COVID-19 and childhood asthma: First considerations

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Abstract

In these last months, besides the apprehensions that normally arise in asthmatic patients during the flu period, there is the fear of COVID-19 infection and its effects on their health. What can patients suffering asthma, both adults and children, do to better protect their health? Are they really at greater risk of infection? And if they are infected by the virus, how should behave? These are some of the questions made by scientific community. Even allergologists ask themselves these questions, but many aspects of this new disease are unknown now. From the epidemiologic data currently available it is clear that the subjects most at risk are the elderly, the immunosuppressed and the chronic patients, but it isn't equally clear whether, among these, asthmatic patients are included, even if COVID-19 is considered to be majorly responsible for respiratory disease. We can say that COVID-19 does not have a significant impact on childhood asthma, and there is no indication to radically change treatment strategies for asthmatic children. New data are emerging daily, rapidly updating our understanding of this novel coronavirus and further research is now needed to focus on different aspects of COVID-19.

Keywords: COVID-19, Children, Coronavirus

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Introduction

Between December 2019 and the first months of 2020 a novel coronavirus, initially called nCoV2019 and then SARS-CoV-2, rapidly spreads from the city of Wuhan (China) to every country around the world, causing Coronavirus Disease 2019 (COVID-19). Consequently, the World Health Organization (WHO) declared COVID-19 a pandemic infection on March 11, 2020 [1]. Thus, in these last months, besides the apprehensions that normally arise in asthmatic patients during the flu period, there is the fear of COVID-19 infection and its effects on their health [2]. What can patients suffering asthma, both adults and children, do to better protect their health? Are they really at greater risk of infection? And if they are infected by the virus, how should behave? These are some of the questions made by scientific community [3]. Even allergologists ask themselves these questions, but many aspects of this new disease are unknown now [4]. From the epidemiologic data currently available it is clear that the subjects most at risk are the elderly, the immunosuppressed and the chronic patients, but it isn't equally clear whether, among these, asthmatic patients are included, even if COVID-19 is considered to be majorly responsible for respiratory disease [5].

Literature Review

Brief overview on COVID-19 features

Seven species of coronavirus that can infect humans are currently known *CoV-229E, CoV-NL63, CoV-OC43, CoV-HKU1, MERS-CoV, SARS-CoV, SARS-CoV-2* and among them *SARS-CoV-2* is the most closely related to SARS-CoV, the coronavirus that caused the Severe Acute Respiratory Syndrome (SARS) epidemic outbreak between November 2002 and July 2003 [6]. Phylogenetic analysis has revealed that *SARS-CoV-2* and SARS-CoV share the similar functional receptor on human cells, the Angiotensin-Converting Enzyme 2 (ACE2) and this fact hints that COVID-19 may partly mimic SARS infection. ACE2 is above all expressed on type I and type II alveolar epithelial cells of the normal human lung, but also on cells of other organs. Men have a higher ACE2 level in their alveolar cells than women and Asians have higher level than Caucasian and African American populations [7].

ACE2 protects lungs from Acute Respiratory Distress Syndrome (ARDS), and when is decreased, due to interaction with virus, favours this syndrome. Reduction of pulmonary ACE2 activity contributes to the pathogenesis of lung inflammation, accompanied by the expression of cytokines that cooperate with the direct effects of viral infection [8]. Damages to alveolar cells can, consequently, trigger many systemic reactions that can lead to death. Accumulating evidence suggests that patients with severe COVID-19 infection might have a 'cytokine storm' syndrome, as seen for SARS [9,10]. Cytokines are hormonal messengers responsible for many biological effects of the immune system, such as cell mediated immunity and allergic type responses. T lymphocytes are a major source of cytokines and they have antigen specific receptors on their surface to recognize foreign pathogens, but in the case of autoimmune diseases, they can also recognize normal tissue. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as T helper cells (Th), and these are regarded as being the most prolific cytokine producers. This subset can be further subdivided into Th1 and Th2, and the cytokines they produce are known as Th1-type cytokines and Th2-type cytokines. Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. Interferon gamma (INF-γ)

