Neurologic and cognitive outcomes in children with congenital heart disease

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Advances in congenital heart surgery have resulted in the increased survival of infants born with complex congenital heart disease. Questions remain, however, about how these patients will develop and whether they will have normal, productive lives. To date, studies have shown that although the vast majority of children with congenital heart disease have normal outcomes, as a group they generally have higher rates of neurodevelopmental problems. The developmental sequelae include mild problems in cognition, attention, and neuromotor functioning. The etiology of neurologic deficits in this population appears to be multifactorial with preoperative, operative, and postoperative factors all contributing to outcome. Continued research and attempts to minimize neurologic injury and associated sequelae are of primary importance. Recent data suggest that advances in care already may be improving outcome after congenital heart surgery. Ongoing documentation of the long-term outcome in this population needs to be mandated, as does the implementation of environmental enrichment programs to help ameliorate the long-term consequences of congenital heart disease. Curr Opin Pediatr 2001, 13:482–486

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Abbreviations

CHD	congenital heart disease
DHCA	deep hypothermic circulatory arrest
HLHS	hypoplastic left heart syndrome

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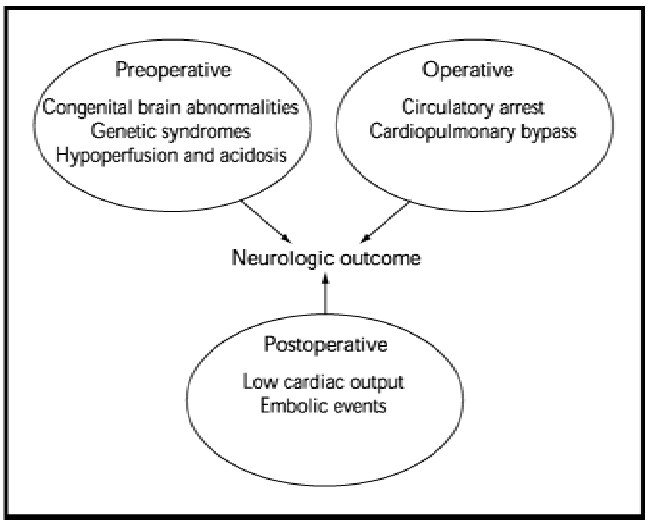
The last several decades have witnessed remarkable improvements in surgical outcome and long-term survival for children with congenital heart disease (CHD). With an increasing number of survivors, interest in functional outcome has grown. Neurologic impairment is one area that deserves particular attention. It has long been recognized that patients with CHD may have cognitive and neurologic dysfunction. To date, greatest attention has been focused on the potential for intraoperative cerebral injury. However, there appear to be many factors that influence neurocognitive outcome in patients with complex heart disease (Fig. 1). This article summarizes research on neurologic injury in children with CHD and the factors that influence outcome.

Preoperative factors

Structural brain abnormalities are more common in children with CHD than in the general population. Glauser *et al.* [1] reported postmortem data in 39 infants with CHD and found increased operculum in 8 (20%) and absent corpus callosum in 3 (8%). Importantly, many of these abnormalities were found in patients without obvious dysmorphism. Neuroimaging studies have demonstrated callosal agenesis, abnormal neuronal migration, temporal lobar hypoplasia, and Chiari I malformations. Microcephaly also has been reported in as many as 36% of newborns with CHD [2•]. Preliminary data have suggested that hypoplasia of the ascending aorta may be one factor limiting brain growth *in utero*, presumably through abnormal cerebral blood flow [3].

In addition to structural brain abnormalities, genetic syndromes with associated cognitive deficits are present in many children with CHD. Trisomy 21 syndrome or Down syndrome, which has an incidence of 1 in 660 newborns, is relatively common in children with CHD. Approximately 40% of patients with trisomy 21 have CHD. Neurodevelopmental delay is found in all patients. Another chromosomal defect found in a significant proportion of patients with CHD is microdeletion of 22q11.2, or DiGeorge syndrome, which is associated with conotruncal defects. Several investigators have reported mean full-scale intelligence quotient scores in the 70s [4]. Patients with microdeletion of 22q11.2 demonstrate a unique profile of neurocognitive deficits. Both expressive and receptive language deficits are common in these patients and may be caused in part by associated palatal abnormalities.

