ISSN-e [2675-5602]

Global Academic Nursing Journal

REVIEW ARTICLE

Impact of early diagnosis and management of Tetralogy of Fallot

Impacto del diagnóstico precoz y el tratamiento de la tetralogía de Fallot

Impacto do diagnóstico e abordagem precoce da Tetralogia de Fallot

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How to cite this article:
Sequenzia AA, Anschau JKP, Schmidt JOS, Pinto MP, Guimarães PPR, Miranda VF, Resende YGC, Ferreira DS, Marques JM. Impact of early diagnosis and management of Tetralogy of Fallot. Glob Acad Nurs. 2024;5(2):e432. https://dx.doi.org/10.5935/2675-5602.20200432

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Submission: 04-04-2024
Approval: 05-26-2024

Abstract

Tetralogy of Fallot accounts for 10% of cyanotic congenital heart diseases. Clinically, symptoms depend on blood flow and, consequently, the degree of hypoxemia. The objective of this article is to gather evidence to support the need for early diagnosis and, consequently, intervention in children born with Tetralogy of Fallot congenital heart disease. The methodology used was an integrative literature review, considering articles published since 2017, with a QUALIS score of A1 to B3, in Portuguese and English. The results indicate that the techniques used to treat Tetralogy of Fallot have been thriving and offering increasingly satisfactory long-term results. However, residual problems require monitoring and may result in reinterventions, such as ventricular arrhythmia, pulmonary regurgitation, and right ventricular outflow tract obstruction. Surgery remains the gold standard, with low early mortality after valve replacement and good long-term results. Given the facts raised, we can conclude that the studies raised showed that late diagnosis is a predictor of worse outcomes and that the success of curative techniques is, evidently, influenced by the existence and quality of early diagnosis.

Descriptors: Tetralogy of Fallot; Diagnosis; Treatment; Heart Defects, Congenital; Heart Septal Defects, Ventricular.

Resumén

La tetralogía de Fallot representa el 10% de las cardiopatías congénitas cianóticas. Clínicamente, los síntomas dependen del flujo sanguíneo y, en consecuencia, del grado de hipoxemia. El objetivo de este artículo es recopilar evidencia que respalde la necesidad de un diagnóstico precoz y, en consecuencia, de una intervención en niños nacidos con tetralogía de Fallot. La metodología empleada fue una revisión bibliográfica integradora, considerando artículos publicados desde 2017, con una puntuación QUALIS de A1 a B3, en portugués e inglés. Los resultados indican que las técnicas utilizadas para tratar la tetralogía de Fallot han prosperado y ofrecen resultados cada vez más satisfactorios a largo plazo. Sin embargo, los problemas residuales requieren seguimiento y pueden dar lugar a reintervenciones, como la arritmia ventricular, la insuficiencia pulmonar y la obstrucción del tracto de salida del ventrículo derecho. La cirugía sigue siendo el estándar de oro, con baja mortalidad temprana después del reemplazo valvular y buenos resultados a largo plazo. A la vista de los hechos planteados, podemos concluir que los estudios planteados demuestran que el diagnóstico tardío es un predictor de peores resultados y que el éxito de las técnicas curativas está, evidentemente, influido por la existencia y calidad del diagnóstico precoz.

Descriptores: Tetralogía de Fallot; Diagnóstico; Tratamiento; Cardiopatías Congénitas; Defectos del Septo Intraventricular.

Resumo

A Tetralogia de Fallot compreende 10% das cardiopatias congênitas cianóticas. Clinicamente, a sintomatologia depende do fluxo e, consequentemente, do grau de hipoxemia. O objetivo desse artigo é reunir evidências que sustentem a necessidade do diagnóstico e, consequentemente, intervenção precoce nas crianças nascidas com a cardiopatia congênita Tetralogia de Fallot. Como metodologia foi realizada uma revisão integrativa da literatura, na qual foram considerados artigos publicados a partir de 2017, com QUALIS de A1 a B3, nos idiomas português e inglês. Os resultados apontam que as técnicas empregadas no tratamento da Tetralogia de Fallot vêm prosperando e oferecendo cada vez mais resultados satisfatórios a longo prazo. Entretanto, problemas residuais exigem acompanhamento e podem resultar em reintervenções, como no caso da arritmia ventricular, regurgitação pulmonar e da obstrução da via de saída do ventrículo direito. A cirurgia ainda se mantém como padrão-ouro, apresentando baixa mortalidade precoce após troca da valva e bons resultados a longo prazo. Diante dos fatos levantados podemos concluir que os estudos levantados expuseram que o diagnóstico em tempo tardio é preditor de piores desfechos e que o sucesso das técnicas curativas é, evidentemente, influenciado pela existência e qualidade do diagnóstico precoce.

