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REVIEW

Asthma, allergies and COVID-19: a review of what we know

Asma, alergias y COVID-19: un repaso a lo que sabemos

Carlos Alfredo Miló Valdés[1], Adrián Alejandro Vitón Castillo[1,2], Lidia Cecilia Pérez Acevedo[3]

[1]Universidad de Ciencias Médicas de Pinar del Río, Hospital Pediátrico Provincial Docente "Pepe Portilla". Pinar del Río, Cuba.
[2]AG Editor. Ciudad Autónoma de Buenos Aires, Argentina.
[3]Centro de Inmunología Molecular. La Habana, Cuba.

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Corresponding author: Carlos Alfredo Miló Valdés

ABSTRACT

Introduction: allergies are exaggerated reactions of the immune system to normally harmless substances, while asthma is a chronic disease that inflames the airways. Although people with asthma may be more susceptible to respiratory infections, the relationship between COVID-19 and asthma and allergies is contradictory and a matter of debate.
Objective: to summarize the theoretical background on the relationship between allergic diseases, such as asthma, and COVID-19.
Development: there is no conclusive evidence on the relationship between asthma, especially the allergic phenotype, and COVID-19. However, several aspects of immunopathogenesis may influence this interaction. The type I interferon response in asthmatics does not seem defective, and ACE2 underexpression could slow down the infection, allowing an adequate antiviral response. Eosinophils, which protect against viral infections, could compensate for the eosinopenia observed in COVID-19. The elevated presence of Th2 cells in asthmatics could also offer protection against severe forms of the disease. Despite this, asthma can predispose to severe symptoms due to inflammation and changes in the respiratory microbiota.
Conclusions: the relationship between asthma, allergies and COVID-19 is complex and subject to debate, influenced by multiple factors. Additional studies are needed to better understand these interactions and the genetic and environmental factors that may affect the prevalence and response to these diseases.

Keywords: COVID-19; SARS-CoV-2; Allergies; Asthma; Infection.

RESUMEN

Introducción: las alergias son reacciones exageradas del sistema inmunológico a sustancias normalmente inofensivas, mientras que el asma es una enfermedad crónica que inflama las vías respiratorias. Aunque las personas con asma pueden ser más susceptibles a infecciones respiratorias, la relación entre la COVID-19 y el asma y las alergias es contradictoria y tema de debate.
Objetivo: resumir los antecedentes teóricos sobre la relación entre las enfermedades alérgicas como el asma y la COVID-19.
Desarrollo: no hay evidencia concluyente sobre la relación entre el asma, especialmente el fenotipo alérgico, y la COVID-19. Sin embargo, varios aspectos de la inmunopatogenia pueden influir en esta interacción. La respuesta de interferón tipo I en asmáticos no parece defectuosa, y la subexpresión de ACE2 podría ralentizar la infección, permitiendo una respuesta antiviral adecuada. Los eosinófilos, que protegen contra infecciones virales, podrían compensar la eosinopenia observada en COVID-19. La elevada presencia de células Th2 en asmáticos podría también ofrecer protección frente a formas graves de la enfermedad. A pesar de esto, el

asma puede predisponer a síntomas graves debido a la inflamación y cambios en la microbiota respiratoria. **Conclusiones:** la relación entre asma, alergias y COVID-19 es compleja y está sujeta a debate, influenciada por múltiples factores. Estudios adicionales son necesarios para entender mejor estas interacciones y los factores genéticos y ambientales que pueden afectar la prevalencia y respuesta a estas enfermedades.

Palabras clave: COVID-19; SARS-CoV-2; Alergias; Asma; Infección.

INTRODUCTION

Coronavirus (CoV) disease 2019 (COVID-19, from the acronym *coronavirus disease 2019*) is a contagious disease caused by SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*, severe acute *respiratory* syndrome coronavirus 2).[1,2,3] The first case was identified in Wuhan, Hubei, China, in December 2019.[1,2,4,5,6,] The disease spread rapidly globally resulting in the COVID-19 pandemic. The World Health Organization (WHO) designated the outbreak as a Public Health Emergency of International Concern from January 30, 2020 to May 5, 2023.[1,7]

SARS-CoV-2 is an enveloped, spherical virus belonging to the betacoronavirus family, with a positive linear single-stranded RNA genome, and is considered to be of zoonotic origin, due to the initial outbreak and similarity to other coronavirus outbreaks.[1,6,8,9]

