COVID-19 and Pediatric Asthma

Subjects: Allergy

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A more robust innate immunity and lower ACE-2 receptors expression underlies a lower severity of COVID-19 in children. Moreover, diverse studies suggest that children with asthma do not appear to be disproportionately more affected by COVID-19. This review address the lower severity of COVID-19 in children and the relationships with asthma, atopy and obesity.

Keywords: COVID-19 ; SARS-CoV-2 ; childhood ; pediatric ; asthma ; atopy ; obesity ; treatment ; vaccines

1. Introduction

In December 2019 a new infectious disease started in Wuhan in the Hubei Province of China, as a cluster of severe pneumonia cases, at first of unknown etiology. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known as 2019-nCoV, is the cause of Coronavirus Disease 2019 (COVID-19)[1][2]. The first case series in 10 children were reported by Jiehao et al. and date back to January 2020[3]. On March 11, 2020, when SARS-COV-2 infection had reached more than 100,000 people, over 4000 lethal cases, in more than 100 countries around the world, the World Health Organization (WHO) classified the outbreak as a pandemic[4]. At the time of this writing, more than 90,335,000 confirmed cases and over 1,954,000 deaths associated with SARS-CoV-2 infection have been reported around the world[5].

All epidemiologic data until now suggest that SARS-CoV-2 infection is less severe and prevalent in children than in adults. An alternative explanation for this fact is that COVID-19 has not been diagnosed that often in children because many in this age group remain asymptomatic[1].

2. Pediatric Asthma and SARS-CoV-2 Infection

Human coronaviruses (hCoVs) circulate globally, commonly infecting children and generally causing mild, self-limiting upper respiratory tract infections (rhinorrhea, nasal congestion, sore throat and fever). Asymptomatic infection also occurs. Of the seven coronaviruses identified in humans, hCoV-229E and hCoV-NL63 belong to α-coronaviruses, and hCoV-OC43, MERS-CoV, SARS-CoV-1 and SARS-CoV-2 belong to β-coronaviruses. Both SARS-CoV-1 and SARS-CoV-2 first emerged in China[6].

Up to 80% of asthma exacerbations are due to viral infections, including common coronaviruses [7]. Two large population based-studies in hospitalized children, one in Norway[8] and the other in China[9], found that, respectively, 10 and 4.3% of hospitalized children tested positive for hCoVs, with the most common type being hCoV-OC43 (a β-coronavirus) in both studies.

This fact draws attention to the possibility of these previous infections with hCoVs in children conferring partial protection against SARS-CoV-2. Despite lower respiratory tract infections with hCoVs have been described, severe illness is rare in the absence of additional risk factors (age < 12 months, immunodeficiency, presence of previous chronic pulmonary disease and co-infection with other pathogens)[9][10]. No clear association between hCoVs infections and Kawasaki disease has been identified[11][12].

Children infected during the SARS-CoV-1 epidemic were sporadic (<5% of confirmed cases) and had a clear history of exposure. The most common symptoms were fever (98%) and cough (60%), and the majority of children have a good prognosis. However, age > 12 years predicted a worse outcome[13]. The most common laboratory abnormalities in SARS-CoV-1 were similar to those seen in SARS-CoV-2, and included lymphopenia, thrombocytopenia and elevated LDH. Regardless of age, sore throat and elevated neutrophil count at presentation were independent risk factors for severe illness. Radiographic abnormalities consisted primarily of ground-glass opacities and/or areas of consolidation (similar to COVID-19)[14]. However, no cases of SARS-CoV-1 have been reported since early 2004.

MERS data on prevalence, clinical presentation and outcome in childhood are scarce. The most common symptoms in children were fever, cough, shortness of breath and vomiting/diarrhea. In chest radiographs, diffuse bilateral infiltrates were the most common abnormality[15].

The clinical and laboratorial data described above reinforce the idea that: (1) pre-existing cellular immunity to SARS-CoV-2 in unexposed patients (mainly children) may drive from previous exposure to beta hCoVs (OC43 being the most likely candidate) and (2) a great similarity (79%) exists between SARS-CoV-1 and SARS-CoV-2, as demonstrated by genetic analysis, which may reflect in the pathophysiology and clinical/laboratorial manifestations of both diseases[16][17].

