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An Overview on Diagnosis and Management of Cardiac Defects in Down Syndrome in Pediatric Age

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Abstract

Background: Down syndrome (DS) is one of the commonest disorders associated with chromosomal abnormality with a huge medical and social cost. DS is associated with several phenotypes including congenital heart defects, the point of our discussion. DS individuals are affected by these phenotypes to a variable extent thus understanding the cause of this variation is a key challenge. In this review, we will talk about the common congenital cardiac disease running in patients with down syndrome. **Objectives:** We aimed to review the literature on cardiac defects associated with Down's syndrome, along with the etiology, clinical features, evaluation, diagnosis, and management of these types. **Methodology:** PubMed database was used for articles selection, papers were obtained and reviewed. **Conclusion:** Down syndrome is associated with a variety of congenital cardiac defects. Proper knowledge of these defects with the management approach is essential. Due to advancements in technology, prenatal diagnosis is possible. Almost all these conditions are cured by surgical repair and carry an excellent prognosis.

Keywords: Down syndrome, Common AV canal., Endocardial Cushion defect.

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Introduction

Down syndrome, the common term for trisomy 21, is the most common chromosomal anomaly in humans and the most common cause of intellectual disability. This condition gives rise to many complications that affect the entire body. Of particular note, cardiovascular anomalies in down syndrome are the leading cause of mortality and morbidity during early life. (Benhaourech et al., 2016) It has been estimated that almost 40-63.5% of patients with down syndrome have congenital cardiac defects. Also, about ¼ of them have more than one defect. (Bergstrom et al., 2016) The percentage of cardiovascular anomalies are different based on seasonal, geographical, and sex differences. (Bergstrom et al., 2016; Santoro et al., 2018; Zahari et al., 2019) Despite these differences, the frequency of cardiac defects is, in descending order, common atrioventricular (AV) canal, also termed endocardial cushion defect, isolated ventricular septal defect (VSD), isolated atrial septal defect (ASD), and tetralogy of Fallot (TOF). (Bergstrom et al., 2016; Santoro et al., 2018; Zahari et al., 2019) In this review, we will go through each type covering the clinical presentation, diagnosis, and management. We will also try to cover the concept of the prenatal screen for both down syndrome and cardiovascular anomalies.

Methodology

PubMed database was used for articles selection, and the following keys used in the mesh ((Down syndrome) AND (Cardiac defects))

OR (Congenital cardiac anomalies). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; Down syndrome, Endocardial cushion defect, ASD, VSD, TOF. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Atrioventricular Canal Defects

- *Etiology and Classification*

Failure of the endocardial cushion to fuse and form the atrioventricular (AV) septa. If the AV septum does not develop, the valves will also be affected, as there is no medical support. It affects around 40-50% of children born with down syndrome. (Calcagni et al., 2017) The classification of AV canal defects can be done in two ways, anatomical and effect on the heart. As for anatomical classification, AV canal defects can be classified into complete, partial, and transitional. (Versacci et al., 2018)

In a complete AV canal defect, there is a complete failure of fusion between the superior and inferior endocardial cushions. It is characterized by a primum ASD that is contiguous with a posterior VSD and a common AV valve. In the partial variant, there is an incomplete fusion of the superior and inferior endocardial cushions. This leads to a primum ASD and a single AV valve annulus with two separate valve orifices. Transitional AV canal defects are similar to partial defects physiologically. However, they have a large primum ASD, cleft mitral valve, and inlet VSD, which is not present in partial AV canal defect. Also, there are dense chordal attachments to the VSD that prevent or, at the very least, reduce the amount of shunting of blood. This is why it is similar to that of partial defects. (Calcagni et al., 2017) Another way to classify AV canal defects is based on the size of the ventricles. If they are equal in size, this is termed a balanced defect that is amenable to repair. If the ventricles are not equal in size, this is termed unbalanced. Commonly, the right ventricle is hypoplastic compared to the left ventricle. This reduces or eliminates, in severe cases, the possibility of biventricular repair. (Calcagni et al., 2017)

- *Clinical Presentation*

During the fetal period, the common AV canal is usually asymptomatic and does not interfere with the development of the fetus. However, if there is severe aortic regurgitation associated with a common AV canal defect, the fetus develops hydrops fetalis. In such cases, echocardiography is indicated to determine the cause of hydrops fetalis and, if found to be due to common AV canal, genetic and chromosomal testing of the fetus is indicated. (Donofrio et al., 2014)

