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Characteristics of COVID-19 Infection in Paediatric Patients: A Narrative Review

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ABSTRACT

Aims The COVID-19 pandemic has been a global crisis for more than two years, which caused an immense global burden on economy, health care and education. More than 250 million people have been infected with this novel virus, among which more than 5 million have died. Prevention is the best strategy against COVID-19 infection in both children and adults. This narrative review aimed at summarizing the important epidemiological and clinical findings of COVID-19 infection and its transmission, clinical manifestation, laboratory findings, radiographic findings, and diagnosis.

Conclusion Reports have shown that paediatric patients are often exposed to the SARS-CoV-2 virus through a family member, and that COVID-19 infection is a serious threat to this vulnerable age group. Milder or asymptomatic manifestations of this new disease in younger patients should not cause this population to be neglected. Numerous epidemiological and clinical studies have reported the burden of this novel infection in children and the chance of severe forms of infection, hospitalisation, and admission to ICU. However, many aspects of pathophysiological and immunological mechanisms regarding COVID-19 infection in children are still unexplained. Clinical characteristics of COVID-19 infection is different in children compared to adults, and a comprehensive knowledge regarding this distinction can lead to timely diagnosis and successful management of COVID-19 in these patients.

Keywords COVID-19; SARS-COV-2; Pediatrics; Patients; Diagnosis; Clinical Manifestation; Transmission

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Introduction

Since late December, 2019, the COVID-19 outbreak has put a high burden on health care systems globally. The symptoms of the infected patients were reported to be similar to those with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1, 2]. Further investigations of the first case-reports discovered a link between these patients and a local market in Wuhan, Hubei, China [3]. The World Health Organization (WHO) reported the outbreak in China on December 31, 2019. It soon spread to other countries and crossed the continent, and by March 2020, the WHO declared the situation as a global pandemic of the disease COVID-19. Since then, more than 270 million people have been infected and more than 5 million have died [4].

SARS-Cov-2 is a single strand RNA virus from the Coronaviridae family. SARS-Cov-2 is a single strand RNA virus from the Coronaviridae family (Figure 1). The genus of this family includes α-CoV, β-CoV, λ-CoV, and δ-CoV [5]. The name belongs to the distinct shape of this virus under electron microscope, which gives it a crown-like shape due to its papillomas [6]. This protein also has a spike glycoprotein that is responsible for virus entry into host cells [6, 7] (Figure 1).

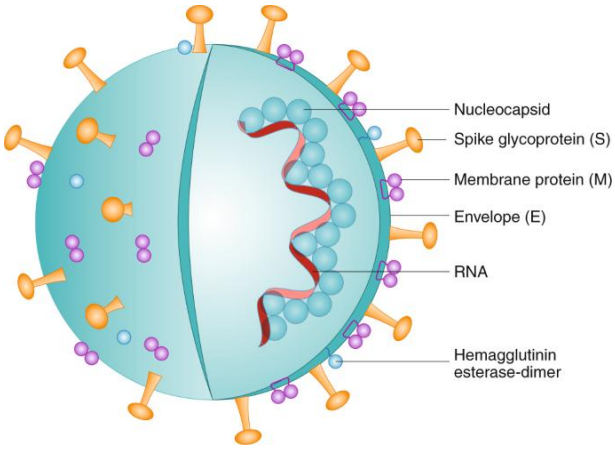

Figure 1) Schematic representation of SARS-CoV-2 structure [8]

Symptoms of this novel infection include fever, cough, chest pain, dyspnoea, fatigue, and anosmia or ageusia [9]. The elderly population, patients with underlying diseases and comorbidities such as Diabetes Mellitus (DM), hypertension, cardiovascular and ischemic diseases, Chronic Kidney Disease (CKD), cancer, and immunodeficiency disorders along with people using immunosuppressants are an increased risk for COVID-19 infection and its severe outcomes including hospitalization, need for ventilation, and death [10, 11]. Although the risk of a severe COVID-19 infection is higher for people over 40 years old, however, the possibility of infection in the paediatric population is the same as in the adult population [12, 13]. Multicenter observational cohort studies report a high prevalence of COVID-19 infection among children and adolescents [12, 14, 15].

