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INFLUENCE OF INFLUENZA ON THE PATHOPHYSIOLOGY OF ACUTE MYOCARDIAL INFARCTION AND VACCINATION AS A PROTECTIVE MEASURE

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Abstract: Introduction: Coronary heart disease, especially acute myocardial infarction (AMI), is one of the leading global causes of death. Since the 1930s, the hypothesis that influenza can trigger acute cardiovascular events and death has been considered. Confirming this association is crucial, as fatal cardiovascular events resulting from influenza may be preventable through vaccination. The literature review aims to understand the influence of influenza on the pathophysiology of AMI, exploring the interconnections between cardiovascular health and immunological response, emphasizing the importance of vaccination as an essential protective measure against mortality associated with AMI. Method: A narrative review of the databases was carried out: PubMed, Virtual Health Library (VHL), Scielo and National Center for Biotechnology Information (NCBI). The key words used were "myocardial infarction", "human influenza", "vaccination", "atherosclerosis" and "inflammation" to select the 19 articles used. **Discussion:** It is currently known that there is an interconnection between influenza and AMI, which occurs through the production of cytokines, cellular transformation and platelet activation. Furthermore, the influenza virus prefers vascular structures, contributing to cardiovascular dysfunction. Furthermore, several studies support the protective efficacy of vaccination, indicating its relevance as a preventive and therapeutic measure in the context of influenza-associated AMI. **Conclusion:** Based on the evidence presented, we conclude that influenza can trigger myocardial infarction through the induction of inflammation and platelet activation. It is important to highlight the crucial role of vaccination as a protective factor, capable of significantly reducing the mortality rate from cardiovascular events.

Keywords: myocardial infarction; human influenza; vaccination; atherosclerosis; inflammation.

INTRODUCTION

Acute Myocardial Infarction occurs when there is cell death in the myocardium due to the formation of a clot, resulting in a total or partial obstruction of the coronary artery and triggering ischemia. (SANTOS, V. E. F. A. DOS, et al., 2011) Ischemia, generally It results from thrombosis and/or vasospasm around an atherosclerotic plaque. Most cases occur due to the sudden rupture of these plaques, leading to the formation of thrombi in vulnerable, inflamed areas, with high lipid content and a thin fibrous layer. (PESARO, A. E. P., et al., 2004)

Globally, coronary disease, particularly acute myocardial infarction, is the leading cause of death and disability. (BARNES, M., et al., 2015) The idea that influenza can trigger acute cardiovascular events and lead to death has emerged in the 1930s, when the relationship between the incidence of seasonal flu and increased cardiovascular mortality was initially identified. (KWONG, J. C., et al., 2018)

It is believed that influenza virus infection can trigger IAM by causing an acute coronary occlusion, triggered by thrombosis of an existing subcritical atherosclerotic plaque.. (BARNES, M., et al., 2015) Several pathogenic agents, such as influenza viruses, have the ability to influence the inflammatory response, affecting the dynamics of the atherosclerotic plaque and contributing to its rupture, which culminates in the development of a type 1 AMI.(MOHAMMAD, M. A., et al., 2020) Furthermore, clinically relevant viral infections can aggravate pre-existing cardiovascular conditions, contributing to the development of a type 2 AMI.(MOHAMMAD, M. A., et al., 2020) This sequence of events occurs due to the increased metabolic needs in the

heart tissue caused by fever and tachycardia, associated with the possible occurrence of hypoxemia.(BARNES, M., et al., 2015)

Currently, vaccination coverage is lower than ideal, especially among those at high risk of acute myocardial infarction. It is crucial to highlight the association between influenza and acute myocardial infarction, as fatal influenza-related cardiovascular events are potentially preventable through vaccination. If more substantial evidence confirms that influenza is a triggering factor for worsening cardiovascular events, this could impact health practices, promoting an improvement in vaccination coverage. (KWONG, J. C., et al., 2018)

The general objective of this literature review is to understand the influence of influenza on the pathophysiology of acute myocardial infarction, covering the connections between cardiovascular health and the immunological response, outlining, therefore, the significance of vaccination as an essential protective measure against mortality resulting from of acute myocardial infarction.

METHODOLOGY

This study consists of a literature analysis, using a review approach that incorporates the evaluation of 16 bibliographic sources. To conduct this review, the following databases were consulted: Pubmed, Scientific Eletronic Library On-line (Scielo), Virtual Health Library (VHL) and the National Center for Biotechnology Information (NCBI). The search for articles was through the application of specific keywords, which were, "myocardial infarction", "human influenza", "vaccination", "atherosclerosis" and "inflammation", which were verified in the descriptors DECS/ MESH. After this outcome, the following steps were followed in sequence: careful selection and choice of material relevant to the research objectives; thorough analysis and evaluation of texts; interpretation of reading and elaboration of the text. The selected articles were subjected to a joint analysis by the four authors, and in cases of divergence of opinions, one of the authors played the role of referee, deciding whether to include or exclude the articles, in order to ensure consensus and cohesion in the process. Among the works identified, 16 presented relevant contributions to the research in question, 6 of which are recent, dating between 2019 and 2022, while the other 10 belong to periods prior to 2019.

