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Genetic Contribution to Neurodevelopmental Outcomes in Congenital Heart Disease: Are Some Patients Pre-Determined to Have Developmental Delay?

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Abstract

Purpose of review—Neurodevelopmental impairment is common in children with moderate to severe congenital heart disease. As children live longer and healthier lives, research has focused on identifying causes of neurodevelopmental morbidity that significantly impact long-term quality of life. This review will address the role of genetic factors in predicting neurodevelopmental outcome in CHD.

Recent findings—A robust literature suggests that among children with various forms of congenital heart disease, those with known genetic/extracardiac anomalies are at highest risk of neurodevelopmental impairment. Advances in genetic technology have identified genetic causes of congenital heart disease in an increasing percentage of patients. Further, emerging data suggest substantial overlap between mutations in children with congenital heart disease and those that have previously been associated with neurodevelopmental disorders.

Summary—Innate and patient factors appear to be more important in predicting neurodevelopmental outcome than medical/surgical variables. Future research is needed to establish a broader understanding of the mutations that contribute to neurodevelopmental disorders and the variations in expressivity and penetrance.

Keywords

congenital heart disease; genetics; brain; neurodevelopment

Introduction

Congenital heart disease (CHD) is the most common birth defect, with moderate or severe disease occurring in six per 1000 live births.[1] Greater survival in recent decades has shifted the focus to improving long-term quality of life, and in particular, reducing the burden of neurodevelopmental disability. In 2012, the American Heart Association released a statement endorsed by the American Academy of Pediatrics highlighting the high

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prevalence of neurodevelopmental disorders in this population and recommending routine evaluation and treatment in certain subgroups of children with CHD.[2]

Paralleling the enhanced interest in neurodevelopmental outcomes has been a remarkable leap in genetic technology, providing insight into the mechanisms of disease. Genetic factors have long been considered a dominant cause of CHD, in part due to strong heritability.[3] Recent advances have accelerated the identification of specific disorders, ranging from single gene disorders causing isolated CHD (e.g., GATA4) to complex multi-system disease.[3, 4] Whereas genetic abnormalities are identified in up to 50% of children with CHD and recognizable syndromes, even among non-syndromic, sporadic cases, up to 10% of patients demonstrate deleterious *de novo* mutations when tested with whole exome sequencing. That percentage increases to 20% when the analysis is confined to those with co-existing neurodevelopmental disorders and extracardiac anomalies.[5]

This review will address the role of genetic factors in predicting neurodevelopmental outcome in CHD. We will describe not only the known associations between syndromic CHD and neurodevelopment but also emerging research that harnesses advanced technology to demonstrate shared genetic pathways between heart and brain development. Ultimately, this line of research has the potential to identify high-risk patients early and facilitate neurodevelopmental risk stratification, thereby improving targeted treatment.

Neurodevelopment and CHD

Neurodevelopmental disabilities are common among children with CHD, with the prevalence varying widely depending upon the severity of heart disease and co-existing conditions. Domains frequently affected include executive function, attention and self-regulation, visuospatial skills, and social cognition.[6–10] Psychiatric morbidity (e.g., anxiety) is also emerging as an important consideration.[11] These neurodevelopmental and behavioral challenges significantly impact academic achievement. In one large cohort of adolescents with single ventricle, nearly 90% of subjects required developmental/educational services; over one-third had received special education and nearly a quarter experienced grade retention.[12] Given the burgeoning number of survivors with critical CHD, neurodevelopmental and behavioral disabilities affect not only the individual child and family, but also exert a significant societal burden.

Influences on Neurodevelopment

Early studies examined perioperative and surgical factors, yet increasingly data suggest that non-modifiable patient factors are important influences on neurodevelopment.[8, 13] Not surprisingly, maternal education and socioeconomic status are frequently associated with neurodevelopmental outcome in CHD.[7] Similarly, birth weight and gestational age, even near-term birth, are important predictors.[7, 14, 15] Worse neurodevelopmental outcome has also been associated with medical and surgical factors, for example, elevated lactate and S100B (a sensitive biomarker for acute brain injury), longer total support time, or need for extracorporeal membranous oxygenation or a ventricular assist device. Neuroresilience genotypes, particularly the apolipoprotein ε2 allele, also appear to contribute to development after open heart surgery.[13, 15, 16]

Fetal Brain Development

Recently, neonatal and fetal brain MRI studies have indicated that brain structure appears altered in CHD even before birth. Brain MRI studies evaluating microstructural, macrostructural, and metabolic indicators of brain maturity in preoperative term neonates with CHD suggest dysmature/immature brain development, with a total brain maturational score equivalent to that of infants born approximately one month earlier.[17–20] Similarly, fetuses with CHD have approximately 10% smaller total brain volumes than healthy fetuses *in utero*, with delays in cortical development detected in fetuses with hypoplastic left heart syndrome as early as 25 weeks gestation.[21–23] Thus, pathophysiologic processes impeding structural brain development likely precede birth.

