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Review Article

Tetralogy of Fallot

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History of the Disorder

Tetralogy of Fallot was first discovered in 1673, when Nils Stensen documented the earliest account of the cardiac malformation that we now know as Tetralogy of Fallot (ToF) on a stillborn infant. In 1777, Eduard Sandifort described a "blue boy" who experienced "sinking spells", saying it was "a very rare disease of the heart"; the boy's anatomical findings align with those of Tetralogy Fallot. About seven years later, William Hunter tracked the abnormal growth pattern and cyanotic spells of a young boy, noting that he was remarkably thin and would experience fits where he fell down and came out sobbing and fatigued. In analyzing an autopsy with similar findings to this boy, Hunter commented on how clear it was that only a very small quantity of blood ever passed through the lungs. In the 1850s, Peacock was the first to note a cardiac murmur of pulmonary stenosis, another common characteristic of ToF, furthering the research on the topic. In 1888, French physician Étienne-Louis Arthur Fallot published a revolutionary description of the disease that established and outlined the four major defects in the disease. Thirty-six years later, in 1924, Maude Abbott coined the name "Tetralogy of Fallot" after the four defects and the man who linked them together [1].

As new diagnostic tools were developed in the late 19th and early 20th centuries, they were quickly determined to be very beneficial in cardiac practice. For example, in 1936, Abbott used circulatory and auscultatory diagrams, chest radiographs, and the 3-lead electrocardiogram to determine that each cardiac defect, including ToF, had a specific clinicopathologic profile. Only eight years later, Alfred Blalock, Helen Taussig, and Vivien Thomas performed the first successful palliative surgery for ToF at Johns Hopkins, where they placed a Blalock-Taussig Shunt to increase blood flow to the lungs. In 1954, though, as open-heart surgeries became more popular, Walton Lillehei performed the first total repair of ToF, using the cardiopulmonary bypass. In the mid-late 20th century, the development of echocardiograms, was a major contribution to the diagnosis of ToF. As this technology developed, physicians were soon able to see fetuses' hearts, allowing for a deeper understanding of cardiac development, and thus congenital heart defects like ToF. Today, we continue to learn more about the disease and how to treat it and mortality rates due to ToF are very low [1].

Pathology

As indicated by the name, Tetralogy of Fallot consists of four main defects: a ventricular septal defect, pulmonary stenosis, an overriding aorta, and right ventricular hypertrophy [2]. However, all of these issues stem from one single misalignment that occurs during fetal development, of which the cause is unknown. This is the anterior and cephalad deviation of the conal (infundibular) septum-the tissue that separates the aortic and pulmonary outlets-making it detached from the rest of the ventricular septum. It is clear that this misalignment can cause a ventricular septal defect, given that the conal septum does not meet the septal band, leaving the patient with an open area between their ventricles [3, 4]. Pulmonary stenosis is also a result of this misplacement because the conal septum is deviated toward the pulmonary artery, thus squeezing it and narrowing the sub pulmonary outflow tract. This narrowing causes resistance of blood flow through the pulmonary artery, forcing the right ventricle to have to pump harder to conquer that resistance. As a result, the muscle of the right ventricle hypertrophies due to the extra work needed to exert blood through the pulmonary valve. Finally, since the conal septum is displaced into the right ventricle, the aortic root sits directly above the ventricular septal defect (overriding aorta), taking blood from both ventricles [5].

Due to four defects that define ToF, the blood flow within the heart becomes more complicated; given the ventricular septal defect, blood can flow between ventricles, causing the oxygen-rich and oxygen-poor blood to mix [6]. There is mostly a right-to-left shunt, though, because there is significant resistance in the pulmonary artery, which is a result of the pulmonary stenosis and the thickened wall in the right ventricle due to ventricular hypertrophy [7]. The blood naturally pumps through the path of less resistance that, in this case, is through the ventricular septal defect, rather than through the pulmonary artery. Therefore, less blood is being sent to the lungs and being oxygenated, while more oxygen-poor blood is being sent across the septum. Additionally, since the aorta is placed directly over the ventricular septal defect, most of the oxygen-poor blood that is pumped across the ventricular septal defect is sent straight through the aorta. The blood that is pumped through the aorta and throughout the body, then, is a mixture of oxygen-rich and oxygen-poor blood, which results in a reduction of arterial oxygen saturation [8].