Descritores: Tetralogia de Fallot; Diagnóstico; Tratamento; Cardiopatias Congênitas; Defeitos do Septo Ventricular.

Introduction

First described by Bishop and anatomist Nicolas Steno in 1673 and with its anatomy better elucidated in 1888 by physician Etienne Louis Arthur Fallot, whose surname gave the disease its eponym, Tetralogy of Fallot comprises 10% of cyanotic congenital heart diseases, making it the most prevalent[1,2]. As a tetrad, the four abnormalities present in Tetralogy include pulmonary valve stenosis, right ventricular hypertrophy, aortic overshoot, and interventricular septal defect. This complex condition generates the clinical picture of hypoxemia, which presents with the cyanosis so characteristic of the disease, identifiable even at an early age as "blue babies"[3].

It is essential to note that although the condition mentioned above is common, cyanosis and the general clinical presentation vary according to the severity of right ventricular outflow tract (RVOTO) stenosis and the anatomy of the pulmonary artery. Hypoxemia is caused by the passage of deoxygenated blood from pulmonary circulation to the systemic circulation, primarily due to a ventricular septal defect and dextroposition of the aorta. When hypoxemia is severe, palliative Blalock-Taussig surgery can be performed to improve blood oxygenation by increasing pulmonary blood flow[4]. Therefore, the phenotype can range from ‘‘classic Fallot’’ with pulmonary artery stenosis to more severe forms with pulmonary atresia and double outlet right ventricle[2].

Clinically, symptoms depend on the flow and, consequently, the degree of hypoxemia. Therefore, patients can be described as having 'Pink Fallot' due to pink/acyanotic skin and long asymptomatic periods. Alternatively, patients who are constantly cyanotic and hypoxic may present with dyspnea at specific moments, heart murmurs, loss of consciousness, digital clubbing, developmental delays, and manifestations of 'compensatory' characteristics, such as the child squatting due to the feeling of improvement brought on by venous return. Furthermore, it is still worth mentioning cases in which the hypoflow is not as significant, but there is a large interventricular communication that can culminate in congestive heart failure (CHF)[1,3].

The objective of this study is to gather evidence supporting the need for early diagnosis and intervention in children born with the heart disease known as Tetralogy of Fallot. By presenting the relationship between disease duration and outcome, we will address the mortality and survival rates of untreated patients, as well as the main signs and symptoms that enable early diagnosis, in addition to the challenges involved. We assume that Tetralogy of Fallot represents 10% of all congenital heart diseases and that most untreated children die in infancy[1].

