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Review Article

Laterality Defects of the Heart: A Review of the Anatomical and Cardiological Approaches

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Abstract

Heart is of mesodermal origin which undergoes a complex process of development. A number of congenital anomalies were encountered at the time of its development. Very little is known about the embryological background of these anomalies. We only encountered the congenital anomalies that was occurred at the time of establishment of the left-right axis of the embryo. This review includes causes, clinical presentations, diagnostic approaches, existing treatment and preventive measures if any persist for the followings: Dextrocardia, isomerism, transposition of great arteries or other forms of heterotaxy.

Keywords: *Congenital anomalies, Laterality defects, Dextrocardia, Isomerism, Transposition of great artery*

Generalization

Embryologically, cardiovascular system is the first major system to function in the embryo which appears first in the middle of the third week when the embryo is no longer able to satisfy its nutritional requirements by diffusion alone.[1] During development of this complex system, a number of anomalies are encountered in the developing heart. The term congenital anomalies are often used to describe structural, functional, behavioral and functional disorders present at birth.[2] Lin et al[3] mentioned that main causes of mortality in early childhood in most of the developed countries are congenital anomalies that accounting for one fifth of the total deaths and in Brazil, 19% of the mortality in children under one year old in 2008. Almost half of the anomalies that encountered at the time of birth are cardiac anomalies and approximately 0.8% of all live births represent it.[4] It is thought that most of the congenital heart diseases denoted multifactorial origin involving anomalous gene expressions and epigenetic factors. However, the origin of cardiac anomalies has been directly related to chromosomal anomalies or single gene defects. The single gene defects can be explained by polymorphic presentation if the gene controls an embryonic process such as genes control the establishment of laterality.[5] Malposition of embryonic left-right axis patterning is known as laterality defects which involves a spectrum of disorders that ranging from isolated dextrocardia or situs inversus (SI) abdominis to situs inversus totalis (SIT) or heterotaxy as well as more severe laterality defects may include situs ambiguous, complex congenital heart defects (CHD).[6] The spectrum of laterality defective phenotypes like heterotaxy, in more than 90% cases, is accompanied by complex and severe cardiovascular anomalies such as atrioventricular canal defects or transposition of the great vessels which is common with situs solitus with or without genetic syndromes.[7]

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Embryological aspects

Establishment of the laterality or right-left asymmetry was initiated on the Hensen or primitive node when the embryonic symmetry broken by cascades of gene activation.[5] The genes that establishes laterality is orchestrated by a cascade of signal molecules and genes such as PITX-2, LEFTY-2, Fibroblast Growth Factor-8 (FGF-8), Sonic hedgehog (SHH), Nodal and 5-hydroxy triptamine (5HT). It was the 16-day of intrauterine life when primitive streak appeared and nodal cells of the streak secreted FGF-8 which induced the expression of Nodal, only in the left side of the embryo. LEFTY-2 genes up regulate PITX2 which is responsible for establishing left-sidedness and its repeated expression on the left side of the embryo concluding heart, stomach, and gut primordial etc, their normal asymmetrical body positions. Ectopic expression of these genes results in laterality defects not only in the form of dextrocardia as well as more severe laterality defects may include situs ambiguous, complex and severe cardiovascular anomalies such as transposition of the great vessels. Moreover, LEFTY 2 expression on the left side of the neural tube may act as a barrier to prevent left-sided signals from crossing over. Sonic hedgehog (SHH) is a repressor for left-sided gene expression on the right. The role of 5HT is also important not only in establishing laterality but also in the development of some congenital anomalies like situs inversus, dextrocardia, and a variety of cardiac malformations. The reason that lies behind the concentration of 5HT only on the left side may be due to hydrolysis of it, by metabolizing enzyme Monoamine oxidase (MAO) on the right, and is upstream from FGF8 signaling.[2]

