

Atrial Septal Defect with Atrioventricular Block – an Overview

Introduction

Atrial septal defects (ASDs), with a prevalence of 1 of 1,000 individuals, account for ~10% of all congenital heart disease and are one of the most common congenital defects seen in adults (1,2). ASDs are characterized by an opening in the atrial septum that creates a connection between the systemic and pulmonary circulation, allowing oxygenated blood to be shunted into the lower pressure pulmonary circuit (3,4). Over time, this shunting can cause irreversible damage to the heart and lungs (1). In addition, the communication between the right and left atria provides a site for small blood clots to move from the venous circulation into the arterial bed where they can cause strokes (1). Early treatment, typically by surgical or percutaneous device closure, is therefore critical (1). However, isolated ASDs are often not recognized until adulthood, after irreversible damage to the heart and lungs or stroke injury has already occurred (3).

About 8-19% of familial ASDs are due to autosomal dominant mutations in the gene *NKX2-5* (5-7). Genetic testing can therefore allow early diagnosis and treatment in family members of patients with *NKX2-5*-related ASD. In addition, identification of *NKX2-5* mutations as the underlying cause of ASD can alert patients and physicians to the high risk of atrioventricular (AV) block, a cardiac conduction defect that is also associated with mutations in *NKX2-5* (8,9). AV block can lead to life-threatening cardiac arrhythmias, but, if diagnosed early, can be treated effectively by the implantation of a pacemaker (10).

Molecular Pathophysiology

ASDs occur during the development of the heart, as a result of defective formation and closure of the septum between the two atria (1). During normal embryonic development, the heart initially forms as a linear tube, which

then undergoes a program of looping and septation to create the four chambers of the heart that accommodate the parallel systemic and pulmonary circulatory systems (11). Atrial septation is a complex, multi-staged process extending into the postnatal period (12). Three major types of ASD are distinguished. Ostium primum defects (10% of ASDs) are located low in the atrial septum, often affecting the mitral valve; sinus venosus defects (5% of ASDs) are located high in the atrial septum, often affecting the atrial connection of the pulmonary vein; in contrast, ostium secundum defects (85% of ASDs) only affect the atrial septum (1). Mutations in *NKX2-5* are typically associated with ostium secundum ASDs (1).

NKX2-5 encodes a homeobox transcription factor involved in regulation of cardiac development in concert with other transcription factors, including *TBX5* and *GATA4* (13). *NKX2-5* is also required for maintenance of the AV node, a critical component of the cardiac conduction system (14). The AV node transduces the electrical signal that coordinates the beating of the ventricles with the atria (10). Defects in the AV node (AV block) interrupt this conduction, leading to delayed or skipped ventricular beats relative to atrial beats (10). Germline truncations and missense mutations in the homeodomain of the *NKX2-5*-encoded transcription factor are associated with highly penetrant familial ASD with AV block (6,7). In contrast, missense mutations outside of the homeodomain are typically not associated with AV block, and tend to have low penetrance (7). *NKX2-5* mutations have also been associated with additional structural cardiac defects including tetralogy of Fallot (15,16). Somatic *NKX2-5* mutations, which have been found in diseased, but not in healthy heart tissue from deceased patients, may play a role in non-familial congenital heart defects (17,18).

Clinical Presentation

ASDs are usually well tolerated in children and adolescents and may not be diagnosed until adulthood, unless detected during routine physical examination during childhood (1). The most common initial clinical manifestations are dyspnea, fatigue, and exercise intolerance; less commonly, palpitations and syncope may be the first symptoms expressed (1). Patients with familial *NKX2-5*-related ASDs may also present initially with symptoms of AV block, such as dizziness, lightheadedness, or syncope (10). The severity of symptoms of both ASD and AV block increases with age; older untreated patients may experience cyanosis, congestive heart failure, stroke, or life-threatening cardiac arrhythmia (1,10). While ASDs in general are more likely to occur in females than in males, at a ratio of 2:1, familial *NKX2-5*-related ASDs affect males and females equally (1,8).

Diagnosis

Clinical diagnosis of ASD is based on physical examination, but the absence of characteristic clinical signs does not always exclude ASD (1). A right ventricular lift may be palpable on held expiration, as well as a dilated pulmonary artery (1). In addition, a wide and fixed split in the second heart sound and a systolic ejection murmur may be heard (1). A diastolic rumble may also be present if there is a large shunt, and a loud P₂ sound is indicative of pulmonary hypertension (1). Characteristically enlarged pulmonary arteries may be observed in chest X-ray films (1). Transthoracic echocardiogra-

phy or cardiac MRI may reveal the magnitude of the ASD, its type, and the direction of the shunt. The functional significance of the defect can also be gauged by the size of the right atrium and right ventricle. In older (>40 years) untreated patients, more severe manifestations occur frequently, including atrial fibrillation or flutter, congestive failure of the right heart, stroke, or Eisenmenger's syndrome – an end stage condition in which pulmonary hypertension causes reversal of the shunt, allowing unoxygenated blood to enter the systemic circulation through the ASD (1). Diagnosis of AV block by physical examination is based on the presence of bradycardia, irregularity of the heartbeat, or irregularities in the EKG (19). Since published studies have established a causal relationship between certain variants of *NKX2-5* and familial ASD with AV block, diagnosis can be confirmed or established through genetic testing (8).

Treatment

ASDs in young, asymptomatic patients are promptly treated by surgical or percutaneous device closure, and the prognosis for such patients is excellent (1). Closure is less effective in older patients whose hearts are irreversibly damaged by decades of shunting (1). In end stage patients suffering from Eisenmenger's syndrome or severe pulmonary hypertension, closure is contraindicated, as the ASD serves as a release valve that prevents heart failure from the afterload on the right ventricle (1). Patients with advanced AV block are at high risk for sudden cardiac death unless implanted with a pacemaker (10,19).

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