Diagnostics

While some patients are diagnosed antenatally by fetal echocardiography [3], most patients with Tetralogy of Fallot are diagnosed in the neonatal period when they present with cyanosis and/or a loud murmur [5]. When a newborn with significant cyanosis is birthed, he or she is usually placed on supplemental oxygen; lung disease is often assumed with cyanotic babies, as it is clear that they are not getting enough oxygen. However, since patients with ToF typically have functioning respiratory systems, breathing extra oxygen will have little effect on them, and they will remain cyanotic. Failure to respond to the hyperoxia test is an indication that the patient has a congenital heart defect, not a defect of the lungs [8]. Upon auscultation, patients with ToF typically present with a harsh systolic ejection murmur from the stenotic sub pulmonary outflow tract [5]. This is typically the first indicator of a congenital heart defect in newborns who do not present as cyanotic. If the patient is not diagnosed at birth, at around four to six months of age, he or she will exhibit "tet spells" [3]. These are episodes, typically during crying or feeding [2]. Which consist of cyanosis, dyspnea, agitation, and syncope. They are triggered by either a decrease in systemic vascular resistance or an increase in pulmonary resistance, which contributes to the right-to-left shunt of blood, dropping the arterial oxygen saturation [3]. These "spells" are one of the most characteristic traits of ToF. Slightly later in life, toddlers with untreated ToF are often seen squatting after exercise, which is another indicator of ToF. This is because, during exercise, one's arteries dilate, causing the systemic vascular resistance to drop, which encourages right-to-left shunting, rather than having oxygen-poor blood travel through the more resistant pulmonary artery. This causes the arterial oxygen saturation to drop, and the patient subsequently receives less oxygen. By squatting, however, the patient is cutting off circulation to their legs, increasing the systemic vascular resistance, and making oxygen-poor blood more likely to travel through the pulmonary artery, raising the arterial oxygen saturation [9]. This makes the patient feel better. Other indicators of ToF include clubbed digits, delayed physical growth, easy fatigability and poor appetite [10].

Once a congenital heart defect or ToF is suspected, an echocardiogram will confirm the suspicions. The echocardiogram, will visualize the four heart defects and how the heart responds to them [6]. It can detect the degree of septal malalignment and thus sub pulmonary obstruction, enabling physicians to decide what kind of repair is needed and when to do it [11]. A chest radiograph is also a helpful tool in diagnosing ToF; in a patient with ToF, the radiograph would display an upturned apex due to the right ventricular hypertrophy, as well as the absence of the main pulmonary artery segment. This is commonly referred to as a "boot shaped heart" [12]. The electrocardiogram would usually show the right ventricular hypertrophy as a right bundle branch block [13,14]. A final test that is often performed in the diagnosis of ToF is cardiac catheterization; this procedure can help determine whether there is a right to left shunt and its severity [6].

Statistics

Tetralogy of Fallot is the most common cyanotic heart defect in children who survive past the neonatal age without treatment, and it accounts for 10% of all congenital heart defects. It is believed to affect males and females equally [3]. The CDC estimates that 1,660 babies are born in the United States each year with ToF, meaning that about one in every 2,518 babies born in the United States each year have ToF [2]. Worldwide, ToF occurs in three to five of every 10,000 live births [3]. Which is almost exactly the same rate as in the US, as it is not more common in some areas over others.

