Familial Incidence of Cardiovascular Malformations in Hypoplastic Left Heart Syndrome

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Obstructive left-sided congenital heart lesions exhibit familial clustering, and familial echocardiographic screening for bicuspid aortic valve has become standard practice. Hypoplastic left heart syndrome (HLHS) is a severe left-sided obstructive lesion; however, familial screening is not universally recommended. The purpose of this study was to define the incidence of cardiovascular malformations (CVMs) in first-degree relatives of HLHS probands. First-degree relatives were screened for CVM by transthoracic echocardiography. Screening was completed in 152 family members (97 parents and 55 siblings) of 52 probands. Of these, 17 of 152 (11%) had CVM. Anomalies detected included: bicuspid aortic valve in 5 (3%), isolated dilated ascending aorta in 4 (3%), coarctation of the aorta in 1, partial anomalous pulmonary venous connection in 1, anomalous, intramural coronary artery in 1, bicuspid pulmonary valve in 1, and other anomalies in 4. Most were previously undiagnosed (11 of 17, 65%). Fourteen of 52 families (27%) had ≥1 relative with CVM. Overall, 7 of 55 siblings (13%), 5 of 46 fathers (11%) and 5 of 51 mothers (10%) had CVM. Although the incidence of CVM in first-degree relatives of HLHS probands was lower in this cohort than previously reported, it remained substantial, with at least one additional member having CVM in 27% of families. The frequent occurrence of undiagnosed CVM highlights the importance of routine familial screening in HLHS. In fact, even if screening was done in childhood, it may be appropriate to screen again in the third or fourth decade to exclude isolated enlargement of the ascending aorta. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;116:1762−1766)

Obstructive left-sided congenital heart lesions include hypoplastic left heart syndrome (HLHS), Shone complex, coarctation of the aorta (COA), congenital aortic valve stenosis, and bicuspid aortic valve (BAV). These lesions exhibit familial clustering in epidemiologic studies such as the Baltimore Washington Infant Study[1] and in prospective studies of patients' first-degree family members.[2−7] The incidence of BAV in first-degree relatives of affected family members has been reported to be as high as 9% to 10%.[2,8] Familial echocardiographic screening for BAV and associated aortopathy has thus become standard clinical practice.[9,10] The incidence of congenital cardiovascular malformations (CVMs) in first-degree relatives of patients with HLHS has been reported to be even higher than that of BAV, up to 19%.[3] Despite this, familial screening has not been universally adopted. This study prospectively assessed the cardiac morphology of first-degree family members of HLHS probands using 2-dimensional transthoracic echocardiography. The purpose was to define the incidence of CVM and to determine if routine family screening is warranted in this population.

Methods

The Institutional Review Board at Mayo Clinic approved this study. Prospective enrollment was performed after obtaining informed consent from all participants or their legal guardians. Participants included HLHS probands and their first-degree family members, defined as parents and full siblings. Consenting probands or guardians were interviewed, and family pedigrees were constructed for all probands.

Electronic medical records of probands, including surgical reports and echocardiographic images, were reviewed to confirm HLHS diagnosis. For this study, HLHS was strictly defined to include only aortic valve stenosis or atresia, mitral valve stenosis or atresia, left ventricular hypoplasia, and hypoplasia of the ascending aorta.[11] All probands in this cohort underwent single ventricle palliative procedures or cardiac transplantation; none were determined eligible for biventricular repair. There were no patients with known genetic syndromes (e.g., Turner syndrome, trisomy 13, and trisomy 18) included in our cohort. Chromosomal microarray was performed on all available and consenting probands.

All available and consenting first-degree family members underwent transthoracic echocardiographic examination in the Mayo Clinic Congenital Echocardiography Laboratory. All studies were reviewed by staff pediatric cardiologists; reviewing physicians were not blinded as to the screening nature of the study. Complete studies were performed in accordance with institutional protocol using 2-dimensional,

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See page 1765 for disclosure information.

