Review Article

Neurodevelopmental outcomes secondary to congenital heart disease

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ABSTRACT

Congenital heart disease (CHD) affects millions of newborns every year which is about 6–8 per 1000 live births. CHD has a considerable impact on mortality and morbidity, with a global death rate of 3.9 per 100,000 live births as of 2017. CHD is a broad term that includes cyanotic-acyanotic defects, conotruncal and non-conotruncal defects, hypoplastic left heart syndrome (HLHS), valvular anomalies, total anomalous pulmonary venous return (TAPVR) and cardiac septal defects. The lengthy hospitalization required for CHD patients limits experience-dependent adaptability and experience-dependent motor development, increasing their risk of neurodevelopmental delays. About 25% of CHD cases require surgical management which by itself increases the risk of these delays. Early identification and consistent follow-up have been shown to enhance neurodevelopmental outcomes. The use of Cardiac Neurodevelopmental Outcome Collaborative 0-5 neurodevelopmental assessment improves the accuracy of the diagnosis of developmental delay in CHD patients and opens the door to early intervention, improving behavioral, psychological, and academic functioning. To improve the quality of life the AHA has endorsed the importance of early intervention through the use of surveillance, screening, evaluation, and re-evaluation for neurodevelopmental delays. This review article focuses on the pathophysiology of neurodevelopmental delays in CHD patients, its diagnosis as well as its management to improve neurodevelopmental outcomes.

Key words: Congenital heart disease, genetic syndrome, Hypoplastic left heart syndrome, Valvular anomalies

Congenital heart disease (CHD) is a structural abnormality of the heart and affects millions of newborn infants annually (6-8 per 1000 live births) [1]. CHD contributes significantly to mortality and morbidity [2] and the global adjusted standardized mortality rate as of 2017 is 3.9 per 100,000 live births. Approximately 20% of CHD incidence is attributed to genetic syndromes (30% of pediatric patients) [3], teratogen exposure, or maternal diabetes. Still, the causes of the remaining 80% of cases are uncertain [4]**.** CHD shows an ethnic variation of being more common in Blacks and Asians, more in Asian Muslims than Asian Hindus, which might be attributed to consanguineous marriages [5, 6]. Mild CHD lesions are more prevalent in Asia than in Europe and America [7]. The spectrum of CHD is vast, including cyanotic-acyanotic defects, conotruncal and non-conotruncal defects, hypoplastic left heart syndrome (HLHS), valvular anomalies, total anomalous pulmonary venous return (TAPVR) [8] and cardiac septation defects, such as atrial septal defects (ASD), ventricular septal defects (VSD), and atrioventricular septal defects (AVSD) [9]**.**

Isolated septal defects such as VSD (3570 per million births) and ASD (941 per million births) are the most common anomalies [10]. Depending on the mild, moderate, or severe lesions category, a child may require no medical or surgical intervention at birth. Children with CHD have to undergo prolonged treatment and hospitalization, which prevents adaptability and motor development. [11, 12] and thus are at increased risk of developing neurodevelopmental delays. A characteristic pattern of a high frequency of low-severity or combined disabilities in the sectors of visual motor integration, language, motor skills, attention, executive function, and behavior has been narrated in numerous studies [13, 14]. The highest risk is present in infants of a single ventricle physiology (SVP), especially those with HLHS [15]. Around 25% of all CHDs require an early diagnosis and surgical correction in the first few months after birth [16]. Following surgical treatment of CHD, several risk factors can lead to developmental delays, which include prenatal,

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preoperative and perioperative factors, which can be nonmodifiable like genetic diseases.

Some are modifiable like cardiopulmonary bypass time, use of deep hypothermic circulatory arrest, and perioperative hemodynamic instability or cardiac arrest [17-19]. Children possess altered micro brain structures with reduced connectivity leading to various impairments including cognitive impairments persisting of low IQ, impaired visuospatial skills, reduced executive function, impaired attention, and working memory; motor impairments (especially in children with single ventricle anomaly) such as impaired balance, reduced manual dexterity, and decreased strength [20-22]. Neurodevelopmental impairments such as motor delays, problems with visual-motor integration, mental retardation, and learning disabilities as well as behavioral abnormalities, including inattention and hyperactivity can also be caused due to CHD [23].

Due to advances in diagnostic, medical, and surgical management modalities over the past several decades, mortality rates from CHD have declined. Improved survival rates have led to an increase in the number of people living with CHD (18.7% increase from 1990), thereby increasing the risk of developing long-term morbidities and an adverse neuro-developmental outcome. Even a child whose anomaly has been corrected by surgical methods at an early period may develop long-term longitudinal developmental delays, which may have seemed to sprout due to preoperative factors (majority), intraoperative techniques (5-8%) [24] and postoperative factors [25].

