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Leftward Displacement of Septum Primum in Hypoplastic Left Heart Syndrome

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Abstract

Embryologic development of atrial septum primum antedates formation of the atrioventricular and semilunar valves. Leftward displacement of the superior attachment of septum primum (LDSP) has only been described in hypoplastic left heart syndrome (HLHS). This study reports the frequency of LDSP in HLHS and correlates LDSP with other echocardiographic features of HLHS. Preoperative echocardiograms for 72 consecutive patients with classic HLHS from 1996 to 2002 at Children's Hospital of Wisconsin were reviewed. One patient was excluded for inadequate imaging. Data for the 71 patients included the following: size, location, and Doppler gradient across the atrial septal defect (ASD); location of attachment of septum primum; size and patency of the aortic valve (AoV) annulus; size and patency of the mitral valve (MV) annulus; ascending aorta diameter (AAD); and left-ventricular end diastolic dimension (LVEDD). Patients were categorized into three groups: aortic atresia/mitral atresia (AA/MA), aortic atresia/mitral stenosis (AA/MS), and aortic stenosis/mitral stenosis (AS/MS). LDSP was seen in 46 of 71 patients (64 %). By diagnostic group, 32 of 35 patients with AA/MA had LDSP (91 %) compared with 10 of

19 AA/MS patients (53 %) and 4 of 17 AS/MS patients (24 %), $p < 0.05$. AoV patency was seen in 4 of 46 (9 %) patients with LDSP compared with 13 of 25 (52 %) patients with normal atrial attachment, $p < 0.005$. Mean left heart dimensions in infants with LDSP compared with normal attachment were as follows: AoV annulus 2.24 versus 3.83 mm, AAD 2.34 versus 4.1 mm, MV annulus 3.21 versus 6.48 mm, and LVEDD 6.38 versus 13.83 mm. By two-way analysis of variance of diagnostic category versus atrial septal attachment with interaction, MV annulus and AAD were independently predicted smaller by LDSP versus normal atrial attachment, $p < 0.05$. Nonsignificant factors included AoV annulus, LVEDD, ASD size, and Doppler gradient. LDSP correlates with more severe maldevelopment of the left heart in patients with HLHS. Because formation of septum primum precedes development and growth of the intracardiac valves, we speculate that LDSP may be an initiating event in the development of HLHS. In addition, prenatal identification of LDSP may help direct planning of potential in utero therapies.

Keywords

Hypoplastic left heart syndrome; Atrial septal defect; Aortic atresia

Hypoplastic left heart syndrome (HLHS) is a well described form of congenital heart disease with varying degrees of underdevelopment of left heart structures leading to insufficient systemic cardiac output shortly after birth and, if left untreated, death. More than 2000 infants/y are born with HLHS in the United States, and HLHS accounts for approximately 25 % of cardiac deaths during the first year of life [12]. Recent advances in surgical technique and postoperative care have significantly decreased the morbidity and mortality associated with this lesion [18].

The cause of HLHS is not yet known. One theory suggests that severe fetal aortic stenosis results in subsequent lack of flow through the left heart needed to provide proper development of the mitral valve and left ventricle [14]. Recent improvements in prenatal diagnosis and fetal intervention have allowed for attempted balloon valvotomy of critical aortic stenosis in the fetus [10, 13]. Although there has been technical success with this procedure, some patients develop HLHS despite successful fetal aortic valvotomy. Animal models have also shown that fetal limitation to the left-ventricular outflow is not sufficient to develop HLHS and that other factors may be important in the embryogenesis of this lesion [3].

An additional factor in the embryogenesis of HLHS may involve the flow of blood across the atrial septum in utero [11]. Weinberg et al. in 1988 described four subtypes of the atrial level communication in HLHS: (1) normal atrial septum with secundum ASD; (2) congenitally small foramen ovale; (3) malaligned atrioventricular canal with hypoplastic left ventricle; and (4) leftward displacement of superior attachment of septum primum (LDSP; flap valve of foramen ovale) relative to septum secundum [20]. These same investigators also described that echocardiography can accurately differentiate between these subtypes [1].

LDSP (Fig. 1) is not known to occur in other forms of congenital heart disease. Its association with other anatomic features of HLHS has not previously been described. The

purpose of this study was to report the frequency of LDSP in patients with HLHS and to correlate LDSP with other anatomic features of HLHS using echocardiography.