The route of human-to-human transmission is airborne, through droplets and aerosols released during coughing, sneezing, and speaking. An inoculum of 200 to 800 viable virions is thought to be sufficient to initiate infection. In addition, transmission of the virus through the ocular surface and the prolonged presence of viral RNA in fecal samples have been documented. CoV can persist on inanimate surfaces for days, which could also be the case for SARS-CoV-2, thus posing a prolonged risk of infection.[1,6,10]

Human SARS-CoV-2 infection has a classic clinical course similar to that of a respiratory virus in more than 80 % of patients, with a mild to moderate, self-limiting course.[11,12] It appears that the population of all ages is susceptible to SARS-CoV-2 infection and the median age of infection is around 50 years. However, clinical manifestations differ with age. In general, men over 60 years of age with comorbidities are more likely to develop severe respiratory illness requiring hospitalization or even death, while most young people and children are asymptomatic, or have only mild disease (no pneumonia or mild pneumonia). For pregnant women in particular, the risk of disease does not appear to be higher. However, evidence of transplacental transmission of SARS-CoV-2 has been reported.[1,13,14,15]

In case of infection, the most common symptoms are fever, fatigue, and dry cough. Less common symptoms include expectoration, headache, hemoptysis, diarrhea, anorexia, pharyngitis, chest pain, chills, nausea, and vomiting. Patients have also reported loss or disturbances of smell and taste. Most people show signs of illness after an incubation period of 1 to 14 days (commonly around 5 days), and dyspnea and pneumonia develop in an average time of 8 days after onset of illness.[1,6,12,13,14,16,17,18]

In most countries, more deaths were observed in infected men than in infected women.[13,14,29,20,21] Also, a higher mortality rate from COVID-19 was observed in smokers,[22] obese persons, and patients with chronic kidney disease, cardiovascular disease, or cancer.[4,6,12,13,23] The major change in mortality is associated with the emergence of the highly transmissible Omicron variant, with a lower mortality rate than other variants.[13]

Currently, no curative therapy is recommended for COVID-19, except for personalized supportive care.[20]

A literature review was conducted with the aim of summarizing the theoretical background on the relationship between allergic diseases such as asthma and COVID-19.

METHOD

A search for information was conducted in the databases *Redalyc*, *Elsevier Science Direct*, *PubMed/Medline*, *SciELO*, as well as in the *ClinicalKeys* services and the Google Scholar search engine. Advanced search strategies were used to retrieve the information by structuring search formulas using the terms “SARS-CoV-2”, “COVID-19”, “T cells”, “IgE antibodies”, “allergy”, “asthma”, “atopy”, etc. as well as their equivalents in English. From the search results, we selected those documents that provided theoretical and empirical information, in Spanish or English, prioritizing those published in the period 2020-2024.

DEVELOPMENT

Allergic disease, in a broad sense, refers to immunomediated diseases due to contact with agents or substances that are innocuous for most of the subjects in the population. However, in the clinical setting, diseases due to type I hypersensitivity mechanisms, characterized by a type 2 immune response involving Th2 cells, IgE-producing B cells, ILC2, M2 macrophages, IL-4-secreting NK and NKT cells, basophils, eosinophils and mast cells and elevated serum levels of IL-4, IL-5, IL-9, IL-13, IL-31 and allergen-specific IgE, are recognized as

"allergies".[24,25,26,27,28] Atopic dermatitis, food allergies, allergic rhinitis and asthma belong to this spectrum; as the most frequent entities and may be transient.[29,30,31,32]

It is likely that individuals who eventually develop allergic asthma suffer or have suffered from any of the other entities of the atopic march. Certainly, this could be a confusing factor and a source of bias: the history of allergy could be masked by that of asthma, an entity with a more striking clinical picture, better defined, and of possible immediate risk to life, as well as by the effect of intercrisis pharmacological treatment used on a sustained basis.

The grouping of allergic diseases (atopic dermatitis, allergic rhinitis, etc.) under the general label of "allergy" made it difficult to compare the results obtained with those of other studies where the entities are distinguished separately and the repercussions of specific allergic pathophysiology of the respiratory system and others of a systemic nature are analyzed in the context of COVID-19.

