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Echocardiographic Evaluation of Asymptomatic Parental and Sibling Cardiovascular Anomalies Associated With Congenital Left Ventricular Outflow Tract Lesions

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Abstract

Objective—Left ventricular outflow tract obstructive (LVOTO) malformations are a leading cause of infant mortality from birth defects. Genetic mechanisms are likely, and there may be a higher rate of asymptomatic LVOTO anomalies in relatives of affected children. This study sought to define the incidence of cardiac anomalies in first-degree relatives of children with congenital aortic valve stenosis (AVS), coarctation of the aorta (CoA), and hypoplastic left heart syndrome (HLHS).

Methods—A total of 113 probands with a nonsyndromic LVOTO malformation of AVS (n = 25), BAV (n = 3), CoA (n = 52), HLHS (n = 30), and aortic hypoplasia with mitral valve atresia (n = 2) were ascertained through chart review or enrolled at the time of diagnosis. Echocardiography was performed on 282 asymptomatic first-degree relatives.

Results—Four studies had poor acoustic windows, leaving 278 studies for analysis. BAV were found in 13 (4.68%) first-degree relatives. The relative risk of BAV in the relatives was 5.05 (95% confidence interval: 2.2–11.7), and the broad sense heritability was 0.49, based on a general population frequency of 0.9%. BAV was more common in multiplex families compared with sporadic cases. An additional 32 relatives had anomalies of the aorta, aortic valve, left ventricle, or mitral valve.

Conclusions—The presence of an LVOTO lesion greatly increases the risk of identifying BAV in a parent or sibling, providing additional support for a complex genetic cause. The parents and siblings of affected patients should be screened by echocardiography as the presence of an asymptomatic BAV may carry a significant long-term health risk.

Keywords

congenital heart disease; genetics; recurrence risk; aortic valve; coarctation; hypoplastic left heart syndrome

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ABBREVIATIONS

CCVM, congenital cardiovascular malformation; LVOTO, left ventricular outflow tract obstruction; HLHS, hypoplastic left heart syndrome; AVS, aortic valve stenosis; CoA, coarctation of the aorta; BAV, bicuspid aortic valve; CI, confidence interval

Congenital cardiovascular malformations (CCVMs) are among the most common of all medically significant birth defects (birth incidence of 0.5%–0.7%) and are a leading contributor to infant mortality in the United States.[1] Left ventricular outflow tract obstruction (LVOTO) malformations include hypoplastic left heart syndrome (HLHS) and Shone complex, congenital aortic valve stenosis (AVS), coarctation of the aorta (CoA), and bicuspid aortic valve (BAV). Although the frequency of HLHS is only ~1.7 per 10 000 live births, it is the leading cause of death from CCVM in infancy.[2,3] Known teratogenic exposures, cytogenetic abnormalities, and single-gene disorders account for only a small fraction of LVOTO defects.[4] Familial clustering, the sibling recurrence risk of 2% to 9%,[5] and the seemingly higher offspring recurrence risk of 7% to 13% suggest that most LVOTO malformations behave as a threshold trait with multifactorial genetic cause.[6]

Epidemiologic evidence from the Baltimore Washington Infant Study clearly linked these malformations together.[7] In that study, HLHS, AVS, and CoA occur in families much more commonly with each other than with any other CCVM. Observations of family clustering of LVOTO malformations support the hypothesis that LVOTO lesions share a common cause[8–11] that may involve abnormal intracardiac flow-induced morphogenetic alterations as a convergent mechanism.[12] Additional independent lines of evidence for genetic susceptibility include ethnic predilection in white individuals, specific associations with various chromosomal disorders including Turner and Jacobsen syndromes, and association with some single-gene defects.