PATHOPHYSIOLOGY

Congenital heart diseases are structural defects that can result in the mixing of oxygenated and deoxygenated blood. They are broadly classified into Cyanotic and Acyanotic, depending upon the type of shunting [26]. The pathophysiology of neurodevelopmental delay in CHDs is not completely understood but multiple factors, both pre and post-surgical correction of CHD can contribute towards it. These include genetic abnormalities, fetal cerebral blood flow, cerebrovascular resistance, and environmental factors [18]. A recent study, using exome sequencing found that CHD patients, who had neurodevelopmental delay had the presence of mutations in specific genes that were expressed in both the heart and brain, thus making genetic cause a possibility [22]. Several mutations were identified including mRNA splicing, chromatin and transcriptional modification, RBFOX gene responsible for epithelial to mesenchymal differentiation [22]. APOE2 allele has been associated with poor neurological outcomes after CHD repair surgery. It has been found that fetuses with congenital heart disease have altered cerebral vascular resistance which contributes to neurodevelopmental delay.

Fetuses with left-sided heart lesions such as hypoplastic left heart syndrome have decreased cardiac output, which in turn leads to decreased cerebral vascular resistance to allow adequate blood and oxygen delivery to the brain. In contrast, fetuses with right-sided obstructive lesions such as tetralogy of Fallot, have increased cerebrovascular resistance [17]. During fetal life, CHD leads to a decrease in blood supply and oxygen content causing delayed brain maturation which further increases susceptibility to brain injury, especially white matter [3]. Few studies suggest that there is an increased incidence of microcephaly in infants with complex congenital heart diseases and underdevelopment of the operculum, an insular area responsible for feeding problems and language delay [17].

After birth, infants with severe CHD presenting with cyanosis and hemodynamic instability, along with risk factors such as prematurity and low birth weight are at increased risk for neurodevelopmental delay. Peri and post-operative circumstances influence the outcomes in patients undergoing surgical correction of CHD. Use of Cardiopulmonary bypass, the possibility of circulatory arrest, hypothermia, hemodynamic instability, and decreased cerebral perfusion during surgery can negatively impact developmental outcomes. Longer duration of hospital stays, post-operative hemodynamic instability, seizures, need for mechanical ventilation and ECMO can augment brain injury post-operatively [27]. *Table 1* summarizes the factors associated with an increased risk of neurodevelopmental delay.

Table 1: **Factors associated with increased risk of neurodevelopmental delay.**

Intrinsic	Genetic alteration -Protein damaging De-novo mutations, APOE2 allele is associated with poor neurological outcome Altered cerebrovascular resistance
Neonatal	Low birth weight Pre-maturity
Perioperative	Cerebral Hypoxemia Air embolism Continuous Cardiopulmonary bypass Hyperglycemia Deep hypothermic circulatory arrest pH-stat management during CPB
Post-operative	Post-operative pain Fever Agitation Length of hospital stay

Disability is seen in around 40% of adults with CHDs, the most common being cognitive impairment (memory, concentration, and difficulty making decisions [28]. The

neurodevelopmental impairments include but are not limited to delayed developmental milestones which improve as the child becomes older, decrease in overall IQ scores, language and memory impairment, and decreased processing speed. Executive functions are also affected leading to difficulty in academics and daily activities [29]. The developmental outcome is not only influenced by the disease itself but also the environmental and familial factors. High socioeconomic status, maternal education, good maternal mental health, and parenting style can help achieve milestones [27].

DIAGNOSIS AND TREATMENT

Diagnosis

Knowing this fact that infants with CHD are at increased risk of atypical neurodevelopment, especially those needing an open-heart surgery (42% exhibited fine/gross motor delay) or showing blue heart (cyanotic) lesions or other conditions determined by a medical home provider, it has become a necessity to identify in early life which infant is particularly at risk. CHD associations with neonatal conditions such as prematurity, suspected genetic abnormality (i.e Down Syndrome, Noonan Syndrome, autism spectrum disorder in children with 22q11 deletion syndrome), history of mechanical support (ECMO or ventricular assist device), abnormal brain imaging findings, perioperative seizures or a hospital stay of more than 2 weeks all point towards our high-risk category. The prevalence of "internalizing problems" (i.e. anxiety, depression, withdrawal, somatization) and "externalizing problems" (i.e. attention, aggression) are similar and range between 15-25% by parent report in the CHD population.

