

From asymptomatic to critical illness - different clinical manifestations of COVID-19 in children

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Abstract: The global pandemic infectious disease that was named the new coronavirus disease (COVID 19), spread throughout the world, causing a major public health emergency. The causative virus of COVID-19, called SARS CoV-2, can infect all age groups. Various clinical signs and symptoms have been observed in neonates, children, and adolescents during the COVID-19 outbreak. The clinical manifestations of COVID-19 might be different due to the medical conditions and comorbid status in elderly and pediatric patients. The rise in cases among children has been reported during the COVID-19 pandemic. Although infected children generally appear to be asymptomatic or have only mild symptoms, COVID-19 in children may also involve a wide spectrum of clinical manifestations ranging from asymptomatic carriers to life-threatening and fatal diseases, as COVID-19 is a systemic disease that can affect multiple organs. Due to the lack of knowledge in the current literature, it is necessary to describe the atypical clinical features, including extrapulmonary manifestations, in pediatric patients with COVID-19. This review is conducted to identify knowledge gaps regarding the broad spectrum of clinical signs and symptoms of children with COVID-19.

Key words: COVID-19, multisystem inflammatory syndrome in children (MIS-C), SARS CoV-2, children

1. Introduction

The new coronavirus disease 2019 (COVID-19) of which the etiologic agent is Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) was reported as a pandemic by the World Health Organization (WHO) in March 2020 and resulted in a major public health crisis in worldwide¹ [1]. In the initial phase of the pandemic, most cases occurred in middle-aged and elderly people [2].

Nevertheless, SARS-CoV-2 can infect all age groups, including children [3]. During the outbreak, numerous pediatric studies have described various atypical clinical presentations of children with COVID-19 [4]. Although the disease seems to be milder in children than adults, fatal cases have also been reported in the pediatric age group [3].

COVID-19 is a systemic disease affecting multiple organs since ACE2, the SARS CoV-2 receptor, is also found

in other organs such as kidneys, adipocytes, heart, brain, enterocytes, and liver. ACE2-linked signaling pathways might cause extrapulmonary manifestations of COVID-19 [5].

The clinical presentation of COVID-19 in children includes pulmonary, dermatological, ophthalmological, neurological, renal, cardiovascular, and gastrointestinal manifestations as shown in the table below [6]. In addition, a rare severe form of the disease, COVID-19 associated multisystem inflammatory syndrome requiring inotropic support, has also been reported².

The spectrum of COVID-19 ranges from an asymptomatic carrier state to a life-threatening and fatal condition [4]. The purpose of this review is to explain the different clinical manifestations of neonates, infants, and children with COVID-19. Comprehensive research for extrapulmonary manifestations in pediatric cases

¹ World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19-- 11 March 2020. Available at: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020> (Accessed on May 21, 2021).

² European Centre for Disease Prevention and Control Rapid Risk Assessment: Paediatric inflammatory multisystem syndrome and SARS CoV 2 infection in children. Available at: <https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf> (Accessed on May 17, 2021).

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Table. Most common signs and symptoms in children with different organ involvement of COVID-19.

General manifestations	Pulmonary manifestations	Cardiovascular manifestations	Gastrointestinal manifestations	Neurological manifestations	Ocular manifestations	Renal manifestatios	Dermatologic manifestations	MIS-C
Fever	Acute respiratory distress syndrome	Myocardial injury, myocarditis	Abdominal pain	Severe encephalopathy	Conjunctival discharge/ Conjunctival congestion	Acute kidney injury	Maculopapular, urticarial and vesicular eruptions	Persistent fever [four to six days]
Cough	Respiratory failure	Submassive pulmonary embolism	Diarrhea	Ischemic stroke	Eye rubbing		Reddish-purple nodules	Rash,erythroderma
Shortness of breath, dyspnea	Pneumonia	Arrhythmia	Vomiting	Central nervous system infection	Eye pain		Transient livedo reticularis	Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)
Myalgia	Bronchiolitis	Cardiac arrest	Pancreatitis	Guillain-Barre syndrome/ variants	Teary eyes		Acral peeling	Bilateral bulbar conjunctivitis
Sore throat		Cardiomyopathy	Hepatitis	Acute fulminant cerebral edema	Eyelid swelling			Mucosal findings (red or swollen lips, strawberry tongue)
Fatigue		Heart failure	Cholestasis	Cerebral central venous sinus thrombosis				Arrhythmia, myocardial dysfunction, shock, hypotension
Myalgia		Cardiogenic shock		Focal cerebral arteriopathy				Acute renal failure
Nasal congestion/ rhinorrhoea		Coagulation abnormalities		ADEM				Acute respiratory failure, pneumonia, pulmonary embolism
Loss of smell or taste		Acute pericarditis						Cervical lymphadenopathy
Nausea/vomiting								Serositis
								Encephalopathy,coma
								Seizures,meningoencephalitis, aseptic meningitis
								Coagulopathy

of COVID-19 has been conducted. The most common extrapulmonary and pulmonary manifestations in pediatric patients with COVID-19 are summarized in this review.