The aim of this narrative review was to illustrate the epidemiology, clinical presentation, diagnosis, and laboratory or radiographic findings of COVID-19 infection in paediatric patients based on the current literature.

Epidemiology of COVID-19 in paediatric population

Susceptibility to COVID-19 infection does not differ between different age groups. Although COVID-19 infection is more prevalent among older paediatric patients, infant patients experience more severe forms of infection due to their high rate of hospitalization [16, 17]. The incubation period for paediatric patients is reported to be about 1 day longer compared to adults. The incubation period for adults is 5.2 in comparison to 6.5 for paediatric patients [18, 19]. Case-reports of incubation period more than 15 days are also available [20].

Current literature reports no gender-related differences in the prevalence of COVID-19 among paediatric populations. A case series study from China reported that among 2135 patients, 94% experienced mild, moderate, or asymptomatic COVID-19 infection, and only 6% suffered from severe infection compared to 18% for the adult population [16]. Factors contributing to severe infection among paediatric patients comprise congenital heart disease, congenital lung disease, malnutrition, chronic kidney disease, immunodeficiency disorders, and diabetes mellitus. Also, age less than 3 months can be another risk factor for severe forms of infection [21].

Viral load and transmission

Virological studies indicate that there is no significant difference between asymptomatic and symptomatic COVID-19 patients regarding the viral load of SAR-CoV-2, which is suggestive of the viability of asymptomatic patients as a source of disease transmission [22, 23]. An important study compared the nasopharyngeal viral loads of paediatric patients with adult patients. There was no significant difference between adults and paediatric patients in different age groups, which indicates an equal chance of infection for both populations [24]. However, further studies have reported that transmission of COVID-19 infection from paediatric patients to adults is rare [25]. The incidence of COVID-19 infection in paediatric patients varies between similar studies from different populations, probably due to testing policy and availability of tests. In the USA, 10% of cases were paediatric patients with a mortality rate of less than 1% [26].

Infection in paediatric patients commonly occurs through exposure to a family member previously

infected or exposed to SARS-COV-2 [27]. An important study in England on the transmission of COVID-19 in educational settings has concluded that of the 1 million students that attended to an educational setting every day during the summer half-term, only 113 cases of COVID-19 infection were reported. The source of infection is believed to be staff members, and prevention protocols are focused on reducing the likelihood of infection through timely detection of infection among the staff members. These results suggest that the paediatric population probably does not play a major role in the transmission of COVID-19 [28, 29]. However, contrary to the previous results, Polymerase Chain Reaction (PCR) test of rectal swabs was positive even in the absence of a positive test of nasopharyngeal swabs. High expression of Angiotensin-Converting Enzyme 2 (ACE2) in cells of colon may be a possible explanation for the consistent positive results. Although faecal-oral transmission of SARS-COV-2 has not been affirmed, it should be noted that poor hygiene among children (toilet training) may increase the chance of transmission, as reported for other viral infections such as influenza [29-32]. This result bolds the importance of hygiene among the paediatric population during the pandemic.

Clinical manifestation

Common symptoms in paediatric patients with COVID-19 include: respiratory symptoms such as cough along with fever, fatigue, and myalgia. However, clinical symptoms are often uncommon in paediatric population and the disease is mild or asymptomatic [20, 29, 33, 34]. Also, paediatric patients experience a short duration of fever compared to adult patients [35]. Other symptoms such as sore throat and rhinitis have been seen in a small number of patients. Several studies have also reported that gastrointestinal symptoms such as abdominal pain, diarrhoea, and vomiting are more common in paediatric patients, and they have concluded that those patients who manifest such symptoms are at greater risk for severe form of COVID-19 infection. Also, neonatal COVID-19 infection can present with weakness, anorexia, and dyspnoea [36-39]. The severe form of disease has been reported to present with dyspnoea, hypoxia, sepsis, acute respiratory distress syndrome, acidosis, multiple organ dysfunction syndrome, and thrombocytosis [21, 22, 40].