is the main Th1 cytokine. Excessive proinflammatory responses can lead to uncontrolled tissue damage, so there needs to be a mechanism to counteract this. The Th2-type cytokines include interleukins (IL) IL-4, IL-5, and IL-13, which are associated with the promotion of IgE and eosinophilic responses in atopy, and IL-10, which has more of an anti-inflammatory response. In excess, Th2 responses will counteract the Th1 mediated microbicidal action. The optimal scenario would therefore seem to be that humans should produce a well-balanced Th1 and Th2 response, suited to the immune challenge [11]. As shown some years ago by a study on anatomopathological examinations of SARS victims, high levels of proinflammatory cytokines were present in ACE-2 expressing cells infected by SARS-CoV. Plasma cytokine profiles showed Th1 dominated responses with markedly elevated proinflammatory cytokine levels (INF-γ, IL-1β, IL-6, IL-8, IL-12, and Tumor Necrosis Factor-α) and were associated with the development of ARDS [12]. Although *SARS-CoV-2* is very related to SARS-CoV and so maybe have very similar mechanisms, it is a new disease that can present with varying degrees of severity, from flu-like symptoms to death and more research is needed to understand how it really acts and how these pathophysiological mechanisms can be stopped.

Asthma and viral infections

Asthma is one of the most common respiratory disease. It is a chronic inflammatory airway disease, susceptible to triggering factors, such as allergens, air pollution, and viral infections rather than bacterial one [13]. Even though advances in prevention and management, asthma is still incurable and remains a global healthcare problem and, at the same time, it is a challenge for medical scientists [14]. In the period from 1990 to 2015, the prevalence of asthma has increased by 12.6%. Now there are over than 350 million cases of asthma globally and it is estimated that about 400.000 people died from asthma in 2015 [15]. Approximately 8-9% of children and adults suffer from asthma in Europe, and it is estimated that an equal number of individuals have asthma-like symptoms [16].

Viral infections caused by different families of viruses have been scientifically proven to cause asthma exacerbations and to have an impact on the development of asthma [17-19]. A review of sixty previous studies, in 2018, examined the prevalence of viral infection in asthmatic patients, stratified by age. The results indicated that the viruses much involved during asthma exacerbations were rhinovirus (42.1%), respiratory syncytial virus (13.6%), herpes simplex virus (12.3%), enterovirus (10.1%), influenza virus (10.0%), coronavirus (8.4%), cytomegalovirus (7.2%), bocavirus (6.9%), parainfluenza virus (5.6%), metapneumovirus (5.3%) and adenovirus (3.8%). Enterovirus, metapneumovirus, rhinovirus, respiratory syncytial virus was more prevalent in children, whereas adenovirus, bocavirus, coronavirus, influenza virus and parainfluenza virus were more frequently present in adults [20]. Asthma has long been considered a Th2 cell-mediated disease. Indeed, it often occurs in patients who have atopy, the genetic tendency to produce immunoglobulin E (IgE) to common allergens, a process driven by IL-4. Eosinophils and CD4 cells producing IL-5 are frequently found in the blood and lung lavage fluid of asthma patients. In the past years, trials on mouse models of asthma convincingly showed that many of asthma features were abolished in animals genetically lacking the Th2 cell cytokines IL-4, IL-5, and/or IL-13 [21]. On the other side, in other studies, administration of IL-12 had the potential to suppress asthma in mice, by producing IFN-γ from Th1 [22].

This concept of Th2 cell-mediated immunity to allergens driving asthma pathogenesis has dominated over the last 30 years and, importantly, has pushed forward treatments that target Th2 cell cytokines [23]. However, asthma is a much more complex syndrome with various pathophysiological mechanisms, and it has also been found that besides Th2 cells, other innate immune cells like basophils, mast cells, and type 2 innate lymphoid cells can produce Th2 cell-associated cytokines in asthma [24]. Asthma is also highly heritable disease and genetics can, then, be considered an important tool to better understand its mechanisms. The knowledge of genetic background of asthma has rapidly increased, during recent years, thanks to advances that allow Genome Wide Association Studies (GWAS) with whom millions of genetic variants, covering the entire genome, can be tested without a prior hypothesis about underlying mechanisms. As result, scientists have now identified more than 100 genes/loci associated with asthma [25]. Other studies are necessary to completely understand the genomics of asthma, in fact, more information's on gene variants, gene expression and epigenetics are needed. These studies are a challenge and have the potential to reveal unknown pathophysiological mechanisms and functional subtypes of asthma, that is essential to personalize and improve treatment and prevention of the disease [26].

