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LEADING ARTICLE

Impact of COVID-19 on the Symptoms of Asthma in Children and Its Management

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Introduction

The current outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started in or around December, 2019, in Wuhan.[1] On January 30th, 2020 the World Health Organization (WHO) declared COVID-19 a pandemic health emergency.[2] Since then, COVID-19 has continued to spread quickly and has now become the most dangerous pandemic in over 100 years. Chronically diseased patients are particularly vulnerable to severe complications and so need special attention to prevent increased morbidity and mortality.[3] Asthma is a chronic disease, and patients may experience decreased access to healthcare due to restrictions on public movements, lockdowns and diversion of healthcare resources to the care of patients affected by COVID-19.[4] Patients with asthma are hypothesised to have high susceptibility to, and increased severity of, SARS-CoV-2 infection due to their impaired immune response and the likelihood of respiratory exacerbation when infected by respiratory viruses, but little evidence has supported this theoretical risk.[5]

Based on the available literature, it is believed that children could be spared from COVID-19 likely due to the highly expressed thymic repertoire and efficiently activated immune response against SARS-COV-2.[6] Out of the total cases, children accounted for only 1.2% in Italy, 5% in the USA and 2% in China.[7]

Several factors have been hypothesized to offer an explanation on the low severity of the disease in the pediatric age group. First, seasonal coronaviruses may give a protective immune response toward SARS-CoV-2.[8] Second, children show low expression or function of the angiotensin-converting enzyme 2 (ACE 2) receptor.[9] Third, in children there are "innate" B cells, called immune naïve cells, that respond to novel antigens, producing effective immune responses against the pathogen and possibly contributing to the lower pathogenicity of SARS-COV-2 in the pediatric age.[10] Fourth, in the pediatric age immature B cells secrete anti-inflammatory cytokines such as IL-10, which may contribute to reducing the immune-mediated tissue damage.[11] Moreover, the lower severity of COVID-19 in children with respect to adults could be explained by a stronger innate immune response and by the lack of co-morbid conditions in most subjects.[7]

Therefore, in asthmatic patients some potential protective mechanisms against SARS-COV-2 have been hypothesized, like type 2 immune response, number of eosinophils, overproduction of mucus, and asthma treatment, along with behavioral factors not strictly related to asthma, such as social distancing, hygiene measures and wearing facemasks, that contribute to reduce the individual susceptibility to SARS-COV-2 infection.

Pathogenesis of COVID-19

SARS-COV-2 necessitates two proteins for entry into the host cell. The virus attaches to the ACE 2 receptor; subsequently, the host trans-membrane protease serine 2 (TMPRSS2) splits up the spike protein, expressed on the viral envelope, into two segments, allowing fusion of SARS-COV-2 to the cellular membrane and its penetration into the cell. The binding of SARSCoV-2 to ACE 2 receptors produces a marked down-regulation of these molecules, whose protective effects on the human body have been recognized. In fact, after its entry into the host cells, the activated innate immune

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response prompts release of pro-inflammatory cytokines, which recruit effector cells like neutrophils, macrophages, etc. In the context of the adaptive immune response, antigen-presenting cells (APCs) present viral antigens to T cells, eliciting differentiation from immature cells to mature cells (Cytotoxic T cells and Natural Killer cells) that might contribute to killing virus-infected cells. If the adaptive immune responses are insufficient, innate immune responses can be reinforced through a cytokine storm that is responsible for severe multi-organ damage.[12,13] In case of low-dose virus infection, efficient T- and B-cells responses and neutralizing antibodies could lead to rapid viral clearance. By contrast, high-dose virus exposure may account for severe disease and delayed viral clearance. This can be attributed to lymphopenia, which determines inadequate T- and B-cells responses, eventually followed by a cytokine storm and multiorgan failure.[14]

Pathogenesis of Asthma

Asthma is a respiratory disease characterized by chronic inflammation of the airways with bronchial hyper-responsiveness to several stimuli, mucus overproduction, recurrent episodes of wheezing, respiratory distress, and cough, associated with reversible airway obstruction. Asthma is one of the most common chronic diseases worldwide, affecting more than 300 million individuals, and the incidence is growing, particularly in developed countries.[15] Asthma remains one of the highest causes for school absence and hospital admissions, imposing a high socioeconomic burden, and impairing quality of life of children and their families.[16,17]