According to a nationwide study in China, no gender differences were observed. This study also reported that children under seven years of age were more likely to experience a severe form of infection [16]. A possible explanation could be the immaturity of their innate and adaptive immune system. Another important finding is the emergence of Kawasaki-like clinical manifestations in children with COVID-19, which presents with non-exudative conjunctivitis, lymphadenopathy, polymorphic rash, firm indurations in hand or feet, cardiac involvement, and macrophage activations syndrome. The disease is also called Paediatric Inflammatory Multisystem Syndrome (PIMS) or Multisystem Inflammatory Syndrome in Children (MIS-C). Several studies from Italy, France, and Iran have reported Kawasaki outbreaks and were seeking immediate attention [41-43]. Ultimately, although rare and very uncommon, testicular involvement has also been suggested to present in paediatric COVID-19 patients [44].

There is still no definitive explanation for the mild manifestations of COVID-19 in paediatric patients. However, some possible explanations have been suggested in the literature. ACE-2 expression is increased in paediatric patients compared to adults. One study reported that the elderly with more severe COVID-19 infection express lower levels of ACE-2 along with reduced numbers of lymphocytes and lung progenitor cells compared to paediatric patients, which may prolong recovery duration from severe pneumonia. In older adults, due to aging, ACE-2 expression is lower in the bronchi and higher or similar in the alveolar region, which enhances the chance of lower respiratory tract infection in adults and upper respiratory tract infection in children. Lower respiratory tract infection may then progress to severe pneumonia, thus increasing morbidity and mortality in the adult population [45, 46].

Lung progenitor cells are crucial components of regenerative potency of lung tissue. They play a vital role in regeneration and repair following lung injury in COVID-19 infection and other respiratory disorders such as MERS-COV and influenza [5, 47, 48]. The function of these cells can be evaluated by the expression of their associated markers, often called markers of progenitor lung cells, such as *KRT5, KRT8, TP63, NKX2.1, SOX2, SOX9, ATNX1, and SCGB1A1*. In adult patients, the expression of these markers is reduced compared to paediatric patients, which makes adult patients more susceptible to severe forms of infection due to diminished regenerative potential of lung tissue [45].

Based on the epidemiological findings regarding SARS-CoV-2, SARS-CoV-1, MERS, Respiratory Syncytial Virus (RSV), and influenza outbreaks, paediatric patients are susceptible to RSV and influenza infection but are less infected with SARS-CoV-2, SARS-CoV-1, and MERS [49, 50]. According to data from the 2009 influenza pandemic in the United States, paediatric patients were initially the most affected by the H1N1 pandemic [51]. However, in the SARS-CoV-2, SARS-CoV-1, and MERS outbreaks, the paediatric population had a lower risk of infection. The distinct difference in the pathophysiology of SARS-CoV-2, SARS-CoV-1, and MERS compared to RSV and influenza, along with the explanation given in previous paragraphs, can justify the lower prevalence and severity of COVID-19 infection in paediatric patients. Other possible explanations include innate and adaptive immunity differences

between adult and paediatric patients along with lower chance of transmission to paediatric patients due to closure of schools and day-care centres at the start and during the COVID-19 pandemic [39, 49, 52]. However, no robust evidence supports the latter justifications and further investigations should inquire the pathophysiological and epidemiological distinctions between SARS-CoV-2 pandemic and previous pandemics.