Asthma is a heterogeneous disease, with important patient-specific differences in age of onset, associated risk factors and degrees of severity, comorbidity and response to treatment.[25]

Currently, asthma is considered a general diagnosis consisting of several clinical presentations (phenotypes) and different pathophysiological mechanisms (endotypes). Allergic asthma is the most common asthma phenotype with early onset, Th2- and IgE-mediated.[33]

Airway inflammation occurs due to an allergic response that aggravates and reduces lung function. Cytokines are mainly responsible for this process. According to the predominance of the Th2 pattern, the pathophysiology of asthma can be classified into two endotypes: T2 "high" or T2 "low".[24]

Allergic asthma (type 2 "high") tends to begin in childhood and is associated with Th2 cell responses, which are also seen in other allergic conditions such as atopic dermatitis or allergic rhinitis.[25] These nosological entities belong to the so-called "atopic march."[28,29,30]

This form of asthma is induced by early encounters with environmental allergens such as house dust mites (APD), pollen, cockroaches or animal dander, although it can be induced later in life when a new allergen is encountered.[25]

In asthma, there is increased permeability of the epithelial cell barrier, due to the existence of hypomorphic variants of tight junction proteins that consolidate the unity of the respiratory epithelium. Allergens such as APD or cockroach, endowed with enzymatic activity, are able to break intercellular junctions causing the loss of intercellular contacts. Damage to epithelial cells is a feature present in all asthma phenotypes and correlates with the severity of the disease.[25]

Lung epithelial cells express a wide variety of PRRs. These enable epithelial cells to respond to a wide variety of external triggers by producing chemokines and cytokines. In mice, allergen exposure can trigger the production of IL-1a, GM-CSF, M-CSF, and TGF-ß, but the best described cytokines in the context of asthma are IL-33, TSLP, and IL-25. The production of these "alarmins" is dependent on the TLR4/MyD88 pathway and is increased in the respiratory mucosa of "high" type 2 asthmatic patients, and their levels correlate positively with disease severity.[25] Patients with eosinophilic allergic asthma have elevated serum levels of IL-33 and increased expression of ST2 in blood and sputum eosinophils compared with non-allergic and non-eosinophilic phenotypes. Higher IL-25 levels are associated with greater bronchial hyperreactivity (HRB), blood and mucosal eosinophilia, higher serum IgE, subepithelial thickening and increased expression of the Th2 gene signature. For its part, TSLP contributes to ILC2 longevity and resistance to corticosteroid treatment.[24,25]

ILCs perform tissue-specific functions that depend on the signals they receive. ILC2s respond primarily to epithelium-derived cytokines IL-33, IL-25 and TSLP, which induce their proliferation and activation. ILC2s resemble Th2 cells in that they also express GATA-3, a prototypical Th2-associated transcription factor, and produce IL-5, IL-9 and IL-13.[25]

The initiation of Th2 responses in the lungs and other organs has been attributed to the cDC2 population. Epithelium-derived cytokines stimulate CD11b+ cDC2 CD11b+ cDC2s involved in Th2 cell differentiation. In contrast, lung-resident CD103+ cDC1 CD103+ and Mo-DC are not able to induce Th2 responses and have even been shown to protect against the development of asthma through the production of IL-12, associated with the Th1 pattern and inhibitory of Th2 responses.[25]

In order to induce adequate Th2 immunity, cDC2s need to migrate from lung tissue to the draining lymph nodes, a process controlled by ILC2-derived IL-13 and type I IFN. The role of type I IFN, normally associated with antimicrobial responses, is still not clear.[25]

The number of DCs increases in the airways of patients with asthma. In the lung, most CD1c+ cDCs express high-affinity crystallizable ε-fraction receptor 1 (FcεRI), suggesting a role for IgE and these DCs in airway Th2 inflammation, and suggesting that they are highly related to cDC2. Mo-DCs, which accumulate after allergen exposure, produce chemokines involved in attracting Th2 cells and eosinophils to the lungs.[25]

Upon recognition of allergens, specific Th2 cells produce IL-4, IL-5, IL-9, and IL-13, which lead to eosinophil accumulation in the airway wall, overproduction of mucus, and synthesis of IgE by allergen-specific B cells, which can be detected in serum or by skin test.[24,25]

