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Seminars in
Pediatric
Neurology

Neurological Complications of Cardiac Disease

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This article focuses on the complex interactions between the cardiovascular and neurologic systems. Initially, we focus on neurological complications in children with congenital heart disease both secondary to the underlying cardiac disease and complications of interventions. We later discuss diagnosis and management of common syncope syndromes with emphasis on vasovagal syncope. We also review the diagnosis, classification, and management of children and adolescents with postural orthostatic tachycardia syndrome. Lastly, we discuss long QT syndrome and sudden unexpected death in epilepsy (SUDEP), reviewing advances in genetics and current knowledge of pathophysiology of these conditions. This article attempts to provide an overview of these disorders with focus on pathophysiology, advances in molecular genetics, and current medical interventions.
Semin Pediatr Neurol 24:3-13

Introduction

The brain controls the heart directly through the sympathetic and parasympathetic branches of the autonomic nervous system, which consists of multisynaptic pathways from myocardial cells back to peripheral ganglion neurons and further to central preganglionic and premotor neurons. Cardiac function can be profoundly altered by the reflex activation of autonomic nerves in response to inputs from baroreceptor, chemoreceptor, nasopharyngeal, and other receptors as well as by central autonomic commands, including those associated with stress, physical activity, arousal, and sleep. On the contrary, cardiac function directly affects the nervous system. Cardiac diseases can cause neurological deficit directly through hemodynamic instability, hypoxemia, as well as precipitating a hypercoagulable state. Cardiac arrhythmias have been long implicated in a variety of neurological abnormalities such as syncope, mental status changes, and seizures. More recently, a genetic link with dysfunctional ion channels has been discovered. The heart and the brain are now the target of efforts to better understand a group of conditions called channelopathies and expand available options to manage these diseases.

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Congenital Heart Disease

Children with congenital heart disease (CHD) are at increased risk for neurological complications, including cerebrovascular accidents, brain abscesses, developmental delay, and retinopathies, which may occur in as many as 25% of all affected children.[1]

It has been well documented in the literature that children and adults with CHD are at increased risk for stroke.[2] Long-term follow-up studies have shown that over a period of 20 years, 0.54% of patients with CHD were diagnosed with an ischemic stroke, which is 10-fold higher than age-matched controls. Studies estimate that CHD accounts for 7%-31% of all pediatric ischemic strokes with the highest incidence reported in large referral centers, probably reflecting referral bias in populations with more severe heart defects.[3,4]

Stroke in the setting of CHD can be embolic or thrombotic, with or without hemorrhagic transformation.[5] Patients with cyanotic CHD (CCHD) have a higher prevalence of thrombosis, the most frequently described locations being the cerebral and the pulmonary vessels.[6] Prothrombotic conditions, such as dilated and slow-flow cardiac chambers and vessels and arrhythmias, are thought to play an important role; however, erythrocytosis secondary to hypoxemia can also contribute to thrombogenesis.[6–8] Horigome et al[8] suggested that in patients

http://dx.doi.org/10.1016/j.spen.2017.01.001
1071-9091/11/

with CCHD and erythrocytosis, there is chronic activation of platelets and suppression of the thrombomodulin-protein C and S pathway, and that these factors are implicated in the procoagulant cascade.[4] They speculate that the grade of erythrocytosis itself (hematocrit level) may be one of the major determinants.

Cerebral abscesses arise from local suppurative infection of the brain parenchyma. Several mechanisms exist for bacteria to enter the brain, and the hematogenous route is the one seen in children with CHD. The incidence of brain abscess in CHD has been reported to be approximately 5% and is very unusual under the age of 2 when stroke usually predominates.[9,10] Most patients have CCHD. Chakraborty et al[11] reviewed 28 cases with CCHD complicated with brain abscess. Tetralogy of Fallot was the most common CCHD found in 75% of them. Transposition of great arteries, tricuspid atresia with ventricular septum defect, and double-outlet right ventricle with ventricular septum defect comprised the remaining of the cardiac lesions. Febrile illness was the most common mode of presentation, and frontal lobe the main site of abscess localization, followed by parietal lobe. Multiple abscesses were seen in a third of the patients.

