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Acute Respiratory Syndrome Associated with a Novel Coronavirus (COVID-19): A Threat to Bronchial Asthma in Children and Adult

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Abstract

The coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection. Theoretically, asthmatic patients should have increased susceptibility and severity for SARS-CoV-2 infection due to a deficient antiviral immune response and the tendency for exacerbation elicited by common respiratory viruses. However, existing studies have not shown an expected prevalence of asthmatic individuals among COVID-19 patients. The interactions between COVID-19 and asthma deserve further attention and clarification.

Keywords: Asthma, COVID-19, Antiviral, SARS-CoV-2

INTRODUCTION

The coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection [1]. The World Health Organization (WHO) used the term 2019 novel coronavirus to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December 2019 [2–4]. In the early 2020, the novel corona virus originated in Wuhan, China and spread to many countries across the globe [5]. This finding is consistent with trends during the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic, caused by a virus with close sequence homology to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), during which diabetes and heart disease and not asthma were the leading comorbidities[6]. However, comorbidities found with COVID-19 fatalities may reflect confounding by age, and the Centers for Disease Control and Prevention has reported that among younger patients hospitalized for COVID-19 the most common comorbidities were obesity, asthma, and diabetes[7]. Although the role of asthma in increasing the severity of COVID-19 infections remains unclear, anxiety continues to be high among patients and their caregivers. For patients with asthma treated with inhaled corticosteroids, both the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology recommend that patients continue to use their maintenance medications even during the pandemic[8]. Continuation of therapy even with potential exposure to COVID-19 is extremely important because poorly controlled asthma is always the greatest risk factor for exacerbations with any viral infection. Elderly persons are at high risk of corona virus infection, morbidity, serious complications, and mortality. The data reported in highly affected counties such as China and Italy are highlighting the same point [9]. The main objective of this study was to identify bronchial asthma, the most common chronic respiratory disease in children and adult population, is a risk factor for COVID-19.

METHODS

Literature for this review was identified by searching the following online databases: BioRxiv, MedRxiv, ChemRxiv, Google scholar, PubMed. These online databases contain archives of most English and Chinese biomedical journals. We repeated searching the online databases to evaluate whether existing preprints may have relevant asthma information. The last update of the searches was on June 20, 2020. If sufficient studies with relevant data were found, the plan was to perform a meta-analysis by bronchial asthma status.

RESULTS AND DISCUSSION

Approximately 300 million individuals worldwide have asthma[10]. Considering that a significant proportion of asthmatics is confronted with COVID-19, it is crucial to understand which asthma patients are particularly at risk and how inhaled corticosteroids (ICS) - the cornerstone of asthma treatment - may influence morbidity and mortality associated with COVID-19. Long-term treatment with systemic corticosteroids (e.g. in transplant patients) is immunosuppressive, increasing the risk and severity of viral infections. Due to the potential risk for worse disease outcomes, the World Health Organization (WHO) does not recommend systemic corticosteroid treatment in COVID-19[11], unless if indicated for other reasons such as acute asthma or COPD exacerbations requiring a short course of oral corticosteroids. These recommendations have caused doubt and uncertainty among asthma patients and physicians on whether ICS therapy should be maintained during this pandemic. However, withdrawal of ICS treatment puts asthma patients at risk of severe exacerbations. A recent metaanalysis on COVID-19 outcomes in patients with chronic respiratory diseases using ICS concluded that there is currently insufficient evidence to abandon the well-established ICS-treatment in asthma[12].

Asthma versus COVID-19

Symptoms of COVID-19 can be similar to those of worsening asthma, or an asthma exacerbation. Dry cough and shortness of breath, commonly seen in asthma, are among the most common presenting symptoms of COVID-19 in case series of children admitted to the hospital in China, as well as in available data from the Centers for Disease Control and Prevention (CDC) in the US[14-16]. Fever, a common presenting symptom of COVID-19, may help to differentiate COVID-19 from an asthma exacerbation, although fever can be present in other virus-triggered asthma exacerbations as well[13-16]. Other less common symptoms of COVID-19, better described in the adult population, may help to differentiate COVID-19 from asthma and include myalgia, confusion headache, pharyngitis, rhinorrhea, loss of sense of smell and taste, diarrhea, nausea, and vomiting[16]. A travel history, close contact with someone infected with COVID-19, and absence of a prior atopic history in a child also help to differentiate the two.

Pathophysiology of COVID-19

SARS-CoV-2 enters the host cell through targeting angiotensin-converting enzyme II (ACE2), the same receptor as SARS-CoV [17], which might further trigger host immune responses based on previous knowledge of CoVs. After entering the cytoplasm, SARS-CoV releases genomic RNA and begins replication in the host cell. The presence of doublestranded RNA (dsRNA) can elicit an innate immune response through sensitizing Toll-like receptor (TLR)-3 and then activating type 1 interferon (IFN) production by signalling pathway cascades [19]. Type 1 IFNs are important antiviral cytokines that can induce the expression of interferon-stimulated genes (ISGs) [18]. On the other hand, the spike protein (S protein) of the virus might be recognized by TLR-4 and leadto activation of pro inflammatory cytokines through the MyD88-dependent signalling pathway, recruiting lymphocytes and leukocytes to the infection site [18]. Regarding adaptive immune responses, CoV antigens are presented to T cells by antigen-presenting cells (APCs), which leads to T cell activation and differentiation [19]. This process, which may be accompanied by massive release of pro-inflammatory cytokines, is vital for viral clearance but has the potential to induce overactivated inflammation. The pathological understanding of COVID-19 is still growing. The first published pathological report generated in 2 patients from Wuhan, China, showed edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration and multinucleated giant cells, suggesting early phase pulmonary changes [20].