BAV is a risk factor for aortic valve disease in adults. It may be the most common CCVM, with an estimated incidence of 0.6% to 1.36%. In 2 large, published autopsy series, the incidence of BAV was 0.9% and 1.36%, with the higher figure from a tertiary care center noted for cardiovascular surgery.[13,14] Echocardiography studies in healthy military aviators and pediatric subjects in sport participation evaluations had BAV incidences of 0.9% and 0.6%, respectively.[15,16]

Two previous echocardiography studies attempted to investigate the hypothesis that clinically asymptomatic LVOTO malformations may occur at a higher rate in families with a known LVOTO malformation. Brenner et al[7] performed echocardiograms on relatives of 11 infants with HLHS, where they observed 5 of 41 first-degree relatives with unrecognized BAV. Huntington et al[5] performed echocardiography on 186 first-degree relatives of 30 adults with BAV. They found 17 subjects (9.1%) with BAV, with at least 1 other affected subject in 11 of the 30 families.

Progress in echocardiographic methods over the last decade has made it possible to reevaluate the incidence of anatomic anomalies in families of LVOTO probands with greater confidence and precision. Seeking to investigate further the genetic components of LVOTO malformations, we conducted a prospective echocardiographic study of the cardiac morphology in relatives of infants and children ascertained with LVOTO malformations. We used broader criteria than previous studies to include not only HLHS but also AVS and CoA, as these defects are both epidemiologically and developmentally linked.

METHODS

Patient Population

Pediatric patients who carried a diagnosis of a left heart obstructive lesion were identified by chart review via a search of the patient databases of the Division of Cardiology, Department of Pediatrics at Baylor College of Medicine, or by referral. Once these affected children (also called the proband) were identified, we contacted the families and enrolled them after obtaining informed consent. Inclusion criteria for proband subjects were based on an anatomic diagnosis documented by echocardiography or cardiac catheterization. Children with a left ventricular outflow tract lesion in which the causative basis was known were excluded (eg, Turner syndrome). Previous Institutional Review Board approval for this study was obtained from Baylor College of Medicine.

Echocardiography

We performed 2-dimensional and Doppler echocardiographic imaging modalities using an Acuson Sequoia Imaging System (Mountain View, CA), in accordance with institutional guidelines. Studies were performed by a pediatric cardiac sonographer, pediatric cardiology fellow, or board certified pediatric cardiologist. Two staff cardiologists subsequently reviewed all studies (M.B.L. and L.I.B.). This evaluation included qualitative depiction of anatomic anomalies and 2-dimensional quantitative assessment of left heart dimensions. Left heart structures were measured online, using widely accepted criteria. These structures included mitral and aortic valve annulus dimensions; aortic root; sinotubular junction; ascending, transverse, and isthmic portions of the aortic arch; and left ventricular wall and chamber dimensions. These values were compared with normal values, using a database developed via collaboration with Boston Children's Hospital/Harvard University Department of Pediatric Cardiology. Interobserver variability was analyzed on the initial 55 studies. After interpretation of the studies by the initial cardiologist, a second cardiologist overread these studies in a blinded manner. Agreement with the initial interpretation was 100%, and the subsequent reader made no previously undetected diagnoses.

Statistical Analysis

Analysis was performed on Stata v7.0 (Stata Corp, College Station, TX). Comparisons of proportions were analyzed by the χ^2 statistic with the appropriate degrees of freedom or Fisher exact test. Relative risk is defined by the formula $\lambda_R = K_R/K$, where K_R is the probability that a relative is affected given the occurrence of an affected relative and K is the frequency of the condition in the population; 95% confidence intervals (CIs) for relative risk were calculated as described.[17]

RESULTS

Characteristics of Probands and First-Degree Relatives

We were able to identify and contact 324 families. All parents of affected children were interviewed to obtain a 3-generation pedigree, and echocardiographic data were subsequently collected on asymptomatic parents and siblings in the consenting families. A total of 211 families participated in acquisition of family history and development of a biological sample research resource. Family history was positive for a CCVM in an extended family member in 44 (20.9%) of these families. Of the 211 families that provided family histories and biological samples, 113 were available for enrollment in the echocardiography study. A description of the probands is provided in Table 1.