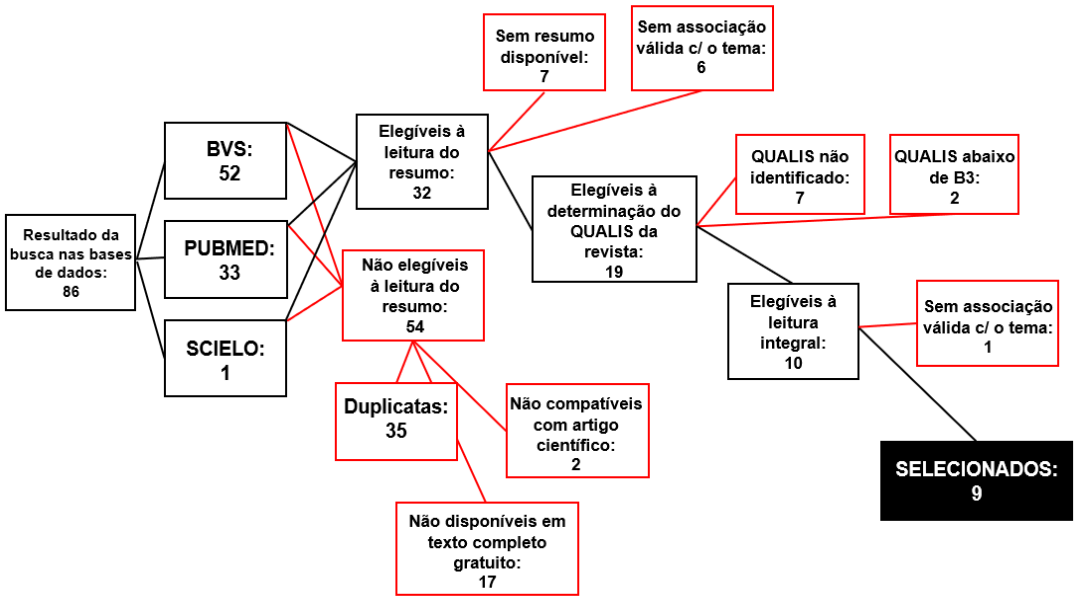
Methodology

This is a comprehensive, multidisciplinary, integrative literature review with an exploratory and descriptive approach. The guiding question of the study is to investigate the importance of early diagnosis and intervention in Tetralogy of Fallot.

An integrative review is a broad methodological approach to literature reviews, allowing for the inclusion of experimental and non-experimental studies for a comprehensive understanding of the phenomenon under analysis. It combines data from theoretical and empirical literature and incorporates a comprehensive range of purposes, such as defining concepts, reviewing theories and evidence, and analyzing methodological issues within a particular topic[5].

The broad sample, together with the multiplicity of proposals, should generate a consistent and comprehensible overview of complex concepts, theories, or health problems relevant to the health-disease context[6,7]. To answer the objective of the study, the acronym PVO was used as the method, where “P” indicates the disease under study; “V” the variables, and “O” the outcome, which are described below: P: Tetralogy of Fallot, V: Technologies, O: Diagnosis.

Figure 1. Flowchart of the article selection process for integrative review. Angra dos Reis, RJ, Brazil, 2023



Articles published since 2017, in Portuguese and English, and available in free full text, were considered for analysis. A search was performed in the databases by article title and subsequent reading of the abstract, using the descriptors "Tetralogy of Fallot, diagnosis and treatment" defined according to the Health Sciences Descriptors (DeCS/MeSH), which in English are described as "Tetralogy of Fallot, diagnosis and treatment." Using Boolean operators, the search was conducted as follows: "(Tetralogy of Fallot) AND ((diagnosis) OR (treatment))", on November 9, 2023.

Thus, the aim was to identify articles with diverse study designs that discussed the diagnosis and intervention of Tetralogy of Fallot. After selection for reading the abstract of each article, these were classified according to the QUALIS of each journal. Of these, only those with a QUALIS score of A1 to B3 and most appropriate to the proposed topic were selected for full reading. This narrowed the sample size to those works truly consistent with the research objective, excluding the others. To better visualize the material used, after reading and critical analysis, a summary table of the articles was created, highlighting the author/year, objective, methodology, main result, and main outcome.

Results and Discussion

In total, the search found (86) articles from all the databases used. Namely, (52) from BVS (Virtual Health Library), (50) from MEDLINE, (1) from LILACS, and (1) from the São Paulo State Health Department. Of the remainder, (33) were found in PubMed and (1) in SciELO. After excluding (35) duplicates, (17) articles not available in free full text, and (2) publications not compatible with scientific articles, 32 articles remained eligible for abstract reading and subsequent QUALIS classification of the journals. Thus, (7) articles without an available abstract and (6) articles in which the abstracts did not demonstrate a valid association with the theme were removed from the content. Of the (19) articles whose journals were subjected to QUALIS classification, (7) were excluded due to unidentifiable QUALIS and (2) due to QUALIS below B3. At the end of the selection, (10) articles were assigned for full reading, filing, and composition of the synthesis matrix of the integrative review, and in the process, (1) article was excluded for not presenting a valid association with the theme. Finalizing the selection with (9) papers.