2.1. Asthma and COVID-19

Two questions remain crucial regarding the association of asthma and COVID-19. Are asthmatic patients more susceptible to be infected by SARS-CoV-2? If infected, are asthmatic patients at higher-risk of severe COVID-19? Another question revolves around if the relationship between asthma and COVID-19 is different according to age (adults vs. children) and asthma endotypes (eosinophilic vs. non-eosinophilic asthma).

In a recent review, Skevaki et al.[18] found large country-differences in asthma prevalence among patients (mainly adults) with COVID-19. In most countries, such as China, Brazil, India, Mexico, Saudi Arabia, Spain and Italy, the prevalence of asthma among COVID-19 patients is lower than that observed in the general population, while the opposite is observed in the USA, Australia, UK and Ireland. The lack of more detailed information about asthma severity and phenotypes in most of these studies limits further conclusions.

Data in children are very scarce. Du H et al.[19] reported data from 182 children with COVID-19 hospitalized in Wuhan; although 23.6% had some form of allergic disease, only one child had asthma. In this study, no difference in clinical symptoms, severity and complications was observed between those with and without allergy[19]. On the other hand, in Brazil, asthma was found to be the most common comorbidity among 115 children with COVID-19[20]; nevertheless, the prevalence of asthma among infected children was lower than that found in local epidemiological studies (13.0% vs. 20–25%)[21] and asthma was not associated with more severe COVID-19 leading to hospitalization. Data from 46 children admitted due to COVID-19 in a New York hospital showed that asthma was a frequent comorbidity (24%), but was not associated with the need for intensive care treatment[22].

Some studies have reported the effects of the COVID-19 pandemic among asthmatic children. In a recent online survey of 91 asthma experts, caring for more than 133,000 asthmatic children in five continents, only 14% of the responders reported suspected cases of COVID-19 among their patients; asthmatic children had mild symptoms in 73% of the cases and only one child required hospitalization[23]. Ruano et al.[24] described clinical data from 29 allergic asthmatic children with probable COVID-19 (suggestive symptoms in the child and in one adult living in the house) from a single center in Madrid, Spain. All children had mild symptoms of COVID-19 and there were no hospitalizations. Mild bronchospasm was observed in 24%, and oral corticosteroids were prescribed in only one case.

Severity and complications of SARS-CoV-2 infection are associated with hyper-inflammation. In asthmatics such hyper-inflammation could be down regulated by several mechanisms including the delayed and inefficient antiviral response due to lower IFN-α production by dendritic and epithelial cells, protective role of eosinophils in the airway, and antiviral and immunomodulatory proprieties of inhaled steroids[25]. Interesting, according to these explanations, such mechanisms that contribute to higher morbidity and higher lung involvement in most respiratory viral infections in asthmatics, are the same ones that are responsible for protecting them during SARS-CoV-2 infection.

In a systematic review of the literature, Castro-Rodriguez et al.[26]concluded that there are almost no data to assess whether asthma, or other pediatric respiratory diseases, constitutes a risk factor for SARS-CoV-2 infection or the severity of COVID-19, and emphasized the need for studies to address this issue in childhood. These authors discuss whether the lower prevalence of asthma among cases of COVID-19 may be due to a bias, since patients with chronic lung diseases may be more cautious when practicing social distancing and other measures to prevent infection, or even more reluctant to seek medical attention, even when sick, and so not being accounted for in health statistics[26].

In the real world, COVID-19 has not been implicated as an important driver of viral wheeze or asthma exacerbations in children. According to data from some hospitals, the number of presentations and/or admissions due to wheezing/asthma during the COVID-19 pandemic were either similar or lower than that observed in previous years [27][28]. Within this context, Abrams et al. [29]argue that although non-epidemic coronaviruses are commonly found in the respiratory tract of children, with exacerbation of asthma and contribution to bronchial hyperreactivity and eosinophilic inflammation,

paradoxically, asthma exacerbations actually decreased during the COVID-19 epidemic, which can be attributed to greater attention being paid in relation to hygiene measures in this population. Obviously, the impact of the generalized lockdowns must be considered as a confounding factor.