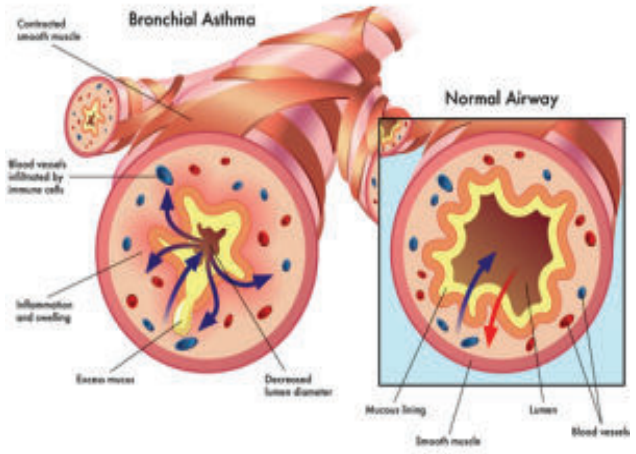

Fig.-1: Airway changes in Asthma

Because of the tendency for disease exacerbation elicited by common respiratory viruses including Rhinovirus, Respiratory Syncytial Virus, Influenza virus, Parainfluenza virus, Adenovirus, human Bocavirus, and Coronaviruses[18] and a deficient antiviral immune response that is evident in asthmatic patients.[19,20] the latter should potentially have increased vulnerability to SARS-COV-2 infection. This could be sustained by the deficient type I Interferon (IFN) responses observed in patients with severe asthma. However, some studies have shown that asthma is not a risk factor in patients with COVID-19.[21] In the study by Zhang et al[22] involving 140 community infected COVID-19 subjects, asthma was not reported by any of the patients. Similarly, Dong et al[23] in a case series of 2,135 pediatric patients with COVID-19, did not report any case of asthma. In the Confidence study, which included 100 pediatric patients with COVID-19, chronic respiratory diseases did not appear as risk factors.[24]

Protective factors against SARS-COV-2 infection in children with Asthma

Some protective factors against SARS-COV-2 infection have been hypothesized in patients with allergic asthma, such as T2 immune response (Fig.-1), overproduction of mucus, and asthma treatment.

Type 2 immune response

The T2 immune response in asthmatic patients might counteract the COVID-19 cytokine storm. According to Kimura et al[25] in airway epithelial cells of patients with allergic asthma ACE 2 is reduced and TMPRSS2 is increased thanks to IL-13 exposure. In addition, patients with activated Th2 immune responses showed decreased expression of ACE 2 in airway epithelial cells, inversely correlated with T2 cytokine levels and Th2 signature molecule expression.[25] In the study by Sajuthi et al[26] nasal airway transcriptome and network co-expression analysis were used to detect cellular and transcriptional factors of ACE 2 and TMPRSS2 genes in a cohort of 695 subjects with asthma and healthy controls between 8 and 21 years of age. They found that Th2 inflammation had a major role in ACE 2 down-regulation as well as in TMPRSS2 up-regulation. The study also showed that ACE 2 expression was marked only in secretory cells and ciliated cells, whereas TMPRSS2 was expressed in all epithelial cell types. Overall, these results suggest that Th2 immune responses may be a protective factor against SARS-COV-2 infection by causing ACE 2 down-regulation.[26]

