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Etiology of Atrial Septal Defect: Review

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ABSTRACT. *Atrial septal defect is caused by malformation of the septum between left and right atrium. This paper will firstly review the embryology and classification of atrial septal defect, then the etiology of atrial septal defect will be discussed according to various studies. Even atrial septal defects are treatable, the underlying cause of such defects is not clear, therefore, the research into them must be continued.*

KEYWORDS: *Atrial septal defect, Ostium primum, Ostium secundum, Sinus venosus, Unroofed coronary sinus, Tbx5*

1. Introduction

Atrial septal defects (ASDs) are one of the most common congenital heart defects [1]. It is caused by the malformation of the atrial septum, leading to a hole between left and right atrium. Consequently, a shunting of oxygenated blood between left and right atrium happens after birth. Generally, ASDs are tolerated during fetal life. However, in later life, it will cause arrhythmia, intolerance of exercise and even pulmonary vascular obstructive disease. Therefore, the understanding and prevention of it become important.

2. Embryology and Classification of Atrial Septal Defects

2.1 Formation of the Atrial Septum

The septum primum is first formed by growing from atrial roof towards the endocardial cushion. The space between the septum primum and the endocardial cushion is called the ostium primum (Figure 1a). The primum septum then starts to fuse with the endocardial cushion [2]. Before the ostium primum is completely obliterated by the fusing between endocardial cushion and septum primum, the septum primum undergoes apoptosis at the site where it originates thereby forming this secondary interatrial communication, the ostium secundum (Figure 1b). At Carnegie stage 21, the secondary septum is not yet formed (Figure 2a), however, the infolding of the atrial wall begins, and the primitive pulmonary vein becomes part of the developing left atrium (Figure 2b). About 4 weeks later, the right part of pulmonary vein becomes a separate tributary of the left atrium. As such change

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happens, the anterior and superior parts of the foramen ovale margin are formed by the infolding of the atrial roof. After the atrium expands to both sides of truncus arteriosus, an invagination is formed passively next to the septum primum, the septum secundum. In order to maintain the blood circulation within the atrial level, the crescent-shaped leading edge of septum secundum contact the superior margin of the septum primum. The leading edge of the septum secundum is curving inward, therefore the oval space is called foramen ovale (Figure 1c). As a result, the septum primum exists as the flap valve of the foramen ovale and it only allows right-left shunting of the blood. However, once after birth, the lungs can be used as gas exchange. With the onset of blood flow from the lungs to the left atrium, the pressure in left atrium will be higher than that in the right atrium, high pressure in left atrium will push the flap valve of foramen ovale thereby closing it.

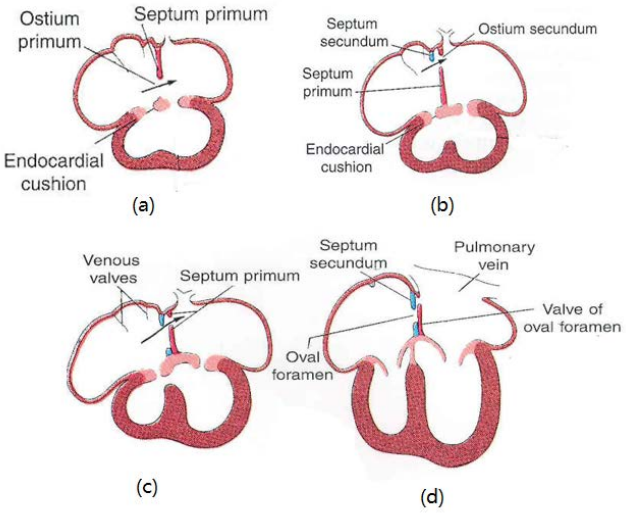

Fig.1 The Formation of (a) Ostium Primum, (B) Ostium Secundum and (C)(d) Foramen Ovale (Retrieved on Amc Academic Systems, 2014)