Multiplex families composed 18 (16.1%) of the total 113 families enrolled, which was not significantly different from the families in which echocardiography was not obtained. There

were 8 sibling–sibling, 5 parent–offspring, and 5 second- or third-degree relative–affected proband multiplex families. Diagnoses in the relatives in these multiplex families were HLHS (5), BAV (diagnosed by aortic regurgitation needing valve replacement, endocarditis, or murmur; 4), AVS (3), CoA (2), pulmonic valve stenosis (1), and ventricular septal defect (1) These relatives were not included in subsequent analyses.

Echocardiography Results

There were 328 first-degree relatives in the 113 families, 282 of whom consented for the study. Eight parents and 38 siblings either were unavailable or did not consent. Three mothers and 1 father were excluded from analysis because of poor quality echocardiographic images secondary to lack of acoustic window. A total of 45 anomalies were identified among the 278 individuals studied (Table 2). The most common finding was BAV (n = 13; 4.68%). The male:female ratio was 1:1 for BAV, comparable to that observed in population-based studies,[18] and 1:1 for all cardiac anomalies.

Anomalies were found in 20.2% (21 of 104) of mothers, 14.7% (14 of 95) of fathers, 21.6% (8 of 37) of brothers, and 4.8% (2 of 42) of sisters. The proportions were not significantly different by Fisher exact test (P = .38). The proportion of left heart anomalies for mothers, fathers, sisters, and brothers was also not significantly different when compared by the proband's diagnosis (Fisher exact P = .80) or gender (Fisher exact P = .39).

Subgroup analysis was performed by comparing the frequency of BAV in the first-degree relatives on the basis of the diagnosis of the proband (Table 3). The number of first-degree relatives with BAV was not statistically different when the proband had AVS with or without BAV (χ^2 = 2.582, df = 1, P = .108), but there were significantly more first-degree relatives with BAV when the proband had CoA with a BAV compared with a proband with CoA alone (χ^2 = 4.71, df = 1, P = .030).

Relatives were also compared by all anomaly types found by echocardiography, on the basis of the anatomic location of the anomaly (Fig 1). There was a trend for first-degree relatives to have more left ventricle and mitral valve anomalies when the proband had HLHS, and more aortic valve anomalies when the relatives had a proband with AVS. There was no excess of aortic arch anomalies among relatives of probands with CoA, but as noted above, there were more aortic valve anomalies. This trend for a difference in types of anomalies in the first-degree relatives on the basis of the proband's diagnosis did not reach statistical significance (Fisher exact P = .10).

Echocardiographic anomalies were noted in 10 (35.7%) of 28 AVS families, 22 (42.3%) of 52 CoA families, and 11 (29.1%) of 32 families of HLHS probands, for a total 33 (29.5%) of 113 families. This included 9 of the 16 previously identified multiplex families; thus, 42 (37.5%) of 113 families had relatives with LVOTO anomalies. Multiplex and sporadic families differed significantly in the frequency of BAV and non-BAV anomalies (Fisher exact P = .001; Table 4). In the multiplex families, 5 of the first-degree relatives with BAV occurred in families that were ascertained by symptomatic BAV in another relative.

Risk and Heritability

Relative risk and heritability were calculated assuming a population frequency of BAV = 0.9% (27 cases in 2916 individuals[13]) and the study frequency of BAV = 4.68% for all families, 2.54% for single affected case nuclear families, and 16.67% for multiplex families. This gave relative risks (λ_R) of 5.05 (95% CI: 2.18 –11.7) for all families, 2.75 (95% CI: 0.8 –8.9) for single affected case families, and 18.0 (95% CI: 6.4 –50.3) for the multiplex families. When the multiplex families that were ascertained on the basis of symptomatic BAV are included

with the single affected case families, the incidence and relative risk of BAV in first-degree relatives changes: single affected case families, BAV = 11/249 (4.42%), with (λ_R = 4.77 (95% CI: 1.9 –11.7) and multiplex families BAV = 2/29 (6.90%), with (λ_R = 7.45 (95% CI: 1.1–51.2). Heritability, calculated by the method of Edwards,[19] which assumes a normally distributed underlying quantitative liability with a threshold for trait expression, was 0.49.