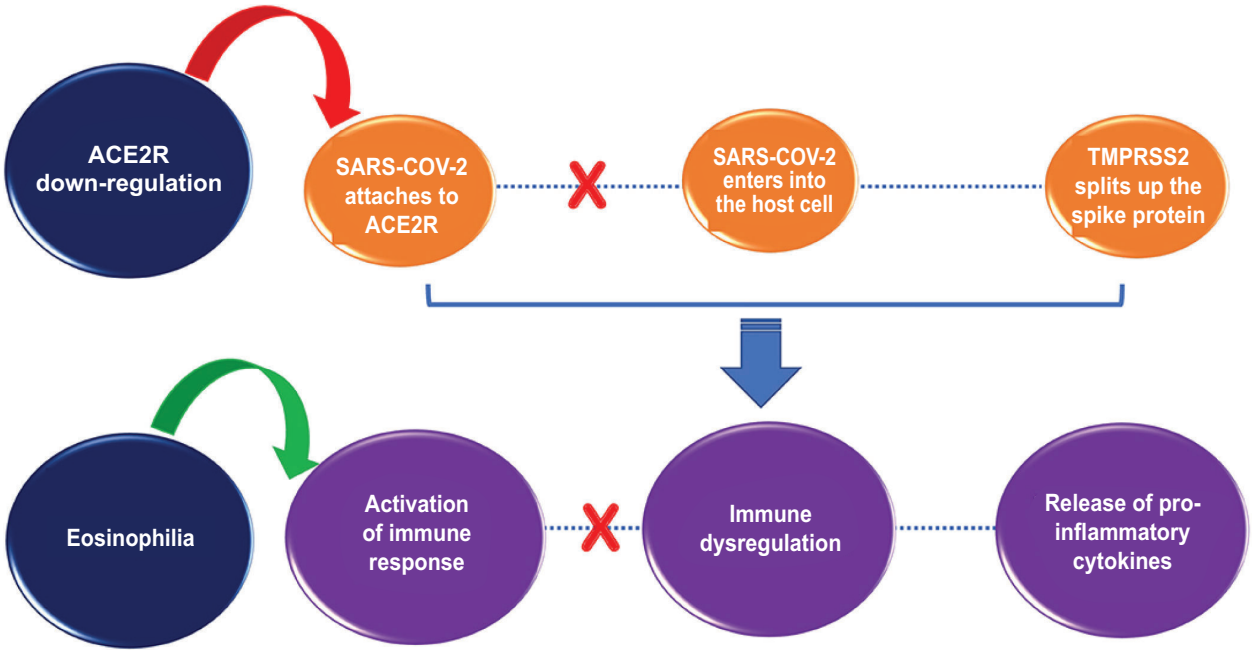

Fig.-2: *T2 immune response*

Additionally, since eosinopenia has been observed in COVID-19 patients, the increased number of eosinophils in asthmatic patients could have a protective role against SARS-COV-2. Though the relationship between eosinophil levels and COVID-19 is still not clear, during the pandemic it is important to monitor eosinophil counts and the clinical course of COVID-19 in patients with asthma treated with biological drugs responsible for decreased eosinophil levels.[27]

Overproduction of mucus

Mucus hypersecretion could be recognized as another hypothetical protective factor against COVID-19 because it acts as the first line of defense against infection, thereby preventing SARS-COV-2 from reaching the distal airways and entry into the alveolar type 2 cells, which predominantly express ACE 2 in the lung. In asthma there is increased expression of MUC5AC,[28] which has been proved to give protection against influenza infection in a murine model. However, not all patients with asthma show mucus overproduction; thus, mucus hyperproduction may only give protection in some patients.

Impact of Asthma treatment during COVID pandemic

Inhaled corticosteroids (ICS) are the first line treatment of asthma. One study hypothesized that ICS could increase antiviral immunity in treated patients.[29] There is also evidence that ICS may down-regulate both ACE 2 and TMPRSS2 expression, thereby decreasing binding of SARS-COV-2 to receptors on the airway epithelium cells.[30] Moreover, ICS suppress virus replication and cytokine production. Additionally, the combination of formoterol, glycopyrronium and budesonide has been shown to inhibit seasonal coronavirus replication and cytokine production.[31]

Allergen immunotherapy (AIT) suppresses T2 immune responses and controls allergic inflammation by stimulating T regulator cell responses and preventing tissue homing and degranulation of mast cells, basophils and eosinophils.[32] Therefore, it could be supposed that AIT might play a role in preventing a cytokine storm. In recent studies, the monoclonal antibody against human IgE Omalizumab has been suggested to have a potential effect on antiviral responses by reducing susceptibility to respiratory virus infections.[29]

Therefore, in light of the abovementioned data and according to the Global Initiative for Asthma Guidelines (GINA) recommendations, children with asthma should continue their treatment to prevent asthma exacerbations due to SARS-COV-2 infection, undergoing pulmonary function tests when needed to guide management.[33]

Impact of the implementation of lockdown measures on asthma outcomes

The ongoing COVID-19 pandemic has had a significant impact on access to and use of health services. Data from US hospital records and online surveys of health-care providers have documented major reductions in emergency room (ER) visits, uptakes of follow-up visits, prescriptions, treatment adherence, and asthma control.[34] Similarly, hospital records analysis in Japan revealed a decrease in asthma hospitalisations during the pandemic.[35] Such reductions likely reflect the combined effects of stay-at-home orders, reassignment of health services, fear of contagion or reduction of severe asthma attacks. A recent multicentre case-control analysis of asthmatic children attending outpatient visits showed improved asthma outcomes and control during the COVID-19 pandemic. Control measures during lockdown likely would have reduced exposures to respiratory viruses that have been associated with 80% of asthma exacerbations in children, with rhinoviruses being particularly important.[36]

Effect of preventable measures of COVID -19 in child with Asthma

In order to mitigate COVID-19 disease transmission, unprecedented disease prevention measures were implemented wordwide. Children have adopted different more hygienic lifestyles such as wearing masks and frequently using disinfectants. Undoubtably, these practices can effectively curb viral transmission. However, there are studies showing that using N95 or KF94 masks increases the risk for chronic disease patients with impaired pulmonary function and that frequent disinfectant usage may affect the respiratory tract of newborns, increasing the risk of pediatric asthma.[37] Zok et al[38] showed that weekly usage of air fresheners may also be a risk factor of severe asthma onset. Considering the fact that 60–80% of allergic asthma cases involve pulmonary asthma, minimizing exposure to allergens should be the most effective method to control asthma. The frequent usage of alcoholic and chlorinated allergic disease prevention materials may be a risk factor of severe asthma attacks, contributing to the increase in the incidence of severe asthma attacks among children during the COVID-19 pandemic. Since certain disease prevention practices such as masks and disinfection are expected to persist even after the pandemic, we have to design ways to minimize the impacts of these measures on pediatric asthma patients so as to achieve effective asthma management.[39]

Conclusion

Based on the available literature, whether asthma could really be considered a protective condition against SARS-COV-2 infection in children is still not clear. Therefore, further studies are required to clarify the impact of asthma on COVID-19 susceptibility and severity, especially in pediatric population where the available evidence is very limited.

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