Chart 1. Summary of articles included in the integrative review. Angra dos Reis, RJ, Brazil, 2023

Author / Year	Qualis	Objective	Methodology	Main Results	Conclusion
Aguirrezabalaga, *et al*. 2020	A4	Evaluate and compare transcatheter pulmonary valve implantation and surgical valve replacement.	Review Article	Both techniques yield excellent results. There are currently no studies directly comparing them. Surgery remains the gold standard; however, percutaneous pulmonary valve implantation (PPVI) has shown safety and good results.	There is still a need for better monitoring of cohorts regarding PPVI, to compare them with pre-existing studies of the surgery, as well as studies that directly compare them. Ultimately, it is necessary to understand both techniques as complementary, not competing. In the future, the hybrid form may become the gold standard.
Chelliah, *et al.* 2021	A1	Identify risk factors for mortality in patients with tetralogy of Fallot and absent pulmonary valve.	Multicenter retrospective cohort	Early gestational age at delivery, mediastinal shift, ventricular dilation, left ventricular dysfunction, tricuspid regurgitation, and Doppler abnormalities were associated with fetal and postnatal mortality.	Perinatal mortality in tetralogy of Fallot with absent pulmonary valve remains high, with an overall survival rate of 64% in fetuses with intended treatment. Right ventricular dysfunction is an independent predictor of mortality. Left ventricular dysfunction predicts mortality, influences prenatal management, and birth planning. Mediastinal shift can influence airway obstruction, abnormal lung development, and is associated with high mortality.
Gou, *et al*. 2022	A1	Gather important information for formulating targeted therapy and biomarkers useful for diagnosing Tetralogy of Fallot, based on a comparison of lncRNA and mRNA expression in healthy fetal myocardial tissues and those with Tetralogy of Fallot.	Prospective study	These abnormal lncRNAs, selected in cardiac tissue with tetralogy, are promising biomarkers and gene therapy targets for early diagnosis and treatment. Further studies are still needed due to the limited sample size.	Further studies are still needed due to the limited sample size.
Karapurkar, *et al*. 2023	B1	Report a case of tetralogy of Fallot with a disconnected	Case report	The report presents the benefit of advanced STIC 3D/4D rendering accurate	Prenatal diagnosis and accurate analysis of anatomy are possible using fetal echocardiography with newer

		branch of the pulmonary arteries.		prenatal diagnosis of this rare condition, leading to early neonatal intervention.	techniques such as STIC 3D/4D rendering, allowing perinatal care to be better developed.
Moscatelli, *et al.* 2023	A4	Provide a more comprehensive view of the role of protocols used for the clinical evaluation of patients with Tetralogy of Fallot.	Review Article	Cardiopulmonary exercise testing is valid for monitoring patients with repaired tetralogy of Fallot, but standardized protocols and the use of the technique in practice are necessary to promote risk stratification and determine outcomes.	Cardiac computed tomography (CT) is becoming increasingly popular in the management of patients with Tetralogy of Fallot. Cardiopulmonary exercise testing is a useful tool for therapy and prognosis. Choosing the most appropriate modality is multifactorial.
Valdigem, *et al*. 2018	A4	Report the case of a 16-year-old girl with delayed repair of Tetralogy of Fallot and drug-refractory implantable cardioverter defibrillator (ICD) shocks.	Case report	The patient underwent successful ablation of ventricular tachycardia using radiographs and anatomical landmarks, without the use of electroanatomical mapping. Medications were reduced one month after the procedure, reducing symptoms and improving the patient's quality of life.	Ventricular tachycardia ablation in these patients is feasible and should be considered when there is no anatomical or hemodynamic impairment or prosthesis failure.
Van der Ven*, et al*. 2019	A3	Present an overview of Tetralogy of Fallot, current treatment strategies, long-term survival delineation, residual lesions, and remaining challenges.	Review Article	Tetralogy has a chance of being repaired with low short- and long-term mortality, and patients surviving into adulthood.	The key to favorable outcomes is to expand understanding of right ventricular adaptation.
Yeo, *et al.* 2019	A4	Report, for the first time, two cases of TOF with pulmonary atresia with variable pulmonary arterial anatomy, in which fetal intelligent navigation echocardiography detected the condition early prenatally.	Case series	Even with the evolution of intervention in Tetralogy of Fallot with pulmonary atresia, inadequate growth of the pulmonary vasculature is still present in some patients, even when treated appropriately.	Tetralogy of Fallot with pulmonary atresia is a highly complex and anatomically variable heart defect, particularly in the pulmonary arterial circulation. The fetal intelligent navigation ultrasound successfully detected the characteristics of the abnormality prenatally.
Yuan, *et al*. 2021	A2	Evaluate the predictive value of the pulmonary vein index in the early prognosis of patients who underwent total repair of tetralogy of Fallot.	Retrospective study	A lower pulmonary vein index better predicted prolonged postoperative hospital stay, ICU stay, and ventilation time. Furthermore, it was a significant risk factor for a higher 24-h maximum vasoactive inotropic score, serous effusion, delayed sternal closure, and the need for peritoneal dialysis.	The pulmonary vein index is therefore a good predictor of early prognosis for surgical treatment in Tetralogy of Fallot.

