A Review on the Novel Coronavirus and Its Effects on Children

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Abstract

BACKGROUND: The outbreak of the new coronavirus was first reported in China and then spread to other parts of the world. The number of people infected with the virus is significantly increasing, making the disease an international concern.

AIM: The present study aimed to investigate the coronavirus and its effects on children.

MATERIALS AND METHODS: In the present study, search engines, and scientific databases of Google Scholar, Science Direct, PubMed, Medline, and Cochrane were searched to examine the effect of coronavirus on children. To collect information, keywords were also searched in the databases.

RESULTS: In spite of contradictory results, among the children, those under 5 years old are the high-risk group.

CONCLUSION: Some researchers believe that the virus shows fewer symptoms in children. However, the immune system of infants under six months develops pneumonia in rare cases.

Introduction

Coronavirus (CoV) is a severe infectious agent in human and animal, which causes systemic disorder in respiratory and gastrointestinal tracts. CoV can infect certain species of animals, including mammals, bird, and reptiles [1]. On January 3, 2020, a new member of the CoV enveloped RNA was identified in bronchoalveolar lavage fluid samples of a patient in Wuhan and subsequently confirmed as the cause of the disease by the Centers for Disease Control and Prevention (CDC, China) [2]. The pathogenicity of this virus is that after the virus enters the body, it first binds to specific receptors on the cells with proper binding feature. Then, it enters the cell and uses its transcription machinery, multiplying it in large numbers and causing cellular damage [3].

Most of the patients are adults, with a small number of children. Out of 44,672 laboratory-confirmed cases of COVID-19 in China, only 2.1% are under 19 years old.

Studies have shown that COVID-19 has the highest mortality in the elderly. It also causes mild-to-severe respiratory problems in children, with mortality and morbidity lower than other age groups. Most children patients show mild symptoms, with no fever or signs of pneumonia [4], [5], [6], [7].

Given that one of the concerns of the health sector regarding the dangerous consequences of CoV is the dangers of this disease in a vulnerable community of children. There are many questions about the effect of the virus and ways to prevent children from getting the disease. An important issue is recognizing the virus and providing a reliable treatment strategy such as vaccination. Therefore, in the present study, an attempt is made to examine its effect on children and the proposed treatment options by examining the published articles on COVID-19 and the development of new CoV in children.

Materials and Methods

Search strategy

This evaluation was conducted in January and February 2020. Search engines and scientific databases of Google Scholar, Science Direct, PubMed, Medline, and Cochrane were used for obtaining papers on CoV and its effect on children. The keywords were also searched in the databases to collect information on the CoV, including corona, CoV and children, CoV pathogenesis, the virus structure, and COVID-19.

Priority was given to articles from the past year. A reference list of relevant articles was searched to identify additional articles. In addition, search engines such as Google and Google Scholar were used to identify all potential eligible publications. The operators were used to find related articles. The study was conducted from July 5, 2020, to September 5, 2020.

Inclusion and exclusion criteria

Inclusion criteria included articles published after December 1997 to the end of January 2020, qualitative, descriptive, analytical study and articles published in English and Persian. Editorial letters, case studies, and clinical studies were excluded. Furthermore, articles with inadequate reports and a study whose full text was not available were excluded from the study.

Screening and data mining

A trained author performed search strategies. In the first stage, the titles and abstracts were reviewed for the selection of articles, in the next stage, an author independently reviewed the full text of the articles. Differences in findings were resolved through the criterion method of general conclusion of articles and in this study, were organized. Qualitative evaluation of articles was done by preparing a list of titles and summaries of studies in databases and selecting them based on the purpose of the study and content.

CoVs

CoVs are a large family of viruses that cause a flu-like illness in birds and mammals, accounting for 15–30% of common colds. They are spherical or polymorphic viruses containing a positive-sense single-stranded RNA with protein capsid nucleoprotein. There are several CoVs common between human and animal that usually cause mild-to-moderate infections in upper respiratory tract, such as the common cold. The virus rarely evolves and transmits from other animals to human. COVID-19 is a mutant of the CoVs family [2], [8].

The recombination rate of the virus is high because of the RNA-dependent RNA polymerase transcription (RdRPs) and constant transcription errors. However, despite the high mutation, CoVs are a zoonotic pathogens that vary between human and animal with a wide range of clinical manifestation from asymptomatic to requiring hospitalization due to infection in the respiratory, gastrointestinal, liver, and nervous systems [9], [10]. CoV is structurally related to middle East respiratory syndrome and severe acute respiratory syndrome (SARS).