During the postnatal period, endocardial cushion defects would either present with signs and symptoms of heart failure or found incidentally in a physical examination in mild forms of the defects (Abbas et al., 2019; AL-Shakhshir et al., 2019; Aboud, et al., 2019). In balanced complete AV canal defect (CAVC), heart failure would manifest with hyperactive precordium with inferior and laterally displaced precordial impulse, increased pulmonary component S2 due to pulmonary artery hypertension, and systolic ejection murmur heard at the left upper sternal border because of increased blood flow across the pulmonary valve. (Ramamoorthy, 2011) If the defect is not fixed at this stage, the child will go on to develop pulmonary vascular resistance with the possibility of the development of Eisenmenger's syndrome. (Morales-Demori, 2017)

In unbalanced CAVC, symptoms depend on the chamber affected. If LV hypoplasia is severe, the presentation may manifest as a variant of hypoplastic left heart syndrome or left-sided obstructed lesions and would present with signs of low cardiac output as the PDA closes. If the RV is hypoplastic, the presentation is similar to that of tricuspid atresia with cyanosis and signs of decreased blood flow into the lungs. (Ramamoorthy, 2011)

- *Diagnostics*

During the fetal period, due to the advancements in ultrasound technology, the diagnosis of CAVC can be made in the first trimester. (Donofrio et al., 2014; Hopkins et al., 2019) postnatally, if patients are symptomatic they usually undergo three tests, chest X-ray, electrocardiogram, and echocardiography. CXR and ECG studies will not show any specific changes and signs. However, they are suggestive of heart failure. Echocardiography is diagnostic of AV canal defects as it can show the site of the defect, motion abnormalities, size of ventricles, and size of the shunt. (Versacci et al., 2018)

- *Management*

As discussed earlier, children born with CAVC will go on and develop heart failure by the sixth week of life. So, it is important to manage the heart failure of these patients. Management of heart failure includes diuretic therapy with furosemide and thiazides, inotropic support with digoxin, afterload reduction with ACE-inhibitors, and promoting optimal nutrition as they are usually underweight. (Donofrio et al., 2014) In balanced CAVC, surgical repair is possible.

However, in unbalanced CAVC, we cannot repair the defects. Instead, we will go for single ventricle palliative surgery, in which a single ventricle pumps out blood into the systemic circulation and blood flows into the pulmonary circulation passively, or go for cardiac transplant. (Santos et al., 2019) In cases of balanced CAVC, if the patient develops symptoms of heart failure, we will go for surgical repair once stabilized and is older than 6 weeks of life. If the patient does not develop symptoms, however, we will go for elective surgical repair between 3 and 6 months of life. (Donofrio et al., 2014)

There are a variety of techniques for surgical repair include; single-patch repair, in which one synthetic patch is used to close both ASD and VSD; two-patch repair, in which we use 2 patches to close the ASD and VSD, with suturing of the common AV valve; and modified single-patch repair, in which the common AV valve is sutured to a component of the ventricular septum, along with the closure of the ASD by that component followed by patch repair of the VSD. (Santos et al., 2019) In partial and transitional AV canal defects, symptoms are not apparent and can be clinically silent for years. Surgical management is with patch repair of the defect. It is usually done between the age of 18 months to 3 years. If found

later, the repair is done at the time of diagnosis. (Santos et al., 2019)

- *Outcome*

Generally, the outcome is excellent when diagnosis and proper surgical repair is achieved early in life, with a ten-year survival rate after repair approaching 90%. However, about 1/5 of patients may require reintervention due to the development of complications such as severe mitral regurgitation, severe mitral stenosis, and severe left tract outflow obstruction. Thus, all patients must be followed up after surgical repair to monitor for the possibility of reintervention. (Morales-Demori, 2017)

Ventricular Septal Defect

- *Etiology and Classification*

Ventricular septal defects are the most common congenital cardiac defects second only to the bicuspid aortic valve. In down syndrome, isolated VSD is the second most common congenital cardiac defect second to common AV canal and affecting around 30-35% of children with down syndrome. The interventricular septum has three components, septum of the AV canal, muscular septum, and the distal conal septum. The septum closes starting from the projection of the endocardial cushion into the AV canal, then followed by the downward projection into the rest of the septum. (Calcagni et al., 2017)

While the symptoms are determined by the size of the defect, the location is important in knowing the associated valvular compromises or attachments. The size of the defect can be determined in two ways, the anatomic size, and the size of the shunt. Anatomically, small defects are less than 4 mm wide at the widest area, moderate defects are between 4–6 mm wide, and large defects are wider than 6 mm. The other way is by dividing the ratio of pulmonary flow over the systemic flow (Qp: Qs). Small defects have a ratio of less than 1.5, while moderate defects are between 1.5–2.3, lastly, large defects 'ratio is larger than 2.3. (Calcagni et al., 2017)

