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Review Article

Pathophysiology, Presentation and Management of Tetralogy of Fallot

Abdullah S Alqahtani[1]*, Aljawharah Muidh Asiri[2], Sahar Sameer Al-Jubali[3], Abdulrahman Abdullah Dobaie[4], Nouf Nasser Albalawi[5], Abdulrahman Sharaf Althobaiti[6], Abdullah Mohammed Alshehri[7], Olfa Ahmed Halawani[8], Sarah Emad Alsayed[9], Maryam Awad Allah Alkhormani[10] and Fatima Mohammed Zabani[10]

[1]Consultant of Pediatric Cardiology, East Jeddah General Hospital, Jeddah, Saudi Arabia

[2]East Jeddah General Hospital, Jeddah, Saudi Arabia

[3]Hera General Hospital, Mecca, Saudi Arabia

[4]King Abdulaziz Hospital, Jeddah, Saudi Arabia

[5]Maternity and Children's Hospital, Jeddah, Saudi Arabia

[6]Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[7]King Khalid University, Abha, Saudi Arabia

[8]Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia

[9]Arabian Gulf University, Bahrain, Saudi Arabia

[10]Batterjee Medical College, Jeddah, Saudi Arabia

***Corresponding Author**: Abdullah S Alqahtani, Consultant of Pediatric Cardiology, East Jeddah General Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: Tetralogy of Fallot (TOF) is one of the most common congenital cardiac malformations with multifactorial etiology that may comprise of interventricular communication known as ventricular septum defect, obstruction of right ventricular outflow tract, override of ventricular septum by aortic root and right ventricular hypertrophy. Combination of lesion occurs in every 3 out of 10,000 births, and the mortality rate reached 50% for untreated patients by age six years. But in the present era of advanced cardiac surgery and progressed strategies for surgical and medical management, the morbidity and mortality rate of patient born with TOF has significantly reduced with improvement in long-term survival rate of simple form of TOF.

Aim of the Study: The review helps us to understand the presentation, pathophysiology, diagnosis, and management of Tetralogy of Fallot.

Methodology: The review is comprehensive research of PUBMED since the year 1994 to 2019.

Conclusion: TOF is a congenital heart defect which results in decreased blood flow to pulmonary system, the neonates usually present with cyanosis of varying intensity due to obstruction of blood flow to lungs. Multifactorial etiology and congenital malformation (chromosomal anomalies) are associated with disease. But with definitive diagnostics, initial palliative therapy, surgical correction in infancy, creation of systemic-to-pulmonary arterial shunt is allowing most of the patients to lead a healthy lifestyle. However, lifelong follow-up is important to watch out any abnormal heart rhythm, leaking of pulmonary valve or poor functioning of right ventricle. The continued research in gaining new knowledge and treatments for congenital heart disease will improve the child health care in future.

Keywords: *Tetralogy of Fallot; Etiology; Diagnosis; Management*

Anatomy

The classical anatomy feature of TOF are as follow [1]:

- Outlet septal defect
- Right ventricular outflow tract obstruction
- Overriding of aorta
- Right ventricular hypertrophy

The ventricular septal defect

The interventricular communication found in TOF is because of anterior and cephalad malalignment of the outlet portion of the muscular ventricular septum or its fibrous remnant fail to muscularize during the embryonic stages. In majority, the posterior-inferior margin of the hole between ventricles is formed by an area of fibrous continuity between the leaflets of aortic and tricuspid valves, involving the interventricular portion of membranous septum; thus these defects are appropriately called as peri-membranous [1].