The most important mechanism, which increases the vulnerability to this phenomenon in patients with CHD, is the right-to-left shunting of blood, bypassing the filtering lungs. In addition, the increased blood viscosity leads to microinfarcts causing areas of encephalomalacia, which may serve as sites for bacterial proliferation as do other previous hypoxic insults. Mortality is high in almost half of the patients according to Chakraborty's study.[11] Interestingly, they found no correlation of mortality with age, sex, type of microorganism, site of abscess localization, and nature of heart disease. Multiple abscesses, increased intracranial pressure, and associated meningitis or ventriculitis are predictors of poor outcome.[11] Treatment is directed toward the common bacteria causing symptoms, which usually are gram-positive *Streptococcus*, *Staphylococcus*, or *Hemophilus*.[12] Steroids and anticonvulsants may be used as adjuvant therapy. Occasionally, operative intervention is needed. Long-term sequelae include intellectual impairment, focal deficits, and epilepsy.

Children with CHD are at risk for having lower intelligence quotient (IQ) scores than other age-matched controls. This risk is independent of concomitant genetic abnormalities, surgical interventions, and complications. It appears to be greatest for children with CCHD.[13] Several hypotheses explain the worse functional status associated with CCHD. The experience of Newburger et al[14] convincingly demonstrated that the duration of chronic hypoxemia is important in reducing IQ scores. They discovered an inverse relationship between the age of surgery and IQ scores. A similar age-related decline in IQ scores was not found in acyanotic heart disease such as ventricular septal defects.[14]

Acute and chronic neurological dysfunction is well known to be associated with cardiac surgery, especially in patients with CHD. Puntis and Green[15] identified 37 children with cardiovascular disease who underwent cardiothoracic surgery and developed chronic neurological deficit. In two-thirds of diseases, they occurred in association with cardiovascular surgery; in the remaining, neurological sequelae were thought to be unrelated to intervention. Most patients (94%) had motor deficits. Severe motor and intellectual impairment were found in half of the patients.[15]

Small studies at individual institutions have shown that children with CHD undergoing surgery in infancy have more problems with reasoning, learning, executive function, inattention and impulsive behavior, language, and social skills compared with peers without CHD.[16–18] Lower abilities in these areas may lead to poor school performance, strained interpersonal relationships, and behavior problems. Survivors of cardiac surgery during infancy are more likely than the general population to require remedial services, including tutoring and special education, as well as physical, occupational, and speech therapy.[16,19] As they reach adulthood, neurodevelopmental disabilities can limit educational achievements, employability, and quality of life.[20] Unfortunately, despite robust literature, very few modifiable risk factors for adverse neurodevelopmental outcomes following cardiac procedure have been identified.

Early efforts were targeted at decreasing neurological injury by modifying intraoperative techniques and maximizing neuroprotection.[21] However, we now recognize that there are nonmodifiable patient-related factors that may be more important determinants of adverse neurodevelopment outcome.[22] Studies have described abnormal fetal brain development and brain perfusion, and many cases are accompanied by structural congenital brain disease.[23–26] These findings emphasize the importance of brain imaging in high-risk subjects prior to proposed surgical interventions. Many radiographically identified perioperative infarcts in children undergoing cardiopulmonary bypass for CHD are clinically silent in the acute period and may manifest as neuropsychological deficits later in life. In a series of children who had magnetic resonance imaging performed after a cardiac operation with cardiopulmonary bypass, 10% of them had ischemic infarcts; half of them thought to be preoperative insults based on the magnetic resonance imaging appearance.[27]

Children with CHD after cardiac procedures need to be followed carefully. Early intervention when needed is paramount to optimize long-term neurodevelopmental status. As operative mortality after surgery for CHD continues to decrease, efforts have shifted to recognize and mitigate other short- and long-term morbidities. Unfortunately, adverse neurodevelopment outcomes and other signs of brain injury remain common sequelae in this population.

Syncope

Pediatric syncope is a common problem that peaks in adolescence, for which there are few data or evidence-based consensus on investigation and management.[28] As many as 15% of children and adolescents may have a syncopal episode between the ages of 8 and 18 years. These patients often seek evaluation at emergency department (ED) and outpatient clinics.[29,30] Therefore, it is important that ED physicians, pediatricians, neurologists, and cardiologists know how to evaluate, refer, and properly manage these patients.