Diagnosis, laboratory, and radiographic findings

Several studies have compared laboratory findings in paediatric COVID-19 patients with severe or mild forms of the infection. Mostly, the laboratory findings were not specific and no consensus trend has been reported in the literature. However, C-Reactive Protein (CRP) elevation, erythrocyte sedimentation rate elevation, creatine phosphokinase elevation, lactate dehydrogenase elevation, and increased potassium levels were the most common laboratory findings in paediatric COVID-19 patients. Compared to adults, white blood cell, neutrophil and lymphocyte count were typically normal and CRP was found to be more commonly elevated in adults, suggesting more serious forms of infection in adult population and mild or asymptomatic disease in paediatric patients with diminished immunological damage. In paediatric patients with severe COVID-19 infection, bilirubin and hepatic enzymes were the best diagnostic markers, indicating the chance of PIMS in children. Paediatric patients admitted to the Intensive Care Unit (ICU) had higher levels of all the aforementioned indicators along with inflammatory markers such as Interleukin 6 (IL-6), Interleukin 4 (IL-4), and Tumour Necrosis Factor-α (TNF-α) [41, 53-55].

Similar to adult patients, Reverse Transcription Polymerase Chain Reaction (RT-PCR) test is the most accurate test to detect COVID-19 infection. Nasopharyngeal and oropharyngeal samples are mostly used for RT-PCR tests, however, other samples such as stool, urine, serum, and bronchoalveolar lavage can also be used for this test [56, 57].

A chest X-ray is usually normal in the early stages of COVID-19 infection and mild infection in paediatric patients, and only those with severe COVID-19 infection have abnormal chest X-ray findings. Bilateral or unilateral ground glass opacity, lung consolidation, and pleural effusion are among the common findings of paediatric patients admitted to ICU. The most characteristic findings in paediatric patients admitted to the ICU are unilateral or bilateral white lung patterns [21, 55, 58]. Computed Tomography (CT) findings are different in early, progressive, and severe stages of COVID-19 infection. Multiple ground glass opacities along with localized consolidation and blood vessel thickening were the common manifestation in early COVID-19 infection. Rarely, large consolidations along with increased ground glass opacities can present in progressive stages of infection. Similar to chest X-ray findings, CT findings in paediatric patients with severe COVID-19 infection show pleural effusion, bilateral or unilateral ground-glass opacities, and lung inflation [59, 60]. Table 1 summarizes useful diagnostic criteria regarding the diagnosis of COVID-19 infection in paediatric patients.

Table1) Suggested protocol for diagnosing paediatric patients with COVID-19 [61]

Disease severity	Diagnostic criteria
Asymptomatic	- No clinical signs, normal chest X-ray and CT imaging, positive RT-PCR
Mild	- Symptoms such as fever, fatigue, cough, myalgia, sore throat, rhinitis, and sneezing - Normal pulmonary examination - Gastrointestinal signs such as nauseas, diarrhoea, vomiting, and abdominal discomfort
Moderate	- Signs of pneumonia in clinical examination - Persistent fever, dry and productive cough, wheezing or crackles during auscultation and without signs of respiratory distress - Typical pulmonary involvement in Chest CT
Severe	- Initial respiratory and gastrointestinal symptoms - Clinical deterioration within 7 days followed by dyspnoea and hypoxemia (O_2 < 94%)
Critical	- Progressive and fast deterioration with ARDS (Acute Respiratory Distress Syndrome), respiratory failure, septic shock, encephalopathy, myocardial damage, coagulopathy, acute kidney damage, and multiple organ dysfunction

Conclusion

Although paediatric patients suffer from mild or asymptomatic forms of COVID-19 infection, susceptibility to COVID-19 infection does not differ between different age groups. They may also experience a longer incubation period in comparison to adults. No consensus has been found in the literature regarding the underlying reason for the lower prevalence of COVID-19 infection in younger patients. However, some explanations such as the role of ACE-2, distinct characteristics of immune system, and higher regenerative potential of lung tissue have been suggested, which are not definitive. Paediatric patients with underlying conditions such as heart disease, diabetes mellitus, or immunosuppressive disorders suffer from severer forms of disease and have an increased chance of hospitalization or admission to ICU. Importantly, signs and symptoms similar to Kawasaki have been observed in children with Covid-19. Further research should clarify the precise pathophysiology of COVID-19 in paediatric patients.

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