- *Clinical Features*

Most patients present during neonatal life. However, symptoms depend largely on the size of the VSD. In small VSDs, children will present with an asymptomatic murmur. This murmur is a harsh, pansystolic murmur with mid-diastolic rumbling heard best over the upper left sternal border. The murmur becomes detectable at 4–10 days of life as pulmonary vascular resistance decreases. The intensity of the murmur increases as the size decreases. In moderate to large VSDs, infants typically present with signs and symptoms of heart failure at the 4^{th} week of life. The severity of the symptoms also increases with the increase in left-to-right shunting. (Donofrio et al., 2014)

- *Diagnostics*

During pregnancy, diagnosis is possible as early as 14 weeks of gestation. Once the diagnosis is made in a pregnant woman, genetic and chromosomal studies are indicated to determine the association. Similar to CAVC, if the patient presents with heart failure, CXR, ECG, and echocardiography are indicated. Color flow doppler will clearly show the shunting of blood and determine the physiological size of the defect, as well as the anatomical location and size. (Calcagni et al., 2017; Donofrio et al., 2014; Hopkins et al., 2019)

- *Management*

Small VSD is expected to close spontaneously within 2 years after birth. If the patient is symptomatic, it is advised to manage those patients with medical therapy, similar to the treatment of heart failure in CAVC. As for moderate and large defects, they carry a high risk for the development of pulmonary vascular resistance in down syndrome. So those patients are generally treated medically for symptoms of heart failure, then the estimation of the pulmonary vascular resistance should be made along with its index. If the index is less than 8, then close is indicated. If the index is larger than 12, then the child has a high risk of developing persistent pulmonary hypertension with a high risk of perioperative mortality due to low cardiac output. Surgical repair is contraindicated in this case and should be managed accordingly. If the index is between 8–12, then further evaluation should be done to determine whether to treat surgically or medically. (Versacci et al., 2018; Ramamoorthy et al., 2011) Surgical repair of VSD is done via patch closure of the defect. (Santos et al., 2019)

- *Outcome*

The outcome in repaired VSDs is excellent. It has been reported in most centers that the rate of operative mortality after surgical repair is less than 1%. Also, in patients who were not managed surgically, the outcome was excellent. Those patients, on further, follow up, either had spontaneous closure of the defect or the condition remained at the same stage and did not develop complications. (Santos et al., 2019)

Atrial Septal Defect

- *Etiology*

Atria septal defects (ASD) are common congenital cardiac defects in all populations. In down syndrome, almost 15% of all children born have an ASD. It develops due to the failure of the fusion of the atrial septa during its stages of development. (Ramamoorthy, 2011)

- *Classification*

We can classify ASDs depending on which stage did it fail to close, or by the size of the defect. Primum defects occur when the primum-septum fails to fuse with the endocardial cushion. Secundum defects are due to defects within the fossa ovalis, the remnant of foramen ovale in the right atrium. By size, we can classify it as trivial if less than 3 mm wide, small if 3–6 mm wide, moderate if 6–8 mm wide, and large if it is wider than 8 mm. However, these measurements are not precise and often we use the relative size of an ASD to the size of the heart. (Bergstrom et al., 2016; Ramamoorthy, 2011)

- *Clinical Features*

Most children born with an ASD are asymptomatic except for a murmur due to the shunt. However, the murmur by itself is faint and very hard to hear unless there is increased shunting. It is a midsystolic murmur that is best heard over the left second intercostal space. There is also fixed, wide splitting of the S2 due to the equalization of the right and left diastolic pressure. (Hopkins et al., 2019) In large defects, signs of heart failure might be present.

- *Diagnostics*

The diagnosis can be made prenatally because of the advancement in ultrasonography. ASDs can be picked up as early as 18 weeks of gestation. After birth, the diagnosis of ASD can be suspected in a child with the typical clinical features of ASD. Echocardiography can confirm the diagnosis, measure the size, and location of the defect, and it can measure the degree of shunting using a doppler scan. (Hopkins et al., 2019)

- *Management*

The majority of small ASDs close spontaneously by the age of 2. (Donofrio et al., 2014) While Secundum defects are usually larger than primum defects, it is still advised to wait and see because there is a possibility, albeit small, that this defect will close spontaneously in asymptomatic patients. (Morales-Demori, 2017) If the defect persists, however, closure is still only indicated in large defects with a high shunt, i.e. Qp: Qs =2:1. (Donofrio et al., 2014) symptomatic defects should always be closed surgically. The intervention is to patch up the defect with a synthetic patch. All patients who have not opted for surgical intervention should be monitored for any signs of increased shunting, right chamber enlargement, and pulmonary over circulation, as these are indications for surgical closure. (Donofrio et al., 2014) Of particular importance, children with a repaired ASD should receive antibiotic prophylaxis for endocarditis in cases where the repair required the use of prosthetic material and where a residual defect was left. Those populations should receive prophylaxis for dental and respiratory tract procedures for 6 months for the first group and life for the second group. (Donofrio et al., 2014; Pierpont et al., 2018) The outcome is excellent whether the defect was repaired or closed spontaneously.

