Genetics Corner: Genetic Counseling and Family Screening after Prenatal Diagnosis Of Hypoplastic Left Heart Syndrome: Is It Warranted?

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Case Summary:

A 33-year old G2P1 Lebanese woman was referred for consultation to high-risk obstetrics at an outside hospital because of preterm delivery at 34 weeks gestation in her first pregnancy. The nuchal translucency measurement and first trimester maternal serum screening tests were normal in the current pregnancy. A comprehensive fetal ultrasound exam at 18 weeks gestation revealed a small left ventricle, suggesting hypoplastic left heart syndrome in an otherwise normal male fetus. The patient was referred to our institution for a fetal echocardiogram that confirmed hypoplastic left heart syndrome with severe hypoplasia of the left ventricle, mitral hypoplasia, aortic atresia, and endocardial fibroelastosis. In anticipation of the need for cardiac surgery after delivery, her prenatal care was transferred to our tertiary care facility. Although tricuspid regurgitation was noted on subsequent fetal echocardiograms, interval fetal growth was appropriate, and no extracardiac anomalies were present. The patient and her partner, who is also Lebanese, were counseled about the poor prognosis for survival, and, at 36.5-weeks' gestation, they are considering palliative care versus surgical repair. The patient denied other affected relatives. The pediatric cardiologist recommended genetic testing after delivery.

The Challenge:

The prenatal genetic counselor suggested a genetic counseling appointment and screening echocardiograms for family members, but the maternal-fetal medicine attending physician felt that this was not indicated. We took up the challenge posed by our MFM colleague and sought data to address his concerns:

1. Is genetic counseling warranted in families with prenatally diagnosed isolated HLHS in the absence of other anomalies or positive family history?

2. Is a screening echocardiogram justified in the first-degree relatives of patients with HLHS?

Summary of Medical Literature:

Hypoplastic left heart syndrome (HLHS) is the most severe expression of left ventricular outflow tract obstruction (LVOTO), which describes a related group of congenital left-sided heart defects that includes Shone complex, coarctation of the aorta (COA), congenital aortic valve stenosis (AVS) and bicuspid aortic valve (BAV). Familial clustering of LVOTO lesions has been reported in many epidemiologic studies and prospective studies of first-degree relatives of affected patients.

BAV and/or thoracic aortic aneurysm (TAA) are inherited in an autosomal dominant manner with variable expression and incomplete penetrance (OMIM 109730). Isolated aortopathy or TAA has been reported in first-degree relatives of patients with BAV. The incidence of BAV in first-degree family members of individuals with BAV is as high as 9-10%, and routine echocardiographic screening of all first-degree relatives has become standard practice at many institutions. The 2010 guidelines endorsed by the American College of Cardiology/American Heart Association and the American Association for Thoracic Surgery include a class I recommendation that first-degree relatives of patients with BAV undergo screening for BAV and asymptomatic thoracic aortic disease. Given the risk of early dissection and death, ongoing echocardiographic screening of relatives at regular intervals is recommended by some authors whether BAV is present or not.

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The incidence of congenital cardiovascular malformations in first-degree relatives of patients with HLHS is even higher. An increased incidence of congenital cardiovascular malformations in family members of HLHS probands was first reported by Brenner et al. (1989) in the Baltimore-Washington Infant Study. These authors found cardiac anomalies in 5/41 relatives (12%) of 11 patients with isolated HLHS. Since that time, a variety of primarily left-sided cardiac lesions has been reported in up to 17% of family members of HLHS probands.

Hypoplastic left heart syndrome has been described in families with both autosomal dominant and autosomal recessive inheritance patterns (OMIM 241550, 614435). Wessels et al. (2005) described four families with a presumed autosomal dominant inheritance of LVOTO: some members had severe anomalies such as HLHS, and others had only AVS. The authors concluded that all anomalies of the LVOTO spectrum are developmentally related.

Hinton et al. (2007) studied 38 probands with HLHS and their families. Overall, 21 of 38 (55%) families had more than one affected individual. The heritability of HLHS alone and with associated cardiovascular malformations was 99% and 74%, respectively. The sibling recurrence risk for HLHS was 8% (4/51), and for cardiovascular malformations, 22% (11/51).

McBride et al. (2005) studied 124 families ascertained by an index case with AVS, COA, or HLHS. Results were positive in 32/413 relatives (7.7%): LVOTO malformations were detected in 30 relatives, and significant congenital heart defects in 2 others. The relative risk for first-degree relatives in this group was 36.9, with a heritability of 0.71-0.90, implying a complex but most likely oligogenic pattern of inheritance.

In their review of 52 HLHS probands, Kelle et al. (2015) obtained echocardiograms on 152/188 first-degree relatives, with complete screening performed on 34/52 families. A cardiovascular anomaly was identified by echocardiography in 17/152 (11.2%), and 11/17 diagnoses (65%) were previously unknown. Overall, at least one affected family member was identified with a cardiovascular malformation in 14/52 families (26.9%). There was more than one affected relative in 3/52 families. Abnormalities were found in 5/46

fathers (10.9%), 5/51 mothers (9.8%), and 7/55 siblings (12.7%). Four relatives had isolated BAV, and one relative had BAV with dilated aortic root and COA for a total incidence of BAV in 3.3% (5/152). Four family members had aortic dilation with normal valves. One mother, who had a history of chest pain with exercise, had an anomalous origin of the right coronary artery that required surgery. Interestingly, chromosome microarray identified duplications or deletions in 9/48 probands, but no significant difference in the occurrence of familial cardiac lesions was observed based on proband microarray anomaly.

"This supports our recommendation for genetic counseling and screening first-degree relatives following the prenatal or postnatal diagnosis of HLHS, even when it is present as an isolated anomaly and without a significant family history. "

Conclusions:

Data from various reports in the medical literature support the high heritability of LVOTO lesions and specifically the genetic nature of HLHS. This supports our recommendation for genetic counseling and screening first-degree relatives following the prenatal or postnatal diagnosis of HLHS, even when it is present as an isolated anomaly and without a significant family history. Genetic counselors have an important role in the management of HLHS by documenting the family history, counseling families about the increased recurrence risks for cardiovascular malformations in general, and HLHS in particular and supporting efforts to screen first-degree relatives.

Practical Applications:

1. Recognize that HLHS is a genetic disorder with an increased recurrence risk for HLHS and other cardiovascular malformations in future pregnancies.
2. Refer families of patients with HLHS for genetic counseling.
3. Document congenital cardiovascular malformations in the family by taking a careful three-generation family history.
4. Inform family members of individuals with HLHS and other LVOTO about the increased risk of asymptomatic thoracic aortic dilation and/or BAV and subsequent increased risk for aortic aneurysm and dissection
5. Recommend screening echocardiograms for first-degree relatives of patients with HLHS and other LVOTO lesions

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References:

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The authors have no relevant disclosures.

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