COVID-19 infection: Differences between children and adults

In March 2020 the first important epidemiological report from China on 2135 paediatric cases (728 confirmed and 1407 suspected) reported a lower frequency of serious (5.2%) or critical (0.6%) cases in children compared to the adult population (18.5%), but among them has been reported a high percentage (10.6%) of infants. Almost 13% of confirmed cases were asymptomatic. Only one death has been reported. These are the first numerically consistent, but still raw, data on the spread of this disease in childhood (2/3 of children had just clinical diagnosis and cannot be excluded they had other viral infections) [27]. Further reports from Wuhan area confirm that paediatric positive cases show often asymptomaticity (15.8%), indeed, more than half (58.5%) of these children presented apyrexia, which probably has been the cause for the low percentage of children diagnosed with COVID-19 infection in the first weeks of the epidemic (only 1% of patients under 10 years old reported on 44,672 cases till February). At the end of March, the population under 18 years old in China constituted 2.4% of all reported cases (over 80,000). In the most serious cases that have been described, the prevalent symptoms are polypnea, fever and cough with multiform radiological pictures ranging from unilateral pneumonia (19%) to 'frosted-glass'

images (32%) typical of interstitial disease. Plasma increase of proinflammatory cytokines (IL-6, IL10, IFN-γ): the so-called 'cytokine storm' responsible for lung damage, as we have seen before [28]. Cardiovascular, endocrine, and digestive system diseases are commonly reported co-morbidities; however, cases of pre-existing chronic respiratory diseases are surprisingly low at this time (<2% of patients from China) [29]. Thus, there is no evidence, till now, that asthmatic patients, either children or adults, can be majorly at risk, neither that can develop pneumonia more easily nor be more prone to hospitalization for COVID-19 [30-32]. For what concerns asthmatic patients, a group of researchers has speculated that their Th2 immune response may counter the inflammation process induced by COVID-19, that is the Th1-mediated 'cytokine storm', reducing de facto the severity of infection. Further studies are of course required to describe the human immune response to inflammation caused by the virus [33]. To summarize, clinical manifestations of paediatric patients are generally less severe than those of adult patients. At now, we can say that children of all ages are susceptible to COVID-19, but no significant gender difference has been found. However, a young child, particularly infants, seems more vulnerable to COVID-19 infection than elder children and asthmatic patients seem not more at risk than other patients [34]. There are, however, many urgent questions that need answers: why does COVID-19 preferentially affect adults, particularly the aged? Are there differences in immune response between adults and children to COVID-19? If yes, which ones? We know that, even during SARS epidemic outbreak of 2003, children appeared to be less susceptible to the SARS coronavirus than adults. From an anatomopathological study on lung samples of SARS adult patients, a giant-cell infiltrate, composed by cells of monocyte or macrophage lineage fused together was seen with a pronounced increase in macrophages in the alveoli and the interstitial of the lungs [35]. This infiltrate was different from the infiltrate seen in non-SARS ARDS, which comprises activated neutrophils (with increased IL-8 levels) and which can occur in both adults and children [36]. It has been supposed, therefore, that activated macrophages played an important role in severe SARS and maybe the lack of activation of macrophages by SARS-CoV would be the reason why children do not develop severe SARS. Although children are vulnerable to non-SARS coronaviruses, it was rightly thought that SARS-CoV used different receptors from other coronaviruses [37].

Macrophages are cells with phagocytic activity that can be stimulated and activated by bacterial products, neuropeptides, neurohormones, cytokines, and other stimuli and can release large amounts of proinflammatory cytokines, nitric oxide, biogenic amines, neuropeptides, hormones, among others. According to a very interesting theory called "Inflamm-aging", macrophage plays as central actor not only in the inflammatory response and immunity, but also in the stress response. This hypothesis suggests the existence of a direct relation between stress and age with macrophage activation, mostly responsible for the presence of a subclinical chronic inflammatory process in the elderly. This phenomenon is only part of the whole spectrum of change characteristic of immune-senescence, and indeed the macrophage is not the only cell involved in the aging process [38]. Another aspect that has been proved in the aging process are the increased plasma levels of IL-6. These levels are low or undetectable in most young people and start to increase in healthy people at about 50-60 years of age and the increment of IL-6 plasma levels appears to be unexpectedly present in both persons who enjoyed good aging and those who suffered pathological aging. Very high levels of IL-6 are found in a high percentage of centenarians in good shape and even proinflammatory cytokines are similarly increased. These high levels have been referred to as the most powerful predictors of morbidity and mortality in the elderly [39].

