

PATHOGENESIS OF ABDOMINAL AORTIC ANEURYSM

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ABSTRACT

An aneurysm is a chronic and complex inflammatory process of the arterial wall that causes permanent dilation of the vessel wall in a localized area, with several complications. It can result from degenerative, inflammatory, or infectious processes, genetic alterations, or even trauma. Some studies report a relationship between the development of inflammatory aortic aneurysms (IAA) and immunoglobulin G4-related disease (IgG4-RD). Based on this parallel, the present study aims to identify the target of this immunoglobulin within AAA pathology, as well as how to reverse the action of IgG4 in these blood vessels, whether medically or surgically. Thus, this project is justified by the perspective of elucidating the forms of treatment for abdominal aortic aneurysms, in order to contribute to the conduct of vascular surgeons when faced with cases involving AAA. To this end, this study consists of an integrative review that aims to document the findings that contribute to the relationship between IgG4 and abdominal aortic aneurysm, in order to provide knowledge on how to approach and treat it appropriately.

Keywords: Aneurysm; Aortic aneurysm; Abdominal aorta; Immunoglobulin G4-related disease.

INTRODUCTION

Despite being a science that studies human health, the human body is still unknown to medicine in many ways. Following this idea, one of the areas that remains largely unexplored is the action of subtype 4 of Immunoglobulin G (IgG4) in arterial diseases. IgG4-related disease (IgG4-RD) is a new clinical entity characterized by elevated serum IgG4 concentrations and tissue swelling or infiltration by IgG4-secreting plasma cells (Umehara *et al.*, 2011). It is a pathology that affects any organ or system of the human body and is associated with the cardiovascular system, affecting the aorta and its main branches (Nikiphorou *et al.*, 2020). In the context of cardiovascular involvement, IgG4-related aortitis or periaortitis can lead to thoracic or abdominal aortic aneurysms (Oyama-manabe *et al.*, 2018). The histopathological characteristics of IgG4-related disease include, in addition to IgG4-positive plasma cell infiltration, stellate fibrosis, and obliterative phlebitis (Mizushima *et al.*, 2019; Sedhom; Ramy, 2017). However, given that vascular lesions related to this immunoglobulin can cause life-threatening situations due to the formation of ruptured aneurysms () (Kasashima *et al.*, 2018), attention

and elucidation of the pathogenesis involved is necessary, one of the main lesions being Abdominal Aortic Aneurysm (AAA).

On the other hand, AAA is a relatively common condition and the 15th leading cause of death in the United States, with an increased likelihood in people who already have a family history of the disease. Nevertheless, there is a higher incidence in adults over 50 years of age, more frequent in men, and it is the 10th leading cause of death in this group, being even more prevalent among white individual than among black, Asian, or Hispanic population. Finally, smoking is the main modifiable risk factor (Kasashima *et al.*, 2018).

When analyzing AAA, this lesion is often associated with IgG4, which, in many cases, manifests as an Inflammatory Abdominal Aortic Aneurysm (IAAA) (Kasashima *et al.*, 2018). IAAA presents as a thickening of the aneurysmal wall with peri-aneurysmal adhesions, in addition to having results that confirm its association with IgG4, which are supported by clinical, laboratory, histopathological, imaging, pathogenesis, and treatment aspects, even though its etiology is not yet fully clear (Nikiphorou *et al.*, 2020).

The prevalence of IgG4-related systemic disease among thoracic aortic aneurysms/aortitis was estimated at around 4% in a Japanese study (Ishizaka *et al.*, 2012). In addition, IgG4-related lesions comprised 4% of all surgical cases for thoracic aortic lesions, with a similar frequency among surgical cases of abdominal aneurysm (Kasashima & Zen, 2011). Furthermore, IgG4-related disease should be considered in all patients with aortitis of unknown etiology (An *et al.*, 2022; Stone *et al.*, 2009).

Thus, as demonstrated above, the action of IgG4 is still unknown in several pathologies. Therefore, understanding the action of this immunoglobulin in AAA is of utmost importance, since it is a disease that is directly linked to patient mortality rates. Regarding this scenario, elucidating this pathogenesis is important for the medical community in terms of shedding light on how this situation occurs in this disease, thereby promoting studies that guide treatment and conduct in such situations.

METHODOLOGY

This study consists of an integrative literature review that sought to analyze and compare data related to the activity of immunoglobulin G4 in the pathophysiology of AAA. To conduct the study, we used the PICOT strategy, which can be used to construct research questions of various natures, originating from clinical practice, human resource management, and material management, by answering a guiding question, in this case, "What is the role of IgG4 in the pathogenesis of aortic aneurysm?", in order to enable the definition of correct information and evidence necessary for the resolution of a clinical situation (Santos *et al.*, 2007).

Articles were searched in the PubMed database using health science descriptors (DeCS), "*Immunoglobulin G4-Related Disease*," "*Immunoglobulin G*," "*Aortic Aneurysm, Abdominal*," and "*Treatment*," using the Boolean descriptor "*and*" and selecting only articles in English. In the search, articles that were outside the 10-year period and that, based on the abstract, did not present a relationship between immunoglobulin 4 and abdominal aortic aneurysm, i.e., that did not answer the guiding question, were excluded.

In addition, external references were also used to provide theoretical support for the clinical findings in the literature review, also following the 10-year time criterion.

