

IMPACT OF COVID-19 ON CHRONIC LUNG DISEASE IN CHILDREN: ASTHMA AND CYSTIC FIBROSIS

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ABSTRACT

In December 2019, the WHO identified a novel coronavirus that leads to severe acute respiratory syndrome (SARS-CoV-2). COVID-19, the disease produced by the novel coronavirus, seem to less affect children and cause severe disease compared to adults, being associated with lower case-fatality rates.

Asthma and cystic fibrosis (CF) are the most common chronic lung diseases that affect children and adolescents. It is not well established if there is a higher risk of poor outcomes due to infection with SARS-CoV-2.

Research that demonstrated that the angiotensin-converting enzyme 2 (ACE2) receptor required for coronavirus recognition and infection may be under-expressed in airways of atopic children, led to a paradox that sets asthma as being a protective condition for COVID-19. Patients with CF manifest cytokine dysfunction and chronic inflammation enhanced by the diversity of pathogens in the airways, mechanisms that overlap with the pathophysiology of COVID-19. International data suggest that very few CF patients experienced symptoms and complications due to COVID-19 and, if the disease is milder than anticipated in CF, this could be related to some protection due to the cellular effect of CFTR mutations associated with viral processing.

Taken together, asthma and cystic fibrosis, chronic diseases with significant impact on morbidity and mortality in both children and adults, may serve as a model of factors that may mitigate the impact of SARS-CoV-2 and creates opportunities for developing research.

Keywords: asthma, cystic fibrosis, COVID-19

INTRODUCTION

In December 2019, the World Health Organization (WHO), after being notified of an unusual cluster of pneumonia cases in Wuhan, China, investigated subsequently and identified a novel beta-coronavirus that leads to severe acute respiratory syndrome coronavirus (SARS-CoV-2) (1).

Coronaviruses (CoVs) are a large family of zoonotic RNA viruses that encompass four common circulating viruses among humans (HCoV-229E, -HKU1, -NL63 and OC43), and novel CoVs that are mutating and recombined viruses that rapidly spread from animals to humans (severe acute respiratory syndrome coronavirus – SARS-CoV, that emerged in 2002, and Middle East respiratory syndrome coronavirus – MERS-CoV, that emerged in 2012) (2,3).

CHARACTERISTICS. TRANSMISSIBILITY OF SARS-COV-2 IN CHILDREN

The 2019 novel coronavirus (SARS-CoV-2) is currently causing a severe outbreak of disease, COVID-19, that led to a global pandemic.

CoVs cause mainly gastrointestinal and respiratory symptoms that can be expressed by a range of clinical manifestations as common cold, bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure and even death (3). To date, all CoVs seem to less affect children and to cause severe disease compared to adults, being associated with lower case-fatality rates. The likelihood of infection is similar in children, but preliminary evidence suggests that they are less likely to be symptomatic or develop severe disease. Transmissibility

of SARS-CoV-2 remains uncertain and is a still debated problem and, among majority of cases of infected children, there have been documented household contacts with previous symptoms.

The novel virus is more likely to infect older people, more so, those with chronic comorbidities that have greater risk for severe outcome and even, death (4).

Since the beginning of the COVID-19 pandemic, symptomatic infection in children and adolescents is lower than in adults and data remains scarce, despite the number of confirmed cases (5,6).

Most data originate from China and several studies are already published on smaller series in Europe and North America, clinical and epidemiological data being of little relevance due to the benign outcome of most children. Symptomatic children infected with SARS-CoV-2 less commonly require hospitalization (7,8).

Documented data from the Centers of Disease Control (CDC) updated in August 2020, show that from the known COVID-19 cases (96%), only 8% were children under 18 years of age. Mortality in several series was less than 0.1% of all COVID-19 mortality (9,10).

From those who were hospitalized and died being infected with SARS-CoV-2, the majority had profound comorbidities. When speaking of poor outcomes in COVID-19 mainly in children, identification of risk factors is paramount for developing prevention strategies and new treatments, which is important in all age groups.

A special interest and approach has been directed towards the impact of COVID-19 on chronic lung disease (CLD) in children, based on previous reports that showed that CLD may be seriously impacted by infection with influenza, or other viruses, depending on the specific lung disease and virus aggressivity (11).

ASTHMA AND COVID-19

Asthma, and cystic fibrosis are the most common CLDs that affect children and adolescents. There is not well established if there is a higher risk of poor outcomes due to infection with SARS-CoV-2.

Multiple international medical and scientific organizations, list asthma among an important risk factor for morbidity and mortality due to COVID-19, but data result as based more on observational studies and reports, mounting evidence being still necessary (12). Only two reports among several systematic reviews, listed pediatric asthma as a risk factor for COVID-19 severity, among others, being stated that

there is a theoretical risk for asthma exacerbations in SARS-CoV-2 infection, as it is demonstrated with other viruses (13,14).