Although studies on asthma and COVID-19 in children have so far been reassuring, the European Academy of Allergy and Clinical Immunology (EAACI) declared that “based on common sense, rather than mounting evidence” children with asthma, particularly severe or uncontrolled, should be considered to be at increased risk of developing severe COVID-19[30].

2.2. Risk and Protective Factors Associated with Pediatric Asthma

2.2.1. Atopy

Several mechanisms have been proposed to explain the lower morbidity of COVID-19 observed in patients with type 2 asthma.

As previously described, ACE2 is a host molecule used in cell entry by SARS-CoV-2 and other coronaviruses [31][32]. Data from three different cohorts of children and adults have shown that asthma and respiratory allergy were associated with lower expression of ACE2 gene in airway cells[32], as type 2 inflammatory mediators (such as IL-13) and allergen exposures may decrease ACE2 expression in bronchial epithelial cells[31][32].

The South Korean nationwide cohort tested almost 220,000 adults for SARS-CoV-2, with 7340 positive cases, and information regarding asthma, allergic rhinitis and atopic dermatitis was obtained from the health insurance records. Asthma was associated with an increased risk of SARS-CoV-2 test positivity (12.7% vs. 7.6%) and severe COVID-19 infection (ICU admission, mechanical ventilation, or death: 6.9% vs. 4.5%). Interesting and of note, was the report that both risks were higher in non-allergic asthma, with no significant risk being found when allergic asthma was compared to the non-infected group[33].

Du Y et al.[34] reported that about 80% of patients who died of COVID-19 had eosinopenia, a finding considered as a biomarker of poor prognosis of the disease and one of the best predictors for the severity when screening patients with COVID-19[35]. It has been speculated that the eosinopenia was independent of the use of corticosteroids, and is related to the depletion of CD8+ T cells and the consumption of eosinophils caused by SARS-CoV-2[36]. On the other hand, a minority of patients with COVID-19 have eosinophilic inflammation, suggestive that a type 2 inflammatory predominance plays a protective role against SARS-CoV-2[37].

2.2.2. Obesity

Obesity has been identified as an independent risk factor for serious disease and fatal outcomes in adults with COVID-19[38]. Possible mechanisms for these findings include endothelial dysfunction associated with metabolic syndrome, increased expression of SARS-CoV-2 entry receptors ACE2, TMPRSS2 and CD147 in adipose tissue, and deficient pulmonary mechanics [39][40]. Interestingly, in a cohort of adults with COVID-19 it was reported that CD147 expression in the whole blood correlated positively with body mass index (BMI), and its upregulation by high glucose concentrations, which might reflect a correlation with obesity and also potentially with diabetes, another relevant COVID-19 comorbidity[41]. In contrast to other risk comorbidities for COVID-19 in adults, obesity is nowadays a worldwide epidemic in children[42]. Asthma and obesity are among the most prevalent diseases of children, and both are pro-inflammatory conditions. Systemic inflammation, related to excess visceral adiposity, has been identified as a possible mechanism for the development of the obesity–asthma endotype[43][44].

Although considered as factors of greater susceptibility and severity for COVID-19, studies in adults and children with both conditions have shown controversial results[45]. Most studies on asthma and COVID-19 were carried out in elderly people with many comorbidities as obesity, hypertension and diabetes, not clarifying whether asthmatic patients with COVID-19 have isolated asthma or asthma as a multimorbidity[46]. Thus, studies focused on asthma–obesity comorbidity are needed to establish the real role of asthma as a risk or protective factor in obese patients with COVID-19 in different age groups.

A study conducted by Lovinsky-Desir et al.[39]in New York City (NY), with the aim of determining whether asthma was associated with unfavorable outcomes, evaluated 1298 patients, 65 years or younger, hospitalized with severe COVID-19. The authors concluded that outcomes did not differ between obese and non-obese patients, with and without asthma, suggesting no change in risk attributed to asthma alone[39]. In another study, involving 1747 children and adolescents who visited an NY emergency department, 67 (34.5%) tested positive for SARS-CoV-2 infection, with 46 subsequent hospital admissions, and 13 (28.3%) patients needing ICU. Obesity and asthma were highly prevalent but not significantly associated with ICU admission[22].

