods

Forty-one patients operated on at the National Heart Hospital between December 1962 and May 1973 were selected for this study. All had isolated aortic valve disease which was considered to be congenital by both the surgeon and pathologist. None had a history of rheumatism or had any other valve lesion. In all the anatomy of the valve was sufficiently well preserved to identify cusps and commissures. During the same period a further 11 patients were operated on for isolated congenital aortic valve disease, but were excluded as the anatomy of the valve was distorted, generally by calcification, to a degree that made identification of cusps and commissures impossible.

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Fig. Pedigrees of 14 families with more than one member with evidence or 'doubtful' evidence of a bicuspid aortic valve (BAV) or aortic valve disease.
Two relatives (14.II.2 and 18.IV.2) who were normal on clinical examination had asymmetric septal hypertrophy (ASH).
Families 34, 36, 43, and 56, though mentioned in the text, are not shown above as no relative other than the propositus was considered to have aortic valve disease.

As in previous studies (Emanuel *et al.*, 1968, 1971, 1975, 1977) arrangements were made to interview the propositus or a close relative at home and a family pedigree was drawn up which included all first and second degree relatives and first cousins.

Relevant information when available on more distant relatives was also recorded. During the interview, specific questions were asked to ascertain whether any relative was known to have cardiac abnormalities.

All first degree relatives who were willing to co-operate were examined at the National Heart Hospital or a convenient regional hospital. This involved a physical examination, chest radiograph, and an electrocardiogram. All chest radiographs and electrocardiograms were seen by one of us (R.E.). If the clinical findings were in any doubt, for example there was an isolated ejection sound or an apparently insignificant ejection murmur, an echocardiogram was performed on the relative concerned, and on all other first degree relatives in that particular family. In addition, in families with one or more affected first degree relatives, all available relatives had echocardiograms. Altogether 52 first degree relatives (from 13 families) were investigated by this technique.

Diagnostic criteria for congenital bicuspid aortic valve without obstruction to left ventricular outflow presented difficulties. The diagnosis was only accepted if 3 of the following 4 abnormalities were present: an ejection sound, an ejection murmur, an abnormal eccentricity index in the echocardiogram of 1.3 or more (Nanda *et al.*, 1974; Radford *et al.*, 1976), or dilatation of the ascending aorta on the chest radiograph. If only 2 of the 4 findings were present, the diagnosis was considered 'doubtful'.

In addition, signs of aortic stenosis with obstruction to left ventricular outflow in relatives without a previous rheumatic history were accepted as evidence of a bicuspid valve. It was appreciated that this assumption might well lead to overdiagnosis of bicuspid valves, particularly in the elderly (Vollebergh and Becker, 1977).

Results

(A) PROPOSITI

The 41 propoiti consisted of 30 males and 11 females. Their age at the time of operation was between 13 and 64 years, with a mean of 36.3, and in 21 a murmur was noted before the age of 15 years. In 34 the dominant lesion was stenosis and in 7 regurgitation, of whom 2, possibly 3, had had infective endocarditis. In 38 of the propoiti the valve was bicuspid because of fusion of the inter-coronary commissure. In 2, the commissure between the right coronary and non-coronary cusp was fused, and in the remaining 1 there was fusion of the inter-coronary commissure and the commissure between the right coronary cusp and non-coronary cusp. At the time of operation, the valve was calcified in 26 patients, 25 of whom were over the age of 35 years. As expected, there was an inverse relation between valve calcification and the presence of an aortic ejection sound.

Additional congenital cardiac lesions noted in the propoiti included hypertrophic cardiomyopathy in 1 (Family 7)¹ and asymmetric septal hypertrophy with supra valve aortic stenosis in another (Family 36). A third also had supra valve aortic stenosis but without any evidence of disproportionate inter-ventricular septal hypertrophy (Family 56).

(B) FIRST DEGREE RELATIVES

In the 41 families there were 275 first degree relatives (82 parents, 124 sibs, and 69 children); 220 (40 parents, 111 sibs, 69 children) were living and 188 (85.5%) of these were examined (36 parents, 88 sibs, 64 children).

Among the 55 first degree relatives who had died, 2 (parents) were known to have had aortic valve disease before death. In the remaining 53 (with the exception of 1 who had a normal aortic valve at necropsy) there was inadequate evidence to comment on the structure of the aortic valve.

There were 5 (1 parent, 4 children) living and 2 dead (parents) first degree relatives with aortic valve disease, which gives a frequency of 2.7 per cent affected for living parents who were examined, and 6.3 per cent for living children examined. In the 88 sibs examined there was no definite evidence of aortic valve disease. In addition, there were 11 (2 parents, 4 sibs, 5 children) in whom the diagnosis was 'doubtful'. In 6 families there was more than one affected member and in an additional 7 families there was 1 or more 'doubtful' first degree relatives. Thus there was a minimum family incidence of 14.6 per cent, or 31.7 per cent if 'doubtful' cases were included. Diagnostic details of the 7 affected (5 living and 2 dead) first degree relatives and 11 'doubtfuls' are shown in Tables 1 and 2.