CoV, SARS, and MERS

6LU7 is the COVID-19 main protease (Mpro), which been structured and repositioned in PDB and can be accessed by the public, as of early February 2020. The Mpro of 2019-nCov shares 96% similarity with the Mpro of the SARS-CoV [11]. The Mpro in CoV is essential for the proteolytic maturation of the virus and has been examined as a potential target protein to prevent the spread of infection by inhibiting the cleavage of the viral polyprotein [12]. The discovery of the structure of the Mpro proteinase in COVID-19 provides an excellent opportunity to identify potential drug candidates for treatment.

Proteins represent potential targets for the inhibition of CoV replication, and the protein sequences of the SARS-CoV Mpro and 2019-nCoV Mpro are 96% identical, and the active sites in both proteins remain free from mutation. Thr24, Thr26, and Asn119 amino acids are predicted to be involved in drug interactions [13]. Therefore, usually, host proteases can be used as potential therapeutic targets. In many viruses, proteases play important roles in viral replication; therefore, proteases are commonly used as protein targets during the development of antiviral drug treatment [14].

Nelfinavir and lopinavir are protease inhibitors with high cytotoxic against HIV-infected cells. Lopinavir and ritonavir are protease inhibitors recommended for the treatment of SARS and MERS, which have similar mechanisms of action as HIV. The antiviral effects of nelfinavir on CoV have been studied *in vitro*, in Vero cells infected with SARS-CoV [15], [16]. It is important to pay attention to how infection develops in COVID-19 disease.

Infection

Scientists exploring how CoVs like COVID-19 infect human cells have shown that the SARS-CoV-2 spike (S) glycoprotein binds to the cell membrane protein angiotensin-converting enzyme 2 (ACE2) to enter human cells. COVID-19 has been shown to bind to ACE2 through the S protein on its surface. During infection, the S protein is cleaved into subunits, S1 and S2. S1 contains the receptor binding domain (RBD) which allows CoVs to directly bind to the peptidase domain (PD) of ACE2. S2 then likely plays a role in membrane fusion. Chinese researchers have now used cryogenic electron microscopy to study the structure of the ACE2 when it is bound to one of its typical ligands, the amino acid transporter B0AT1, and also how the COVID-19 RBD may bind to the ACE2-B0AT1 complex. These structures have previously not been identified and could aid in producing antivirals or a vaccine that can block CoV infection by targeting ACE2 (Figure 1) [3].
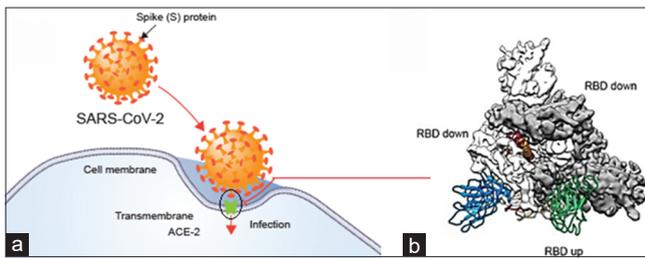
Figure 1: (a) Connection of the S1 receptor to the ACE2 receptor on the pulmonary cells. (b) Three-dimensional structure of the coupled receptor. S1 contains the receptor binding domain which allows coronaviruses to directly bind to the peptidase domain of ACE2

The signs, symptoms, disease progression, and severity

Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. As of February 20, 2020, and based on 55,924 laboratory-confirmed cases, typical signs and symptoms include fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%) (WHO, 2019).

People with COVID-19 generally develop signs and symptoms, including mild respiratory symptoms and fever, on an average of 5–6 days after infection (mean incubation period 5–6 days, range 1–14 days) (WHO, 2019).

Most people infected with COVID-19 virus have mild disease and recover. Approximately 80% of laboratory confirmed patients have had mild–to-moderate disease, including non-pneumonia and pneumonia cases, 13.8% have severe disease. Asymptomatic infection has been reported, but the majority of the relatively rare cases who are asymptomatic on the date of identification/report went on to develop disease. The proportion of truly asymptomatic infections is unclear but appears to be relatively rare and does not appear to be a major driver of transmission. People at high risk for serious illness and death include people over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer. Disease in children appears to be relatively rare and mild, with approximately 2.4% of all reported cases among cases under 19 years old. A very small proportion of those under 19 had severe (2.5%) or critical (0.2%) disease [17], [18], [19].