DISCUSSION

These data demonstrate a significant excess occurrence of BAV among first-degree relatives of children who are affected with clinically severe LVOTO malformations. Familial clustering was initially noted in epidemiologic studies, in which a high sibling pre- or recurrence risk of 3% for serious LVOTO malformations was found. Offspring recurrence risks among affected parents were also found to be elevated, ranging from > 3% for paternal to 8% to 12% for maternal offspring recurrence risk.[20–22] Similar to the families ascertained in this study, most recurrences of CCVMs in the relatives of children with LVOTO defects are of the same mechanistic class.[7] Considering the population frequency and the sibling recurrence risk for a congenital heart defect, the sibling relative risk (λ_s) is ~20 to 25. Family studies of the frequency of BAV using infants with HLHS[7] and adults with BAV[5] as index cases also showed an excess of family members with BAV. Results of the current study, the first to use a sample from the complete spectrum of serious LVOTO malformations, confirms the findings for probands with HLHS and expands this to include similar findings of excess BAV with other left-sided lesions.

We also found a number of other left-sided anomalies in this group. Some, such as aortic dilation, are clinically important, whereas others detail minor anatomic variation that may nevertheless be part of the phenotypic spectrum of LVOTO malformations. Dilation of the ascending aorta is a common finding in patients with BAV, even in the absence of valve dysfunction.[23] Cases of dissecting thoracic aortic aneurysm have not been reported in any of the family studies of LVOTO, but there is an association between BAV and CoA and subsequent thoracic aortic dissection.[24,25] Natural history studies have also noted an increase in aortic root size over time in individuals with BAV.[26] The presumed mechanism is early loss of smooth muscle cells manifest as cystic medial necrosis.[27] Huntington et al,[5] in a study of familial clustering of BAV, found dilation of the ascending aorta in the absence of BAV or other valve abnormality in 5 (2.9%) of 169 subjects. The present study noted significant aortic dilation, defined as a body mass index–, gender-, and age-calculated *z* score of 2.5, in 5 (1.8%) of 278 subjects, not different from expected from the *z* score range. Our study included mostly children and young adults, so it is unknown whether the proportion with aortic dilation would change over time.

Co-occurrence of some of the other anomalies that we noted with AVS, CoA, or HLHS is known, but familial occurrence has not been reported. Thickening of the interventricular septum and hypertrophic cardiomyopathy have been reported together with bicuspid aortic valve, most often as a secondary consequence of aortic stenosis. These 2 conditions have been found to coexist in individuals from several families, separately or in combination.[28,29] The demonstration of septal anomalies in family members of children with AVS, CoA, or HLHS has not been previously reported. Congenital mitral valve abnormalities, notably parachute valve or valve hypoplasia but including mitral valve prolapse, can be seen in association with CoA.[30,31]

The significance of these other left-sided findings is difficult to interpret. These lesions may represent congenital or acquired findings; thus, the exact incidence may vary depending on the age of the population studied. The frequency of most of these lesions in the general population is unknown, making a direct comparison with the relatives in this study impossible. This also

complicates recommendations for screening for these particular lesions, including dilated aorta and hypertrophic cardiomyopathy, until more evidence can be gathered on the lifetime risk for the first-degree relatives. Follow-up will be required to assess the risk and define the natural history of aortic dilation and septal hypertrophy in these pedigrees, along with restudy of individuals with normal echocardiograms to determine whether some will develop these lesions later.

The high frequency of BAV in families with LVOTO malformations raises important clinical questions. BAV is estimated to lead to significant complications in one third of cases.[32] Our data support this figure, as 8 of 21 known individuals with BAV in our young families have had significant medical problems related to their valve. It is the leading cause of endocarditis in children and adolescents,[33] aortic regurgitation in young adults,[34] and aortic stenosis in older adults.[35] As there seems to be limited ability to predict risk on the basis of severity or type of lesion in the proband, any LVOTO malformation in the proband should prompt echocardiographic screening of first-degree relatives for the presence of BAV. Although the subgroup analysis suggests a greater risk to relatives when the proband has CoA with BAV, the small numbers of individuals in each subgroup and the use of multiple tests dictates caution in interpreting these results until this can be confirmed in future studies.

