Review Article

RHEUMATIC FEVER AND INFECTIVE ENDOCARDITIS: A REVIEW

Abstract

Aims: Gather relevant literature, understand and expose the mechanism by which Rheumatic Fever can trigger Endocarditis Method: This is a narrative review, where the following descriptors were used as a source of research: Endocarditis; Rheumatic Fever; Bacterial Endocarditis; in the Scielo, PubMed, LILACS, BVS and MEDLINE databases.
Methodology: This is a narrative review, where the following descriptors were used as a source of research: Endocarditis; Rheumatic Fever; Bacterial Endocarditis; in the Scielo, PubMed, LILACS, BVS and MEDLINE databases.
Results: Rheumatic fever can be classified as an autoimmune disease because it develops a response against the body's normal constituents. It is noticed that it mostly affects children and adolescents. Endocarditis is one of the main complications of rheumatic fever, and can affect the mural endocardium and frequently the heart valves. The pathophysiology of both diseases and the existing epidemiological data show that the alteration of the blood flow near the heart valves damaged by RF, results in a lesion of the endocardium and migration of bacteria present in the circulation.
Conclusion: Patients affected by rheumatic fever, as it is characterized as a pathology resulting from an autoimmune process secondary to a bacterial infection, present a close relationship with the development of infective endocarditis. From the literature review, it is clear how both conditions are related and require attention because of their complications.

Keywords: Endocarditis; Rheumatic Fever; Epidemiology; Carditis.

1. INTRODUCTION

Rheumatic fever (RF) is an autoimmune disorder that primarily affects the human body by causing upper respiratory tract infections. This infectious condition is caused by the beta-hemolytic group A streptococcus Lancefield (EBHGA), which has a chemically structural tropism for cardiac, articular, neurological, cutaneous, and subcutaneous cells. Among these preferred tissues, the myocardium is the most affected by the mentioned infection [1].
Globally, an estimated 15 to 20 million new cases are reported annually [2]. Cases diagnosed before the age of 5 or after the age of 15, or during adulthood, are rare since this age group is at higher risk of developing EBHGA pharyngitis. However, both primary and recurrent contacts can also affect adults [3].
The most common clinical manifestations include polyarthritis, carditis, subcutaneous nodules, erythema marginatum, and variable chorea (involuntary and repetitive movements that are brief, irregular, relatively fast, unpredictable, and continuous). Consequently, valve sequelae (mitral and aortic) can be chronic and irreversible, leading to cardiac dysfunction or even death. Infectious endocarditis (IE) is the most severe manifestation of RF, occurring in about 40% to 70% of initial episodes, and it is the only one that can result in sequelae and death [4].

Thus, the significant morbidity and mortality associated with RF demonstrate the importance of prevention and early identification. Therefore, this study aims to understand and explain the mechanism by which Rheumatic Fever can trigger Endocarditis through a narrative review.

2. MATERIAL AND METHODS

A literature review was conducted in April and May of 2023, based on a total of 23 sources. The articles used in this study were selected using the following keywords: Rheumatic fever; endocarditis; Cardiac Valve Diseases. In addition, academic books were consulted to supplement the information.
The study period was set from 1996 to 2023, and the articles were searched in the databases of the Virtual Health Library (BVS), Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), MEDLINE, and PubMed. After the search and selection stage, the reading and production of this narrative review began.

3. RESULTS AND DISCUSSION

3.1 Rheumatic Fever (RF)

Streptococcus pyogenes, a gram-positive bacterium, or EBHGA, has an incredible ability to adapt to the human body and can cause various infectious conditions, with pharyngotonsillitis being the most predominant infection. After infection with S. pyogenes, which occurs through direct contact with secretions from contaminated individuals, the infection can remain localized to the primary focus, causing symptoms such as fever, dysphagia, general malaise, vomiting, edema, and erythema in the oropharyngeal region, among others. However, if the infection spreads to other areas of the body, it can cause serious complications, such as RF, the most concerning sequelae of infection by this bacterium [5].

