Research, Society and Development, v. 10, n. 12, e17101220110, 2021
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Asthma and COVID-19: who wins the contested territory of the lower airways?

Asma e COVID-19: quem ganha o disputado território das vias aéreas inferiores

Asma y COVID-19: ¿quién gana el territorio en disputa de las vías respiratorias inferiores?

Received: 09/01/2021 | Reviewed: 09/08/2021 | Accept: 09/09/2021 | Published: 09/12/2021

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Abstract
Among the numerous published studies on COVID-19 in a pandemic year, few listed asthma as a comorbidity, making it therefore difficult to draw any solid conclusions. The respiratory allergy and controlled exposures to allergens are associated with significant reductions in the expression of angiotensin-converting enzyme 2 (ACE2), receptor for SARS-CoV-2 entry into human cells. There is a hypothesis that patients with chronic asthma, due to the type 2 inflammatory profile, may be potentially resistant to developing a severe clinical course of COVID-19. The low IFN-γ-mediated response in the respiratory tract of asthmatic patients could limit ACE2 expression in the target cells of SARS-CoV-2 infection. The inflammatory profile of the airways in patients with chronic asthma is mainly related to a Th2 response in type-2 asthma, with production of IL-4, IL-13 and IL-5, presenting antagonistic relationship with pro-inflammatory cytokines such as IFN-γ, produced at high levels in severe COVID-19. Published studies, for the most part, are retrospective and may have loss of information or present material with limited possibility for more robust and conclusive analysis. It is important to discuss how patients with atopic or nonatopic asthma seem to protect themselves from new coronavirus infection and how asthma affects COVID-19 and the course of the disease, since there is no increased mortality in asthmatic patients with COVID-19 compared to non-asthmatic patients.
Keywords: Asthma; COVID-19; Lower Airways; SARS-CoV-2.

Resumo
Entre os numerosos estudos publicados sobre a COVID-19 em um ano de pandemia, poucos listaram a asma como comorbidade, tornando, portanto, difícil tirar conclusões sólidas. A alergia respiratória e as exposições controladas a alérgenos estão associadas a reduções significativas na expressão da enzima conversora de angiotensina 2 (ACE2), receptor para a entrada do SARS-CoV-2 nas células humanas. Há uma hipótese de que pacientes com asma crônica, em função do perfil inflamatório do tipo 2, podem ser potencialmente resistentes a desenvolver um curso clínico grave da COVID-19. A baixa resposta mediada por IFN-γ no trato respiratório de pacientes asmáticos pode limitar a expressão de ACE2 nas células-alvo da infecção por SARS-CoV-2. O perfil inflamatório das vias aéreas em pacientes com asma crônica está relacionado principalmente a uma resposta Th2 na asma tipo 2, com produção de IL-4, IL-13 e IL-5, que apresentam relação antagônica com citocinas pró-inflamatórias como IFN-γ, produzido em níveis elevados na COVID-19 grave. Os estudos publicados, em sua maioria, são retrospectivos e podem apresentar perda de informações ou material com possibilidades limitadas de uma análise mais robusta e conclusiva. É importante discutir como os pacientes com asma atópica ou não atópica parecem se proteger de novas infecções por coronavírus, e como a asma afeta COVID-19 e o curso da doença, uma vez que não há aumento da mortalidade em pacientes asmáticos com COVID-19 em comparação com não -pacientes asmáticos.
Palavras-chave: Asma; COVID-19; Vias aéreas inferiores; SARS-CoV-2.

Resumen
Entre los numerosos estudios publicados sobre COVID-19 en un año de pandemia, pocos mencionaron el asma como una comorbilidad, lo que dificulta tener conclusiones sólidas. Las alergias respiratorias y las exposiciones controladas por alérgenos se asocian con reducciones significativas en la expresión de la enzima convertidora de angiotensina-2 (ACE2), el receptor para la entrada del SARS-CoV-2 en las células humanas. Existe la hipótesis de que los pacientes