Pathophysiology of Asthma

Asthma is a common respiratory disease characterized by airway chronic inflammation, mucus overproduction, hyperresponsiveness, and remodelling. Normally, the majority of the disease is predominantly mediated by type 2 immune responses. The type 2 immune response involves T helper (Th) 2 cells, type 2 B cells, group 2 innate lymphoid cells, type 2 macrophages, IL-4-secreting nature killer (NK) and natural killer T (NKT) cells, basophils, eosinophils, and mast cells [21]. A variety of cytokines produced by immune system and epithelial cells contribute to the regulatory network. For example, IL-4 and IL-13 have essential roles in allergenspecific immunoglobin (Ig) E production and accumulation of Th2 cells and eosinophils in local tissues, as well as epithelial barrier regulation, while IL-5, IL-9, and IL-13 contribute to eosinophilia and mucus production [22].

Morbidity and Mortality

The evidence on COVID-19 risk factors derives largely from the adult population. Four case series, all from Wuhan, China, of adults admitted to hospital with COVID-19 did not list asthma as an underlying preexisting condition in any of those patients [24-27]. In contrast, recent data released from the CDC of US hospitalizations in March 2020 notes that 27.3% of adults 18-49 years of age who were hospitalized with COVID-19 had a history of asthma[23]. In adults aged 50-64 years of age hospitalized for COVID-19 asthma was present in 13.2% and in those 65 years or older asthma was present in 12.9% [23,28]. As a result, the American Academy of Allergy, Asthma & Immunology notes that “those with asthma in the 18-49 year old age range may be at increased risk of hospitalization owing to COVID-19.”[28] Additional major concerns are whether therapeutics for asthma (including corticosteroids, allergen-specific immunotherapy (AIT), monoclonal antibodies, leukotriene antagonists, bronchodilators) affect the immune system, which in turn reduces COVID-19 infection, and whether these medications would influence the biological behavior of SARS-CoV-2 in the human body.

Vaccines for SARS-CoV-2

There is no available vaccine against COVID-19, while previous vaccines or strategies used to develop a vaccine against SARS-CoV can be effective. Recombinant protein from the Urbani (AY278741) strain of SARS-CoV was administered to mice and hamsters, resulted in the production of neutralizing antibodies and protection against SARS-CoV [29,30]. The DNA fragment, inactivated whole virus or live-vectored strain of SARS-CoV (AY278741), significantly reduced the viral infection in various animal models [31–36]. Different other strains of SARS-CoV were also used to produce inactivated or live-vectored vaccines which efficientlyreduced the viral load in animal models. These strains include, Tor2 (AY274119) [37,38], Utah (AY714217) [39], FRA (AY310120) [32], HKU-39849 (AY278491) [30,40], BJ01 (AY278488) [41,42], NS1 (AY508724) [43], ZJ01 (AY297028) [43], GD01 (AY278489) [42] and GZ50 (AY304495) [44]. However, there are few vaccines in the pipeline against SARS-CoV-2. The mRNA based vaccine prepared by the US National Institute of Allergy and Infectious Diseases against SARS-CoV-2 is under phase 1 trial [45]. INO-4800-DNA based vaccine will be soon available for human testing [46].

One of the RNA based vaccines (LNP-encapsulated mRNA) has been made available for the phase 1 clinical trial in humans. This vaccine has been developed by collaborative effort of scientists at NIAID/NIH and a biotechnology company (Moderna Therapeutics) in USA.

The clinical trial began in mid March 2020 and has already enrolled few patients in Seattle, USA (NCT04283461). It will study the efficacy and adverse reactions of the candidate vaccine in 45 adult volunteers from 18 to 55 years of age. Another vaccine that has gone in phase 1 clinical trial is a nonreplicating viral vector vaccine (ChiCTR2000030906). It has been bioengineered by using an adenovirus vector (type 5) at Beijing Institute of Biotechnology and CanSino Biological Inc. It uses the same platform as was used for developing a vaccine for Ebola virus. However this is just the beginning and it will take 12-18 months for the trial to complete and have the data to interpret for antibody response and long term efficacy [47].

CONCLUSION

Despite deficient antiviral immune responses and the tendency for acute exacerbation, there is little evidence showing that asthma patients have increased susceptibility or severity of SARSCoV-2 infection than others. It is particularly intriguing to explore whether features of the disease, type 2 immune response, asthma therapeutics, or all of them are capable of providing certain protective effects against COVID-19. Notably, further clinical and basic studies are expected to explore the relationship between COVID-19 and asthma and/or other allergic diseases. However, existing studies have not shown an expected prevalence of asthmatic individuals among COVID-19 patients. The interactions between COVID-19 and asthma deserve further attention and clarification.

This review summarizes scientific foundations, identifies literature gaps, and suggests some evidence for future research directions on COVID-19 which will provide information for research community, policymakers, and health professionals to adjust and/or come up with new research, policies, and practices.

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