Genetics of Hypoplastic Left Heart Syndrome

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Hypoplastic left heart syndrome (HLHS; MIM#241550) is a severe congenital heart defect (CHD). Hypoplasia of the left ventricle (LV) and aorta are cardinal features, but the pathologic definition also includes atresia or stenosis of both the aortic and mitral valves.[1] However, in HLHS the ventricular septum is intact and the great arteries are normally related. Although emphasis has been on left-sided heart structures, dysplasia of both tricuspid and pulmonary valves is frequently reported.

The prevalence of HLHS is 2.6 per 10 000 births, but only 1.6 per 10 000 live births.[2] However, despite the low prevalence, HLHS accounts for approximately 4%-8% of all CHD.[3,4] HLHS is slightly more common in males, but there is no ethnic or geographic association. HLHS usually results in a viable fetus in utero, but without surgical intervention, it is lethal during infancy. Although heart transplantation is a treatment option, therapy usually revolves around a 3-stage palliative surgical strategy (Figure 1). The right ventricle is recruited to be the systemic ventricle and pulmonary circulation is driven by gravity and atrial pulsations. Thus, this palliative surgery creates a circulatory system with a single ventricle that directs oxygenated blood to the systemic circulation and most unoxygenated blood to the pulmonary circulation.

Despite Progress in Management, Concerns Persist

Even though there are only ~2000 HLHS live births annually in the US, the HLHS burden is substantial. HLHS accounts for ~25% of deaths among infants with CHD,[5] and only 50%-70% of newborns survive to age 5 years.[1] The majority of these deaths occur prior to the first surgical stage,[6] but interstage mortality occurs in 12% of patients.[7] The mortality, morbidity, and utilization of a disproportionate share of pediatric resources make HLHS a central problem in pediatric cardiology.

Longer term prognosis for patients with HLHS is disappointing. Compared with healthy controls, infants with HLHS have delayed motor development[8,9] and worse cognitive functioning[10-12] across all ages. The Single Ventricle Reconstruction Trial sponsored by the Pediatric Heart Network demonstrated that the poor neurodevelopmental outcomes were associated more with innate patient factors than intraoperative management.[13] In addition to the surgical interventions, survivors with HLHS face long-term health care burden and comorbid conditions resulting in high health care resource utilization.[14-16]

It is noteworthy that the delineation of the extended natural history of HLHS has just begun as the current surgical intervention was first implemented in the 1980s. Some long-term survivors with HLHS are now in their mid-30 years of age.[17] Since the inception of the staged surgical reconstruction, reductions in mortality have occurred, further increasing the survivorship to adulthood. Indeed, comparing the prevalence of adults with HLHS in 2000 with 2010, there is an increase of 2 per 10 000 cases.[18,19] The adult population with HLHS is expected to grow in the next decade.[17] Thus, post-intervention natural history is a concern.

Strategies to Address Present Concerns

The challenge facing the field is whether refinements in current management approaches in the fetus[20] and/or neonate, which focus primarily on restoring the blood flow pattern, can ameliorate the present concerns regarding outcomes. Alternatively, it may be that a substantial barrier to further progress in HLHS management is the lack of an understanding of the pathogenic mechanism for this heart malformation. For example, it has been speculated that the origins of underlying CHD are not limited to the obvious heart defect but may have additional manifestations that become evident later in postnatal life.[21,22] As such, future advances in clinical management of HLHS may be limited until better understanding of the pathogenic mechanisms leading to the cause of this clinically important birth defect.

Current Understanding in the Pathogenesis of HLHS

Concepts of cardiac development have greatly influenced our understanding of the formation of the mesoderm derived, 4-chambered vertebrate heart. Human genetic studies have identified mutations in genes important for early heart formation that cause CHD, supporting the idea that these birth defects are caused by alterations during cardiogenesis.[3-27]

BAV	Bicuspid aortic valve
CHD	Congenital heart defect
CNV	Copy number variants
HLHS	Hypoplastic left heart syndrome
LV	Left ventricle

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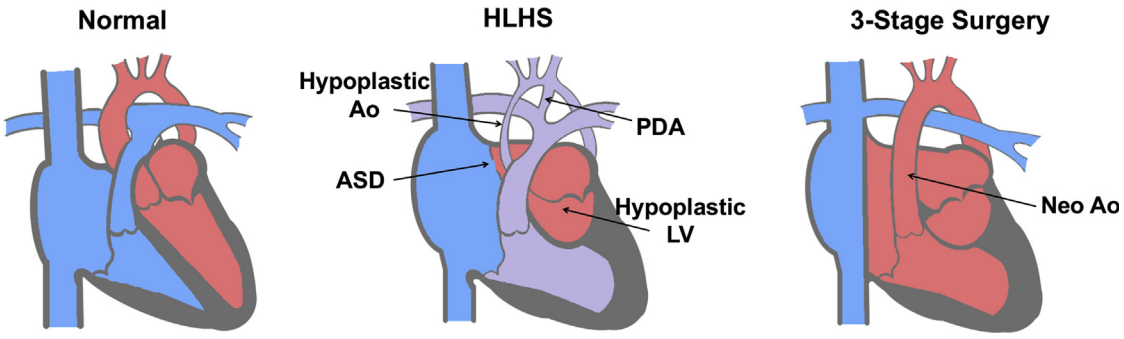