Figure 1.



Factors influencing neurologic outcome in patients with congenital heart disease

In addition to congenital neurologic abnormalities, infants with complex CHD are at risk for preoperative neurologic insult. In particular, newborns with ductal-dependent systemic blood flow may show symptoms of profound acidosis, hypoxic-ischemic injury, or shock upon closure of the ductus arteriosus. Preoperative seizures, intraventricular hemorrhage, and periventricular leukomalacia can occur as a consequence of hypoperfusion in these ductal-dependent lesions. Intraventricular hemorrhage has been documented in many neonates with CHD [5]. Intraventricular hemorrhage, which has been reported in as many as 24% of term infants with CHD, may be related to hemodynamic instability.

Thus, even before the newborn or infant undergoes cardiac surgery, a number of factors place the child at increased risk for abnormal neurologic and cognitive development. Recent studies have confirmed the presence of neurologic abnormalities in many patients with CHD before any surgical intervention. Limperopoulos *et al.* [2•] studied newborns with a variety of congenital heart defects and demonstrated that more than 50% had at least one abnormal finding on preoperative neurologic examination. Some of the more common problems noted in neonates with CHD were abnormalities in tone, jitteriness, and poor oromotor coordination. Feeding difficulties were noted in more than one third of patients.

Intraoperative factors

Cardiopulmonary bypass is used in many neonatal and infant cardiac surgical procedures. Cardiopulmonary bypass allows for perfusion of vital organs by providing oxygenated blood via a mechanical pump. During procedures using cardiopulmonary bypass, especially at low-flow rates, neuroprotection is achieved with concomitant use of hypothermia. Hypothermia protects the brain by decreasing cerebral metabolism. In principle, therefore, if cerebral blood flow can be maintained during cardiopulmonary bypass at the level adequate for metabolic demands of the hypothermic brain, ischemia can be minimized.

One risk factor intrinsic to cardiopulmonary bypass is the potential for embolic complications. There are considerable data from adults suggesting that microemboli, mainly bubbles and small particulate matter, occur during cardiopulmonary bypass and lodge in the microcirculation, causing short-lived infarcts in the organs. In addition, cardiovascular surgery with cardiopulmonary bypass leads to activation of a variety of inflammatory pathways. The clinical effects of bypass on the central nervous system in adults are well known. Cognitive deficits have been reported in more than half of adult patients at hospital discharge after open heart surgery [6•]. More worrisome is the recent suggestion that the risk of neurodevelopmental deficits may not be apparent until several years after cardiopulmonary bypass [6•]. It is important to recognize, however, that cardiopulmonary bypass generally is used in the setting of only mild hypothermia in the adult population and may be complicated by comorbidities such as diabetes or atherosclerosis. Investigators have shown that microemboli can be detected in the carotid arteries of children undergoing repair of CHD [7]. The significance of these findings is unclear, however. A recent retrospective study suggested that children who have an atrial septal defect closed surgically have lower intelligence quotient scores at follow-up than those who undergo transcatheter closure [8•]. Further prospective studies examining the impact of cardiopulmonary bypass on cognitive outcome in children are warranted.

Deep hypothermic circulatory arrest (DHCA) is a support technique used in some forms of congenital heart surgery, especially when interventions on the aortic arch are required. The infant is cooled and the circulation arrested. Therefore, DHCA represents a clinical situation of planned, total-body ischemia-reperfusion. The relation between the use and duration of DHCA and the risk for neurologic injury has been a matter of considerable controversy. Data obtained from animal studies have suggested that a total DHCA duration of less than 30 minutes is not likely to result in significant damage to the central nervous system. Many clinical studies have attempted to address the importance of the duration of DHCA on subsequent cognitive function. Several studies have suggested that the risk of neurologic compromise increases significantly when the duration of DHCA exceeds 45 to 50 minutes. Wells *et al.* [9] evaluated 31 patients who underwent heart surgery with DHCA at a mean age of 15 months of age and compared them with siblings. The subjects who underwent surgery with DHCA had significantly lower scores on the McCarthy