Additional cardiac lesions were seen in 3 first-degree relatives. One (34.IV.1) had a ventricular septal defect confirmed at operation. Another (7.IV.1), with evidence of a bicuspid aortic valve without obstruction to the left ventricular outflow, had asymmetric septal hypertrophy with a ratio of the interventricular septum to the posterior left ventricular wall of 1.4; his mother (7.III.1), the propoitus, had a cardiomyopathy. The third (14.III.5), with 'doubtful' evidence of a bicuspid aortic valve (systolic murmur and a dilated ascending aorta) had asymmetric septal hypertrophy with a ratio of the interventricular septum to the posterior left ventricular wall of 1.4.

Additional isolated echocardiographic findings in the first-degree relatives included 6 (9.III.2,

¹Confirmed by histological examination of septal biopsy obtained at operation and by haemodynamic study 2 years 5 months after surgery.

Table 1 Diagnostic data from 10 affected relatives with evidence of bicuspid aortic valve or aortic valve disease

Relation to propositus	Pedigree no.	Age/Sex	Aortic ejection sound	Aortic systolic murmur	X-ray ascending aorta	Echo eccentricity index	Other data
<i>First degree</i>							
Son	7.IV.1	20/M	+	—	+	1.4	
Son	9.IV.1	41/M	+	+	+	0	Aortic diastolic murmur
+ Father	38.II.1	68/M	Not examined				Necropsy; aortic valve stenosis
Son	38.IV.7	11/M	+	+	—	1.6	
Son	53.IV.3	16/M	—	+	—	0	Cardiac catheterisation AoV gradient 20 to 30 mmHg
Mother	58.II.2	93/F	+	+	+	0	Aortic valve calcification; complete heart block
+ Mother	59.II.2	97/F	+	+	+	0	Electrocardiogram, LV hypertrophy
<i>Second degree</i>							
+ Uncle	7.II.3	62/M	Not examined				Necropsy, aortic valve calcification
Nephew	38.IV.1	8/M	+	+	—	1.3	
Niece	38.IV.3	18/F	+	+	+	1.0	

Table 2 Diagnostic data from 14 relatives with 'doubtful' evidence of a bicuspid aortic valve or aortic valve disease

Relation to propositus	Pedigree no.	Age/Sex	Aortic ejection sound	Aortic systolic murmur	X-ray ascending aorta	Echo eccentricity index	Other data
<i>First degree</i>							
Son	9.IV.3	28/M	+	—	+	1.1	
Daughter	10.IV.1	41/F	+	—	—	1.5	
Sister	13.III.8	26/F	+	—	+	0.9	
Brother	14.III.5	39/M	—	+	+	1.0	Electrocardiogram, T inverted aVL
Sister	18.III.7	46/F	+	—	+	0	
Daughter	18.IV.1	30/F	+	+	—	1.1	Metacarpal index 8-9, forme fruste Marfan
Mother	32.II.2	33/M	+	+	—	1.0	
Son	38.IV.6	13/M	+	+	—	1.1	
Mother	40.II.2	53/F	+	+	—	1.2	
Sister	54.III.3	52/F	+	+	0	1.1	
Son	54.IV.2	14/M	+	+	—	1.2	
<i>Second degree</i>							
Nephew	38.IV.4	14/M	+	—	+	1.0	
Niece	38.IV.5	12/F	—	+	—	1.4	
<i>Third degree</i>							
+ Grandfather	4.I.1	88/M	Not examined				Aortic valve stenosis; clinical information from general practitioner

AoV gradient = Peak systolic aortic valve gradient. O = Investigation not done.

14.III.4, 14.IV.2, 40.III.3, 43.II.2, 53.IV.1) with eccentricity indices of 1.3 or more (1.3 to 1.5, mean 1.4); none had an ejection sound or ejection murmur. A further 2 had asymmetric hypertrophy with ratios of the interventricular septum to the posterior left ventricular wall of 1.3 (14.II.2) and 1.7 (18.IV.2).

SECOND AND THIRD DEGREE RELATIVES

Although there was no systematic examination of second and third degree relatives, 3 (7.II.3, 38.IV.1,

38.IV.3) were thought to have aortic valve disease; 1 of these was confirmed at necropsy. In a further 3 (4.I.1, 38.IV.4, 38.IV.5) there was 'doubtful' evidence of aortic valve disease (Table 2).

Discussion

Certain congenital defects, including aortic stenosis and coarctation of the aorta, are significantly more common in the male (Watson, 1968). In both these

conditions the chromosomes are normal (Anders *et al.*, 1965) and a multifactorial mode of inheritance has been suggested. In this context it is interesting to note that in Turner's syndrome (XO), where those affected are phenotypically female but there is only one X chromosome present, the same two cardiac lesions predominate, which suggests that some of the genetic component is X-linked (Emanuel, 1970).