The clinical manifestations of RF can be observed 2 to 6 weeks after upper respiratory tract infection by EBHGA, when throat cultures for bacterial infection become negative and the antibodies produced by the body to fight the bacteria increase. This disease has an autoimmune nature and occurs in genetically susceptible hosts, characterized by non-suppurative inflammatory lesions involving cardiac tissue, joints, subcutaneous cellular tissue, and the central nervous system. Therefore, RF causes long-term permanent cardiac damage, almost invariably resulting in rheumatic carditis [6].

RF and its sequel, rheumatic heart disease (RHD), are poorly recognized as a global health problem, despite causing significant morbidity and mortality in underdeveloped countries. Worldwide, the incidence of RF is higher among individuals aged 5 to 15 years and is rare above 30 years of age, with approximately 60% of these individuals in endemic communities developing RHD as a sequel. The incidence is similar between men and women, but women have a 1.6 to 2.0 times higher chance of developing RHD. Furthermore, the most recent estimates of the global burden of RHD conclude that there are about 33 million prevalent cases and around 275,000 deaths per year, predominantly occurring in developing countries [7].

The prevalence of RF cases has significantly decreased over the years, especially in developed countries and high-income populations, but it remains a relevant health problem in Brazil, causing high costs for the Unified Health System (SUS). Between 2016 and 2020,

a total of 10,458 hospitalizations for RF were documented, with the predominant age group being between 50 and 69 years. During the same period, among the hospitalized patients, there were 256 deaths. Although RF has decreased in cases worldwide, it remains the leading cause of heart disease among children and young adults in Brazil and other developing countries [8].

The pathophysiology of RF is still poorly understood but certainly involves autoimmune mechanisms, where self-recognizing antibodies, called autoantibodies, cross-react with the M protein of EBHGA and the cardiac tissue proteins of the host. EBHGA infection generates an immune response by neutrophils, macrophages, and dendritic cells, which phagocytize the bacteria. Thus, an inflammatory process occurs through B and T lymphocyte-mediated responses. If the infection is recurrent, the host tissue is degraded through molecular mimicry, which involves the sharing of antibody or T-cell areas between the host and the organism. Finally, the antibody generated to fight the pathogen also recognizes the host antigen, leading to inflammation of the heart valves, which, upon healing, results in permanent damage, and inflammation of the basal ganglia in the brain, causing Sydenham's chorea [1].

The treatment of acute rheumatic fever aims to suppress the inflammatory process and minimize its impact on the heart, joints, and central nervous system, as well as eradicate EBHGA from the oropharynx and provide symptom relief. General measures include hospitalization in cases of moderate or severe carditis, disabling arthritis, and severe chorea. Relative rest for an initial period of two weeks, temperature control with paracetamol or dipyrone in cases of high fever.[21] Corticosteroid use as anti-inflammatory therapy in cases of severe and refractory rheumatic carditis, with alternating pulse therapy or oral therapy gradually decreasing the dose each week, with a total treatment time of approximately 12 weeks for moderate to severe carditis and 4-8 weeks for mild carditis when corticosteroids are used in this category. In cases of chorea, some more recent studies have shown the effectiveness of corticosteroid use in symptomatic treatment, but there is still insufficient evidence to recommend other therapies [9].

3.5 Infective Endocarditis (IE)

Infective endocarditis (IE) is an inflammatory disease of the mural endocardium or heart valves [10], which occurs when bacteria, fungi, or other microorganisms invade the bloodstream and deposit on the heart valves, which are the structures that control blood flow within the heart [11]. These deposits are called vegetations and are composed of thrombotic fragments, amorphous masses of varying size that consist of a significant amount of microorganisms, which can generate an inflammatory process when they adhere to the valves [2].

Many microbial agents can cause IE, although the most frequent ones are gram-positive bacteria, mainly Staphylococcus and Streptococcus, and more recently, Enterococcus (SOUSA; PINTO., 2022). However, in addition to bacteria, infections by fungi such as Mycoplasma, Chlamydiae, and Rickettsiae are also observed [12]. Furthermore, the etiology and development of this pathology also depend on the risk factors to which the patient is exposed. Immunocompromised patients, intravenous drug users, children with congenital heart disease (the most affected group), individuals undergoing invasive procedures of any kind, and those with prosthetic valves constitute the most affected epidemiological profile [13]. Thus, it is understood that the genesis of IE is closely related to the patient's exposure or lack of exposure to certain infectious agents, the presence of comorbidities, and immunological factors.