con asma crónica, debido al perfil inflamatorio tipo 2, pueden ser potencialmente resistentes a desarrollar un curso clínico severo de COVID-19. La baja respuesta mediada por IFN-γ en el tracto respiratorio de los pacientes asmáticos pueden limitar la expresión de ACE2 en las células objetivo de la infección por SARS-CoV-2. El perfil inflamatorio de las vías respiratorias en pacientes con asma crónica se relaciona principalmente con una respuesta Th2 en el asma tipo 2, con producción de IL-4, IL-13 e IL-5, que tienen una relación antagónica con citocinas proinflamatorias como IFN- γ, producido en altos niveles en COVID-19 severo. La mayoría de los estudios publicados son retrospectivos y pueden presentar pérdida de información o material con posibilidades limitadas para un análisis más robusto y concluyente. Es importante discutir cómo los pacientes con asma atópica o no atópica parecen protegerse de las nuevas infecciones por coronavirus y cómo el asma afecta al COVID-19 y al curso de la enfermedad, ya que no hay un aumento en la mortalidad en pacientes asmáticos con COVID- 19 en comparación con pacientes no asmáticos.
Palabras clave: Asma; COVID-19; Vías respiratorias inferiores; SARS-CoV-2.

1. Introduction

The coronaviruses (CoVs) are positive-strand RNA viruses that cause respiratory infections and are responsible for the severe acute respiratory syndromes (SARS) in 2002 and 2003 in China and the Middle East in 2012. In late 2019, in Wuhan province, China, the occurrence of an acute respiratory syndrome caused by a new coronavirus, SARS-CoV-2, leading to COVID-19, was demonstrated and reached many countries across several continents in early 2020, being characterized as a pandemic (Cucinotta & Vanelli, 2020; World Health Organization [WHO], 2020).

The typical clinical manifestations of the disease usually begin after 5-7 days of incubation and consist of flu-like symptoms including fever, cough, fatigue and dyspnea (Hu et al., 2021). It is known that compared to other individuals, people with certain comorbidities, including hypertension, diabetes mellitus and cardiovascular disease (Chhiba et al, 2020; Liu et al., 2020; Skevaki et al., 2020) and cerebrovascular disease (Liu et al., 2020), chronic obstructive pulmonary disease and obesity (Chhiba et al, 2020) are more likely to develop severe disease and have a worse prognosis (Liu et al., 2020).

The infection caused by SARS-CoV-2 in humans can manifest itself through mild to severe respiratory symptoms. The binding of the virus to the epithelial cells of the respiratory tract results in its multiplication and migration into the airways with invasion of the epithelial cells of the lung alveoli (Hu et al., 2021). The speed of SARS-CoV-2 replication in the lungs is associated with the development of a strong immune response characterized by a cytokine storm with the possibility of causing acute respiratory distress syndrome and respiratory failure, considered the leading cause of death in patients infected with the new coronavirus (Huang et al., 2020).

Many of the infection symptoms caused by the new coronavirus can be observed in other respiratory diseases, not to mention the exacerbated inflammatory process associated with the pathophysiology of COVID-19. It is worth noting that there are non-infectious airway diseases, such as asthma, that are also associated with intense inflammatory processes, and their increasing prevalence in the world population, despite the existence of guidelines for control and available treatments, still represents a serious public health problem. Considering that the immunological mechanisms, although distinct, in the two pathologies can contribute to the evolution of the clinical picture both in asthma and in COVID-19, studying the relation of overlapping immunopathogenic aspects is fundamental to broaden the understanding of these two associated conditions, with fundamental impact on the contribution to the world public health.

Our aim was to carry out a narrative review of information in the literature about the impact of COVID-19 in patients with allergic asthma.

2. Methodology

This is an exploratory and qualitative study of the narrative review type, appropriate for discuss the state of the art of an issue that still lacks conclusive information. It was carried out through an extensive literature review but without establishing a rigorous and replicable methodology (Correa et al., 2013). Articles indexed in PubMed (US National Library of

Medicine National Institutes of Health Search database), Science Direct and SciELO databases were searched during the month of June 2021, having as reference period the years 2020-2021 for COVID-19 and the last 10 years for asthma. The descriptors terms COVID-19, allergic asthma and SARS-CoV-2 were used in combination. The criterion used for inclusion of publications was to have the expressions used in the searches in the title or keywords, or to have evidenced in the abstract that the text is related to the intended association; language (Portuguese, English and Spanish); Availability (text integral), all kinds of articles and books and also considered the references of these articles or books.The excluded articles did not assemble the established inclusion criteria and/or presented duplicity, that is, publications retrieved in more than one of the databases. After an independent review by three reviewers, of 70 pre-selected articles, 22 articles that referred to the proposed objective were selected, and we proceeded with the analysis of the theoretical foundation of the studies.