The high heritability and increased relative risk is consistent with a significant genetic component for BAV in these families of children with HLHS, CoA, or AVS. An important unanswered question in this and previous studies regards the converse, the risk of occurrence of a serious CCVM in the offspring of a parent with an asymptomatic LVOTO anomaly, particularly BAV. The risk for having an affected child cannot currently be calculated for individuals with BAV, as all available data were obtained by ascertainment through affected probands and not asymptomatic individuals. However, the present data raise the possibility that BAV and other minor structural anomalies of the heart represent very mild manifestations of the genetic risk that underlies severe LVOTO and that consequently individuals who bear these variants are at higher risk for having severely affected offspring.

One limitation of this study could be selection bias. The families enrolled were similar to a larger cohort not studied by echocardiography regarding proband diagnosis and proportion of families that were multiplex; thus, it is unlikely that there is a bias for increased severity of defects or selection for families that might have a Mendelian disorder. Excluding relatives in multiplex families who had symptomatic CCVMs from the analysis avoided overestimation of defects from ascertainment bias. Lumping together the diagnoses of AVS, CoA, and HLHS could have created a second limitation. Our subgroup analysis suggests that CoA with BAV may be a unique group; however, the sample size is small, and the difference needs to be taken with caution. Supporting the amalgamation of these disorders is the common developmental mechanism and previous observation of increased incidence of BAV in families ascertained through individuals affected with BAV and HLHS.[5,7]

The data generated for the relative risk and heritability data are sensitive to the frequency estimate for BAV in the general population. Although estimates of up to 2.25% can be found in the literature, the most reasonable estimate seems to be 0.9%, as the higher frequencies are from studies with selected populations. The BAV incidence was 2.25% in the study by Osler,[36] but this included a number of patients with endocarditis. Larson and Edwards[14] reported an incidence of 1.36% in a large autopsy study, but it was conducted retrospectively in a tertiary care institute noted as a referral center for cardiac surgery. The least biased study seems to be that of another large autopsy study performed by Roberts,[13] in which the incidence of BAV was 0.9%. The data most comparable to our study are from an echocardiographic study of asymptomatic military aviators, in which the incidence of BAV was also 0.9%.[16]

Compelling evidence exists for a large genetic component in the cause of the LVOTO malformations HLHS, AVS, CoA, and BAV. The phenotype in families might also include septal hypertrophy, mitral and aortic valve anomalies, and dilation of the ascending aorta in the absence of significant aortic valve abnormality. The risk of health problems from BAV is significant, and there is potential but unknown risk from the other associated anomalies of dilated ascending aorta and thickened interventricular septum. Current practice has not dictated studying the relatives of children with LVOTO malformations, but on the basis of these results, we recommend echocardiographic screening of all first-degree relatives of LVOTO patients for BAV.

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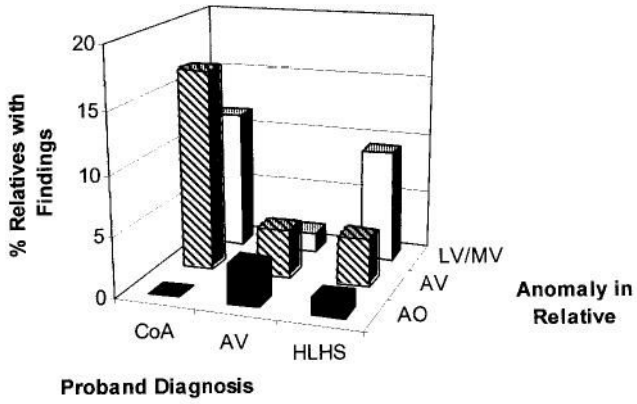

Fig 1.