RESULTS

IgG4-related diseases (IgG4-RD) can affect any system or organ. At the cardiovascular level, IgG4 generally affects large vessels, such as the aorta and its branches (Nikiphorou; Galloway; Fragoulis, 2020). That said, at the cardiovascular level, IgG4 commonly affects large vessels, such as the aorta and its branches, resulting in the pathology Inflammatory Aneurysm of the Aorta, which constitutes the majority of cases of IgG4 Aortitis. However, there is also a description of the term IgG4-chronic periaortitis (IgG4-CP), which is characterized by the presence of fibrotic tissue around the aorta and is often observed in the abdominal aorta, mainly in the infra-abdominal region (Nikiphorou; Galloway; Fragoulis, 2020).

The mechanisms of pathogenesis for IgG4-induced aortic aneurysms are not fully understood. However, several studies have provided *insights* into this condition. First, IgG4-related diseases are systemic inflammatory fibrous lesions characterized

by elevated serum IgG4 and IgG4-positive plasma cell infiltration (Kasashima *et al.*, 2023). Inflammatory abdominal aortic aneurysm (IAAA) is a subtype of AAA that shows thickening of the aortic wall and infiltration of inflammatory cells and is considered to be closely related to idiopathic retroperitoneal fibrosis (IRF) (Prucha *et al.*, 2019). In addition to IAAA and other types of AAA, there is growing evidence that IgG4 may be involved in the autoimmune mechanism of various idiopathic sclerosing lesions, including sclerosing pancreatitis and retroperitoneal fibrosis (Kamisawa; Egawa; Nakajima, 2003).

In patients with AAA, histopathological features consistent with IgG4-related disease and the presence of IgG4+ plasma cells have been observed, suggesting that AAA may be a heterogeneous group of inflammatory diseases with different pathogeneses (Liu; Zhang; Zhang, 2020).

The pathogenesis of abdominal aortic aneurysm is not only due to the action of IgG4. Among the factors that influence this context are: biomechanical aspects (characteristic of the infra-abdominal portion, as already mentioned), intraluminal thrombosis (in cases of occlusive atherosclerosis), oxidative stress, VSMC apoptosis-Vascular Smooth Muscle Cells (from oxygen and nitrogen-derived free radicals and consequent activation of proteolytic enzymes), proteolysis (from the destruction of the three-dimensional network of ECM-Extracellular Matrix Components), and the action of myeloid cells in AAA (Kessler *et al.*, 2022). Therefore, this outline reflects the complexity of the study surrounding abdominal aortic aneurysms and the need to update the knowledge of health professionals not only in the field of IgG4, but also in other aspects that may contribute to an imminently fatal situation.

However, from a perspective focused on the pathogenesis of IAAA and the role of IgG4, inflammation is an intrinsic theme at this point. Starting with the fact that innate and adaptive immune cells enter the aneurysmal tissue of the aortic wall, contributing to an inflammatory process. The action of ectopic adipocytes around the vessel promotes the recruitment and activation of immune cells, releasing pro-inflammatory cytokines such as tumor necrosis factor alpha, IL-6, IL-8, and may also mediate an autoimmune response. This fact corroborates the idea of comorbidities that increase the risk of AAA, such as dyslipidemia, physical inactivity, smoking, etc.

The increase in CD4+ helper T cells, macrophages, increased proteolysis, and oxidative tissue damage are points that contribute to the progression and formation of chronic inflammation. It should be noted that cytokines such as Th1, Th2, Th17, IFN-gamma, TNF-alpha, IL-4, IL-22, and T CD8 are also all increased in AAA. Therefore, this entire situation negatively corroborates the AAA picture when there is activation of macrophages and mast cells stimulated by IgG4 and IgE (Kessler *et al.*, 2022).

Given that IgG4 and IgE production is controlled by Th2 cells, the increase in interleukins 4 and 13 reflects an increase in IgG4 and IgE. In contrast, IL-10, IL-12, and IL-21 alter the balance between IgG4 and IgE, favoring the action of Ig4 (Stone *et al.*, 2012).

More recently, the role of *APRIL* (*a proliferation-inducing ligand*), a cytokine that promotes the activation, proliferation, and survival of B lymphocytes and plasma cells, has been demonstrated in IgG4-induced AAA. In this study comparing patients with IgG4-induced and non-IgG4-induced AAA, there was a significant increase in serum *APRIL* in the former group, in addition to the finding of *APRIL-positive* cells in histological sections. In addition, there was a positive correlation between the number of IgG4-secreting plasma cells and *APRIL-producing* cells infiltrating the histological section of aneurysmal lesions (Mizushima *et al.*, 2014). In conclusion, although further research is needed to fully understand the specific mechanisms by which IgG4 is involved in the development of aortic aneurysms, some points are already clear, such as the involvement of pro-inflammatory cytokines, especially those of the Th2 profile, and B lymphocyte-stimulating cytokines such as *APRIL* in the emergence of the unique histological features of IgG-4-induced AAA.

CONCLUSION

The findings presented in this review highlight the crucial role of IgG4 in the pathogenesis of abdominal aortic aneurysms. The presence of inflammatory infiltrates rich in IgG4-producing plasma cells, associated with elevated serum levels of this immunoglobulin, suggests a specific humoral immune response against the aortic wall, as occurs in other idiopathic sclerosing lesions, including sclerosing pancreatitis and retroperitoneal fibrosis. Understanding these pathogenic

mechanisms opens new perspectives for the diagnosis and treatment of these patients. In addition, early detection of IgG4-related disease and regular monitoring of these patients may help prevent serious complications, such as aneurysm rupture, ultimately leading to a reduction in mortality from these causes.

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