Methods

Study Population

Retrospective review of echocardiograms at diagnosis for 72 consecutive patients who underwent stage 1 palliation with aortic arch reconstruction with Blalock–Taussig shunt for classic HLHS (mitral, left-ventricular, and aortic hypoplasia/atresia inadequate to support systemic circulation) at Children's Hospital of Wisconsin from August 1996 to May 2002 was performed. Patients with unbalanced atrioventricular canal or other types of single-ventricle anatomy requiring stage 1 palliation were excluded from this study. Patients were identified from the Heart Center database and represent the same cohort of patients our group has reported on previously [5]. Institutional Review Board approval from the Children's Hospital of Wisconsin was obtained for this study.

Echocardiographic Measurements

All echocardiographic studies were evaluated in a retrospective manner by two independent reviewers. The orientation of the superior attachment of septum primum (leftward vs. normal) was evaluated from subcostal windows as has been described previously [1, 7]. One patient was excluded due to inadequate imaging of the atrial septum. The remaining 71 patients were included in the analysis, which measured the following: size, location, mean, and peak Doppler gradients across the atrial septal defect (ASD); diameter and patency of the AoV annulus; diameter and patency of the MV annulus; ascending aorta diameter (AAD); and left-ventricular end diastolic dimension (LVEDD).

Patient Grouping

Patients were categorized into three diagnostic categories based on the patency of their aortic and mitral valves: aortic atresia/mitral atresia (AA/MA), aortic atresia/mitral stenosis (AA/MS), and aortic stenosis/mitral stenosis (AS/MS) [5].

Statistical Analysis

Statistical analysis was assessed with one-way analysis of variance (ANOVA), Tukey post hoc comparisons, and Pearson Chi Square analysis. Two-way ANOVA of diagnostic category versus atrial septal attachment with interaction was also performed for independent prediction of diagnostic category by atrial septal attachment.

Results

Atrial Septum

LDSP was seen in 46 of 71 patients (64 %). One patient had an intact atrial septum (no evidence of blood flow across the septum by color Doppler) with normal attachment of the septum primum.

In the 70 patients with an atrial communication, communication size was scored as follows: small communications = 2 mm; medium communications = 3–4 mm; and large communications = 5 mm [16]. Small communications were seen in 22 of 70 (31.4 %) patients (14 of 46 [30.4 %) patients with LDSP versus 8 of 24 [33.3 %) patients with a normally attached atrial septum). Medium communications were seen in 23 of 70 (32.9 %) patients (18 of 46 [39.1 %) patients with LDSP versus 5 of 24 (20.8 %) patients with a normally attached atrial septum). Large communications were seen in 25 of 70 (35.7 %) patients (13 of 46 [28.3 %) patients with LDSP versus 12 of 24 [50 %) patients with a normally attached atrial septum. Atrial septal communication size was not statistically significant between the two groups ($p = 0.165$ by Pearson Chi square analysis).

Atrial communication location in the 70 patients was scored as either being mid-position or superior. Mid-position communications were seen in 23 of 70 (32.9 %) patients (4 of 46 [8.7 %) patients with LDSP versus 19 of 24 [79.2 %) patients with a normal septum primum attachment). Superior level atrial communications were seen in 47 of 70 (67.1 %) patients (42 of 46 [91.3 %) patients with LDSP versus 5 of 24 [20.8 %) patients with a normally attached atrial septum). The association of LDSP with superior level communications was statistically significant ($p < 0.001$).

Pulsed wave peak Doppler gradients across the atrial septum was performed in 44 of 70 (62.9 %) patients (33 of 46 [71.7 %) patients with LDSP and 11 of 24 [45.8 %) patients with a normally attached septum primum). LDSP patients had a mean peak Doppler gradient of 10.2 ± 5.4 mm Hg (range 1.6–26.7), whereas patients with a normally attached septum primum had a mean peak Doppler gradient of 7.8 ± 3.8 mm Hg (range 3.5–15.9). The mean peak Doppler gradient between the two groups was not significantly different ($p = 0.170$).