Tetralogy of Fallot

- *Etiology*

Tetralogy of Fallot (TOF) is the commonest congenital cyanotic heart disease. It is found in 5% of children born with down syndrome. (Versacci et al., 2018; Asim et al., 2015) It is characterized by four defects: right ventricular outflow obstruction (mostly due to pulmonary valve stenosis), right ventricular hypertrophy (caused by the right outflow obstruction), and an aorta that overrides a preexisting ventricular septal defect. (Ramamoorthy, 2011) TOF severity is dependent on two factors: how severe is the right-sided outflow obstruction, and how large is the VSD. Severe pulmonary stenosis accompanied by a large VSD will lead to the development of right-to-left shunt, causing severe cyanosis. The less the degree of obstruction is, the less severe the presentation. (Ramamoorthy, 2011)

- *Clinical Features*

The clinical presentation depends on the degree of the outflow obstruction. Infants with severe obstruction and inadequate pulmonary flow typically present in the immediate newborn period with profound cyanosis that requires intervention. Infants with moderate obstruction may be asymptomatic at first, but due to the progressive nature of the obstruction, they may present later in life with cyanotic “tet” spells due to a sudden increase of the right-sided outflow obstruction from agitation or excitement. Typically, children become severely cyanotic during their tet spells, tachypneic. Commonly, children are found in the squatting position, as this stance reduces the severity of the symptoms due to an increase in the systemic vascular resistance, thus reversing the right-to-left shunt. Infants with minimal right flow obstruction go on to develop heart failure during the 4-6 weeks of life as the pulmonary pressures reduce over time, and pulmonary over circulation occurs. (Donofrio et al., 2014) on physical examination, one can appreciate prominent right ventricular pulsations and an occasional systolic thrill. On auscultation, the second heart sound is single in most cases as the pulmonic component is barely audible. There is also a systolic ejection, crescendo-decrescendo murmur heard over the left second intercostal space. This is the murmur of the pulmonary stenosis, rather than that of the VSD.(Ramamoorthy, 2011)

- *Diagnostics*

The diagnosis of TOF can be made prenatally. The diagnosis is achieved using echocardiography with doppler scanning. These studies must address the location and number of VSDs, the severity of the right-sided outflow obstruction, the coronary artery anatomy, the aorta anatomy, and the presence of any associated anomalies. If the echo fails to achieve this information, cardiac catheterization must be done to provide further information. (Donofrio et al., 2014; Hopkins et al., 2019)

- *Management*

Initially, patients with severe outflow obstruction manifested as profound cyanosis immediately after birth must be managed immediately. Management includes administration of alprostadil, a prostaglandin analog, to keep the patency of the ductus arteriosus while awaiting surgery. (Donofrio et al., 2014) The surgical repair of TOF consists of patch closure of the VSD and enlargement of the stenosed pulmonary valve. The surgery is done within the first year of life if the condition is detected early. However, if the neonate is presented with severe obstruction, they can either undergo primary repair after birth or staged repair, in which palliative surgery is done after birth to keep the ductus arteriosus open or to create an aorticopulmonary shunt until the complete repair is achieved later during the first year. (Santos et al., 2019)

For moderate obstruction, patients may not present until later during childhood with tet spells. To manage tet spells put the child in the knee-chest position and administer oxygen, if these measurements fail, administer a bolus of normal saline with IV morphine. Next in case of failure, administration of IV beta-blockers. Next in line is the administration of IV phenylephrine. If all these medical therapies fail, we must proceed to surgical

intervention, either primary repair or staged repair. (Santos et al., 2019) All patients undergoing surgical repair must take antibiotic prophylaxis for 6 months after the surgery. (Donofrio et al., 2014)

- *Outcome*

Without repair, the outcome of TOF is generally poor. (Bergstrom et al., 2016) Those who have received surgical repair during childhood have an excellent outcome. However, there is some complication that may limit the functionality of the individual, namely pulmonary regurgitation secondary to the surgical repair that may deteriorate into right-sided heart failure. However, quality of life, development, and general survival has been reported to be excellent. (Morales-Demori, 2017)

Conclusion

Down syndrome or Trisomy 21, is the most common chromosomal abnormality among live-born infants is associated with several congenital malformations. Cardiovascular defects associated with the down syndrome include endocardial cushion defects, VSDs, ASDs, and TOF. With the new advancements in ultrasonography, prenatal diagnosis is possible for these conditions. With this knowledge, a proper management plan for patients with down syndrome can be put forth even before the child is born. All these defects can be repaired surgically, with excellent results and outcomes.

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