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SHORT COMMUNICATION

ACE2 expression in allergic airway disease may decrease the risk and severity of COVID-19

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Abstract
The coronavirus disease (COVID-19) is caused by Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and presents with respiratory symptoms which can be life threatening in severe cases. At the start of the pandemic, allergy, asthma, and chronic obstructive pulmonary disease (COPD) were considered as risk factors for COVID-19 as they tend to exacerbate during respiratory viral infections. Recent literature has not shown that airway allergic diseases is a high-risk factor or that it increases the severity of COVID-19. This is due to a decrease in Angiotensin-converting enzyme 2 (ACE2) gene expression in the nose and bronchial cells of allergic airway diseases. Conventional asthma treatment includes inhaled corticosteroids (ICS), allergen immunotherapy (AIT), and biologics, and should be continued as they might reduce the risks of asthmatics for coronavirus infection by enhancing antiviral defence and alleviating inflammation.

Keywords Allergic rhinitis · Asthma · SARS-CoV-2 · COVID-19 · Angiotensin-converting enzyme 2 (ACE2) · Transmembrane protease serine 2 (TMPRSS2) · Inhaled corticosteroids (ICS) · Allergen immunotherapy (AIT)

Introduction

Coronavirus was discovered in 1930. They are enveloped single-stranded RNA virus with spikes on their surface, which looks like a crown and hence the name "Corona". Human coronavirus producing severe symptoms are Severe acute respiratory syndrome coronavirus (SARS-CoV, 2003), Middle East respiratory syndrome coronavirus (MERS-CoV, 2012), and Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019). COronaVIrus Disease 2019 (COVID-19) outbreak was declared a pandemic on 11th March 2020 by World Health Organization. Since then, numerous medical literature is released worldwide to spread awareness about this new infection, its physiology, treatment guidelines, and prevention.

COVID-19 presents with mild to severe respiratory symptoms and is associated with a cytokine storm. Old age and comorbidities such as cardiovascular diseases, hypertension, diabetes, obesity, and tobacco exposure are factors for increased morbidity and mortality [1]. Allergic airway diseases ie allergic rhinitis and allergic asthma is of concern in this pandemic since symptoms of upper respiratory tract viral infection, allergic rhinitis, influenza, etc. overlap during the early stages. Hence, allergists and otolaryngologists are responsible for timely diagnosis and treatment and thus alleviate the patient's anxiety. Respiratory viruses can trigger and cause serious illness in individuals with chronic airway diseases and hence it was thought that individuals with allergies, asthma, and chronic lung diseases (COPD) are at high risk for severe COVID-19. However, multiple studies published recently do not prove that allergy and asthma are risk factors or increases severity for COVID-19.

Pathogenesis of SARS-CoV-2

SARS-CoV-2 needs two proteins for entry in the host cell. It attaches to angiotensin-converting enzyme 2 (ACE2) receptor and then the host transmembrane protease serine 2 (TMPRSS2) divides the spike protein into two subunits leading to virus fusion to the cellular membrane and then the entry in the cell [2]. SARS-CoV-2 has a highly glycosylated spike glycoprotein which binds with ACE2 with a higher affinity to gain entry in the cell [3], explaining its rapid

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spread. High ACE2 expression is present in the nose, lung, heart, intestine, and kidney. Nasopharynx and oropharynx, are the main replication sites of highly infectious aerosol particles that are released during sneezing, coughing, and talking [4].

Radzikowska et al. studied the distribution of ACE2, CD147, CD26 receptors and SARS-CoV-2 in immune cells and respiratory epithelium [5]. High ACE2 expression was seen in bronchoalveolar lavage and bronchial biopsy of patients with old age, high BMI (obesity), asthma, COPD, hypertension, male gender, and skin lesions of atopic dermatitis patients. However, this study did not mention the asthma phenotype (allergic or non-allergic). Similar results were seen in the bronchial biopsy of smokers, and they thus stated smoking to be a strong factor of increased airway epithelium ACE2 expression. He concluded that the altered expression of these receptors is related to age, gender, obesity, smoking, and contributes to severe COVID-19 symptoms and increased morbidity. Brake et al. also suggested smoking increases in vitro susceptibility to SARS-CoV due to high ACE2 expression and related it to the severe form of COVID-19 [6]. Halpin et al. reviewed data and concluded COPD and asthma are not common comorbidities for COVID-19 presentation [7].

Type 2 immune response occurs in atopic diseases such as allergies, asthma, atopic dermatitis, and parasitic helminth infections. They lead to the production of cytokines interleukins like IL-4, IL-5, IL-9, and IL-13. Kimura et al. demonstrated lower ACE2 expression in the nasal epithelial cells of participants with asthma and allergic rhinitis as compared to healthy participants. They further observed that interleukin-13 decreases ACE2 and increases TMPRSS2 expression in the nasal and airway epithelial cells [8]. IL-13 is a cytokine associated with allergic asthma (type 2) and allergic rhinitis.