3. Results and Discussion

Asthma is an immune-mediated inflammatory disease of atopic etiology, multifactorial, highly complex with intermittent and reversible obstruction of the lower airways due to smooth muscle constriction and narrowing by airway inflammation in response to an environmental trigger, often associated with a viral airway infection (Patel & Teach, 2019). The airway epithelium is located between the internal and external environment and plays an important role in the mechanism of asthma onset. The pro-inflammatory cytokines TNF-α, IFN-γ, IL-4 and IL-13 disrupt the airway epithelial barrier (Hardyman et al., 2013; Saatian et al., 2013), facilitating the infiltration of allergens into the airway submucosa (Gon & Hashimoto, 2018).

As the underlying pathophysiology of these symptoms, airway hyperresponsiveness associated with chronic inflammation usually occurs (Gon & Hashimoto, 2018). The airway obstruction associated with narrowing of the lumen diameter caused by chronic inflammation at the site, accompanied by plasma extravasation, edema and influx of inflammatory cells such as eosinophils, neutrophils, lymphocytes, macrophages and mast cells (Lambrecht et al., 2019).

It is known that the vigorous and immediate local innate immune response triggered by the interaction of SARS-CoV-2 single-stranded RNA (ssRNA) with the usual recognition receptors in alveolar and tissue macrophages, induces an IFN-mediated antiviral response and plays a key role in limiting the replication and spread of SARS-CoV-2. The activation of this pathway leads to the production of pro-inflammatory mediators in an intense, massive, amplified, uncontrolled and systemic manner, and cytokines such as IL-2, IL-6, IL-7, TNF-a and the chemokines MCP-1 and MIP-1a induce a cascade of response contributing to local tissue destruction with systemic consequences (Xu et al., 2020). The cytokine storm is associated with coagulopathies as a function of increased vascular permeability and disseminated vascular coagulation (Alipoor et al., 2021). In approximately 20% of infected patients, the excessive inflammatory response in the lower airways, the development of pulmonary inflammatory infiltrate, the dissemination of inflammatory mediators plays a crucial role in clinical worsening (Chowdhury & Oommen, 2020).

The Centers for Disease Control and Prevention (CDC) classifies patients with moderate to severe asthma as a high vulnerability group for severe COVID-19 (Chhiba et al, 2020). However, in people with COVID-19, neither asthma conditions nor potentially pathological changes in the respiratory system have yet been adequately documented.

Interestingly, among the number of published studies on COVID-19 in a pandemic year, few listed asthma as a comorbidity, making it thereby difficult to draw any solid conclusions (Liu et al., 2020). In the study by Chhiba et al. (2020), asthma patients with COVID-19 had a higher prevalence of other comorbidities compared with non-asthmatic patients but reported no difference in mortality between the two groups.

The clinical and pathophysiological association between asthma and COVID-19/ SARS-CoV-2 infection is not yet well established, because they have distinct polarized immunological mechanisms. Depending on the inflammatory nature of asthma, it may influence the outcome of SARS-CoV-2 infection in these patients. Considering that SARS-CoV-2 primarily

affects the upper and lower airways leading to heightened inflammation (Skevaki et al., 2020), as explained above, it seems that, theoretically, pre-existing asthma has a potential influence on SARS-CoV-2 susceptibility and the course of the disease. However, existing studies do not indicate a high prevalence of asthma among COVID-19 patients (Liu et al., 2020; Jackson et al., 2020; Mendes et al., 2021; Green et al., 2020).

The inflammatory profile of the airways in patients with chronic asthma is related mainly to a Th2 response in type-2 asthma, with production of IL-4, IL-13 and IL-5. Considering the antagonistic relationship between these and pro-inflammatory cytokines, such as IFN-γ, it would be important to investigate if there would be any relationship, positive or negative, polarized or regulated, between clinical entities of different etiology, such as asthma and COVID-19, with different pathophysiology and evolution, with one being chronic and the other acute, but that involve the same anatomical region.