Percentage of first-degree relatives with anomaly on echocardiography according to anatomic location of defect and proband diagnosis. Anomalies classified into each anatomic group are AO (aorta: aortic dilation; $n = 5$), AV (aortic valve: aortic valve thickening, aortic regurgitation, bicuspid aortic valve; $n = 21$), LV (left ventricle: segmental thickening of the interventricular septum with protrusion into the left ventricular outflow tract, septal hypertrophy with septal to free wall ratio > 1.4; $n = 10$), and MV (mitral valve: mitral valve thickening, mitral regurgitation, redundant chordae tendinae; $n = 9$). Proband diagnoses are AVS, CoA, and HLHS.

TABLE 1

Proband Diagnoses by Ethnicity and Gender

Diagnosis	White			Hispanic		Black		Asian		Total			Total
	M	F	U	M	F	M	F	M	F	M	F	U	
AVS													
AVS	5	2		1	1	2				8	3		11
AVS-BAV	7	2		3	2					10	4		14
BAV	1	1		1						2	1		3
Total	13	5		5	3	2	0	0	0	20	8		28
CoA													
CoA	9	3		7		1				17	3		20
CoA- BAV	10	4		5	1	1			1	16	6		22
CoA-VSD	2	1		1						3	1		4
CoA-BAV-VSD	3	1		1	1					4	2		6
Total	24	9		14	2	2	0	0	1	40	12		52
HLHS													
HLHS	9	4	1	7	1	1				17	5	1	23
Shone		2		5	1					5	3		8
Total	9	6	1	12	2	1	0	0	0	23	8	1	31
Other*													
Other				2	0					2	0		2
Total				2	0					2	0		2
Total	45	21	1	33	7	5	0	0	1	83	29	1	113

M indicates male; F, female; U, unknown; Shone, Shone complex; VSD, ventricular septal defect.

*Aortic atresia and mitral valve stenosis.

TABLE 2

Left Heart Anomalies in First-Degree Relatives

Anatomic Location	Anomaly	*n* (%)
Aorta		
	Dilated root	5 (1.80%)
	Total	5 (1.80%)
Aortic valve		
	Bicuspid	13 (4.68%)
	Thickened	4 (1.44%)
	Regurgitation	4 (1.44%)
	Total	21 (7.55%)
Left ventricle		
	Protruding IVS	4 (1.44%)
	HCM	4 (1.44%)
	Depressed function	1 (0.36%)
	Enlargement	1 (0.36%)
	Total	10 (3.60%)
Mitral valve		
	Thickened	3 (1.08%)
	Regurgitation	4 (1.44%)
	Redundant chordae tendinae	2 (0.72%)
	Total	9 (3.24%)
Total		45 (16.19%)

IVS indicates interventricular septum; HCM, hypertrophic cardiomyopathy.

TABLE 3

Echocardiography Findings in First-Degree Relatives, Stratified by Anatomic Location and Grouped by the Proband's Diagnosis

Proband Diagnosis	Anatomic Location of Anomaly in Relative						Total
	AO	AV	BAV	LV	MV	Normal	
AVS	0	0	3	0	0	26	29
AVS-BAV	4	0	1	1	0	35	41
BAV	0	1	0	0	0	7	8
CoA-BAV-VSD	0	1	1	0	0	8	10
CoA	0	1	1	3	0	44	49
CoA-BAV	0	4	6	2	3	38	53
CoA-VSD	0	0	0	1	1	11	13
HLHS	1	1	1	1	4	46	54
Other	0	0	0	0	0	5	5
Shone complex	0	0	0	2	0	14	16
Total	5	8	13	10	8	234	278

AO indicates aorta; AV, aortic valve (not BAV); LV, left ventricle; MV, mitral valve; VSD, ventricular septal defect.

TABLE 4

Diagnosis in First-Degree Relatives According to Family Type

Family Type	Non-BAV Abnormality	BAV	Normal	Total
Sporadic*	29 (12.29)	6 (2.54)	201 (85.17)	236
Multiplex†	3 (7.14)	7 (16.67)	32 (76.19)	42
Total	32 (11.15)	13 (4.68)	234 (84.17)	278

*Single affected case in family.

†More than one affected case in family.