Considering the compilation of selected publications, it is possible to answer and discuss the objectives of this research, organized under the topics: diagnostic strategies and tools, treatment and its challenges, modalities, and relationship with mortality and survival. It is a fact that the techniques employed in the treatment of Tetralogy of Fallot have been thriving and offering increasingly satisfactory long-term results. Thirty-year survival rates range from 68.5% to 90.5%. However, even when performed under the best conditions, residual problems require monitoring and may result in reinterventions, as in the case of ventricular arrhythmia, pulmonary regurgitation, and right ventricular outflow tract obstruction, so well elucidated in the literature. On this other point, the study also highlights the need to perform pulmonary valve replacement or stenosis relief before right ventricular dysfunction, caused by long-term regurgitation or pulmonary stenosis, becomes irreversible. However, defining the ideal time frame remains a challenge[2].

Tetralogy of Fallot presents in several ways, with varying degrees of severity. Therefore, some are more difficult to repair, and the after-effects, even after successful intervention, also require management. Pulmonary regurgitation is the most significant after-effect after repair, given its impact on the right ventricle. The best procedure for its resolution is discussed, comparing classic surgery and transcatheter implantation. In short, surgery remains the gold standard, with low early mortality after valve

replacement and good long-term results[8]. But percutaneous implantation emerges as an efficient and safe alternative, which deserves further studies[1].

As previously mentioned, some presentations of Tetralogy of Fallot bring more serious conditions, such as an absent pulmonary valve, with high perinatal mortality and an overall survival rate of 64% in fetuses in which treatment is attempted[9].

Still discussing the influences on mortality, right ventricular dysfunction acts as an independent predictor of overall mortality, that mediastinal shift is associated with increased mortality by influencing airway obstruction and abnormal lung development, and that left ventricular dysfunction also predicts mortality and can influence birth planning and prenatal management[9].

Therefore, the literature strongly emphasizes that due attention should be paid to the high fetal and postnatal mortality, even today, of Tetralogy of Fallot with absent pulmonary valve. They also show that the mortality predictors can be observed in fetal echocardiographic findings and highlight the need for a comprehensive evaluation of the heart and lungs to obtain an early diagnosis of the condition and provide effective pre- and perinatal counseling and management. Improved risk stratification is also aimed at[9].

The clinical heterogeneity of patients with Tetralogy of Fallot challenges therapeutic decision-making and prognostic prediction. Research suggests that some patients may experience prolonged postoperative recovery even with successful surgery. Given this, this study aims to assess the predictive value of the pulmonary vein index for survival or early death and determine postoperative recovery time. Therefore, even with the current low mortality and excellent long-term results of early surgical repair of Tetralogy of Fallot, predicting the prognosis is useful for anticipating the intensive management of patients who require it and modifying/minimizing negative outcomes. The study concludes that a low pulmonary vein index is a risk factor for early death and long postoperative recovery[10].