Other researchers noted that the cytokine profile associated with COVID-19 resembling to Secondary Haemophagocytic Lymphohistiocytosis (sHLH) an under-recognised hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In 7 adults, sHLH is most triggered by viral infections. Its features include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients [40]. Predictors of fatality from a recent retrospective study of 150 confirmed COVID-19 cases included elevated IL-6 levels, suggesting that mortality might be due to virally driven hyperinflammation [41]. Moreover, it is interesting to note that the number of ACE2 receptors normally decreases throughout life and this event can easily expose lungs to damages from stress or from infections [42].

Management of asthma during COVID-19 pandemic

The available data here analysed reveal that patients suffering from asthma seem to be at no greater risk of infection with COVID-19 than others. However, should infection occur, this underlying condition may worsen the disease course of COVID-19. In effect, any lung infection risks worsening the symptoms of asthma, such viral infections that can be a strong trigger for exacerbations. Patients must, first, diligently respect all usual precautionary measures (wash hands often, keep a safe distance, limit movement, etc). Then it is possible and necessary to keep asthma under control through an adequate control plan, which allows reducing exacerbations. This is very important because it is difficult to distinguish if symptoms such cough, wheezes and other related breathing difficulties are potentially caused by asthma or by the virus and if COVID-19 infection is suspected the use of systemic steroids must be avoided [43,44]. In fact, has been reported that 3 patients with asthma that received systemic steroids for a week for presumed asthma exacerbation, were subsequently admitted to the ICU with severe respiratory failure requiring invasive mechanical ventilation [45]. Previous studies have shown that systemic steroids can be associated with a higher subsequent viral load, resulting in worse clinical outcomes in previous coronavirus outbreaks (SARS-CoV and MERS-CoV) [46,47]. There are not many case reports, but it is advisable to continue the normal treatments underway and contact clinicians to check the therapeutic plan or modify it if necessary, even by telemedicine consultation if it is possible. There is only a report with two

paediatric patients with a history of allergic rhinitis and atopic dermatitis, they presented as ordinary types of COVID-19 and were both treated with interferon-α inhalation as a nonspecific antiviral therapy, which was one of the trial methods recommended in the practice guidance of novel coronavirus pneumonia in China. They get well and admission to ICU was not necessary. This shows once again that allergic diseases and young age may not be an aggravating factor of the disease [34,48,49]. Finally, given the current crisis, it is natural for some to feel sad, confused, frightened, or stressed. Anxiety and stress conditions can trigger asthma attacks in asthmatic patients. To better manage these emotionally complex situations it is necessary to maintain a healthy lifestyle (proper diet, sleep, exercise, relaxation exercises), feed contacts with family and friends via email or phone, avoid other triggers such as smoking, alcohol and drugs, stay informed avoiding overexposure to news and seek help when necessary.

Discussion and Conclusion

Children can be affected by COVID-19 and present with mild and, generally, less severe respiratory symptoms than in adults. The percentage of paediatric cases is certainly underestimated. Admission of children to Intensive Care Unit (ICU) is rare and prognosis is almost always favourable except in very few cases. A more difficult course of disease can be present in infants, as well as in children with pre-existing chronic pathologies. Cardiovascular, endocrine, and digestive system diseases are commonly reported co-morbidities (especially hypertension and diabetes), however, cases with pre-existing chronic respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and asthma are, at the moment, surprisingly low. We can say that COVID-19 does not have a significant impact on childhood asthma, and there is no indication to radically change treatment strategies for asthmatic children. Furthermore, regarding asthmatic children, it is recommended to continue their therapies without making any dose adjustments. It is better to avoid systemic steroids, because it has been shown that they can compromise the prognosis of the affected patients. New data are emerging daily, rapidly updating our understanding of this novel coronavirus and further research is now needed to focus on different aspects of COVID-19.

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