IL-4 has a broad spectrum of biological activities and could be considered as the main cytokine involved in the pathogenesis of allergic disorders. IL-4 induces IgE immunoglobulin class switching by B cells, promotes bronchial hyperreactivity and induces the expression of adhesion molecules such as ICAM-1 and VCAM-1; this leads to increased adhesiveness of the endothelium to monocytes, T cells, basophils and eosinophils.[24,25]

IL-5 mobilizes eosinophils from the bone marrow during allergic inflammation. It also drives eosinophil activation, proliferation and survival in peripheral tissues. In general, CCR3, the eotaxin receptor, together with the expression of several adhesion molecules such as VCAM-1, enable the recruitment of eosinophils from the bloodstream to inflamed tissues.[24,25]

IL-13 originates from activated T lymphocytes, B lymphocytes and mast cells. This cytokine acts directly on respiratory epithelial cells and smooth muscles, causing airway hyperreactivity, eosinophilia and increased production of several glycoproteins.[24] A subset of IL-13-producing Tfh cells was recently identified that stimulate IgE production.[25]

IL-9, released by different cells such as mast cells, Th2 cells and ILC2 cells, initiates amplification of activated T cells and mast cell differentiation. It also stimulates IgE secretion from B cells and mainly mast cells to respond to allergens through elevated expression of FcεRI receptors on the cell surface. IL-9 also prevents excessive mucus secretion and amplifies IL-13 regulation of epithelial cell genes.[24,25]

Once Th2 cells are generated in the draining lymph nodes of the lungs, part of them interact locally with B cells, which will develop into antibody-producing plasma cells. Under the influence of IL-4 and IL-13, B cells will preferentially produce IgE. IgE production takes place in the secondary lymphoid organs, and there is evidence that it can also occur in the lung mucosa.[25]

IgE can bind to its high-affinity FcεRI and low-affinity CD23 receptors. FcεRI is expressed on basophils, mast cells, eosinophils, and airway dendritic, endothelial, epithelial, and smooth muscle cells. In allergic asthma, a pool of IgG+ memory B cells switch class to IgE and become long-lived plasma cells in response to IL-4 and/or IL-13.[25]

Cross-linking of two adjacent IgE molecules, triggered by allergen binding, activates mast cells and basophils to release preformed bioactive mediators, such as histamine and neutral proteases (tryptase and chymase). They also produce large amounts of lipid mediators [cysteinyl leukotrienes (LT) or PGD2], and Th2 cytokines, to reinforce the inflammatory environment present.[25]

The interaction of IgE with mast cells and basophils is responsible for the rapid phase of the allergic response, which is characterized by increased vascular permeability and increased cell recruitment in the lung. In the airways, mast cells are located near the mucous glands of the submucosal layer, and the release of PGD2, LTC4, IL-4 and IL-13 triggers the hyperproduction of mucus by goblet cells.[24,25]

Finally, the localization of mast cells in airway smooth muscles is a key feature in the pathogenesis of asthma and contributes to smooth muscle hypertrophy and hyperplasia and HRB.[25]

Proliferation, contraction, and production of cytokines and chemokines, are the direct responses of smooth muscle to IgE, which contributes to airway hyperreactivity.[25]

IgE can also bind to FcεRI on DCs and facilitate allergen presentation to memory Th2 lymphocytes. IgE-mediated allergen presentation lowers the threshold for generating Th2 cell responses; and in turn, leads to increased production of allergen-specific IgE.[25]

IgE, by binding to FcεRI on pDCs also reduces intracellular signaling of type I IFN, which affects proper respiratory virus challenge.[25,34]

Eosinophilic inflammation leads to ongoing damage to lung structural cells given by the release of cytotoxic granular proteins. Eosinophil-associated fibrogenic factors (such as TGF-ß) lead to airway remodeling. In addition, activation of eosinophils and release of their granule contents near airway nerves changes the tone of parasympathetic nerves and promotes HRB.[25]

Successive episodes of epithelium damage and repair lead to airway modification. Such modifications lead to loss of contractility, dilatation due to impaired elasticity and edema.[24]

It has recently been shown that respiratory mucosal epithelial cells from allergy patients express fewer ACE2 molecules than those from healthy donors.[35,36] Type 2 cytokines, such as IL-13, are negatively related to ACE2 expression; and by reducing the expression of the enzyme, they also reduce the anti-inflammatory effect of Ang1-7.[37]