Abnormal fetal perfusion and/or oxygenation may play a role in fetal brain abnormalities. In hypoplastic left heart syndrome, for example, *in utero* blood flow to the brain is abnormal, such that in severe cases, blood must flow retrograde via the ductus to reach the brain. In other lesions, such as D- transposition of the great arteries, relatively deoxygenated blood is recirculated to the fetal brain, while the higher oxygen content blood from the placenta is directed towards the body. These aberrations in cerebral perfusion and oxygen content may be one factor impairing brain growth and development. Supporting this mechanism, infants with D-transposition of the great arteries show smaller head growth relative to somatic size, and a recent phase-contrast fetal MRI study demonstrated correlations between fetal brain weight and fetal cerebral oxygen consumption and ascending aortic arch saturation.[23, 24] Whereas fetal perfusion and oxygenation may play an important role in altered prenatal brain development, innate genetic factors are an alternative, or perhaps additive explanation. Future large, multi-center studies will need to investigate the variability in prenatal brain structure that may be explained by genetic influences.

Genetics Causes of CHD

The genetic basis of CHD is complex and incompletely understood. CHD is highly heritable, with one landmark population-based study in Denmark identifying a more than three-fold risk among first-degree relatives of CHD patients.[3] CHD can occur in isolation or as part of a recognizable phenotype characterizing a syndrome. Among identified syndromes, some have well established neurodevelopmental associations (e.g., trisomy 21) while others are often without coexisting neurodevelopmental issues (e.g., Holt-Oram). Single gene disorders, copy number variants, and chromosomal aneuploidy conditions have been associated with congenital heart disease and neurodevelopmental abnormalities. Several reviews highlight the increasing identification of genetic abnormalities among the cardiac population.[4, 25, 26] To date, it has been shown that approximately 40% of familial CHD, 20% of sporadic CHD, and 50% of CHD with extracardiac congenital anomalies have an identifiable genetic etiology.[25]

Genetics Influences on Neurodevelopment in CHD

Early and long-term neurodevelopmental outcome studies have suggested a strong genetic contribution to neurodevelopment in CHD. Whereas few studies have performed routine

genetic testing or universal clinical exams as part of the study protocol, most stratify for genetic or extracardiac anomaly detected during routine clinical care.

One multi-center study of over 1700 subjects with various forms of moderate/severe CHD evaluated with the Bayley Scales of Infant Development – Second Edition (BSID-II) at 15 months found that definite/suspected genetic or extracardiac abnormality was associated with significantly reduced mental development and psychomotor indices.[7] Similarly, in the Single Ventricle Reconstruction (SVR) trial, approximately 80% of subjects underwent clinical or research genetic evaluations, and those who were classified as having genetic syndrome/other anomalies scored lower on the BSID-II mental development index at 14 months of age.[27] Carey and colleagues evaluated infants who participated in the SVR trial as well as those who participated in the similar Infants with Single Ventricle (ISV) trial to assess the frequency of pathogenic copy number variants and associated outcomes. Infants with putatively pathogenic copy number variants that had been previously associated with known genomic disorders had globally lower scores on the BSID-II than those without pathogenic copy number variants.[28]

Shifting to late outcomes, in a study of adolescents who underwent the Fontan procedure, those with definite or suspected genetic abnormality based upon clinical examination and chromosomal microarray testing had lower full-scale IQ, higher autism spectrum quotient, and were more likely to require special developmental/education services.[12] Similarly, among 91 adolescents with tetralogy of Fallot, approximately one-quarter of whom had a genetic abnormality based on medical history or laboratory testing, those with genetic abnormalities scored broadly lower on measures of intellectual ability, academic achievement, and executive functioning.[6] Those with a genetic abnormality also had lower physical and psychosocial health-related quality of life.[29] Collectively, these data indicate a strong association between genetic abnormalities and neurodevelopmental outcome in CHD that persists from early childhood through adolescence.