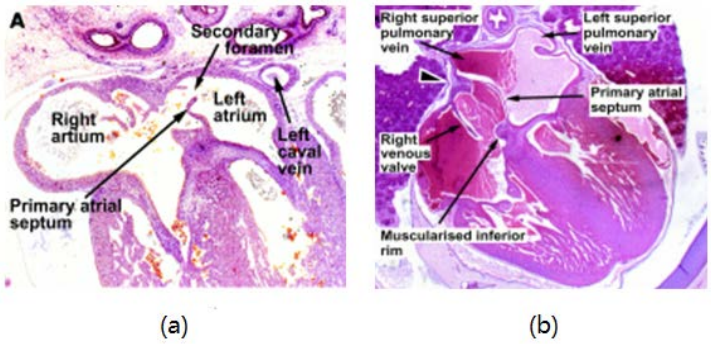

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Fig.2 (a) the Infolding of the Atrial Wall (B) the Primitive Pulmonary Vein Becomes Part of the Developing Left Atrium [2].

2.2 Classification of Atrial Septal Defects

Ostium Primum ASDs: represent 2-3% of all ASDs and they are usually related to Down's syndrome [5]. Ostium primum ASD is defined as being when the defect is only caused by the failure of the fusion between septum primum and the atrioventricular endocardial cushion. An ostium primum ASD is also associated with a partial atrioventricular septal defect (pAVSD). In this case, tricuspid valve and mitral valve fails to separate (Figure 3).

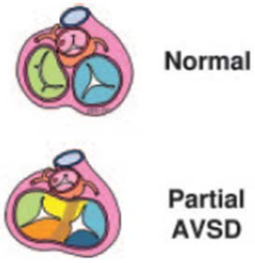

Fig.3 Normal Vs Pavsd. [4]

Ostium Secundum ASDs: represent 80-90% of ASDs [5] and 8-13% of all congenital heart defects [6]. In pathology, such defects are defined by the deficiency around the tissue of septal around fossa ovalis. This could be caused by the abnormal development of the septum primum or excessive absorption of the septum primum which leading to an enlarged ostium secundum.

Sinus Venosus ASDs: constitute approximately 2-10% of ASDs [5]. The embryology of sinus venosus ASDs is not clear [7]. Such a defect is thought to be caused by insufficient septation between the right upper pulmonary veins and the superior vena cava or right atrium adjacent to the cavo-atrial junction [8].

Unroofed Coronary Sinus: also known as coronary sinus septal defect, is the rarest type of ASDs. Such a defect is caused by insufficient septation between the inferior left atrium and the roof of the coronary sinus [10], thereby allowing the shunting between the left and right atria.

3. Etiology of Atrial Septal Defects

3.1 Molecular Genetics of Atrial Septal Defects

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3.1.1 Tbx5

TBX5 is a member of the family of T-box transcription factors. Goetz [12] proved that TBX5 regulates the cell cycle of developing cardial musculature. Camarata [13] stated that the regulation of the activity of TBX5 has significance for the formation of atrioventricular valves. Mutations in TBX5 could lead to Holt-Oram syndrome which manifests as ASDs and ventricular septal defects [14]. Experiments also showed that loss of TBX5 would cause the excessive apoptosis in the septum primum [28].

3.1.2 Nkx2.5

NKX2.5 is a homeobox transcription factor found in adult cardiomyocytes [15]. Schott [16] first proved it is related to isolated ASDs. NKX2.5 is proved to regulate its downstream TBX5 gene [18].

3.1.3 Gata4

GATA4 is a member of the GATA family of zinc-finger transcription factors. In 2003, Garg [21] found an isolated cardiac septal defect which is related to the mutations in the GATA4 gene. One year later, Okubo [22] showed that a deletion of GATA4 caused ASDs in a Japanese family. Evidence shows that GATA4 can also interact with TBX5 therefore contributes to the regulation of atrial septum formation [23].

3.2 Risk Factors of Atrial Septal Defects

3.2.1 Demographic Factors

Ethnic origin: Botto et al. [24] showed that incidence of ASDs per 10,000 births among black people is 5.82, which is higher than 3.84 among white people in Atlanta (Table 1). Two other studies [25][26] also suggested the prevalence of ASDs among whites was lower than other groups.