In agreement, analysis of transgenic murine AMs revealed different susceptibility to SARS-CoV-2 infection depending on their cytokine-induced polarization. *In vitro* treatment with IFN-γ and lipopolysaccharide caused higher infection rates compared to IL-4 pretreated animals.[38,39]

ACE2 expression among asthmatic patients varies according to asthma endotypes. ACE2 expression in "low" type 2 asthmatics is higher than in "high" type 2 asthmatics, this includes phenotypes associated with obesity, smoking and age-associated asthma.[37,40]

ACE2 expression was also significantly inversely associated with type 2 biomarkers, including the number of positive allergen-specific IgE test results, total IgE level, and nasal epithelial IL-13 expression. In children

with asthma, moderate and high allergic sensitization has been associated with reductions in ACE2 expression compared with asthmatic children with minimal or no allergic sensitization. However, it is likely that additional factors beyond ACE2 expression modulate the response to COVID-19 in allergy sensitized individuals.[37,40,41,42]

Low-dose inhaled corticosteroids could exert protective effects in patients with asthma by reducing airway inflammation and ACE2 and TMPRSS2 expression. This was proven for SARS-CoV and could be a factor reducing susceptibility to SARS-CoV-2 infection.[40,43]

However, "high" type 2 asthmatics show significantly higher expression of TMPRSS2, whereas in "low" type 2 asthmatics it is similar to that of healthy participants. TMPRSS2 facilitates infection by human CoV 229E, Middle East respiratory syndrome-related CoV, and H1N1, H3N2 and H7N9 influenza viruses. Therefore, increased expression of TMPRSS2 could override any protective effect of reduced ACE2 expression.[37]

ACE2 expression in nasal epithelial cells is lower in patients with uncontrolled rhinitis and asthma.[37] IFN expression in patients with mild or easily controlled atopic disease is comparable to that in healthy controls, showing the importance of monitoring disease activity.[27]

It has been proposed that people with asthma are predisposed to allergic responses that could override the antiviral response, manifesting as elevated susceptibility and impaired immune response to viral infection.[27,39,44]

Respiratory viruses are the most common triggers of asthma exacerbations, but not all affect patients equally. In asthma exacerbations, human rhinovirus (RV) was identified as the single largest contributor and CoVs do not appear to induce exacerbations frequently.[45]

A substantial number of studies have demonstrated a delay and/or deficiency in IFN induction following RV infection in patients with asthma. This antiviral deficiency manifests *in vivo* as an increased viral load in subjects with asthma compared to healthy subjects. Subjects with asthma show dysregulation of antiviral gene expression.[46] In addition, asthmatics fail to positively regulate several immunosuppressive molecules such as CTLA-4 and CD69.[34] IFN production by bronchial epithelial cells and pDCs is impaired in asthmatic individuals, which explains the impaired apoptosis and increased rhinovirus replication. Impaired IFN-α/ß expression has also been observed in asthmatic patients after viral infection, which is associated with increased viral load and adverse clinical outcomes.[27]

Murine models demonstrate that deficiency in type I IFN signaling leads to dysregulated ILC2 activation and infection-associated type 2 immunopathology. IFN-ß acts directly and significantly decreases cytokine secretion by human ILC2s, inhibits increased pulmonary eosinophilia, and suppresses IL-33-induced HRB. There is also evidence to the contrary: IL-33 plays a buffering role in innate and adaptive type 1 responses, including suppression of IFN-ß.[34]

During virus-induced asthma exacerbation, lung epithelial cells produce large amounts of IL-33, which could suppress antiviral responses by decreasing type I IFN production and favoring asthma exacerbations.[25]

IgE cross-linking, a hallmark of allergic diseases, is able to attenuate antiviral responses by abrogating the IFN-α response, downregulating TLR-7 upregulation and disrupting pDC maturation, whereas serum IgE concentrations inversely correlate with reduced IFN-α secretion. These observations suggest a possible mechanism for the altered antiviral response in asthmatic patients.[27]

In asthmatic preschool children, the same deficiency was found during an asymptomatic phase; however, during virus-induced exacerbations there is a delayed but sufficient production of measurable IFN-α. In turn, epithelial cells from asthmatic subjects infected with respiratory syncytial virus (RSV) show a conserved interferon response.[46]