DISCUSSION

The pathophysiological context that associates influenza as a trigger for myocardial infarction involves the production of cytokines, resulting in the destabilization and rupture of the plaque, triggering, in turn, the coagulation cascade. (MOHAMMAD, M. A., et al., 2020) Recent Data suggest that smooth muscle cells have the ability to transform into foam cells through metaplasia, presenting cellular and molecular characteristics similar to those of mononuclear phagocytes. This concept integrates the proliferative perspective of atherogenesis with inflammatory pathways. (BENNET, M. R.; SINHA, S.; OWENS, G. K., 2020)

Cytokines, which act as proteins that mediate inflammation, play an essential role in the communication between leukocytes and the intrinsic cells of the arterial wall. During the process of atherogenesis, leukocytes and vascular cells in the plaque assume prominent roles in inflammation, and cytokines provide the means by which these protagonists communicate. (LIBBY, P., et al., 2018)

In an infection scenario, the presence of inflammatory cytokines, such as interleukins 1, 6 and 8, and tumor necrosis factor α, is detected in the bloodstream. These substances play a crucial role in activating inflammatory cells located within the atherosclerotic plaque,

influencing its biological dynamics. This process can culminate in plaque rupture, triggering events that lead to the occurrence of a myocardial infarction. This mechanism highlights the interconnection between infectious processes and acute cardiovascular events. (BOCALE, R.; NECOZIONES, S.; DESIDERI, G., 2022)

Furthermore, there is evidence that influenza viruses have a specific preference for vascular structures, as evidenced in experimental models that accelerate atherosclerosis, highlighting their prominent location in fibro lipid plaques. (AIDOUD, A., et al., 2020) This location it is associated with a pronounced local inflammatory response with macrophage infiltration and release of inflammatory cytokines into the circulation. This state of increased systemic inflammatory activity and plaques, hypercoagulability and endothelial and platelet dysfunction/ activation tends to persist even after clinical resolution of the acute infection. (MUSHER, D. M.; ABERS, M. S.; CORRALE MEDINA, V. F., 2019)

Furthermore, it is widely recognized that platelets play a crucial role in the development of myocardial infarction (MI). (ROSE, J. J., et al., 2015) After the release of inflammatory cytokines, the flu syndrome can favor the triggering of a state pro-thrombotic, facilitating platelet activation and endothelial dysfunction. (MUSCENTE, F.; DE CATERINA, F., 2020) Viral infection, especially by the influenza virus, results in a hyperreactive response and activation of platelets in both human models as well as animals. (ROSE, J. J., et al., 2015)

It was confirmed in two independent cohorts that a set of 62 genes, mainly from platelets, form the platelet gene expression profile associated with the response to aspirin. (ROSE, J. J., et al., 2015) Highlighting 31 of these genes coinciding with genes specific to platelets or megakaryocytes, emphasizing their relevance. Exposure to the H1N1 virus changes this profile, providing information about the connection between influenza and platelet activation, identifying genes and proteins associated with this response, contributing to a broader understanding of the interaction. (VOORA, D., et al., 2013)

Vasoconstriction in the coronary arteries, resulting from the narrowing of the vascular lumen, and the increase in frictional stress (shear tension), triggered by sympathetic activation and an increase in the concentration of endogenous catecholamines, promote a hyperdynamic cardiovascular response, causing changes in systemic vascular tone and coronary artery disease and, consequently, intensifying platelet activation. (ARDLIE, N. G.; MCGUINESS, J. A.; GARRET, J. J., 1985) These conditions are aggravated by changes in blood volume, such as hypovolemia or hypervolemia. All of these factors simultaneously contribute to an increase in biomechanical stress on pre-existing atherosclerotic coronary plaques, thus facilitating their rupture. (MUSCENTE, F.; DE CATERINA, F., 2020)

The efficacy of influenza vaccination in supporting the causal relationship between influenza and myocardial infarction has been robustly proven. In a recent double-blind, randomized study involving patients with myocardial infarction or high-risk stable coronary disease, administration of the vaccine soon after the cardiac event revealed a significant reduction in the risk of death from all causes, myocardial infarction or stent thrombosis. (BOCALE, R.; NECOZIONES, S.; DESIDERI, G., 2022) Furthermore, vaccinated patients had a lower risk of cardiovascular death at 12 months compared to those who received placebo. These results suggest considering influenza vaccination as a crucial measure in the hospital treatment of

these patients. (FROBERT, O, et al., 2021)

The protection afforded by influenza vaccination is likely due to several mechanisms. The prevention of flu syndrome plays an essential role in cardiovascular protection, reducing the hemodynamic and metabolic stress associated with serious viral infections. (BOCALE, R.; NECOZIONES, S.; DESIDERI, G., 2022)

In this context, in a study with mice, immunization with the Influenza vaccine (Vaxigrip®) resulted in less development of atherosclerotic lesions and lower lipid content compared to the control and Pneumo23® groups. These findings suggest that influenza vaccination may protect against cardiovascular disease by promoting smaller, more stable atherosclerotic plaques while inducing atheroprotective immune responses. Additionally, mice vaccinated with Vaxigrip showed reduced levels of interferon gamma (IFNγ), interleukin (IL)-2 and tumor necrosis factor alpha (TNFα).(BERMÚDEZ-FAJARDO, A.; OVIEDO-ORTA, E.,2011).

CONCLUSION

Based on the evidence presented, a plausible association between influenza and myocardial infarction is considered based on general medical and scientific knowledge. Influenza infection can trigger a systemic inflammatory response, including the production of cytokines, which have the potential to affect the stability of atherosclerotic plaques in coronary arteries. Influenza viruses demonstrate a preference for vascular structures, contributing to persistent inflammation and cardiovascular dysfunction. Sympathetic activation and coronary vasoconstriction exacerbate biomechanical stress on atherosclerotic plaques. The protective efficacy of vaccination is highlighted, reducing mortality from cardiovascular events. This occurs both due to its positive influence on patients hospitalized due to cardiovascular events, resulting in a lower risk of death, and due to its ability to reduce and stabilize atherosclerotic plaques, thus reducing the risk of a heart attack.

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