Dextrocardia

The condition dextrocardia was first described by Marco Aurelio Severino, an Italian surgeon and anatomist in 1643.[8] Dextrocardia is a condition occurred when laterality being established, roughly at the time of gastrulation or when the heart loops to the left instead of right. In this condition, heart lies on the right side of the thorax instead of the left.[2] The incidence of dextrocardia has been reported previously less than 1% and in a more recent research it is 0.22%. The most common congenital cardiac anomalies associated with dextrocardia includes: Double outlet right ventricle (the aorta connects to the right ventricle instead of to the left ventricle), endocardial cushion defect (the walls separating all 4 chambers of the heart are poorly formed or absent), pulmonary stenosis (narrowing of the pulmonary valve) or atresia (pulmonary valve does not form properly), single ventricle (instead of two ventricles, there is a single ventricle), transposition of the great vessels (the aorta and pulmonary artery are switched) and ventricular septal defect (hole in the wall that separates the right and left ventricles of the heart).[9] Dextrocardia is often accompanied with situs inversus where complete reversal of asymmetry in all organs or with laterality sequence or heterotaxy, in which the positions of some organs are reserved.[2] The cause of dextrocardia is still unknown but it is related to the developmental period, there may have defects in the heart chamber or associated with normal cardiac anatomy. There are variations in the presentations of dextrocardia. Isolated dextrocardia usually have no symptoms but there is increased chance of lung infections due to immotile cilia or sinus infection or pneumonia. Patients usually present with breathing difficulty, cyanosed lips and skin, fatigue or developmental delay or jaundice.[9] The unusual and specific electrocardiographic findings of dextrocardia includes inversion of P waves in leads I and aVL, dominant S waves in leads I and V1 to V6, reversed R wave progression in chest leads, low voltage QRS axis in V4 to V6, extreme QRS axis, flattened T waves in V4 to V6 and aVR and inverted T waves in lead I and aVL.[8] Yusuf et al [10] reported a case where a 67-year-old patient of renal cell carcinoma presented with shortness of breath and after electrocardiography, dextrocardia was incidental finding with situs inversus. Treatment of dextrocardia is necessary if it prevents vital organs from functioning properly such as pacemaker or surgery to repair septal defects, antibiotics to prevent repeated respiratory tract infection. A patient with isolated dextrocardia often live a normal life, on the other hand, a more complicated dextrocardia needs treatment according to symptoms.[9]

Isomerism

Heterotaxy syndrome of the heart includes: Atrial and ventricular isomerism, a condition in which both atria and ventricle have similar characteristics instead of left-right differences.[2] The Greek word '*iso*' means equal and "*meros"* means part, refers to abnormal developmental symmetry on both sides of the body. Affected patients with isomerism will have either two right sides or two left sides instead of distinct left and right sides.[11] Isomerism can be result from both anatomic and functional impairments and affects multi organ system of the body.[12] The diagnostic difficulties due to varied and confusing anatomy of multi organ involvement and patients rarely survive into adulthood due to cardiovascular complications, the etiology and natural history of such conditions are not fully understood although imaging provides the most accurate non invasive method for diagnosis.[13] As a major component of heterotaxy, atrial isomerism causes significant morbidity and mortality due to discordance among the heart, systemic and pulmonary vessels, and other organs. Patients with atrial isomerism present with cyanosis due to right-to-left shunting as a result of pulmonary outflow obstruction and septal defects between the atria and ventricles, most often present during the neonatal period. In severely affected neonates, survival is dependent on maintaining a patent ductus arteriosus. There may be chance of respiratory distress because of pulmonary congestion due to pulmonary venous obstruction.[14] A thorough understanding of the various effects of isomerism can allow for early detection of abnormalities and proactive intervention.[12] Agarwal et al[13] mentioned that among two major categories in the Heterotaxy syndromes are the left isomerism (Polysplenia syndrome) and right isomerism (Asplenia syndromes or Ivemark syndrome). In the left isomerism, females predominance with survival up to mid adolescence is seen and mostly patient present with acyanotic congenital heart disease and characterized by only major fissures in both lungs, bilateral hyparterial bronchi, congenital cardiac anomalies such as ASD and VSD, interrupted IVC with azygous continuation into thorax (the Double-vessel sign), multiple spleens, gut malrotation, and biliary atresia. On the other hand, in right isomerism (Ivemark syndrome) male predominace with most patients with cyanotic heart disease who are immunocompromised due to absent spleen.[15] Majority of the patients are presented with bilateral superior vena cava draining into bilateral atria, both lungs with major and minor fissures, bilateral eparterial bronchi, complex cardiovascular anomalies such as total anomalous pulmonary venous congestion (TAPVC), transposition of great vessels (TGA), common atrio-ventricular (AV) valve etc., absent spleen, midline symmetrical liver with midline gall bladder, gut malrotation, piggy-back inferior vene cava (IVC) and truncated pancreas. Most patients with right isomerism die within the first year of life due to cardiovascular compromise, if survive up to adulthood that's may be due to less severe pulmonary stenosis and absence of arrhythmias.[13] However, according to the best knowledge of the reviewers, there is no convincing literature yet to explain the exact cause of survival in patients that do survive.