Figure 1. Pre- and post-operative HLHS anatomy. Features of HLHS include: (1) hypoplastic ascending aorta (Ao); (2) hypoplastic LV; (3) large patent ductus arteriosus (PDA), supplying the only source of blood flow to the body; and (4) an atrial septal defect (ASD). These abnormalities result in a mixture of oxygenated and unoxygenated blood to the body. The 3 surgical stages result in PDA ligation and creation of a neoaorta (Neo Ao) so that the right ventricle ejects most oxygenated blood to the body. Later, a baffle that guides most unoxygenated blood coming from the lower extremities into the pulmonary arteries is created in the right atrium.

There has been considerable interest in CHD such as HLHS, in which individual chambers or valves of the developing heart are selectively impaired.[23] A widely accepted hypothesis is that HLHS develops as a result of embryonic alterations in blood flow, such as premature narrowing of the foramen ovale[28] or aortic valve obstruction.[29] In this light, it is noteworthy that valve malformation is a prominent part of the HLHS phenotype as evidenced by the frequent occurrence of left- and right-sided valve dysplasia in HLHS probands and the presence of bicuspid aortic valve (BAV) in family members.[30] This "no-flow, no-grow" hypothesis of heart maldevelopment is also supported by studies of altered blood flow during cardiac development.[31-35] An alternative hypothesis for HLHS etiology focuses on the summation of the coordinated actions of signaling pathways and gene regulatory networks that guide the complex process of heart development. Recent studies have investigated chamber-specific regulatory mechanisms, eg, TBX5 and IRX1, leading to formation of morphologically, functionally, and molecularly distinct cardiac chambers.[23,24] In this context, it has been suggested that LV hypoplasia may result from a primary defect in myocardial growth during development. Currently, there are no experimental models to elucidate the relative contribution of these hypotheses, but defining the genetic underpinnings of HLHS should enlighten the debate.

Evidence that HLHS has Genetic Origins

Several lines of evidence support a genetic cause for HLHS. Overall, approximately 30% of fetuses with HLHS have genetic syndromes and/or the presence of extra-cardiac structural abnormalities.[36-38] There are numerous reports linking HLHS occurrence to chromosomal abnormalities, eg, Turner syndrome (monosomy X), trisomy 18, DiGeorge (22q11.21-2 deletion), and Jacobsen syndrome (chromosome 11q deletion).[38-41] Less frequently, microdeletions in 1q211 have been reported.[41] HLHS has also been associated with non-chromosomal genetic syndromes such as Smith-Lemli-Opitz syndrome, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association, Rubinstein-Taybi syndrome, Noonan syndrome, and Holt-Oram syndrome.[42-49] However, incomplete phenotype detail in many of these case reports raises the possibility that rather than HLHS, observed LV hypoplasia was associated with another type of CHD, eg, unbalanced atrioventricular septal defect in Holt-Oram syndrome.

A second line of evidence supporting genetic origins of HLHS is the strong familial clustering of HLHS with other CHD in families. An increased prevalence of CHD in families ascertained by an HLHS proband was identified in the Baltimore-Washington Infant Study over 30 years ago and verified in more recent studies.[3,50-52] Studies have also used heritability (h^2, a statistical measure of genetic effect size) to quantify this familial patterning. In a family-based study where all participants were screened for CHD by echocardiography, Hinton et al[30] determined HLHS heritability was very high (>0.9). Other investigators found high heritability using a family-based analysis of phenotypically related left-sided heart malformations.[51,53]

A third line of evidence comes from use of linkage analysis to identify genomic regions that encode genes influencing the inheritance of HLHS. Hinton et al[54] used nonparametric linkage analysis and identified 2 significant loci on chromosomes 10q22 and 6q23. These findings confirmed that nonsyndromic HLHS is genetically heterogeneous. Interestingly, ~21% of kindreds contributed to linkage at each locus, suggesting these loci account for a substantial number of HLHS cases. Further, a suggestive HLHS locus on 11q22, previously identified in a case of HLHS with a balanced translocation, t (10; 11) (q 24; q 23), validated these analyses.[55] When the linkage approach was extended to a family-based cohort ascertained by either an HLHS or BAV proband, subsets linkage analysis showed a significant improvement in the