2. General clinical manifestations of children with COVID-19

The features of COVID-19 in children are similar to symptoms of viral respiratory infection. Typical manifestations of viral infection have been frequently noted in children with COVID-19, with fever and cough being the most common symptoms [4].

In a retrospective study that included 1156 children with documented SARS CoV-2 infection from 32 different hospitals in Turkey, fever and cough were the most frequently described symptoms. The other symptoms were found to be sore throat, myalgia, dyspnea, diarrhea, abdominal pain, and nasal discharge [7].

COVID-19 surveillance was conducted in the United States and included 5188 children with COVID-19 aged 0–9 years. Fever (46%) was recorded as the most common symptom in this age group, followed by cough (37%). Other clinical findings included shortness of breath (7%), myalgia (10%), rhinorrhea (7%), sore throat (13%), headache (15%), nausea/vomiting (10%), abdominal pain (7%), diarrhea (14%), loss of smell or taste (1%). Of 12689 children aged 10–19 years included in the surveillance, the most common symptom was cough (41%), fever (35%), or shortness of breath (16%). Other symptoms were myalgia, rhinorrhea, sore throat, headache, nausea/vomiting, abdominal pain, diarrhea, or loss of taste [8].

A metaanalysis that included 129 studies from 31 countries found that pediatric COVID-19 has a milder course and better prognosis than adults. 9335 children (0–19 years) with SARS CoV-2 infection participated in the metaanalysis and the median proportion of asymptomatic children was 13%. The most commonly reported symptoms were fever (63%), cough (34%), nausea/vomiting (20%), diarrhea (20%), dyspnea (18%), rash (16%), fatigue (16%), abdominal pain (15%), conjunctivitis (11%), pharyngeal erythema (9%) [9].

Although fever and cough have been the most commonly reported symptoms in children with COVID-19, other clinical syndromes such as pneumonia, bronchiolitis have also been observed. In a study that included 1475 pediatric patients with confirmed COVID-19, 15% of cases were asymptomatic, 42% were mild, 39% were moderate (clinical or radiological evidence of pneumonia without hypoxemia), 2% were severe (dyspnea, central cyanosis, hypoxemia), and 0.7% were critical (acute respiratory distress syndrome, respiratory failure, shock), and six pediatric deaths (0.08%) were reported [10].

Although knowledge about infants with COVID-19 is limited, mild or atypical clinical symptoms have also been described in this age group. In a recent study, which included 63 infants with COVID-19 aged less than three months, the most common clinical finding was fever (73%), followed by cough (38%). Other symptoms included rhinitis (36%), dyspnea (26%), poor feeding (24%), vomiting (14%), and diarrhea (14%) [11].

In a recent study conducted in Greece, 14 infants with COVID-19 under three months of age were examined and 39 °C fever was a common presentation (79%). Other findings included rhinorrhea, cough, diarrhea, drowsiness, difficulty feeding, and tachypnea, and one patient was completely asymptomatic. Although all cases were mild and even asymptomatic, they were all hospitalized because of their age [12].

In addition, SARS CoV-2 has been described as a cause of acute bronchiolitis in children under one year of age [13].

3. Cardiovascular system involvement in children with COVID-19

SARS CoV-2 has cardiotropic properties. Previous studies report that cardiac involvement in adults with COVID-19 is associated with increased mortality [14].

Myocarditis, arrhythmia, cardiac arrest, cardiomyopathy, heart failure, and coagulation abnormalities have been identified as cardiovascular complications related to COVID-19 in the pediatric case series [15].

Acute pericarditis has also been recently reported in children with COVID-19. Pericarditis may be a postinflammatory immune-mediated presentation or an active COVID-19 infection-causing pericarditis [16].

In a case series of pediatric patients with congenital heart disease, the authors noted that cases with acute COVID-19 presented with new or worsening heart failure without the multisystemic inflammatory syndrome. New signs of arrhythmias and myocardial inflammation were found in these patients [17].

Previous studies in adults have shown that severe COVID-19 was associated with increased thrombosis and hypercoagulation. Pediatric patients with COVID-19 presenting with submassive pulmonary embolism have also been reported due to a hypercoagulable state [18].

4. Gastrointestinal system involvement in children with COVID-19

Gastrointestinal symptoms might be observed in pediatric patients with COVID-19 without respiratory symptoms. The most frequently reported gastrointestinal symptoms in children with COVID-19 were diarrhea, and abdominal pain [19].