Allergic airway diseases and SARS-CoV-2

At the beginning of the COVID-19 pandemic, US Centers for Disease Control and Prevention (CDC) mentioned asthma and allergy as risk factors for COVID-19. Since then many studies were conducted to correlate allergic airway disease and COVID-19. Initially, US data suggested a high asthma rate in patients hospitalized for severe COVID-19. However, they did not specify the asthma phenotype ie allergic or nonallergic. The Allergic Rhinitis and its Impact on Asthma (ARIA) and the European Academy of Allergology and Clinical Immunology (EAACI) stated that patients with airway allergies do not worsen or are at high risk of severe COVID-19 [9]. European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) concluded that allergic airway disease is probably not a risk factor for severe COVID infection. However, they did postulate that asthma can worsen with upper respiratory viral infections [10]. Studies from China did not find asthma to be a risk factor for COVID-19 severity [11]. Morais-Almeida et al. in their literature review of 29 studies from USA, China, UK, Italy, Spain, Mexico, Switzerland, and Saudi Arabia did not find evidence of asthmatic patients being at high risk for COVID-19 infection [12].

An upper respiratory tract viral infection can trigger asthma exacerbations in adults and children. A recent review suggested the human rhinovirus is the main reason for asthma exacerbations in adults and children as compared to coronavirus [13], and this was true for all continents [14]. Jackson et al. reported respiratory allergies, allergen exposures, high IgE and allergen sensitization to be associated with a decrease in ACE2 expression in the nasal and bronchial epithelium of asthma patients [15]. Patients with high allergic sensitization and asthma had the lowest ACE2 expression. In addition, low ACE2 expression was not associated with non-atopic asthma. Hence, they concluded reduced ACE2 expression to be one of the strong factors in patients with respiratory allergies for reduced COVID-19 severity. Dong et al. selected adults and children with COVID-19 and studied their profile and clinical presentations [16]. They suggested type 2 immune regulation in COVID-19 as patients with allergic diseases like rhinitis or atopic dermatitis did not progress to severe disease.

Children have mild clinical COVID-19 symptoms than adults [17] and it seems that SARS-CoV-2 may not be an asthmogenic virus. Sajuthi et al. [18] found a strong association of viral infection and T2 inflammation-causing ACE2 downregulation and TMPRSS2 upregulation in children. Thus, it seems that airways of allergic patients have low ACE2 expression which may protect from COVID-19, but higher TMPRSS2 expression may also cause rapid deterioration to severe symptoms. ACE2 and TMPRSS2 gene expression did not differ in healthy and asthmatic patients. The Severe Asthma Research Program-3 (SARP), showed sputum cells of males, diabetics, and African Americans, had a high expression of ACE2 and TMPRSS2, which explains their poor prognosis with COVID-19 [19]. They also demonstrated early evidence that inhaled corticosteroid use is associated with a decrease in sputum ACE2 and TMPRSS2 gene expression.

The anatomical, histological, and inflammatory mediators similarities between allergic rhinitis and asthma gave rise to the "One airway, One disease" concept. Hence, allergic rhinitis should be treated in patients with asthma to prevent asthma exacerbations. An expert consensus statement by ARIA-EAACI (ARIA-MASK group and European Academy of Allergy and Clinical Immunology) was recommended for allergic rhinitis patients infected with COVID-19, and

they suggested to continue intranasal corticosteroids (INS) at the recommended therapeutic dose [9]. Stopping the treatment of allergic rhinitis especially INS may increase sneezing and thus lead to the rapid spread of the virus [20]. INS normalizes the nasal mucosa and mucociliary clearance and does not reduce immunity. Preliminary data suggest ciclesonide blocks in vitro replication of SARS-CoV-2 RNA [21] and inhibits its cytopathic activity [22]. Further research on this is very important as it may reduce the risk and severity of COVID-19.

Global Initiative for Asthma (GINA) guidelines recommends all asthmatic patients to be treated with inhaled corticosteroids (ICS) with or without long-acting beta 2 agonists (LABA) as controllers. Patients with allergic diseases should maintain their inhaled corticosteroids [23], biologics [24], and allergen immunotherapy [25]. Subcutaneous immunotherapy (SCIT) requires repeated visits to allergists or hospitals and may not be possible during this pandemic for all. In such exceptional situations, sublingual immunotherapy (SLIT) may be considered if the allergist and patient agree [10]. Patients should be educated about refraining from stopping the medication or making self dose adjustments as it may precipitate asthma exacerbations and might require hospitalization. Telemedicine and digital platforms are preferred for follow up consultations to minimize the risk of viral spread and at the same time deliver personalized care.

Conclusion

Low ACE2 expression in airway cells of individuals with airway allergies (allergic rhinitis and allergic asthma) decreases their susceptibility to COVID and may not be a risk factor for severe infection. However, this is not true for nonatopic asthma phenotype. Studies are needed to understand the impact of respiratory allergic diseases and T2 inflammatory response on COVID-19 severity and susceptibility. It is paramount to continue asthma and allergic rhinitis treatment with inhaled corticosteroids, biologics, and allergen immunotherapy during the COVID-19 pandemic.

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