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Table 1
Abnormal echocardiographic findings in first-degree family members

Echocardiographic finding	N	Relation to proband (age in years at time of echo)
Bicuspid aortic valve	4	Father (48), mother (31),[1] sister (5),[1] sister (4)
Dilated ascending aorta, normal aortic valve	3	Father (58), father (51), father (39)
Ventricular septal defect	2	Mother (24), sister (5)
COA, bicuspid aortic valve, dilated aortic root, accessory mitral chordal tissue	1	Brother (6)[2]
Dilated aortic root, accessory mitral chordal tissue	1	Brother (7)[2]
Bicuspid pulmonary valve	1	Mother (30)
Mitral valve prolapse with mitral regurgitation	1	Mother (28)
Anomalous origin of RCA	1	Mother (34)
Partial anomalous pulmonary venous return	1	Brother (7)[3]
Papillary fibroelastoma vs. Lambl's	1	Father (29)[3]
Patent ductus arteriosus	1	Brother (9)
Total	17	

[1,2,3]Members of the same family.
COA = coarctation of the aorta; RCA = right coronary artery.

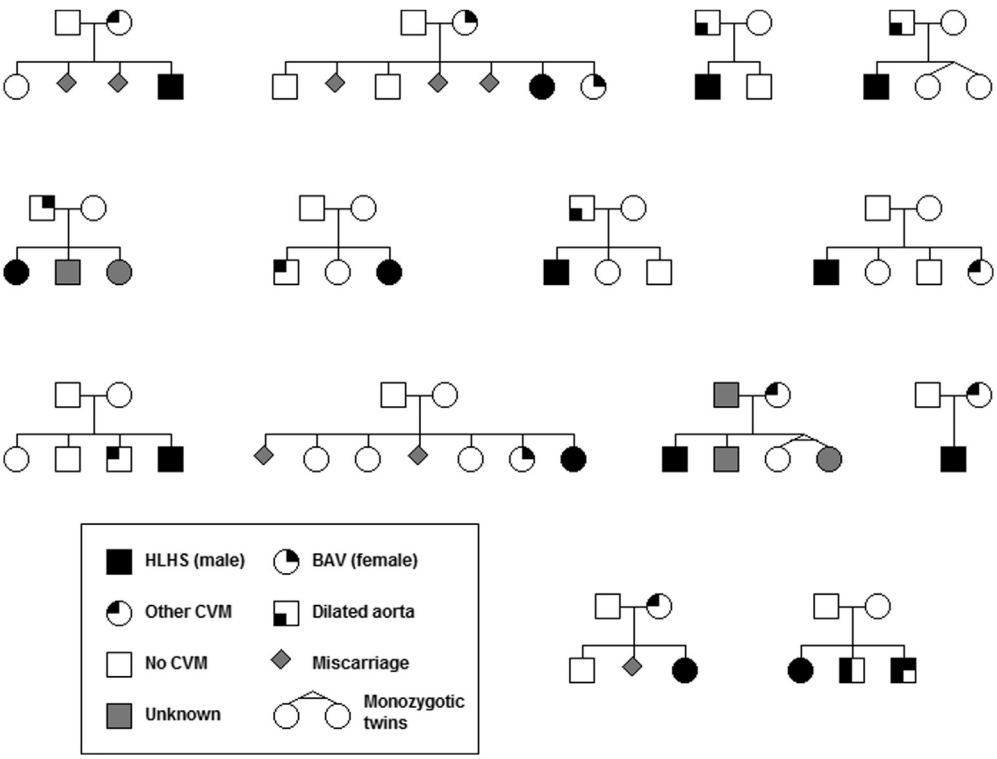

Figure 1. Pedigrees of 14 families of hypoplastic left heart syndrome (HLHS) probands with at least one first-degree relative with cardiovascular malformation (CVM). *Circle shape* represents a female; *square shape*, male; and *diamond shape*, miscarriage. An *empty shape* indicates no identified CVM by echocardiography; *gray shape*, CVM phenotype is unknown; f*ully opacified shape*, HLHS proband. *Individually darkened quadrants* represent specific cardiovascular phenotypes. An *opacified right upper quadrant* indicates bicuspid aortic valve (BAV); *opacified left lower quadrant*, dilated ascending aorta; *opacified left upper quadrant*, other congenital heart disease.

M-mode, and Doppler imaging by experienced congenital cardiac sonographers. Left heart structures including aortic valve annulus, sinus of Valsalva, sinotubular junction, and midascending aortic diameters were measured. Results were indexed to body surface area and compared with published normal values.[12] Pediatric patients were diagnosed with aortic dilatation if computed aortic *Z*-scores were greater than 2.[13,14] BAV was diagnosed in parasternal short-axis view by assessing morphology in both systole and diastole and was classified as previously described.[15]

Statistical analyses were performed using JMP statistical software (version 10.0). Descriptive data are presented as mean ± standard deviation; median with range; or percentage with 95% confidence interval.