The pathophysiology of IE is complex and involves various mechanisms, the main ones being endothelial injury, microbial adhesion, and development. Contact between the subendothelium and blood generates vascular injury, activating the coagulation cascade and exposing plasma proteins that serve as attachment sites for microorganisms. Inflammatory lesions can also initiate the process, and their mechanism is directly related to integrins, as they have the ability to bind to the endothelium [7].

Under normal conditions, the endothelium and heart valves are generally resistant to infections. One of the mechanisms to be highlighted is adhesion, which occurs when microorganisms adhere to previously injured surfaces through adhesion molecules, fimbriae, or other adhesion mechanisms [14]. Adhesion is an important step in establishing infection and is a complex and multifactorial process.

When bacteria adhere to the endothelial cells of the heart valves, they can multiply and form a colony. This colony of bacteria can grow in size and form a complex structure called a biofilm, which is a protective layer of bacterial cells and extracellular material that adheres to the surface of the heart valves [8,10]. This matrix protects microorganisms from the host's immune response, including the action of antibodies and phagocytic cells that would normally eliminate bacteria [22]. The biofilm may also include channels to provide nutrients and oxygen to internal microorganisms, as well as a variety of proteins and enzymes that can help microorganisms resist attacks from the immune system and antibiotics [18].

The presence of microorganisms and biofilms on the heart valves can cause direct tissue damage, leading to destruction of the heart valves. The resulting inflammation can also damage the heart valves. The immune system responds to the presence of microorganisms and biofilms on the heart valves, causing an inflammatory response [22]. Inflammation can lead to fever, chest pain, shortness of breath, and other symptoms. Additionally, inflammation can contribute to the formation of lesions and abscesses in the cardiac tissue. Septic vegetations can detach and affect distant organs such as the kidneys, spleen, and brain [21].

3.3 Relationship between Rheumatic Fever and Infective Endocarditis.

One of the major complications of rheumatic fever is carditis, and among them, endocarditis is the most frequent [23]. To explain this relationship, we must start with the principle of physiology. Firstly, the involvement of the valves by rheumatic fever results in a significant alteration of blood flow [20]. This alteration, by triggering an imbalance in Virchow's triad, leads to the formation of thrombi susceptible to bacterial colonization, ultimately establishing a picture of intracavitary thrombosis [16].

Furthermore, as a result of valve modification, an adaptation is observed where the atrium starts to fibrillate. [17] This fibrillation further alters blood flow and increases intracavitary thrombosis. Finally, the blood, while passing through this valve, may contain bacteria, which will start to colonize the valvular thrombus [18]. This thrombus, now aseptic, infects the endocardium near the valve establishing a picture of endocarditis [19].
Moreover, it is important to note that during the research and writing of this study, scarce literature was found that investigated and defined the relationship between the discussed pathologies.

4. CONCLUSION

Patients affected by rheumatic fever, as it is characterized as a pathology resulting from an autoimmune process secondary to a bacterial infection, have an intimate relationship with

the development of infective endocarditis. The pathophysiology of both diseases and the existing epidemiological data demonstrate that the way in which this connection occurs, the main theory is primarily based on the alteration of blood flow near the cardiac valves affected by RF, resulting in endocardial injury and migration of bacteria present in the circulation.

Therefore, given the correlation between both diseases, it can be affirmed the importance of this understanding for the healthcare professional, who, by being able to recognize and diagnose RF, may suspect a future IE. Thus, healthcare teams will be able to promote a better prognosis for the patient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

REFERENCES

1. Carapetis JR, Beaton A, Cunningham MW, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016;2:15084.

2. Nepomuceno RM, Dias PD, et al. (2019). HEART COMPLICATIONS OF RHEUMATIC FEVER: CASE REPORT. Interdisciplinary Revista Pensamento Científico, 2016;5(4).