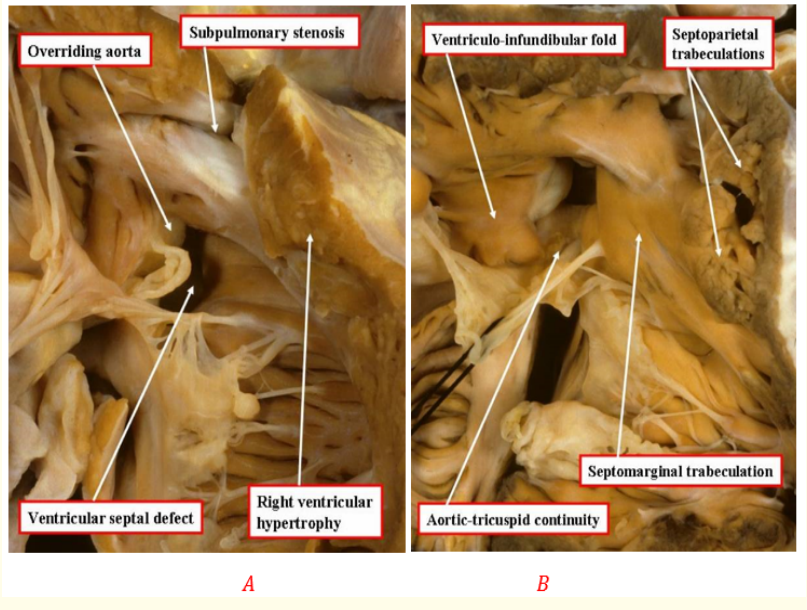

Figure 1: *(A) Autopsy of specimen opened through the anterior wall of right ventricle showing all the cardinal features seen in TOF. (B) Showing fibrous continuity between the leaflets of aortic and tricuspid valves in the postero-inferior margin of ventricular septal defect, making it peri-membranous [2].*

Right-ventricular outflow tract obstruction

In the majority of cases with TOF, there is resistance to right ventricle emptying. The anterior displacement and rotation of infundibular septum causes the obstruction and narrows the outflow tract. This infundibulum obstruction may be associated with pulmonary valve stenosis or atresia which results in further obstruction [1].

Right ventricular hypertrophy

The anatomic lesion created by deviated outlet septum results in hemodynamic consequence such as right ventricular hypertrophy [2].

Overriding of the aorta

The displacement of malaligned outlet septum into right ventricle leads to overriding of aorta root to muscular ventricle septum. Sub-pulmonary obstruction caused shunting across the interventricular communication from right-to-left, promotes ejection of deoxygenated blood into the systemic circulation. The volume load of overriding aorta implicated in dilation of aortic roots in TOF [3].

Methodology

We did a systematic search for tetralogy of Fallot using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Tetralogy of Fallot, etiology, diagnosis, management.

Etiology and pathophysiology

The etiology of TOF multifactorial and is known to be associated with untreated maternal diabetes, maternal intake of retinoic acid, phenylketonuria, chromosomal anomalies such as trisomy of chromosome 21, 13, 18, microdeletion of 22q11.2 and Alagille syndrome, transcription of NKx2.5 mutation in TBX1 and ZFPM2 [4,5].

The exact process that leads to development of TOF is still unknown, and it had been observed that anterior and cephalad deviation of infundibular septum results in misaligned ventricular septal defect with overriding aortic root subsequently causing ventricular outflow obstruction. As discussed above, these ventricular septal defects are peri-membranous and can extend into muscular septum. The physiological process in TOF surrounding the hypercyanotic episodes or "Tet spells" consist of either a decrease in systemic vascular resistance or increase in pulmonary resistance that contributes to right to left shunting across septal defect [6].

Clinical presentation

The patients will mostly present in the neonatal period with mild to moderate cyanosis but without respiratory distress. The initial presentation of TOF also depends on the severity of the obstruction of blood flow to the lungs. The mild right ventricular outflow tract obstruction at birth may take months to be diagnosed and as the situation worsens it represents as cyanosis and louder murmur. There is no sign of heart failure since the patients with TOF present with obstruction to pulmonary blood flow. Other features may include irritability, lethargy, mostly seen in hypercyanotic spell and clubbing which is highly unusual since the patient usually undergo repair before its appearance. The auscultation the second heart sound is often single and loud with presence of harsh systolic murmur [2].

The flow across the interventricular communication is not turbulent and hence not audible. However, in patients with severe obstruction and little antegrade flow across the sub-pulmonary outflow tract will be more cyanotic and have a less prominent murmur [2].

Diagnosis

Chest x-ray

Chest x-ray demonstrates a typical "Boot-shaped" cardiac silhouette with empty hilum. This is due to the upward movement of right ventricular apex because of right ventricular hypertrophy and narrowing of mediastinal shadow due to less pulmonary outflow tract. Right-sided aortic arch is seen in 30% of TOF cases [7].