In 12 reported studies of congenital aortic stenosis the male:female ratio varied from 5.8:1 to 2.4:1 (Lewis and Grant, 1923; Wauchope, 1928; Koletsky, 1941; Kiloh, 1950; Campbell and Kauntze, 1953; Smith and Matthews, 1955; Bacon and Matthews, 1959; Spencer *et al.*, 1960; Braunwald *et al.*, 1963; Lindesmith *et al.*, 1967; Roberts, 1970; Nanda *et al.*, 1974). If the data from these studies were amalgamated there were 380 males and 116 females, giving a male:female sex ratio of 3.3:1. In the present series the ratio was 2.7:1. A similar male:female sex ratio might be expected in affected first degree relatives; this was found to be the case in those with definite evidence of aortic valve disease but was not so in those where the diagnosis was 'doubtful'. In the 7 first degree relatives who had definite evidence of aortic valve disease there were 5 males and 2 females, which gives a male:female sex ratio of 2.5:1 as expected, but in the 11 first degree relatives with 'doubtful' evidence of bicuspid aortic valves there were 5 males and 6 females. This reversal of the usual male predominance would, in itself, have cast doubt on a diagnosis of bicuspid aortic valve in this group.

The most reliable signs of a bicuspid aortic valve, before the development of stenosis, are probably the combination of an aortic ejection sound and ejection murmur (Leatham *et al.*, 1975). The advent of echocardiography and the introduction of the eccentricity index as a diagnostic aid (Nanda *et al.*, 1974; Radford *et al.*, 1976) has provided an additional index, but the frequency of false positive and false negative results has obscured rather than clarified the position. There were 6 first degree relatives with an abnormal eccentricity index without any other sign of a bicuspid aortic valve; none had hypertension and 4 were under the age of 45 years. Conversely there were 7 first degree relatives who had both an ejection sound and an ejection murmur, and only 1 of these had an eccentricity index of 1.3 or more. These findings illustrate the difficulty of diagnosing bicuspid aortic valves before the development of aortic stenosis, and cast doubt on the reliability of the echocardiogram in this context.

The association of bicuspid aortic valve and cardiomyopathy has been reported previously

(Gordon, 1962; Somerville and McDonald, 1968; Parker *et al.*, 1969; Feizi and Emanuel, 1975). It certainly occurred in the proband of one of our families, and may have been present in her son who had asymmetric septal hypertrophy and a bicuspid aortic valve (Family 7). Asymmetric septal hypertrophy was an unexpected finding in a further 3 first degree relatives, involving 2 families. In 2 of these (14.II.2, 14.III.5), where the ratio between the interventricular septum and the posterior left ventricular wall was 1.3 and 1.4, the degree of septal thickness could have been within the normal range (Emanuel, 1977), but in the third (18.IV.2) this seems unlikely as the ratio was 1.7. The only other abnormality in this relative was an aortic ejection sound, so the possibility of an associated bicuspid aortic valve must remain. The exact relation between asymmetric septal hypertrophy and hypertrophic cardiomyopathy still has to be established (Bulkley, 1977), but these relatives could well represent families in which the two conditions co-exist.

The frequent association of bicuspid aortic valve with the *formes frustes* of Marfan's syndrome has also been reported (Emanuel *et al.*, 1977). One relative (18.IV.1) in this study with 'doubtful' evidence of bicuspid aortic valve was noted to have long fingers, with a metacarpal index of 8.9, raising the possibility of Marfan's syndrome. Some support for this diagnosis came from her paternal aunt (18.III.7) who had an aortic ejection sound and slight dilatation of the ascending aorta on the chest radiograph. The proband had severe calcific aortic stenosis, and none of the 8 members of the family who were examined clinically had overt evidence of Marfan's syndrome.

The inheritance of isolated bicuspid aortic valves is almost certainly multifactorial, but in the absence of affected sibs the threshold nature of this common condition cannot be further analysed (Carter, 1961, 1976). Rarely, it appears to be inherited as an autosomal dominant (Families 7 and 38). This study showed a familial incidence of not less than 14.6 per cent, and possibly as high as 31.7 per cent if the 'doubtful' cases are included. The frequency of family aggregates and the pattern of inheritance cannot be determined precisely until more accurate noninvasive techniques are available for diagnosis of bicuspid aortic valves before the development of stenosis with the signs of obstruction to left ventricular outflow.

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Addendum

Since submitting this paper, the brother of one of the proposti (Family 49) has developed an aortic diastolic murmur which, in the absence of any other pathology, suggests a bicuspid aortic valve. If this is so, it would increase the number of affected first degree relatives to 8 and the number of families with more than one affected first degree relative to 7. The minimum familial incidence would then be 17.1 per cent, or 34.1 per cent if 'doubtful' cases were included.

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