The activation of adaptive immunity depends on innate immunity, which is mediated by antigen-presenting cells that, after the virus entry, capture immunogenic proteins and internalize, process and present them in association with MHC or HLA molecules to helper T lymphocytes. However, when the body does not generate an adequate antiviral cellular response, the intense innate response persists, contributing to a polarized and unregulated immune activity (Ahmadpoor & Rostaing, 2020). This is evidenced by the reduced percentage of circulating T lymphocytes and high functional exhaustion, thus determining the severity of the disease in COVID-19 patients (Janssen et al., 2021). Changes in the frequency and activation profile of lymphocyte populations may be a predictor of disease severity. Studies show that patients who died of COVID-19 had a lower percentage of Th2, Th17 and regulatory T (Treg) lymphocytes when compared to recovered patients (Sami et al., 2021).

Asthma is the most prevalent chronic inflammatory lung disease worldwide (Skevaki et al., 2020), and patients have impaired immune responses against viral infection (Liu et al., 2020) and respiratory viral infections have the potential to trigger or worsen asthma symptoms (Liu et al., 2020; Jackson et al., 2020). Considering that SARS-CoV-2 primarily affects the upper and lower airways leading to heightened inflammation (Skevaki et al., 2020), as explained above, it seems that, theoretically, pre-existing asthma has a potential influence on SARS-CoV-2 susceptibility and the course of the disease. However, existing studies do not indicate a high prevalence of asthma among COVID-19 patients (Liu et al., 2020; Jackson et al., 2020; Mendes et al., 2021; Green et al., 2020).

Respiratory viral infections are the most common triggering factor for severe asthma exacerbations in children and adults. Respiratory allergy and controlled exposures to allergens are associated with significant reduction in angiotensin-converting enzyme 2 (ACE2) expression. The expression of ACE2, which is the receptor for SARS-CoV-2 entry into the body, was lower in patients with elevated levels of allergic sensitization and asthma, thereby suggesting a potential mechanism for reducing the severity of COVID-19 in patients with respiratory allergies. This may occur because IL-13 reduces ACE2 gene expression in nasal and bronchial epithelium. However, nonatopic asthma has not been associated with reduced ACE2 expression (Jackson et al., 2020). Another consideration is that the low IFN-γ-mediated response in the respiratory tract of asthmatic patients could limit ACE2 expression in the target cells of SARS-CoV-2 infection (Liu et al., 2020).

The cellular response in the two diseases is also quite distinct, since eosinophils are known to play a central role in allergic diseases, represented by increased eosinophil production in the bone marrow, eosinopoiesis and tissue eosinophilia, which is not the case in COVID-19, in contrast. One study showed eosinopenia in patients with COVID-19, and the positive correlation between the low eosinophil and lymphocyte counts in the blood suggests that eosinopenia, along with the lymphopenia, may be a useful indicator for the diagnosis of COVID-19 in patients with typical symptoms and radiological changes (Zhang et al., 2020). Interestingly, the progressive increase in blood eosinophil count seems to be positively related to recovery from COVID-19 (Mendes et al., 2021). Other different laboratory values in asthma patients observed were significantly lower levels of ferritin, C-reactive protein and lactate dehydrogenase compared to patients without asthma, and they are markers of disease severity in COVID-19. These findings suggest that underlying immune modulation due to asthma

or asthma treatment may have an attenuating effect on COVID-19, but surely, more studies are needed to clearly understand this relationship (Chhiba et al, 2020).

4. Final Considerations

The clinical and pathophysiological association between asthma and COVID-19/SARS-CoV-2 infection is not yet well established. Published studies, for the most part, are retrospective and may have loss of information or present material with limited possibility for more robust and conclusive analysis. It is important to discuss how patients with atopic or nonatopic asthma seem to protect themselves from new coronavirus infection and how asthma affects COVID-19 and the course of the disease, since there is no increase in mortality in asthmatic patients with COVID-19 compared to non-asthmatic patients.

We understand that there are limitations to this type of study, but we believe that this narrative review provides elements that demonstrate the need to analyze the complex relationship of two diseases of different etiologies sharing the same contested territory of the lower airways.

Acknowledgments

The Minas Gerais State Research Foundation (FAPEMIG, Minas Gerais, Brazil), the National Council for Scientific and Technological Development (CNPq, Brazil), and the Coordination of Training of Higher Education Graduate Foundation (CAPES, Brasilia, Brazil).

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