scales of development than their siblings, 91 ± 4.0 versus 106 ± 4.1, respectively. This study suggested that each additional minute of DHCA was associated with a decrease of 0.53 points in developmental testing. Some investigators have found no relation between the duration of DHCA and later cognitive performance. For the most part, these studies have had methodologic limitations, especially in identifying an adequate control group.

Postoperative factors

In the immediate postoperative period, cerebral perfusion and oxygen delivery may be compromised by a variety of factors, including low cardiac output, diminished arterial partial pressure of oxygen, and altered cerebral blood flow. Autoregulation of cerebral blood flow can be impaired after DHCA [10]. As such, the profound changes in blood pressure seen commonly in the postoperative period may impact significantly on cerebral perfusion. Management of body temperature in the postoperative period also may influence cerebral protection in the postoperative period. Several authors have shown that a mild degree of postischemic hypothermia (33–35°C) when initiated within 30 minutes of reperfusion reduces cerebral injury at the histopathologic level [11]. These data must be considered in the approach to temperature control of patients in the intensive care setting. Additional postoperative factors that can influence developmental outcome include congestive heart failure and prolonged hospitalizations. Embolic events, which are of particular concern in patients after the Fontan procedure, can result in significant neurologic deficits [12].

Early neurologic outcomes

Neurologic examinations performed in the postoperative period have identified a variety of abnormalities, including hypotonia, pyramidal findings, and asymmetry of tone. Miller *et al.* [13] performed neurologic examinations on 91 infants undergoing congenital heart surgery. In addition to clinical seizures in 15% of patients, the authors found hypotonia in 34% of patients at hospital discharge. Hypertonia was noted in 7% of infants and asymmetry of tone in 5%. A decreased level of alertness was noted in 19% of patients at hospital discharge. Similarly, Limperopoulos *et al.* [14] reported neurologic abnormalities in more than 50% of infants after open heart surgery. In the Boston randomized study of low-flow cardiopulmonary bypass and DHCA, diffuse motor abnormalities were noted in 45% and cranial nerve abnormalities in 4% of patients at hospital discharge [15•].

Interestingly, several investigators have identified a high incidence of feeding difficulties in neonates after congenital heart surgery. Although factors such as congestive heart failure and respiratory insufficiency may contribute to feeding difficulties, it seems likely that neurologic deficits also may play a role. Because feeding requires integration at several levels of the neuroaxis, feeding difficulties may be a marker for later cognitive dysfunction. Medoff-Cooper and Gennaro [16] have shown that abnormal neonatal sucking behaviors correlated with lower scores on the Bayley Scales of Infant Development at 6 months of age in very low birth weight infants.

Neuroimaging studies performed in the early postoperative period have demonstrated a high incidence of abnormalities, although the clinical significance of these findings is unclear. Focal hemorrhage and infarction have been noted. MRI studies performed in the immediate postoperative period often demonstrate small cystic areas of necrosis dorsal and lateral to the external angle of the lateral ventricle. These cystic lesions usually regress after several months. The cysts often are replaced by an astroglial scar, resulting in periventricular leukomalacia. The factors that lead to the development of periventricular leukomalacia after complex CHD surgery in the neonates have not been well characterized.

Intermediate-term and late neurologic outcome

A number of studies have investigated longer-term cognitive outcome after congenital heart surgery. In general, studies have shown that preschool and school-age survivors with CHD have normal intelligence quotient scores. Some lesions, such as hypoplastic left heart syndrome (HLHS), appear to increase the risk for neurodevelopmental deficits. It is important to recognize that intelligence quotient scores, though reproducible, provide a limited assessment of functional outcome. More comprehensive evaluation may identify abnormalities such as spatial processing deficits in many subjects with normal intelligence quotient scores.