Echocardiogram

Diagnosis of TOF is usually confirmed with echocardiography. The severity of pulmonary obstruction, its dynamic component, size of the right and left pulmonary arteries and sources of flow of blood to lungs can be demonstrated. The degree of aortic overriding, size of interventricular communication, associated lesion can be identified.

Cardiac catheterization is rarely needed these days prior to surgical repair except in case of suspected coronary artery anomalies, assessment of hemodynamics which otherwise is difficult to detect by echocardiography. Coronary angiography is also indicated in case of surgical re-intervention. The cardiac CT can define the cardiac anatomy hence eliminating the need for cardiac catheterization. Balloon dilation of pulmonic valve is also rarely indicated in neonatal surgery [7-9].

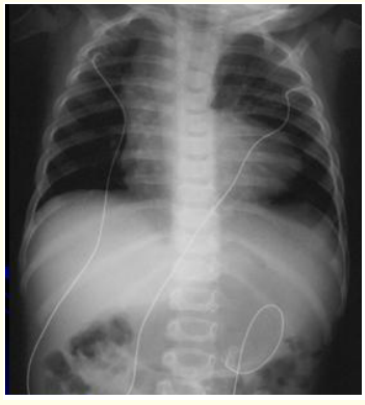

Figure 2: *Chest x-ray of the boot-shaped cardiac silhouette, bilateral decreased/ diminished pulmonary blood flow and right-sided aortic arch are seen [7].*

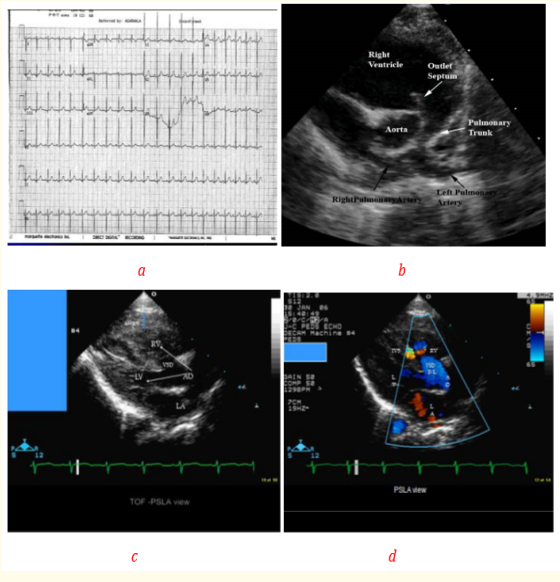

Figure 3: *(A) Showing the right axis deviation and right ventricular hypertrophy with positive T in V1-2 in electrocardiogram. (B) Frame image of parasternal short axis view of echocardiogram of patient with TOF showing antero-cephalad deviation of outlet septum into right ventricular outflow tract [2]. (C) 2D echocardiogram in parasternal Long axis view showing Overriding of the aorta. (D) Colour doppler showing right to left shunt through the VSD [7].*

Management

Medical management

The management of TOF is determined by the degree of pulmonary obstruction. There is no effective medical treatment for pulmonary insufficiency even with the attempt of afterload-reducing agents and diuretics. Patients who develop acute cyanosis are placed in knee-

chest position, oxygen and IV morphine are administer additionally. IV propanol is known to relax infundibulum muscle spasm and relieve right ventricular outflow tract obstruction [10].

Pulmonary Vasodilator drugs- according to research, certain drugs can dilate the pulmonary vasculature and lower the pulmonary insufficiency. Sildenafil has been used to treat patients with TOF. However, there are no long-term studies to prove if this can prevent the progression of pulmonary insufficiency [11].

Surgical management in neonates

Surgical management is according to the centre. Some centers perform complete repair in neonates which is cardiopulmonary bypass while others opt for palliate procedure for symptomatic neonates and later perform the complete repair at the age of 4 to 6 months [2].

Palliation does not frequently require cardiopulmonary bypass. Palliation includes placement of prosthetic tube between systemic and pulmonary artery to establish a secure source of the flow of blood to lungs. The most commonly used aorto-pulmonary shunt is modified Blalock-Taussig shunt consist of communication between subclavian and pulmonary artery on same side [2].

