

EDITORIAL COMMENT

Hypoplastic Left Heart Syndrome

It Is All in the Genes*

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In 1851, the German pathologist Barbedelan reported the autopsy findings of a 6-month-old infant who died from severe asphyxia (1). Evaluation of the cardiac anatomy revealed hypoplasia of the left ventricular cavity without communication to the aorta, severe hypoplasia of the ascending aorta, and a ductus arteriosus. Barbedelan hypothesized that the systemic circulation was dependent on patency of the ductus arteriosus.

One hundred years later, Lev (2) published the first report in the English literature of an infant with hypoplasia of the left sided structures, similar to those described by Barbedelan. In 1958, Noonan and Nadas (3) published a series of 101 patients with hypoplasia of the left heart structures and proposed the term hypoplastic left heart syndrome (HLHS). Currently, HLHS is conventionally defined as hypoplasia of the left ventricular chamber, stenosis and/or atresia of the mitral and aortic valves, and hypoplasia of the aorta.

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Despite remarkable advances in the clinical care of HLHS, this defect remains one of the most challenging and least-understood forms of congenital heart disease. During the last 50 years, there have been increasing reports supporting a genetic etiology for HLHS (4): numerous cases have been reported describing HLHS in siblings, including twins. Several specific chromosomal disorders have been associated with an increased frequency of HLHS, and there is a high frequency of extracardiac defects associated with HLHS. Most recently, 2 studies have identified an increased frequency of congenital heart defects in relatives of patients with HLHS (5,6).

Most forms of inheritance have been described, including autosomal-dominant, autosomal-recessive, and X-linked.

Despite this, some investigators have proposed that HLHS is multifactorial, placing a lesser role on a sole genetic etiology (7). To date there are no genetically engineered animal models for HLHS.

In this issue of the *Journal*, Hinton et al. (8) performed a comprehensive statistical analysis on 38 families of infants with HLHS to determine the heritability component of HLHS. They concluded that HLHS was almost exclusively the result of a genetic cause. Fifty-five percent of the families had more than 1 affected family member. The recurrence rate for HLHS among siblings was 8%. Twenty-two percent of siblings had another cardiovascular malformation (CVM). If a parent had a CVM, 21% of siblings had HLHS, and 26% had another CVM. Overall, the recurrence rate of HLHS in siblings was 515-fold greater than that of the general population, and 1,050-fold higher when a parent had a CVM. Taken together, HLHS has one of the strongest genetic components of any congenital heart defect.

The clinical implications of a genetic etiology for HLHS are substantial. On the basis of the high frequency of first-degree relatives with heart defects, all first-degree relatives should have a baseline echocardiogram. Second, because of the high recurrence rate of CVMs, and in particular HLHS, a detailed fetal echocardiogram should be performed by a pediatric cardiologist on subsequent fetuses in families with a previous child with HLHS. Third, on the basis of the findings of Hinton and previous recent studies, improved genetic counseling can be offered to all families with a child with HLHS.

Although significant advances have been made in the clinical care of patients with HLHS, our understanding of the underlying molecular and genetic mechanisms of HLHS is limited. In 1970, Harh et al. (9) reported the development of a chick model for HLHS. Recently, deAlmeida et al. (10) demonstrated that ligation of the left atrium in the chick, which decreased prograde blood flow to the left ventricle, caused left ventricular hypoplasia in association with cardiac myocyte hypoplasia. Importantly, they demonstrated that increasing prograde flow to the left side of the heart resulted in a "hemodynamic rescue" of the HLHS phenotype.

It is likely that at least some cases of HLHS are due to genetically predisposed decreased inflow to the developing left heart. In the current study, Hinton et al. (8) demonstrated that in virtually all cases of HLHS, the aortic and mitral valves were abnormal. They also frequently found abnormalities in the tricuspid and pulmonary valves. These observations suggest that, in the majority of patients, HLHS may be due to a primary defect in valve development, leading to hypoplasia of the left-sided structures. Alternatively, some forms of HLHS may be due to a primary defect in left ventricular development. For example, in some patients with critical aortic stenosis, relief of aortic valve obstruction does not prevent the development of left ventricular hypoplasia (11).

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To date, putative mutations in only a few genes have been identified in association with HLHS patients: Connexin43 (12) and NKX2.5 (13,14). Connexin43 is a cardiac gap junction protein that is critical for heart development. Mutations in the cardiac transcription factor NKX2.5 have been identified in a small number of patients with HLHS. Most recently, mutations in NOTCH-1 were identified in 2 families with left-sided heart defects, most commonly aortic valve defects (15). One family member had a variant of HLHS. Overall, mutations in these 3 genes comprise a very small subset of patients with HLHS, consistent with multiple causative genes for HLHS.

Clearly, most of the disease-causing genes for HLHS remain to be identified. Significant challenges lie ahead as investigators move toward the identification of new genes for HLHS. First, the number of genes likely to cause HLHS and the paucity of kindreds with a large number of affected individuals makes linkage studies difficult. Second, at least in some cases there is incomplete penetrance for HLHS (see discussion to follow). Consequently, potential disease-causing mutations in affected individuals also may be identified in the normal control population, thereby making it difficult to prove causality for a candidate gene.

Many interesting questions persist: 1) Will most of the genes that cause HLHS be involved in valve development, or could they be involved in other aspects of heart development (e.g., left ventricular development)? 2) What is the basis for the phenotypic variability in families with left-sided heart defects? That is, what determines whether a genetically predisposed individual develops a relatively mild defect such as bicuspid aortic valve, versus the most severe defect, HLHS? 3) What factors determine incomplete penetrance for some cases of HLHS? For example, in the 11q terminal deletion disorder (Jacobsen syndrome), in which 10% of infants are born with HLHS (16), 2 patients with the identical deletion had completely different cardiac phenotypes: a normal heart in 1 and HLHS in the other. Identification of these genetic and/or environmental modifiers should give important additional insights into the mechanisms underlying HLHS.

Despite the formidable challenges, there is cause for optimism. Using a similar approach, Hinton et al. (8) determined previously that a bicuspid aortic valve has a strong genetic component (17). They were able to subsequently identify 3 chromosomal loci that may contain disease-causing genes for bicuspid aortic valve (18). For deletion disorders, recent technical advances allow breakpoint mapping to be performed to single gene resolution. Consequently, potential "critical regions" can be defined with unprecedented resolution, which should facilitate the identification of candidate genes.

Undoubtedly, studies such as those of Hinton et al. (8) will not only help improve genetic counseling for patients with HLHS but also reinforce and validate the importance of efforts to identify new genes for HLHS. Identification of new genes that cause HLHS and the development of genetically engineered animal models for HLHS is certain

to bolster our understanding of this devastating form of congenital heart disease, as well as the other more common but less severe left-sided cardiac defects.

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