Table 1 Distribution of Asds by Ethnic Origin, Metropolitan Atlanta, 1968–1997 [24].

Defect Type	Whites			Blacks			Rate Ratio†	95% Confidence Interval	P‡	Rate Difference§
	No.	%	Rate*	No.	%	Rate				
Atrial septal defect	210	6.5	3.84	200	8.7	5.82	1.51	1.25–1.84	*B	0.3

W indicates excess rate among whites; B, excess rate among blacks.
* Rate per 10 000 births.
† Rate among blacks/rate among whites.
‡ $P < .05$.
§ Rate among blacks minus rate among whites.

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Temporal variation: The study by Botto et al. [24] showed the occurrence rate of ASDs nearly quadrupled in Atlanta from 1970 to 1995. However, this conclusion is controversial as the increased use of echocardiography might have caused more cases of ASDs to be diagnosed.

Gender: Multiple studies showed ASDs were less common among males [29], however, some study showed there was no significant difference between males and females [30]. Thus, the incidence of ASDs might be higher in females, but this remains uncertain.

Regional Difference: A higher rate of ASDs has been found in urban areas than in rural areas [25]. This might be related to maternal exposure to factors such as lower air quality, more frequent consumption of medication and higher stress level in urban areas.

Socioeconomic Status (SES): One study found among the people with cardiac septa malformation, the risk of ASDs was nearly tripled among the deprived compared with the affluent individuals [31]. Thus, there is a strong suggestion that the SES could affect the environmental factors related to the etiology of ASDs.

3.2.2 Reproductive Factors

Birth Order : One study in India by Tandon et al. [32] shows that second born infants have the lowest risk of getting ASDs, and between firstborn and third born or later infants, the risks are identical, which are nearly double the risk of second born infants. However, another report in England only shows first born infants have the highest risk of getting ASDs [33].

Plurality: In terms of plurality, only the risk of twins has been studied. One international study used samples mainly from European and Latin American countries found that twins are more likely to have ASDs than non-twin infants [34].

Consanguinity: A study in Saudi Arabia found the incidence of ASD in infants born to first-cousin marriage is higher than that to non-relative couples [35].

Gestational Factors: A study in Hungary found infants had more risk of getting isolated secundum ASDs with lower birth weight and shorter gestational age [29]. Another study shows that infants with macrosomia also had a higher risk of getting ASDs [3].

3.2.3 Maternal Conditions and Exposures

Overweight: A study by Watkins & Botto [20] shows the rate of ASDs among infants from obese or overweight mothers is higher. A later study in the same region also showed maternal obesity could increase the risk of occurrence of congenial heart defects [19].

Maternal diabetes: A case-control study in Baltimore-Washington from 1981 to 1989 shows increased risk of ASDs with maternal diabetes [17]. Another report shows women with hyperphenylalaninemia might have increased risk of fetal ASDs

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[27]. Elevated rates of ASDs have also been found among infants from mothers with urinary tract infection [25].

Substance use: Studies showed maternal consumption of the following substances could increase the risk of fetal ASDs: corticosteroids [25], alcohol [11], and cigarette smoking [9].

Maternal age: significant increased rate of ASDs has been reported among the infants with from mothers aged ⩾35 years [26].

4. Discussions

The understanding of ASDs still remains on anatomical level and there is no clear explanation of what directly causes such malformation. Most of the risk factors of ASDs are impossible to modify (e.g. gene, ethnic origin, time, gender, birth order, region etc.), but parents could minimize the risk by changing their lifestyle.

5. Conclusions

The formation of the atrial septum is complex and different types of ASDs are related to different stages of its formation. Research has identified some genetic mutations and environmental risk factors associated with ASDs. However, the direct cause of ASDs remains unclear, prevention measures could be taken to reduce environmental risk factors. ASDs can be diagnosed effectively and repaired surgically now, but research into their understanding and prevention must continue.

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