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Extra-cardiac manifestations of adult congenital heart disease

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ABSTRACT

Advancement in correction or palliation of congenital cardiac lesions has greatly improved the lifespan of congenital heart disease patients, resulting in a rapidly growing adult congenital heart disease (ACHD) population. As this group has increased in number and age, emerging science has highlighted the systemic nature of ACHD. Providers caring for these patients are tasked with long-term management of multiple neurologic, pulmonary, hepatic, renal, and endocrine manifestations that arise as syndromic associations with congenital heart defects or as sequelae of primary structural or hemodynamic abnormalities. In this review, we outline the current understanding and recent research into these extra-cardiac manifestations.

Key words: Cardiovascular disease, Adult congenital heart disease, Pulmonary hypertension.

Advances in the diagnosis and management of congenital heart disease (CHD) over the past several decades have greatly improved longevity and quality of life in the CHD population. Palliative or corrective interventions are now available for nearly every type of congenital cardiac lesion, and approximately 90% of affected children now survive to adulthood [1]. Adults with CHD (ACHD) already outnumber pediatric CHD patients, and this population is expected to grow by 5% per year [1,2]. Strikingly, the median age of severe CHD patients has increased from 11 years in 1985 to 25 years in 2010 [3]. Continued improvement in CHD interventions means that new (and more complex) populations will likely reach adulthood in the coming years.

Practitioners who take care of adults with CHD are often charged with the delivery or coordination of comprehensive care for these complex patients, including the management of manifestations and complications that arise later in life. ACHD has many extra-cardiac effects, both as syndromic associations with congenital heart defects, or more commonly, as sequelae of primary structural or hemodynamic abnormalities. The role of genetic predilection remains undefined for nearly all extra-cardiac complications, though their incidence has clearly risen over the past decades. Indeed, more than a third of hospital admissions for ACHD patients are now for non-cardiovascular reasons [4]. Optimal care of ACHD patients, therefore, mandates a thorough understanding of its multi-organ system manifestations. Herein, we will review current understanding of the most common manifestations of ACHD organized by the affected organ systems.

Neurologic/neuropsychiatric

Cerebrovascular complications

A recent study quantified the strikingly high rates of stroke in ACHD [5]. Among nearly 30,000 ACHD patients, 8.9% of men

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and 6.8% of women suffered a stroke before age 65, with an incidence of ischemic and hemorrhagic stroke 12-fold and 6-fold higher than the general population. Ischemic stroke was associated with heart failure, diabetes, and recent MI; CHD lesions predisposing to cyanosis and left-sided CHD lesions had the highest associated stroke rate.

Mechanistically, CHD can directly increase stroke risk through right-to-left shunting, allowing paradoxical embolism of thrombus from venous to arterial circulations. This is most commonly seen in the context of an atrial septal defect (ASD) or patent foramen ovale (PFO), particularly when associated with atrial septal aneurysm, but can also occur with shunting through baffle leaks in d-transposition of the great arteries (TGA) repaired by atrial switch (Mustard or Senning procedures) or in palliated single-ventricle patients with surgical fenestrations. In the presence of these defects, right-to-left shunting can occur due to pathologically elevated right atrial (RA) pressure or with transient physiologic elevation of RA pressure to greater than left atrial (LA) pressure (as with the Valsalva maneuver or briefly during early ventricular systole) [6]. Patients with Ebstein anomaly commonly have associated ASD and are at theoretically higher risk of paradoxical embolism due to blood stasis within an enlarged RA [7]. Current guidelines recommend closure of ASD (either percutaneously or surgically) and repair of baffle leaks following paradoxical embolism [7]. The benefit of PFO closure in cryptogenic stroke remains strongly debated and will not be discussed. *Interested readers are referred to Rohrhoff* et al. [8] *for additional information.*

Cyanotic congenital heart disease (CCHD) patients are at high risk for iatrogenic stroke due to paradoxical embolization of air or thrombus. As such, indwelling venous catheters should be avoided and if necessary precautions taken to avoid introducing air (including use of filters). Specific pathophysiology of stroke in CCHD is discussed below.