The endotype associated with the characteristic late-onset adult obese asthma phenotype, might be an additional risk factor for COVID-19. Studies in obese asthmatic adults have predominantly shown a Th1/Th17 pattern in the airways´ inflammation, with a significant neutrophilia, associated to elevated levels of TNF-α, IFN-γ and IL-6[47]. On the other hand, with the childhood asthma–obesity phenotype, the “classic” atopic Th2 pattern seems to predominate, with eosinophilic inflammatory infiltrate and high levels of IL-4, IL-5 and IL-13, which could hypothetically be a protective factor for severe SARS-CoV-2 infection in children with both conditions[48].

2.3. Management of Asthmatic Children during the SARS-CoV-2 Pandemic

Objective evidence regarding the optimal management of asthmatic children during the SARS-CoV-2 pandemic is still limited and most available information is based on expert recommendations. Weak evidence supports that some asthma medications such as inhaled steroids, montelukast and bronchodilators may have SARS-CoV-2 and/or other coronavirus inhibitory action, or could be beneficial to reduce COVID-19-driven inflammation[49][50][51].

An ex vivo study of an asthmatic’s airway epithelial cells showed that inhaled steroids have suppressive effects on ACE2 and TMPRSS2 expression[52]. A systematic review found no evidence of COVID-19-related adverse outcomes in patients with continuous or pre-morbid inhaled steroid use[53]. This evidence reinforces the recommendation from the Global Initiative for Asthma (GINA) and others that control medication for asthma, including inhaled steroids, should be maintained during the pandemic[54][55]. The decision to reduce or to step down daily controller medication should be carefully considered[55]. Oral corticosteroids were initially not recommended for patients with COVID-19 due to the potential risk of immune depression and a worse viral response[56][57]. However, further studies have shown beneficial effects of systemic corticosteroids in reducing acute respiratory distress syndrome and systemic inflammation[58]. For asthma exacerbations, a short course of oral steroids is recommended—according to clinical judgment—to prevent serious consequences[54][57].

Biologicals for type 2 severe asthma should also be maintained with self-application whenever possible[59]. Nevertheless, in cases of SARS-CoV-2 infection, suspension of biologicals is recommended until clinical recovery and viral clearance[59].

Management of comorbidities to optimize asthma control, mainly rhinitis, may be especially relevant during the COVID-19 pandemic. Uncontrolled rhinitis may mimic viral infection and possibly increase the risk of viral transmission in those infected with SARS-CoV-2[60].

Routine spirometry testing should be suspended[54]. Telehealth and virtual appointments should be stimulated, and face-to-face visits should be limited to severe or uncontrolled patients[55].

Public health measures, as wearing facemasks and maintaining social distancing, if possible, are desirable. There is no evidence that wearing a facemask exacerbates asthma or any other underlying lung condition[60]. The CDC recommends for everyone, but particularly for patients with asthma, to avoid crowds, wash hands often with soap and water or use hand sanitizer that contains at least 60% alcohol, avoid cruise travel and non-essential air travel, stay home during a COVID-19 outbreak in the community and avoidance of people who are sick[61].

3. Conclusions

Despite the fast advances at this moment, there are more questions than answers about SARS-CoV-2 infection, including the still open question why COVID-19 is milder in children. Among the main hypotheses discussed in this review, the more robust innate immunity and the lower expression of SARS-CoV-2 receptors in relation to adults seem the most attractive. On the other hand, SARS-CoV-2 has not been implicated as an important driver of viral wheeze or asthma exacerbations in allergic children. This fact seems to apply even to childhood asthma-obesity phenotype. Despite this, children with severe and uncontrolled asthma should be considered at higher risk for the development of severe COVID-19. Focus on risk stratification and controller medication adherence will be essential to allow children with asthma to return safely to school.

In response to the COVID-19 pandemic, the international scientific community has developed a huge body of research knowledge in record time through mobilization and cooperation, unprecedented for an infectious disease. As a result of this translational approach, guidelines for mitigating the spread of the infection, practical diagnostic investigation tools, therapeutic approaches and vaccines have been developed. Hopefully, these and other pressing questions will be answered soon

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