Early detection promotes referral to early intervention during a growth phase characterized by a high neuroplasticity range leading to a higher recovery rate. Periodic developmental surveillance, screening (using Ages and Stages Questionnaire-3 and Bailey-III), evaluation, and re-evaluation throughout childhood along with age-specific screening tools for children and adolescents (in case of latent delay) may enhance the identification of significant deficits, allowing for suitable therapies to enhance later academic, behavioral, psychosocial, and adaptive functioning. AAP guidelines recommend screening at 9, 18, 30, and 48 months of age. Autism-specific screening is recommended at 18 and 24 months [12]. Pulse oximetry provides a specific screening application [30, 31] followed by cardiac auscultation (in the form of intelligent auscultation) [32], which gives an abnormal murmur that can be pathological (abnormal blood flow through defective valves) or physiological (any physiological condition outside the heart) [33]. Other tests done are electrocardiogram, echocardiogram, chest x-ray, cardiac catheterization, and MRI.

Early diagnosis and regular follow-up are essential for enhancing neurodevelopmental outcomes in patients with congenital heart disease. Introduction of Cardiac Neurodevelopmental Outcome Collaborative 0-5 Neurodevelopmental Assessment would increase correct diagnosis of patients with developmental delay and pave the way for early intervention [33, 34]. Kangaroo mother care accompanied with hospitalization has been proven to be considerably effective in boosting the neurodevelopmental growth of infants with CHD [35].

Treatment

About 25% of children born with a CHD need some kind of medical intervention, and surgery can either be an early corrective or palliation with the help of a shunt [36]. Surgical intervention itself increases the risk of neurodevelopmental delays but with the help of support interventions, timely assessment, and recognition of the patient status, critical care nurses might be able to attenuate the effects of the modifiable factors [37]. This care can be provided after the surgery by using the model of developmentally supportive care which is a family-centered approach and focuses on understanding the social and health effects of CHD on children and their families [38].

Moreover, in CHD patients who undergo a surgical treatment, a neurological examination, documenting any abnormal pattern in EEG, or a cerebral MRI performed before the discharge can help identify children at an increased risk of developing delays and can assist in providing early intervention that might mitigate any long-term effects [39]. The scientific statement from the American Heart Association (AHA) has laid down the algorithm for the management of children with CHD which includes medical home visits, stratifying children as high-risk or low-risk CHD, performing surveillance, periodic re-evaluation, administering screening tools, and referral for early intervention [34].

Early intervention remains the cornerstone for the treatment and a multidisciplinary approach using various providers like developmental educators, and occupational, physical, and speech therapists play a vital role in managing and easing their transition into adulthood [3]. One such approach is The Congenital Heart Disease Intervention Program in which a clinical psychologist and a pediatric cardiac nurse specialist provide tailored psychoeducation, narrative therapy, problem-solving techniques, and parenting skills training to parents assigned to the intervention during six sessions [40]. The outcome of this intervention reported a clinically and statistically significant increase on the Bayleys-II mental scale at the 6-month follow-up [41]. School-going and adolescent age groups are at risk of learning difficulties. Formulating educational programs with the collaboration of medical professionals and a representative from the school may be beneficial. Various accommodations like computer-based learning, occupational therapy for writing difficulties, and increased time to take tests can be created until an individualized plan is characterized [42]. Older children

suffering from anxiety and depression may benefit from psychological interventions.

Various interventions can be undertaken like the Cogmed working memory training program, which was first developed in Sweden for children with ADHD and is thought to generate new neural connections. It consists of computer-based memory training for 5 weeks, 5 days a week for 1 hour each day. A randomized controlled trial studied the application of this program on CHD patients considerably enhanced self-regulation abilities in adolescents with CHD but did not affect other areas of executive function or behavioral outcomes [43]. Another therapy is the Rational Emotive Behaviour Therapy which was observed to alleviate the depression symptoms linked to CHD [44]. The fundamental tenet of therapy is that irrational ideas are a primary source of emotional discomfort [45]. This Therapy actively addresses these irrational beliefs to significantly modify emotional, cognitive, and behavioral patterns [45]. Regular follow-ups at a clinic and individually tailored plans have shown a positive effect on the neurodevelopment of children with CHD.

CONCLUSION

Congenital heart diseases are a group of structural abnormalities of the heart affecting millions of newborns globally. Children with CHD may exhibit altered brain structures and connectivity, leading to cognitive impairments, motor deficits (especially in single ventricle anomalies), and various neurodevelopmental delays. Visual-motor integration, language, learning, attention, and behavior are commonly affected. With an increasing awareness about the signs and symptoms of CHD and neurodevelopmental delay, most of the cases are now being recognized at an early stage and a quarter of these cases are treated surgically. However, certain risk factors associated with the surgical treatment, such as cardiopulmonary bypass time, use of circulatory arrest, and hemodynamic instability, can contribute to developmental delays. This complex situation demands that physicians should explore other management options and a multidisciplinary individualized approach to manage any neurodevelopmental issues. In conclusion, CHD is a complex condition with diverse causes and significant implications for neurodevelopment. Enhancing our understanding of the factors contributing to developmental delays and implementing appropriate interventions can improve the long-term outcomes for children with CHD.

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