3. Kiss MHB. Clinical treatment of rheumatic fever. Rev Soc Cardiol State of São Paulo. 2005;15(1):53-60.

4. By Andrade JP. Brazilian guidelines for the diagnosis, treatment and prevention of rheumatic fever. Arq Bras Cardiol. 2009;93(3 Suppl 4):1-18.

5. Cahill TJ, Prendergast BD. Challenges in infective endocarditis. J Am Coll Cardiol. 2017;69(3):325-344.

6. Ferreira AS. Infectious endocarditis - a suspicion always present. Rev Port Med General Fam. 2013;29(1):54-60.

7. Melo L, Martins S, Ribeiro T, et al. Infectious endocarditis: a casuistic from the Department of Internal Medicine of a Hospital. Internal Med. 2017;24(1):19-23.

8. Medrado AVDS, Costa SA, Ribeiro RHF, et al. Acute rheumatic fever and its epidemiological profile in Brazil over the last 5 years. Rev Ibero-Am Humanid Cienc Educ. 2022;8(4):1175-1184.

9. Do Carmo Carvalho L, de Souza LS, Queiroz CG, et al. Infectious endocarditis: an approach to microbiological variance in the face of different factors. Braz J Health Rev. 2022;5(1):2867-2874.

10. Kumar V, Abbas AK, Aster JC. Robbins & Cotran - Pathology - Pathological Bases of Diseases. 8th ed. Rio de Janeiro: Elsevier; 2010.

11. Galvão JLFM, Santos N, Almeida F. Infectious endocarditis: a review from microorganism to treatment. J Res Dent Maxillofac Sci. 2016;2(3):23-31.

12. Pimenta EA, Silveira FP, Ribeiro CB, et al. Rheumatic fever: literature review on early identification and minimization of complications from the perspective of nursing. Rev Ciênc Saúde Nova Esperança. 2007;5(1):54-59.

13. Neto RA, Lopes MS, Silva PLM. Mitral stenosis as a sequel in patients with rheumatic fever. Braz J Health Rev. 2021;4(5):21099-21111.

14. Lisby G, Gutschik E, Durack DT. Molecular methods for diagnosis of infective endocarditis. Infect Dis Clin North Am. 2002;16(2):393-412.

15. Peixoto A, Martins C, Veiga S. Rheumatic fever: a systematic review. Rev Soc Bras Clin Med. 2011;9(3):234-238.

16. Santaularia-Tomas M, Vega-Sánchez AE, Pérez-Román DI. Infectious endocarditis. Evid Med Invest Salud. 2014;7(2):76-83.

17. Shmuéli H, Cogan E. Right-sided infective endocarditis 2020: challenges and updates in diagnosis and treatment.

18. Neto, Reinaldo Andrade, et al. "Mitral stenosis as a sequel in patients with rheumatic fever Mitral stenosis as a sequel in patients with rheumatic fever." Brazilian Journal of Health Review 4.5 (2021): 21099-21111.

19. de Souza Medrado, Antonio Victor, et al. "RHEUMATIC FEVER AND ITS EPIDEMIOLOGICAL PROFILE IN BRAZIL IN THE LAST 5 YEARS." Ibero-American Journal of Humanities, Sciences and Education 8.4 (2022): 1175-1184.

20. Mosquera, Julia Milhomem. "Child with severe carditis due to rheumatic fever managed in an intensive care unit: A case report." (2021).

21. Jorge, Marcelo Serafim, et al. "Infective Endocarditis Surgery. Analysis of 328 Patients Operated at a Tertiary University Hospital." Brazilian Archives of Cardiology 120 (2023): e20220608.

22. Calcaterra, Giuseppe, et al. "Infective endocarditis triangle.. Is it the time to revisit infective endocarditis susceptibility and indications for its antibiotic prophylaxis?." European Journal of Preventive Cardiology 26.16 (2019): 1771-1774.

23. Komorovsky, Roman R., Oksana R. Boyarchuk, and Vira O. Synytska. "Streptococcus gordonii-associated infective endocarditis in a girl with Barlow's mitral valve disease." Cardiology in the Young 29.8 (2019): 1099-1100.