Treatments

Surgical repair of Tetralogy of Fallot is always necessary [8]. And it greatly improves the patient's health and quality of life [6]. In rare, more severe cases, children require staged treatment before undergoing the full corrective surgery. This includes inserting a Blalock-Taussig shunt - a tube placed between the aorta and pulmonary artery to increase blood flow to the lungs [15]. If no other risk factors are present, however, over 95% of infants diagnosed with ToF undergo successful corrective surgery within their first year [8], typically between three to five months of age [15]. The surgery uses a synthetic Dacron patch to cover and close the ventricular septal defect, so that blood can no longer flow between ventricles. The pulmonary stenosis is fixed by resecting

any obstructive muscle tissue in the right ventricle that was caused by right ventricular hypertrophy. Then, the surgeon will make an incision in the pulmonary outflow pathway and stitch a transannular patch into that incision, enlarging the outflow pathway and relieving sub pulmonary resistance [8]. While this surgery is highly effective and the 1-year survival rate after operation is 98.6% [16]. Teenagers or adults who had a ToF repair during childhood often need additional intervention in stages to correct heart problems that develop over time [6]. Right ventricular outflow tract obstruction and pulmonary regurgitation are common [17]. These issues can be treated by Trans Catheter balloon dilation of the vessels, balloon valvuloplasty, and pulmonary valve implantation, respectively. These are relatively lowr-risk procedures that can increase a patient's quality of life and life expectancy greatly. It is important for adolescents and adults who have had ToF corrective surgery as children to have regular evaluations by cardiac experts to monitor these potential issues [8].

Human Interest Story/Case Study

A previously healthy 11-month old male was reportedly eating when he threw his head back and became unresponsive. Upon arriving at the hospital, the patient was bradycardic and hypotensive and he was intubated for respiratory failure. Even after initial stabilization of the patient, he remained hypotensive. A bedside echocardiogram was performed in the emergency department, which demonstrated poor left ventricular contraction, leading the medical staff to admit him into the Pediatric Intensive Care Unit [PICU] for presumed cardiopulmonary failure. There, he was placed on an oscillator, but his oxygen saturations remained low, and he remained hypotensive. A formal echocardiogram was performed which demonstrated severe right ventricular hypertrophy, reduced left ventricular contractility and an overriding aorta. The right ventricular outflow tract and pulmonary valve were not completely visualized in this exam, which explains why the rest of the characteristics of ToF were not seen. Nevertheless, the findings of the echocardiogram were concerning for potential ToF. The patient was then placed on venoarterial Extracorporeal Membrane Oxygenation [ECMO] [18,19]. After successful ECMO cannulation, another echocardiogram was performed, which demonstrated all the previous findings, in addition to a pulmonary stenosis, which continued to prove the suspicion of ToF. Once stabilized, the patient was transferred to an outside facility for pediatric cardiothoracic surgery services and ultimately underwent surgical repair for ToF [18].

Current Research/Advancements

As of 2020, there has been no report of a complete transcatheter repair for Tetralogy of Fallot. As interventional cardiology becomes more advanced, the possibility of treating ToF by interventional means is raised. A solution would hopefully eliminate the need for open-heart surgery while fixing ToF, as it is a very invasive procedure that takes time to recover from. Developing 3D technology will play a big role in the realization of this idea, as it has been shown to describe vessels' anatomy and can help determine the surgical approach to more complex intra-cardiac anatomy. It can also be used to test possible devices and to rehearse the operation, so that the procedure can be optimally tailored. The current researchers for an interventional approach toward ToF repair suggest using a single device to repair all four abnormalities in the patient's heart. This device would realign the anteriorly and superiorly displaced conal septum, relieving the right ventricular outflow tract obstruction and allowing blood to flow more easily to the lungs. Just this displacement of the conal septum would likely not suffice to close the ventricular septal defect, though, and the use of ventricular septal defect occluders would be required. Otherwise, a single covered device in the shape of a bottleneck or opened with a balloon to obtain a bottleneck shape could be used to treat all of the ToF characteristics simultaneously, as long as the device would long enough to cover the entire ventricular septal defect. Because this device would relieve right ventricular outflow obstruction and, by closing the ventricular septal defect, decrease the right ventricular systolic pressure, the right ventricular hypertrophy would regress. Some issues scientists are facing while trying to develop an interventional approach to ToF repair include the fact that a device standing in the right ventricular outflow tract would be under very high stress and prone to fractures. Despite this, though, it is projected that a fully interventional approach to ToF repair will be achieved within two decades [20, 21].

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