Transpositions of great arteries

Among the cardiac defects that are present at birth, transposition of great arteries is a serious but rare one where the origin of two main arteries leaving the heart are reversed that means the pulmonary artery connected to the left ventricle and the aorta connected to the right ventricle.[16] About 5% to 7% of all congenital cardiac anomalies in Europe are transposition and it is the second most frequent cyanotic CHD after tetralogy of Fallot and if left untreated, causing cardiac death in neonates and infants.[3] The estimated incidence of TGA at 1 in 3,500–5,000 live births, with a male-to-female ratio 1.5 to 3.2:1 where 50% of cases, the ventriculoarterial discordance is an isolated finding and 10% of cases, TGA is associated with noncardiac malformations.[15] TGA involves abnormal development of the outflow tract (OFT) of the embryonic heart and it is strongly linked to laterality gene defects rather than OFT gene defects.[17] Due to transposition, there is a change in the way blood circulates through the body and as a results of circulatory changes, shortage of oxygen in blood flowing from the heart to the rest

of the body and the shortage of adequate supply of oxygen-rich blood, the body can't function properly and child faces serious complications or death without treatment.[16] Some authors also claimed the presence of non-syndromic cases of complete TGA which was principally occurred in two variants: (1) in combination with normal atrioventricular connections, or (2) in combination with abnormal atrio-ventricular connections and the former variant is frequently called TGA, while the latter is called congenitally corrected TGA.[18] In our review, the reviewers used "Transposition (TGA)" as the default term, for all Congenital Heart Defects (CHDs) to describe the clinical presentation, cause, treatment or outcome. The cause of TGA still remains unknown in most cases but it is related to developmental period when laterality being established.[2] There are several factors that may increase the risk of a baby being born with TGA, which includes: history of German measles (rubella) or other viral illness or drinking alcohol or smoking during pregnancy and mother with poorly controlled gestational diabetes, maternal exposure to rodenticides and herbicides, antiepileptic drugs.[16] Association of TGA with genetic syndrome such as Down's, Turner or Noonan syndrome is very rare but cases reported previously.[6] Cardiac anomalies associated with TGA are ventricular septal defect (VSD) and left ventricular outflow tract obstruction more frequent that dictates timing and clinical presentation of TGA, which consists of cyanosis with or without congestive heart failure.[15]

Symptoms of TGA includes cyanosis, shortness of breath, lack of appetite and poor weight gain etc. Diagnosis of the TGA based on the chest X-ray, ECG and echocardiogram and infants with this anomalies required surgical correction. After correction, patient needs to be regular follow-up under a cardiologist for growth monitoring.[17]

Conclusion

Multiple anomalies are encountered during the development of the cardiovascular system. A fair knowledge of different processes of these congenital anomalies along with causes, clinical presentations, diagnostic approaches, existing treatment and preventive measures if any persist for the followings: Dextrocardia, isomerism, transposition of great arteries or other forms of heterotaxy will provide a better insight for future management.

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