Some type 2 cytokines also have anti-inflammatory effects. For example, IL-4 suppresses the development of Th1 cells from the activated Th0 stage, and inhibits the production of IL-1ß, TNF-α, IL-6 and IL-12. IL-13 has regulatory effects by inhibiting the secretion of IL-1α, IL-1ß, IL- 6, TNF-α, IL-8, MIP-1α, MIP-1ß and monocyte chemotactic protein-3. IL-9 reduces the secretion of TNF-α and IL-10, but increases the secretion of TGF-ß in activated monocytes.[27]

Unlike RVs, seasonal CoVs have not been reported as a major trigger of asthma exacerbation. This suggests a fundamental difference in how CoVs and RVs interact and stimulate the asthmatic host immune system.[34]

The results of Yang et al.[47] suggest that patients with respiratory allergic diseases are at increased risk of experiencing worse clinical outcomes from COVID-19. In their investigation, atopic dermatitis did not show a potential association with COVID-19 clinical outcomes, although it is an allergic disease, implying that changes in the local immune environment in the respiratory system, appear to be more important in the progression of infection than systemic immune effects.

The varying effects of SARS-CoV-2 and other respiratory viruses on respiratory allergic diseases may be due to the use of different molecular receptors expressed by respiratory epithelial cells.[40]

It is striking that virus-induced asthma exacerbations are mainly induced in patients with a high body mass index, with eosinophilia ("high" type 2 patients) and with a decreased production of type I IFN.[25]

Taken together, the different studies suggest that the variability of the clinical outcome of coping in asthmatic and allergic individuals with respiratory viruses, such as SARS-CoV-2, is highly dependent on the virus, asthma

endotype, disease control status, patient comorbidities, etc.[46]

The fact that the majority of the asthmatic population does not face any secondary complications or exacerbation due to COVID-19 and that recent research finds evidence against the protective action of allergic/type 2 "high" asthma on COVID-19, is still a matter of controversy.[24]

The inconsistency of findings in the various international studies may be due to the heterogeneity of asthma endotypes (allergic or "high" T2 versus non-allergic or "low" T2 asthma). So a possible protective role of allergic asthma is suggested, whereas non-allergic asthma predisposes to more severe forms of COVID-19.

This idea is in line with studies suggesting that allergic asthma may not be a risk factor for COVID-19, especially when it is well controlled. Immunity "tilted" toward the Th2 pattern may protect against severe COVID-19 disease due to cross-regulation between allergic and interferon-mediated immune responses.[48] In addition, conventional asthma therapies may also reduce the risks of asthmatics suffering from virus infection by alleviating inflammation or enhancing antiviral defense. It is proposed that asthmatics are more compliant with their treatment and respect social distancing to avoid severe lung infection.[49]

Some studies suggest that asthma and allergy medications protect against the development of severe COVID-19 and that patients taking these medications are less prone to SARS-CoV-2 infection. H1 receptor antagonist antihistamines have direct antiviral activity against SARS-CoV-2 by interfering with the early steps of viral replication or by binding to ACE2.[50,51,52] Treatment with H1 receptor antagonists and azithromycin prevents deterioration of pulmonary inflammation in elderly patients with SARS-CoV-2 infection.[50]

Montelukast, a cysteinyl leukotriene receptor 1 antagonist, acts as an antiviral agent by modulating innate and adaptive immunity. It reduces mucus secretion from respiratory glands, affects lymphocyte activation and differentiation, and blocks inflammatory protein expression in the lung by inhibiting the release of pattern 2 cytokines, especially in eosinophils.[53] Levocetirizine, a third-generation antihistamine, and montelukast exhibit remarkable synergistic anti-inflammatory activity across a spectrum of signaling proteins, cell adhesion molecules, and leukocyte, eosinophil, and neutrophil migration, which may prevent disease progression and reduce morbidity and mortality in patients with COVID-19.[50]

There is no conclusive evidence in the literature on this contradictory relationship between asthma (at least the allergic phenotype, more common) and COVID-19. However, several phenomena can be considered in the immunopathogenesis:

- The type I IFN response, although delayed, does not appear to be qualitatively defective in the asthmatic individual. Perhaps, the underexpression of ACE2, which favors a slower infection of the respiratory epithelium, AMs and ECs, would "buy time" until the establishment of the most adequate antiviral response by IFNs.
- Eosinophils are able to protect against viral infections.[27,54] Although peripheral eosinopenia is observed in COVID-19, the pre-existing eosinophilic infiltrate in the asthmatic airways could compensate for the deficit.
- The elevated presence of Th2 cells in the airways could protect the asthmatic subject from the severity of SARS-CoV-2 infection, despite the lymphopenia characteristic of COVID-19.[24]
- The plasticity of T cells, which confers them the ability to express mixed patterns of cytokines (Th2-Th17, Th1-Th17, etc.) could play an important role, yet to be elucidated, in the specific response to SARS-CoV-2.[55,56,57]
- Administration of anti-allergic therapies may directly protect patients' airways from viral spread, considering that some CoV strains are inhibited in vitro by combinations of nebulized asthma drugs.[35,40]

Asthma, and other allergic conditions, may protect infected patients from severe forms of CoVID-19,[58] but not surprisingly, they also provide the conditions for symptom development. This is attested by the wealth of evidence for infection with other respiratory viruses in asthmatic individuals: inflammatory cascades triggered by resident macrophages and lymphocytes, compositional changes in the respiratory microbiota, and diminished antiviral function of interferons and eosinophils.[59]

The heterogeneity of the results yielded by other research on the subject reveals that the relationship between asthma, allergic diseases and SARS-CoV-2 infection and the evolution of COVID-19 is and will be a complex issue subject to intense debate. Several factors can be taken into account in this regard:

Asthma endotypes and phenotypes, and the criteria used to define them, are confounding factors. The predominance of one pattern or another of the immune response has been seen to directly and indirectly influence the individual's response to disease, and the predisposition of asthmatic and atopic individuals to respiratory infections, mainly viral, is a health problem that has been abundantly described.[25,60,61,62]

The performance of complementary laboratory studies would be very useful to determine the atopic status and to have a notion of the asthmatic endotype manifested in the subjects; to establish comparisons and associations between the endotypes and the clinical-epidemiological observations. The cellular and molecular mediators of asthma are not always feasible to study, because of their high cost and the extent of this type of

epidemiological studies; therefore, the better definition of clinical phenotypes could, with the help of a better anamnesis exercise, guide researchers on the underlying mechanisms of asthma.

The geographical origin of the studies may influence the results.[63] The prevalence of allergic diseases and asthma varies between geographical areas and there may even be profound differences between countries in the same area. This may be due to inequalities in access to health services, hygienic practices associated with cultures, presence of sensitizing agents, etc.[64,65]

Genetic factors are closely related to allergic diseases such as allergic rhinitis, atopic dermatitis and asthma, described as multifactorial entities in which the genetic susceptibility of the individual, punctual environmental exposures, and the interaction between them have an impact. Whether genetic predisposition to allergic diseases is also related to susceptibility to SARS-CoV-2 and the evolution of COVID-19 is unknown.[66,67] In addition to genes recognized for their association with allergies and asthma, variants of genes involved in host-SARS-CoV-2 interaction (ACE2, TMPRSS2, etc.) and genes specific to the immune system (IFN, PRRs, etc.) are interesting targets for study. In this regard, blood group genes have been associated with allergic diseases, asthma, atopy and COVID-19.[68,69,70,72,73,74,75]

It would appear that preexisting asthma has a potential influence on susceptibility and disease course to SARS-CoV-2; however, there is no evidence to support this relationship. In fact, reports indicate that allergic diseases, particularly asthma, do not represent a risk factor for COVID-19 morbidity and mortality.[35,40] Nevertheless, in severe asthmatics, COVID-19 may cause worsening of asthma symptoms as with other viral diseases.[24,27,39,76,77]

CONCLUSIONS

The relationship between asthma, allergies, and COVID-19 is complex and subject to debate, influenced by multiple factors. Further studies are needed to better understand these interactions and the genetic and environmental factors that may affect the prevalence and response to these diseases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Conceptualization: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Data curation: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Formal analysis: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Research: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Methodology: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Project administration: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Resources: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Supervision: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Validation: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Visualization: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Writing - original draft: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.
Redaction - original design: Carlos Alfredo Miló Valdés, Adrián Alejandro Vitón Castillo, Lidia Cecilia Pérez Acevedo.