The reason for higher rates of stroke with left-sided lesions (including congenital mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency, and aortic coarctation) is unclear, but may be due to a predisposition to arterial thromboembolism. Regardless of the specific lesion, CHD can predispose to arterial thrombi through heart failure, atrial arrhythmias, mechanical valve prostheses, cardiothoracic surgery, and catheter-based interventions.

Intracranial aneurysms

Intracranial aneurysms (IA) are five times more common in coarctation of the aorta than the general population, occurring in ~10% of screened coarcts [9]. This was previously ascribed to syndromic association, though a recent study has shed new light on this relationship [10]. Screening performed in 80 children prior to early coarctation repair (mean age = 2.6 years) detected no IA. Importantly, no IA was seen at interval screening following repair (mean age = 15.7 years). This suggests that IA in adults with unrepaired coarctation is at least in part a secondary effect of coarctation (and likely the resulting hypertension), rather than a neurodevelopmental abnormality. Another explanation is a two-hit hypothesis, with developmental abnormalities predisposing to IA formation after exposure to longstanding hypertension.

An association between bicuspid aortic valve (BAV) and IA has also been reported [11], but this has also been questioned by recent data. In a retrospective study of adults treated for IA, the prevalence of BAV (1–2%) was similar to the general population [12]. There was, however, an increased prevalence (4.7%) of thoracic aortic aneurysm (TAA). Indeed, the majority of BAV patients with IA in prior studies also had TAA [11]. As with coarctation, the relationship between TAA and IA is likely a manifestation of both developmental predisposition and shared risk factors (hypertension). Although there are no current screening guidelines specific to CHD, these data suggest that cerebral imaging be considered in CHD patients with TAA.

Cerebral complications of cyanosis

CCHD carries an exceptionally high risk for stroke. Also, 47% of adult CCHD patients screened with brain MRI had evidence of prior stroke, with 53% having had multiple events [13]. Importantly, only 13% of patients reported a history of prior stroke, suggesting a high prevalence of clinically silent events. Among CCHD patients, hypoxemia and complexity of CHD were identified as stroke risks. Contrary to common teaching, polycythemia and hemostatic abnormalities were not associated with stroke risk, consistent with emerging science suggesting hypocoagulability in these patients [13,14].

CCHD also carries an increased risk for brain abscess. Though data are limited, one study estimated a 2% incidence over 13-years of follow-up. The most commonly associated CCHD lesions were tetralogy of Fallot (TOF = 61.2%) and TGA (9.6%) [15,16]. Right-to-left shunting carries any increased risk of infective endocarditis and may predispose to brain abscess by both allowing arterial bacteremia (due to bypass of the normal phagocytic filtering ability of the lungs) and a focal ischemic nidus for infection (due to hyperviscosity) [16–18].

Neurodevelopmental issues

Neurodevelopmental abnormalities are common in ACHD, both as innate changes in brain development (as with Down or DiGeorge syndromes) and as acquired abnormalities due to brain injury. Data on cognitive function in ACHD are limited and mixed [19], but a predilection toward neurologic abnormalities in ACHD can be expected given the high frequency of neurodevelopmental abnormalities in pediatric CHD [20]. The prevalence of neurologic abnormalities among school-age CHD patients ranges from 20% in total anomalous pulmonary venous connection and isolated atrioventricular septal defects, to as high as 70% in TGA and hypoplastic left heart syndrome [21]. In general, the prevalence and severity of neurodevelopmental impairment increase with lesion complexity [22].

Acquired brain injury has been associated with cardiopulmonary bypass and circulatory arrest during CHD surgery [20]. Developmental abnormalities can also result from disturbed fetal and/or postnatal cerebral blood flow (seen in hypoplastic left heart syndrome and TGA), hypoxemia (CCHD), failure to thrive, arrhythmias, seizures, or hypotension (often in relation to procedures) [23].