Pulsed wave mean Doppler gradients across the atrial septum was performed in 35 of 70 (50 %) patients (27 of 46 [58.7 %) patients with LDSP and 8 of 24 [33.3 %) patients with a normally attached septum primum). The mean value for patients with LDSP was 4.3 ± 3.3 mm Hg (range 0.4–14.4). The mean value for patients with a normally attached septum primum was 4.5 ± 2.9 mm Hg (range 1.8–10.6). The mean Doppler gradient between the two groups was not statistically significant ($p = 0.918$).

Left Heart Measurements

Mean left heart dimensions in infants with LDSP versus normal attachment, respectively, were as follows: AoV annulus 2.24 mm versus 3.83 mm, AAD 2.34 versus 4.1 mm, MV annulus 3.21 versus 6.48 mm, and LVEDD 6.38 versus 13.83 mm.

Using two-way ANOVA of diagnostic category versus atrial septal attachment with interaction, mitral valve size and ascending aortic diameter were independently predicted as being smaller in HLHS patients with LDSP compared with HLHS patients with a normally attached septum primum ($p < 0.05$) (Fig. 2). Nonsignificant factors included AoV annulus, LVEDD, ASD size, and Doppler gradient across the ASD.

Diagnostic Categories

HLHS patients in the study were divided into three groups based on the patency of their aortic and mitral valves. Atresia of the aortic and/or mitral valves was assigned when no flow by color or pulse wave Doppler could be observed through the aortic or mitral valves, respectively. Thirty-five patients were found to have AA/MA; 19 patients had AA/MS; and 17 patients had AS/MS [5]. The number of patients in each diagnostic category was not statistically significant. When patients were separated into diagnostic groups, 32 of 35 (91 %) patients with AA/MA had LDSP compared with 10 of 19 (53 %) AA/MS patients and 4 of 17 (24 %) AS/MS patients ($p < 0.05$) (Fig. 3).

Aortic and Mitral Valve Patency

In the 71 HLHS patients studied, aortic valve atresia was seen in 42 of 46 (91 %) patients with LDSP versus 12 of 25 (48 %) patients with a normally attached septum primum ($p < 0.005$) (Fig. 4). Mitral valve atresia was seen in 35 of 46 (76 %) patients with LDSP versus 6 of 25 (24 %) patients with a normally attached septum primum ($p < 0.005$) (Fig. 5).

Clinical Outcomes

At the most recent follow-up (mean age at last evaluation 7.6 ± 1.6 years), total cumulative survival for the 71 patients in the study was 56 of 71 (78.9 %). Of the patients with LDSP, 36 of 46 (78.3 %) patients were alive versus 20 of 25 (80 %) patients with a normally attached septum primum (not significant). Overall survival to date by anatomic subgroup was 58 % (11 of 19) of the patients with AA/MS compared with 86 % (30 of 35) with AA/MA and 88 % (15 of 17) with AS/MS. This was statistically significant ($p = 0.015$) and has been reported by our group previously [5].

Of the 10 deaths in the LDSP group, 4 occurred after stage 1 palliation and before hospital discharge; 4 occurred after hospital discharge from stage 1 palliation but before stage 2 palliation; 1 occurred after stage 2 palliation but before stage 3 palliation; and 1 occurred after stage 3 palliation.

Of the 5 deaths in the normally attached septum primum group, 3 occurred after stage 1 palliation and before hospital discharge; 1 occurred after hospital discharge from stage 1 palliation but before stage 2 palliation; and 1 occurred after stage 2 palliation and before stage 3 palliation. There were no deaths in patients with HLHS and those with a normally attached septum primum after stage 3 palliation. No comparison between the groups for mortality or operative outcomes was statistically significant.

Discussion

The development of HLHS is thought to be influenced by altered embryonic blood flow by way of decreased inflow to the developing left ventricle through the foramen ovale [11]. Pathologic studies have shown that the atrial septal anatomy in patients with HLHS has four anatomic subtypes [20]. One of the subtypes, LDSP has been reported to have a high incidence of both MA and AA [19, 20]. In this study of neonates with HLHS, LDSP was much more commonly associated with AA and MA than other anatomic subtypes of HLHS

and had a lower percentage of patency of their mitral and aortic valves than did patients with a normally attached septum primum. In addition, this study showed that HLHS with LDSP had more severe underdevelopment of the left heart than patients with a normally attached septum primum.