More so, infection with seasonal coronaviruses are known to trigger asthma exacerbations annually, albeit less than influenza viruses.

Recent data, based already on older studies that demonstrated that the angiotensin-converting enzyme 2 (ACE2) receptor required for coronavirus recognition and infection may be under-expressed in airways of atopic children, leads to a paradox that sets asthma as being a protective condition for COVID-19 (15,16). More so, epidemiological data from several countries, show decrease of hospitalizations for asthma exacerbations in the period of pandemic, along decrease of admissions for acute respiratory tract infections (17).

Further large scale studies are needed in children in order to establish if asthma is a risk factor for COVID-19 outcomes or, if infection with SARS-CoV-2 increases the risk of poor outcome in asthma (14).

In terms of diagnosis of new cases of pediatric asthma during the actual pandemic, the similarity of presenting symptoms warrants cautions regarding transmissibility of potential SARS-CoV-2 infection. Evaluation of these children should follow international asthma guidelines, and appropriate protective equipment should be worn.

For patients with known asthma, recommendations of international societies are regarding keeping asthma under control with proper medication in conformity with disease staging and to avoid unnecessary risks with maneuvers that contribute to spread of the virus to healthcare workers or other patients. This would be of particular interest when speaking about spirometry (home monitoring is advised under parent's supervision and telemedicine may be used in stable patients), as well indication for use of metered-dose inhaler with valved holding chamber is preferred over nebulizers (18).

Adverse social determinants and impact of COVID-19 outcomes may be amplified in children with asthma, mostly in ethnical and racial affected groups.

Controlled asthma is an issue mentioned in all international guidelines with specification to COVID-19, which means that continuity of medication, mainly the use of inhaled corticosteroids at doses that keeps the child well, should be a rule. A statement of the European Academy of Allergology and Clinical Immunology (EAACI) notes that the regular use of inhaled corticosteroids does not pose an increased risk for pulmonary or systemic infections,

and accordingly, would not represent a further risk for acquiring or increasing the infection with SARS-CoV-2 (7).

Based on lack of observations that demonstrate impairment of immune response to COVID-19 in patients with asthma, all international societies recommend continuation of biologic therapies, and support home-based administration when possible (12).

Managing the comorbidities as rhinitis is mentioned in guidelines and in those patients that need specific allergen immunotherapy, there are recommendations for home-based therapy.

Initial concerns regarding childhood asthma being affected by COVID-19 have not been demonstrated and the reasons may be diverse. This may imply protective mechanisms of allergen exposed airways and lower expression of ACE2 receptors along possible reduction of other causes of asthma exacerbations, as decrease of other viral infections, improved air quality.

CYSTIC FIBROSIS AND COVID-19

Cystic fibrosis (CF) is one of the most common autosomal recessive life-limiting condition affecting Caucasians, multisystemic, in which the genetic defect of the CFTR (cystic fibrosis transmembrane regulator) leads to inefficient mucociliary clearance in the airways resulting in chronic progressive lung disease. Patients with CF also manifest cytokine dysfunction and chronic inflammation enhanced by the diversity of pathogens in the airways. Mechanisms overlap with the pathophysiology of COVID-19, which may be a premise of serious illness in CF patients that undergo infection with SARS-CoV-2. Viruses, as shown in previous studies, are the cause of 60% of pulmonary exacerbations in CF and same as in asthma, rhinoviruses and influenza viruses pose patients to high risk of adverse outcomes (19-21).

Correlated with the observations that CF patients haven't experienced severe COVID-19 illness, with around 90% exhibiting relatively few symptoms and complications (international data), even numbers may reflect effective shielding, countries that were hard hit by negative impact of COVID-19 should have had significant excess deaths in patients with CF. If this will be further demonstrated, and the course of COVID-19 in CF patients is milder than anticipated, this could have the explanation in some protection of the cellular effect associated with viral processing including autophagy, endosomal function and cellular metabolism that is needed by SARS-CoV-2 for replication (22,23). More so, mutations in CFTR, by altering the protein secretory pathway, may alter the glycosylation of ACE, ACE2 and the SARS-CoV-2 spike protein, by this reducing entry and replication of SARS-CoV-2 in CF (24).

CONCLUSIONS

Taken together, asthma and cystic fibrosis, chronic diseases with significant impact on morbidity and mortality in both children and adults, may serve as a model of factors that may mitigate the impact of SARS-CoV-2.

The complex cellular mechanism that are demonstrated to intervene in the physiopathology of COVID-19 in patients with asthma and cystic fibrosis may conduct to identification of several targets for studies that could demonstrate reduction of severity of COVID-19.

This could be leading towards new perspectives in the research of transmissibility of SARS-CoV-2 and of the complex pathogenesis of COVID-19, and finally to innovation and development of prevention strategies and new treatments.

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