Mortality increases with age, with the highest mortality among people over 80 years of age (case fatality rate [CFR] 21.9%). The CFR is higher among males compared to females (4.7% vs. 2.8%). By occupation, patients who reported being retirees had the highest CFR at 8.9%. While patients who reported

no comorbid conditions had a CFR of 1.4%, patients with comorbid conditions had much higher rates: 13.2% for those with cardiovascular disease, 9.2% for diabetes, 8.4% for hypertension, 8.0% for chronic respiratory disease, and 7.6% for cancer [19].

CoVs in children

According to a new study, CoV disease 2019 (COVID-19) has shown mild symptoms among children in China. However, the young age group is not entirely aware of the virus. Infants had a higher disease rate than older children. It is suggested that further investigation is needed to understand the role of children in the spread of the virus in the community. Approximately 75% of suspected children had COVID-19. Regarding the gender, no significant difference was observed. Approximately 4% of children patients were asymptomatic, 51% had mild and 39% had moderate symptoms. Moreover, compared to 18.5% of adults, approximately 6% of children showed severe or critical condition (with a 14-year-old boy dead). The gap is perceived to be confusing to researchers, suggesting that it may be related to both exposure and host factors. Several reasons were proposed, including (a) children's low exposure to the virus; (b) high levels of antibodies against viruses; and (c) developing different immune responses. The virus may also not bind to children's cells. The present study also found that the illness in infants is more serious than in older children. Compared to 7% of children aged 1–5 years, only 11% of infants had severe or critical condition [20]. A similar study suggested that children are more susceptible to upper respiratory tract involvement rather than lower respiratory tract involvement. There is also evidence of stool shedding for several weeks after diagnosis leading to concerns about oral–fecal transmission of the virus, especially in infants and toddlers who are not toilet trained, and for viral replication in the gastrointestinal tract [6].

Data on individuals aged 18 years old and under suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). Within Wuhan, among testing of ILI samples, no children were positive in November and December of 2019 and in the first 2 weeks of January 2020. From available data, and in the absence of results from serologic studies, it is not possible to determine the extent of infection among children, what role children play in transmission, whether children are less susceptible or if they present differently clinically (i.e., generally milder presentations). The Joint Mission learned that infected children have largely been identified through contact tracing in households of adults. Of note, people interviewed by the Joint Mission Team could not recall episodes in which transmission occurred from a child to an adult [19].

Clinical manifestations

The virus was found in pediatric patients, from 1-month-old infants to 19 years old, and based on the evidences, most have been infected by family members [4]. General symptoms of the early patients included fever 98%, cough 76%, muscle aches or fatigue 44%, shortness of breath (in 2 months old infants, with cough, difficulty breathing, and breathing faster than 60/min; in 1–5 years old infants, with cough, difficulty breathing, and breathing faster than 40 breaths/min) 55%, and acute respiratory distress syndrome (ARDS) 29%. In another study, lymphopenia (a decrease in the number of lymphocytes in the blood) was seen in 80% of adult patients, while <25% of children patients had mild lymphopenia, indicating the severity of infection in these patients. Chest computed tomography (CT) of children showed only one patient with bilateral ground-glass opacity, as in adults [5]. In another report by Xia on 20 children, 70% of cases showed leukopenia, 10% leukocytosis, and 35% lymphopenia. Eight cases were found to be infected with other respiratory pathogens such as mycoplasma and influenza. Lung scan also showed 10 abscesses on both sides of the lung. In 6 cases, only one side of the lung had abscess, and in 12 cases, there observed ground-glass opacities [21].

General symptoms include fever 99%, dry cough 59%, and muscle pain or fatigue 70%. Furthermore, 26% of patients were transferred to ICU and 4% of them died. Interestingly, 41% of patients were infected in hospitals. Severe cases of ARDS and acute kidney failure have also been reported. Symptoms the patients may develop include increased C-reactive protein (CRP) protein, erythrocyte sedimentation rate, lactate dehydrogenase, creatinine, and prothrombin clotting time [17]. Another study by Wei *et al*. indicated that all children were infected by their family members, showing mild symptoms [22].