Fetal echocardiography has shown hemodynamic alterations that result in progressive severity of HLHS as seen in fetal critical aortic stenosis [8, 9]. Recent attempts at in utero catheterization of critical aortic stenosis have yielded mixed results because some left ventricles seem to regress or not improve despite improved antegrade blood flow through the left ventricle [10, 13]. In addition, recent attempts at aortic banding in early fetal sheep failed to retard left-ventricular growth [3]. Lev [11] provided one of the first analyses of the pathologic anatomy of HLHS in 1952. In his article, he speculated that decreased blood flow into the left heart during fetal life may be a contributing factor in the embryologic etiology of HLHS. He stated, "It is possible that there is faulty approximation of the septum primum and secundum, with the result that blood from the inferior vena cava may be impeded in its progress through the foramen ovale" [11]. Because formation of septum primum precedes the development and growth of the intracardiac valves [15], maldevelopment of the atrial septum may limit inflow to the left heart. Early studies at creating left-ventricular inflow obstruction in fetal lambs resulted in decreased left-ventricular output and volume. In addition, studies in chick embryos have shown that right atrial clipping to increase blood flow to the left ventricle results in increased left-ventricular end-diastolic volume, left-ventricular myocyte proliferation, and myocardial mass in embryos with experimental left-ventricular hypoplasia [2].

In humans, it is known that HLHS patients with an intact atrial septum have worse outcomes than patients with an atrial level communication. Rychik et al. reported that approximately 6 % of infants with HLHS have intact atrial septal anatomy, and 28 % of patients with intact septum in their study had LDSP with no evidence of Doppler color flow by echocardiography [17]. The HLHS patients in our study who had LDSP had statistically similar survival to patients with a normally attached atrial septum. Only one patient in our cohort had an intact atrial septum with normal attachment. All of the patients in our study who had LDSP had observable blood flow by color Doppler. Our group recently reported that patients with AA had increased mortality only in the presence of a patent mitral valve [5]. We found that LDSP was most often associated with AA/MA, which conferred an 86 % survival rate to date in our previous study. Conversely, only 55 % of patients with LDSP had AA/MS, which conferred the highest mortality rate (42 %) to date of the three anatomic subtypes [5].

LDSP unique in patients with HLHS and has not been reported in other types of congenital heart disease. LDSP can be identified by pathologic specimen or by two-dimensional echocardiography [1]. Previous studies have reported the incidence of LDSP in HLHS to be 37–55 % [1, 7, 20, 21]. Patients with HLHS in our cohort of patients had a greater degree of LDSP compared with previously published results (64 vs. 37–55 %). This is most likely due to our exclusion of patients with anatomical subtypes not classic to HLHS, such as unbalanced atrioventricular canal defects or transposition of the great arteries, as had been included in previous studies [1, 7, 20, 21].

Limitations of this study include its retrospective nature and that all data points, *i.e.*, Doppler gradients across the atrial communication, were not complete for the 71 patients studied. In addition, no fetal echocardiograms were reviewed to follow up the in utero development of these patients with HLHS. Currently, the prenatal identification of LDSP in patients with HLHS has not been reported, and current echocardiographic technology makes assessment of abnormal attachment of septum primum difficult.

We speculate that LDSP may be an initiating event in the development of HLHS and contributes to the most severe forms of underdevelopment of the left ventricle. LDSP defines a substrate of patients that may not be amenable to fetal intervention, including balloon valvuloplasty of the aortic valve. Earlier prenatal identification of LDSP with improved echocardiographic technology may help direct planning of potential in utero therapies for HLHS.

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Fig. 1.

Subcostal sagittal views from patients with HLHS of atrial septal anatomy in a patient with a large secundum ASD **A** and **C** versus a patient with LDSP. **A** HLHS patient with a normally attached septum primum and large ASD. **B** HLHS with LDSP. **C** Patient from [**A**] with color Doppler showing normal pulmonary venous return and left to right flow from the left atrium to the right atrium across the ASD. **D** Patient from [**B**] with color Doppler showing impeded pulmonary venous return to the left atrium with shunting of blood around the leftward-displaced septum primum

Fig. 2.
Differences in left heart dimensions. AVA aortic valve annulus

Fig. 3. Percentage of LDSP by diagnostic categories

Fig. 4.

AA by atrial septal attachment. Normal = normal attachment of septum primum

Fig. 5.
MA by atrial septal attachment. Normal = normal attachment of septum primum