COVID-19 and Children Innate Immunity

Subjects: Respiratory System

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the pandemic viral pneumonia that was first identified in Wuhan, China, in December 2019, and has since rapidly spread around the world. The number of COVID-19 cases recorded in pediatric age is around 1% of the total. The immunological mechanisms that lead to a lower susceptibility or severity of pediatric patients are not entirely clear. At the same time, the immune dysregulation found in those children who developed the multisystem inflammatory syndrome (MIC-S) is not yet fully understood.

Keywords: COVID-19 ; children ; coronavirus ; innate immunity ; SARS-CoV-2 ; pandemic ; MIC-S

1. Introduction

The clinical presentation of SARS-CoV-2 infection in children is mild in most cases [1], although disease progression toward more severe forms is possible. The number of cases recorded in the pediatric age is around 1% of the total. Because of the usually mild clinical presentation, this percentage mainly refers to the few symptomatic patients or tests performed for contact tracing, and could therefore be underestimated [2]. There are several theories about the differences of COVID-19 severity in children and adults, based on the type of immune response, different levels of the expression of angiotensin-converting enzyme (ACE) 2 receptor (necessary for viral adhesion and replication), or the competitive action of other respiratory viruses that colonize the nasopharyngeal mucosa in the pediatric age [3]. However, there is currently insufficient evidence to confirm these hypotheses. It has been shown that children with COVID-19 have a stronger innate immune response in the nasopharyngeal mucosa than adult patients, which is associated with a greater expression of several cytokines (such as IL-17A, interferon (IFN) gamma, IFN-alpha2, IL-1b, IL-8, and IP10) [4], which could partially explain the lower susceptibility to infection. The CONFIDENCE research group [5], analyzing 170 Italian children with a confirmed diagnosis of COVID-19 in 17 different Italian pediatric emergency departments, showed that the most frequent clinical presentation was ill appearance (12%), fever (48%), cough, (73.43%), problems with feeding (42.35%), and rhinorrhea (34.20%); less common symptoms were apnea, cyanosis, headache, and dehydration. Although the SARS-CoV-2 disease mainly affects the respiratory system, gastrointestinal manifestations are also possible (mainly represented by diarrhea and abdominal pain), which may appear at the onset of the disease or later. [1] Similar data on clinical presentation have been reported in other countries [6][7]. In addition to the clinical impact, this disease has had a psychological influence on children: the lack social interactions has increased the incidence of anxiety, lethargy, and depression [8]. Furthermore, the closure of schools in many countries of the world, such as in Italy, has contributed to the exacerbation of these problems [9].

2. Immune Dysregulation and Sars-CoV-2 Infection

A minority of children who contract the infection may develop an intense inflammatory response caused by the cytokine storm induced by Sars-CoV-2, called “multisystem inflammatory syndrome in children and adolescents temporally related to COVID19”, also known as MIS-C [10]. Initially described as a variant of Kawasaki disease, due to frequent cardiac impairment, it has been associated with several other inflammatory diseases such as acute rheumatic fever (ARF) or toxic shock syndrome (TSS) [11]. MIC-S is defined by the presence of more than 3 days of fever in children aged up to 19 years, diagnosed with COVID19 infection or confirmed contact with a positive case, increased inflammation indices in the absence of other microbial cause of inflammation, and at least two clinical signs (skin rash or muco-cutaneous inflammation signs, hypotension or shock, cardiac involvement, coagulopathy, and gastrointestinal symptoms) [12]. In addition to the alterations previously described, this syndrome may cause thrombocytopenia, elevation of the D-dimer, prolonged prothrombin time, and Blood Natriuretic Peptide (BNP) levels correlated inversely with cardiac ejection fraction [13], worsening the prognosis of affected children. Although the immune response, especially the innate immunity, is essential for controlling the early stages of infection, severe forms of MIC-S require modulation to prevent the development of complications [14]. Despite massive systemic involvement, cases of acute respiratory failure are much

rarer than in the adult population, even in severe forms of MIC-S. Among the various theories, we know that there is a distinct antibody response in children with MIS-C compared with adults with severe COVID-19, because MIS-C predominantly generated IsgG antibodies specific for the spike (S) protein but not for the nucleocapsid (N) protein, while the adult COVID-19 cohorts had anti-S IgG, IgM, and IgA Abs, as well as anti-N IgG Abs [15].

Despite the similarities in the clinical presentation of multisystem inflammatory syndrome in children and Kawasaki disease, these two entities differ in biochemical manifestations, like IL-17A-mediated hyperinflammation in vasculitic disease, but not MIS-C [16]. These findings suggest a different endothelial involvement and immunopathology in these two syndromes. MIS-C patients also had a reduced neutralizing activity compared with other COVID-19 patients, probably caused by a reduced protective serological response [15].

3. Vaccination

There is currently no relevant evidence on the safety of Sars-Cov-2 vaccination in children under sixteen/eighteen years of age because the studies necessary for the marketing of the various vaccines did not include, at least in this first phase, the pediatric population or pregnant women. The debate is also open on immunosuppressed patients (children but also adults), who do not seem to manifest more severe forms than the general population [17]. Vaccine strategies for COVID-19, as for some other respiratory viral infections, also require additional safety considerations related to the possibility of antibody-dependent enhancement of the disease [18]. Several scientific societies, such as the Italian Society of Neonatology, have come out in favor of vaccinating pregnant and breastfeeding women [19], while there are no official recommendations for children, although alternative strategies that indirectly focus on protecting children by providing immunization of key categories strictly related to childhood (e.g., doctors, teachers, and grandparents) have been suggested [20].

4. Conclusions

Sars-Cov-2 disease, in the current state of knowledge, often has a mild severity in pediatric age patients. The immune system, especially the innate one, partly explains the lower susceptibility of children to this new pathology; despite this, immune dysregulation can lead to severe forms of COVID-19, even in pediatric patients. To even more complicated the understanding of COVID-19 in the pediatric population even more complicated, recent studies have described the presence of long COVID in children, a scenario possibly characterized by a specific long-lasting inflammatory/immunological dysregulation that still needs to be understood [21]. Future studies should aim to investigate the relationship between the underlying immune profile and susceptibility to infection, disease severity, and development of long COVID, in order to highlight which children are most at risk of contracting the virus and experiencing disease progression, with worsening clinical outcomes, and personalize the management.

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