Inflammatory markers including CRP and procalcitonin showed a 13.6% and 10.6% increase, respectively [10]. After studying four infected children, two showed respiratory disorder and one severe decrease (1 mg/L) in CRP. It is while both proteins in the progressed stages significantly increased in adults [23]. Children CT showed opacity in different regions. The damage was largely similar to that of adults (Figure 2). An important issue was the change in CRP protein and lymphocytes, in which, while the latter had many changes, the former changed a little, indicating a significant difference compared to adults [23], [24].

Important points

There are several salient points from this article. First, although children are less likely than older adults to become severely ill, there are subpopulations of children with an increased risk for more significant illness. These data on disease severity are consistent with data on non-COVID-19 CoVs. The authors of one viral surveillance study in a PICU in China reported that CoV was detected in more children with ARDS than *Human metapneumovirus* [27]. The authors of another study conducted on hospitalized Norwegian children detected CoVs in 10% of hospitalized children with respiratory tract infections [6]. Younger age, underlying pulmonary pathology, and immune compromising conditions have been associated with more severe outcomes with non-COVID-19 CoV infections in children [28].

Second, the attributable risk for severe disease from COVID-19 in children is challenging to discern. The previous studies have revealed that children from whom CoVs are detected from the respiratory tract can have viral coinfections in up to 75% of cases [27]. In the study by Dong *et al*. [4], testing for other viruses was not standardized, and two-thirds of cases were clinically diagnosed, not virologically confirmed. In addition, children without virological confirmation were more likely to have severe disease than children from whom COVID-19 was detected, potentially because their symptoms were caused by other pathogens [29].

Third, children may play an important role in community-based viral transmission.

Fourth, most children are at a high level of immune function. According to studies, while the lymphocytes had many changes, the CRP protein changed a little [24]. Studies showed that an increase in lymphocytes is associated with specific immunity. In people with stronger immune system, lymphocytes, especially T lymphocytes, act more rapidly and specifically eliminate the pathogen. On the other hand, in people with weaker immune system, COVID-19
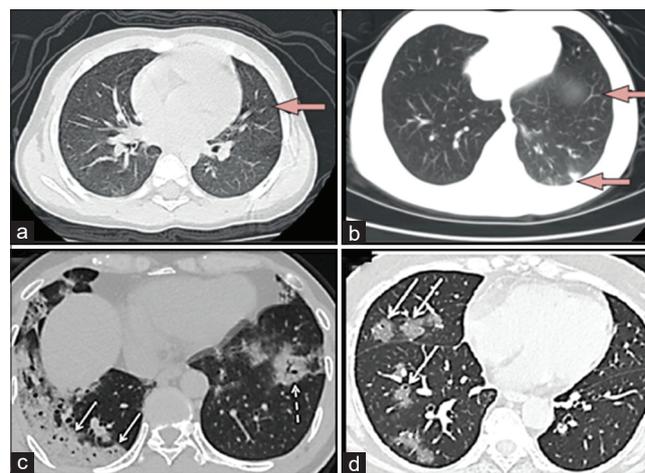

Figure 2: (a) Computed tomography (CT) of a 10-year-old boy showing multiple opacities in lower lobes of both lungs (arrow); (b) CT of a 1.5-year-old girl showing multiple ground-glass opacities with a big patchy opacity in the right lung (arrows); (c) an axial CT image obtained without intravenous contrast in a 42-year-old male in the "late" time group (10 days from symptom onset to this CT) shows bilateral consolidative opacities, with a striking peripheral distribution in the right lower lobe (solid arrows), and with a rounded morphology in the left lower lobe (dashed arrow); (d) an axial CT image obtained without intravenous contrast in a 56-year-old female shows ground-glass opacities with a rounded morphology (arrows) in the right middle and lower lobes. The left lung was normal [25], [26]

exacerbates inflammation by causing pneumonia and increased cytokines. Similarly, the SARS virus is associated with a sharp decrease in the number of T-cells in the blood [30], [31], [32], [33]. The bottom line is that most children produce less inflammatory protein because of their immune system, and instead lymphocytes do their job. However, in people with weaker immune system, especially adults and the elderly, inflammatory proteins are produced, increasing the inflammation and worsening of CoV.