Specific Genetic Abnormalities

Single gene disorders include the RASopathies and commonly identified syndromes such as CHARGE, Alagille, and Kabuki. The most well-known among the RASopathies is Noonan syndrome, often characterized by distinct facial features, short stature, a broad/webbed neck, and widely spaced nipples. The most common cardiac findings are pulmonary valve stenosis, atrial septal defect, or hypertrophic cardiomyopathy. Children with Noonan syndrome may have early motor delays, often secondary to hypotonia. Increasing evidence also suggests that while the majority of children with Noonan syndrome function in the general education setting, reduced executive functioning and high rates of ADHD are often present.[30, 31] Children with cardiofaciocutaneous syndrome may have similar facial, growth, and cardiac features but typically have more severely affected cognitive status.[32] Children with Costello syndrome have cognitive issues that fall on a spectrum between Noonan syndrome and cardiofaciocutaneous syndrome; developmental delay or intellectual disability is present in all individuals.[33] The neurodevelopmental prognosis for children with CHARGE syndrome (an acronym for Coloboma, Heart defects, choanal Atresia, Retardation of growth and development, Genital anomalies, and Ear anomalies) is

complicated by the common complications of significantly compromised vision and/or hearing and it has been shown that microcephaly, brain malformation, and extensive bilateral coloboma resulting in reduced vision are predictive of poor intellectual outcome in 25% of individuals.[34] Finally, Kabuki syndrome, another single gene disorder, is also associated with neurodevelopmental delays; preliminary studies have suggested children have relative strengths in verbal and nonverbal reasoning, with relative weakness in visuospatial skills.[35]

Copy number variants in which chromosomal deletions or duplications alter the gene dosage of multiple genes simultaneously are implicated in multiple well known CHD syndromes including 22q11 deletion syndrome (also known as velocardiofacial or DiGeorge syndrome), Williams syndrome, 1p36 deletion syndrome, and 1q21.1 duplication. All of these disorders are associated with significant developmental delays and cognitive abnormalities as are whole chromosomal aneuploidies including Trisomies 13, 18, and 21 and Turner syndrome (monosomy X). These disorders are well studied, and the specific details of the neurodevelopmental outcomes are beyond the scope of this review.

A number of genes have been reported in association with isolated (non-syndromic) CHD including *NKX2.5, GATA4, ELN, NOTCH1, and TBX20* and are thought to explain about 10% of nonsyndromic CHD.[36] To date these genes have not been linked to an increased risk of neurodevelopmental complications beyond those associated with complex CHD.

Massively Parallel Sequencing

Massively parallel sequencing technology (MPS), such as whole exome and whole genome sequencing, holds great potential for elucidating the genetic connections between heart and brain disease, yet the science remains in its infancy. In one landmark study, more than 350 parent-child trios, comprised of children with sporadic severe CHD and no known genetic diagnosis, underwent whole exome sequencing.[5] Not surprisingly, researchers identified strong enrichment of loss of function/damaging missense mutations particularly among those genes with high heart expression. However, they also identified marked overlap between these “damaging” *de novo* mutations and previously reported mutations associated with neurodevelopmental disorders, particularly those of chromatin modifiers. Among those subjects who had CHD and a neurodevelopmental disorder, the risk was particularly increased. Thus, substantial overlap may occur between the genetic mutations that cause CHD and those that cause neurodevelopmental disorders. In the future, those children with mutations in these shared pathways may be identified as those for whom early developmental services are especially indicated. These emerging findings also provide important mechanistic insight into the overlap of CHD and neurodevelopmental disorders.

Conclusion

Early in the discovery of neurodevelopmental disorders in CHD, medical and particularly operative variables were the focus of prospective and cross-sectional clinical studies because they had the potential to be modified and thereby improve the long-term trajectory for a child with CHD. Over the past ten years, evidence has emerged that abnormalities in brain structure are present at and even before birth, and that further mitigation of

neurodevelopmental sequelae will require not only optimization of postnatal management, but also understanding the innate genetic and prenatal contributors to brain development. Future large, multi-institutional studies will be needed to study the percent variability in neurodevelopmental outcome that is contributed by prenatal hemodynamic and genetic factors on brain development, as well as the interaction between these factors and the postnatal environment in determining outcomes. Moreover, shifting technological advances (e.g., whole exome sequencing) into routine clinical practice will establish a broader understanding of the mutations that contribute to neurodevelopmental disorders and the variations in expressivity and penetrance. Ultimately, refinements in early identification of the patients at highest risk of developmental disorders will allow clinicians to tailor the intensity and focus of early intervention services to neurodevelopmental risk level, a critical triage for a relatively scarce resource, and will improve counseling for families.

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Key Points

- Genetic abnormalities are identified in up to 50% of children with syndromic CHD, and at least 10% of children without a recognizable clinical phenotype.
- Neurodevelopmental impairment is common in children with CHD, and those children who have genetic/extracardiac abnormalities are consistently shown to be at highest risk.
- Smaller brain volumes and dysmature brain structure are seen in neonates and fetuses with CHD suggesting that innate and/or prenatal factors may play an important role in altering brain development.
- Marked overlap exists between deleterious *de novo* mutations and previously reported mutations associated with neurodevelopmental disorders, suggesting that substantial overlap may occur between the genetic mutations that cause CHD and those that cause neurodevelopmental disorders.