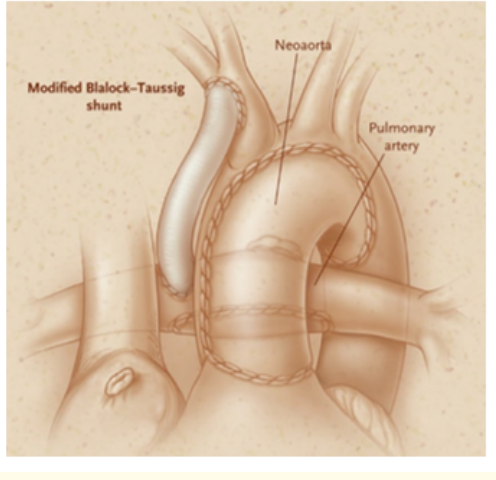

Figure 4: *Modified-Taussig shunt [12].*

Complete repair is performed under cardiopulmonary bypass that includes the closure of interventricular communication with a patch channeling the left ventricle to aortic root, relief of pulmonary obstruction and reconstruction. This provides prompt relief of volume and pressure overload on the right ventricle, minimizes cyanosis, eliminates the risk of stenosis occurring in pulmonary artery due to palliative procedure as well as decreases parental anxiety. The so-called transannular patches placed across the ventriculo-pulmonary junction create a state of chronic pulmonary regurgitation which increases morbidity in young adults producing ventricular arrhythmias. If untreated this increases the risk of sudden death [13]. The cardiopulmonary bypass is also known to have impact on human brain and associated with lower intelligence quotients [14], while some other study proves that cyanosis itself is responsible for cognitive problems in children [15].

Surgical management in adults

For adults, surgery is performed under cardiopulmonary bypass using cardioplegia. Once the heart is arrested the ventricular septal defect is closed with a patch, the infundibulum is widened, and the pulmonary valve is repaired. Transannular patching is rarely performed in adults which leads to pulmonary insufficiency in later stages thus currently pulmonary valve replacement or repair is the choice of

surgical intervention these days. This decreases right ventricle size, improve its function over long term but do not change the incidence of arrhythmias [17].

The timing for surgery is debatable, previously the surgery was recommended based on the presence of QRS interval longer than 180 milliseconds on electrocardiography. Recently it is believed that pulmonary replacement is necessary when right ventricle dysfunction is evident. Regardless of the existing debate, surgery should be undertaken before heart failure develops. However, in case of mild symptoms, surgery is not indicated [17].

Mechanical V/S Bioprosthetic Valve Replacement- For valve replacement bioprosthetic valves such as human tissue (homografts) or animal tissue (bovine pericardium or porcine heart valve is preferred over mechanical prosthetic valve, since the right side of heart and pulmonary artery vessels are a low-flow system, insertion of mechanical valve is associated with high risk of thrombosis and lifelong anticoagulation therapy due to risk of bleeding in case of trauma. Although the bioprosthetic valves eliminate the need for lifelong anticoagulation, they are not durable for young patients and nearly 40 - 55% of bioprosthetic valves fail within the first decade after implantation [18].

The patients may continue to have ventricular arrhythmias are at risk of sudden death, they can benefit from automatic implantable cardioverter-defibrillator [19]. Radiofrequency ablation has also become a good option to treat arrhythmias in TOF [20].

Conclusion

Tetralogy of Fallot is a congenital heart disease which leads to pulmonary insufficiency and obstruction of blood flow to lungs, interventricular septal defect, overriding of the aorta and ventricular hypertrophy. The causative factor is multiple from diabetes during pregnancy to chromosomal anomalies. The diagnosis is based mostly on echocardiography which is also helpful in determining the timing of surgery in adult patient according to some studies, and chest X-rays are another diagnostic method but of less use from surgical point of view. The management in neonates is usually by cardiopulmonary bypass as complete neonatal repair or the palliative procedure which includes systemic-to-pulmonary arterial shunt while the adult requires prosthetic pulmonary valve repair or replacement for correction of pulmonary insufficiency. Continuous research and increase advances in cardiac surgical intervention may benefit the patients with TOF and the post-surgical complication as well as decrease the subsequent mortality and morbidity.

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