Several studies have focused on patients with transposition of the great arteries. Upon examination, many of these patients are profoundly hypoxemic. Currently, the approach to transposition of the great arteries is early reparative surgery with the arterial switch procedure. In a prospective, randomized trial examining two support strategies, the mean full scale intelligence quotient at 4 years of age of patients with was 92.6 ± 14.7, which was mildly but significantly lower than that of the normal population [17]. Deficits were most commonly noted in visual-spatial and visual-motor integration. Definite neurologic abnormalities were noted in 30% of patients. The incidence of speech abnormalities also was higher than that in the general population. Conversely, Hovels-Gurich *et al.* [18] found mean intelligence quotient scores within the normal range in 77 children with transposition of the great arteries who underwent the arterial switch with DHCA. However, abnormalities in fine and gross motor function were noted in 22% and 23% of patients, respectively.

Another group of patients thought to be at considerable risk for neurocognitive impairment are those with a single ventricle who are palliated with the Fontan operation. Risk factors in this population include multiple operations requiring cardiopulmonary bypass with or without DHCA, prolonged hypoxemia, failure to thrive, and an increased risk of thromboembolic complications. Recent studies have investigated the long-term neurocognitive outcome of patients palliated with the Fontan operation. Wernovsky *et al.* [19] evaluated 133 patients palliated with Fontan surgery at a median age of 11.1 years. The mean full-scale intelligence quotient in this cohort (95.7 ± 17.4) was lower than that in the general population. Mental retardation, defined as full-scale intelligence quotient less than 70, was noted in 7.8% of the population. In this and other studies of patients with a single ventricle, subjects with HLHS scored significantly lower on standardized testing [20].

There are several reasons why patients with HLHS may be at higher risk than patients with other forms of single ventricle physiology. A relatively high incidence of microcephaly and congenital brain abnormalities has been reported in neonates with HLHS. In addition, these patients have ductal-dependent systemic blood flow; severe acidosis and end-organ injury upon examination are not uncommon. The duration of DHCA for the stage I Norwood procedure may exceed 45 to 50 minutes. In addition, maintaining adequate systemic blood flow and cerebral perfusion in the postoperative period can be unpredictable.

In 1995, Rogers *et al.*.[19] reported the neurodevelopmental outcome of 11 preschool survivors of reconstructive surgery for HLHS at various stages of palliation. The study documented an alarmingly high incidence of neurodevelopmental deficits. Of the 11 children studied, 7 (64%) were found to have mental retardation. Substantial functional disabilities were present in 8 children (73%). A larger subsequent study of school-age children with HLHS who had undergone staged palliation before 1992 found neurologic and cognitive deficits [20•], although not to the degree reported by Rogers *et al.*[19] In the report by Mahle *et al.* [20•], standardized neurocognitive testing performed in subset of patients demonstrated a median full-scale intelligence quotient of 86. In addition, 18% of subjects had intelligence quotient scores in the mentally retarded range. Minor neurologic abnormalities were detected in 55% of patients. Cerebral palsy was present in 17%.

The neurodevelopmental outlook may be better for patients undergoing staged reconstruction more recently. Prenatal diagnosis has been associated with less preoperative acidosis and a lower incidence of perioperative neurologic events [21]. Intraoperative factors such as shorter duration of DHCA, changes in hematocrit management, and use of modified ultrafiltration may lead to overall improvement in central nervous system function. In 2000, Goldberg *et al.* [22] reported the neurodevelopmental outcome for 26 patients with HLHS who underwent surgery between 1991 and 1996 at their institution. The mean full-scale intelligence quotient was 93.8 ± 7.3, within normal limits.

Conclusions

With improved operative results for CHD, there are an increasing number of survivors. Although the long-term neurologic and cognitive outcome for most children and adolescents with CHD is quite good, some are left with deficits. Caregivers need to be aware which patients are at highest risk. Studies of the mechanisms of neurologic injury continue. Various interventions ranging from prenatal diagnosis to advances in circulatory support should improve outcome for patients with CHD.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

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