Still discussing residual problems after Tetralogy of Fallot repair, studies report ventricular tachycardia, which, although rare, carries a dangerous prognosis. Ventricular arrhythmias, in general, are common in these cases and may reflect prosthetic dysfunction or the need for another cardiac procedure. The study also reports that of approximately 25,000 newborns with congenital heart disease in Brazil in 2010, 973 were born with Tetralogy of Fallot. In summary, the prognosis of the condition is improving, but long-term risks remain[11].

Another severe form of tetralogy is pulmonary atresia, in which there is a lack of blood flow from the right ventricle to the pulmonary arteries. In this case, the study presents two cases with this condition that were diagnosed prenatally with the help of a recently developed method and underwent early surgical correction. The method in question is Fetal Intelligent Navigation Ultrasound (FINE), which demonstrates the impact of early diagnosis and the importance of employing new technologies in this regard[12].

Now in an even more current discussion, we discuss the detection of lncRNAs (long non-coding RNAs) and mRNAs in fetal myocardial tissues with Tetralogy of Fallot and healthy controls, finding 94 different expressed lncRNAs, which may be the future of prevention, diagnosis, and consequent early intervention. We also found 83 abnormal mRNAs in tissues with Tetralogy of Fallot compared to the control group. In summary, these findings, whose role in pathogenesis has not yet been elucidated, may be promising biomarkers and targets for gene therapy in the future, enabling early diagnosis and appropriate treatment[13].

In the search for better methods and tools for timely diagnosis and follow-up after repair of Tetralogy of Fallot, studies compare the modalities employed. This demonstrates the essential role of cardiovascular imaging in diagnosis, treatment, risk stratification, intervention planning, and long-term follow-up. Echocardiography is the first-line diagnostic tool for serial evaluation and evaluation, and in pediatrics, it is often the only one used, given its availability, low cost, and lack of radiation. Cardiovascular magnetic resonance imaging has become the gold standard for guiding interventions and assessing structures that are difficult to visualize with echocardiography. Furthermore, it can indicate the presence of myocardial fibrosis. Also based on data from the same study, cardiac computed tomography is becoming increasingly popular in the periprocedural approach, in the presence of stents, when MRI is contraindicated, or in cases of doubt regarding the coronary arteries. Finally, cardiopulmonary exercise testing is highly useful in guiding therapy and providing prognosis. In short, the choice of modality is multifactorial; all techniques are useful in certain circumstances and can be combined depending on the need[14].

To complete the review, studies report another variation of Tetralogy of Fallot, with a disconnected branch of the pulmonary arteries. This condition, rarely described in the literature, was diagnosed through 3D/4D fetal echocardiography (STIC). Further emphasizing its importance, early neonatal planning and intervention in the case were made possible by prenatal diagnosis. The research highlights the benefit of this diagnostic modality for detecting these anatomical details prenatally, allowing preservation of the pulmonary blood supply and repair, which led to favorable outcomes[15].

Conclusion

In its entirety, it is demonstrated that late diagnosis is a predictor of worse outcomes and that the success of curative techniques is clearly influenced by the availability and quality of early diagnosis. This is especially true during prenatal care, given that highly accurate methods and tools for this detection are currently being used and developed. Furthermore, it is mentioned on numerous occasions that perinatal management is also a major prognostic determinant and that, even with the possibility of late intervention, the results of the latter are demonstrably inferior, which affects the patient's survival and quality of life. Furthermore, it has not yet been defined how early this

intervention should be performed. It is explained that further studies are needed to identify the best timing.

The publications included in the review also highlight the evolution of survival and the need to manage sequelae, which can arise even after successful interventions and are influenced by the length of exposure to the untreated disease. However, the study is limited by the possibility of selection bias, as it included only articles published in Portuguese and English from 2017 onward. Therefore, caution is advised when generalizing the findings to other populations and contexts.

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