Specific safety in children and COVID-19

The human immune system is a complex network of specialized cells, tissues, and organs that are responsible for identifying and eliminating pathogens. Intrinsic and specific immune systems are the two main parts of the immune system. Intrinsic immunity is a general defense system consisting of inhibitory factors such as mucosa and skin and a specific immune system composed of cells that, with advanced mechanisms, identify only certain pathogens. In viral infection, T lymphocytes play the most important role in specific immunity. In summary, these viruses are specifically identified and killed by lymphocytes in a very complex cellular response [34], [35], [36]. Normally, after detection of viral compounds by cellular receptors, an appropriate and effective antiviral response is initiated by the immune system, which includes the production of a variety of cytokines and immune and inflammatory responses. Interferons I (IFN_β and IFN-α molecules) are key cytokines produced after virus infection that induces the onset of an immune response and subsequent adaptation [37], [38]. The immune response to the CoV is that CoV infects macrophages and then the macrophages deliver CoV antigen to the T cell. This process leads to the activation and detection of T cells and the increase in the production of various cytokines, followed by the widespread release of cytokines to enhance the immune response. Continued production of these mediators has a negative effect on NK function and T cell activation [38].

In people with stronger immune systems, lymphocytes, especially T cells, act more rapidly and specifically kill the pathogen. However, in people with a weaker immune system, COVID-19 causes acute inflammation by causing pneumonia and increasing cytokines and decreasing T cells [30], [39], [40].

This suggests a large role for lymphocytes in specific immunity in relation to their impact on the recovery of corona disease. The important results of the reviewed articles show that there are a large number of T cells in children, which have an impact on the quality of function of the specific immune system in children. In many children, milder symptoms have been observed than in adults due to the specific function of the immune system [24]. The reason for the strength of the immune system of children compared to adults can be summarized in several issues. First, children are exposed to a variety of pathogens for the 1st time in the early years of life, and second, children have the ability to rapidly produce natural antibodies with broad reactivity that has not yet been selected and shaped by the reaction to common environmental pathogens that are more prepared to fight T cells in the body [41], [42], [43].

Treatment

A recent paper reports the inhibitory effect of Ramsdevir (a new antiviral drug) and chloroquine (an old antimicrobial drug) on the growth of SARS-CoV-2 *in vitro* and an initial clinical trial conducted on Chinese patients with COVID-19. It was also shown that chloroquine had a significant effect on the clinical outcome and clearance of the virus compared to the control groups [44].

Chinese experts recommend that patients with mild, moderate, and severe COVID-19 pneumonia without chloroquine contraindication be treated with 500 mg of chloroquine twice daily 10 days. On the other hand, 18,264 (24%) reported cases have improved as of February 20. An encouraging report on February 20 from the Guangdong CDC indicated that out of 125 severe cases, 33 (26.4%) were recovered and discharged and 58 (46.4%) recovered and classified as mild/moderate cases (i.e., + mild pneumonia). Of course, there have also been severe cases, with 13.4% of deaths so far. Early detection and contact with physician may improve treatment [19].

Other adjunctive treatments in China with the help of Chinese medicine have been performed on COVID-19 patients, including use of antioxidants. The current studies in China show that antioxidants are effective in boosting the immune system and reducing inflammation in patients with COVID-19 [45], [46], [47]. Another treatment currently under trial is the production of the vaccine; however, because of the consecutive mutations in the viral antigens, the investigations mostly focused on inhibiting the protease enzymes of the virus [15], [48]. Plasma therapy is another solution that the US Food and Drug Administration and WHO are looking for. It uses blood antibodies from the recovered patients, which is still in the experimental phase [49], [50].

Studies on children recommended the use of therapeutic drugs in reasonable and lowest doses at different ages, and like adults, antioxidants are the priority. In a study conducted in Wuhan, China, the use of antioxidants was recommended as adjunctive therapy for the entire high-sensitivity groups [45], [47], [47], [51].

Conclusion

Children are also diagnosed with COVID-19 like adults. Despite the low prevalence of the disease in

children, the issue of prevention and immunosuppression in children is very important. The findings showed that children responded better to CoV than adults because of specific immune function in children.

Many studies have been published focusing on epidemiology, etiology, clinical manifestations, and diagnosis, prevention, and control. However, studies examining prevention and control measures have gradually increased. Government agencies have rapidly incorporated recent scientific findings into public policy at the community, regional, and national levels to slow or prevent further expansion of COVID-19. Our suggestion is to evaluate the difference in children's immune system function in the face of CoV compared to the adults and to provide treatment options for children and those with weaker immune systems. It is also proposed that the scientific community conducts further studies to provide valid and effective ways to manage this type of public health hazard both short and long term.

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