The transmembrane protein angiotensin-converting enzyme (ACE) 2 receptor, which is required for SARS CoV-2 to enter the cell, is expressed in multiple systems (lung, kidney, heart, pancreas) [20]. ACE2 expression, as measured by mRNA levels, is higher in the pancreas than lung [21]. Therefore, acute pancreatitis has been described in children with COVID-19 [22].

Acute hepatitis and cholestasis have also been reported in children infected with SARS CoV-2 [23]. The mechanism underlying this pathogenesis has been investigated [24]. ACE2 expression has been observed in cholangiocytes which are essential cells for liver regeneration and immune response. This may be the underlying process for the acute cholestasis reported in pediatric patients with COVID-19 [24, 25]. Mild cholestasis was first described in a pediatric patient with COVID-19 from Wuhan, China. This case was a 55-day-old baby with COVID-19 with pneumonia and acute cardiac injury. The authors observed that the findings of mild hepatitis and conjugated hyperbilirubinemia resolved with clinical improvement in this patient [26]. Two other reported pediatric cases with acute cholestasis and hepatitis did not have typical clinical signs of COVID-19 such as fever, cough, shortness of breath, myalgia, sore throat, or significant gastrointestinal symptoms or manifestations of multisystemic inflammatory syndrome [23].

5. Neurological involvement in children with COVID-19

The wide spectrum of neurologic diseases associated with COVID-19 in children and adolescents ranges from mild cases to peripheral nerve disorders (Guillain-Barre syndrome (GBS)), focal CNS disorders (ischemic stroke, cerebral central venous sinus thrombosis, and focal cerebral arteriopathy), and widespread central nervous system (CNS) involvement (CNS infection, acute disseminated encephalomyelitis, severe encephalopathy with corpus callosum lesions, acute fulminant cerebral edema). These results demonstrated the fact that more than one mechanism causes a broad spectrum of neurologic manifestations related to COVID-19 [27, 28].

This neurologic involvement may be due to putative mechanisms, such as neuroinvasive or neurotropic (neuronal infection and/or direct viral entry via the ACE2 or olfactory tract), neuroinflammatory (excessive cytokine/immune-mediated response leading to blood-brain barrier disruption), postinfectious immune dysregulation, and/or secondary damage from systemic inflammatory complications or other non-CNS organ failures [29].

Most children with COVID-19 do not have neurological manifestations, but life-threatening neurological complications have also been documented in pediatric studies. A metaanalysis that included 21 studies and 5 case reports consisting of 3707 pediatric

patients reported that neurological complications in children with COVID-19 have been observed in a small number of patients. In this metaanalysis, 581 children had nonspecific neurological features and 42 of the total patients (1%) had neurological severe complications. In this study, encephalopathy has been observed in 25 children and meningeal signs have been reported in 17 children. The mechanism underlying this pathogenesis has been attributed to aseptic neuroinflammation that may cause encephalitis, myelitis, and other complications (e.g., GBS) in children with COVID-19. Cerebrospinal fluid (CSF) analysis in children with SARS CoV-2 CNS disease was found to have lymphocytic pleocytosis and elevated CSF protein concentration with no detection of SARS CoV-2 virus in CSF in most of the cases. Polymerase chain reaction (PCR) test might have low sensitivity in CSF [30].

Nevertheless, in a recent study consisting of 171 Chinese children with COVID-19, neurological manifestations were not observed in patients in all study population [31]. Another study reported from Italy includes 100 Italian children, 4%–28% of children with COVID-19 had non-specific headaches as the only documented neurological symptoms [32].

Unlike those studies, life-threatening neurologic involvement has been reported in children with the multisystem inflammatory syndrome (MIS-C). In a multicenter case series of 1695 children (age < 21 years) hospitalized with confirmed COVID-19 (36% with MIS-C), 365 (22%) had neurologic involvement of whom 88 patients were transiently affected. In this study, severe encephalopathy in 15 patients and acute CNS infection (encephalitis, aseptic meningitis, ADEM) in 8 patients, acute fulminant cerebral edema in 4 patients were observed in children with COVID-19. Among these children, 11 patients died [28].

6. Dermatological involvement in children with COVID-19

Skin lesions may be consequences of inflammation of COVID-19. Skin findings have rarely been described in pediatric patients with COVID-19. This involvement includes maculopapular, urticarial, and vesicular eruptions, transient livedo reticularis, acral peeling, and reddish nodules on the distal fingers [33].

In one study, granular positivity of SARS CoV-2 spike protein was found in the epithelial cells of eccrine glands in two acral biopsies in patients with mild symptoms [34]. In a case series, three cases with COVID-19 with perniois, SARS CoV-2 protein was found in the endothelial cells [35]. SARS CoV-2 RNA was found in the specimens of skin biopsy in a patient with negative nasopharyngeal PCR test [36].

In a study of 378 children with COVID-19, reddish-purple nodules resembling pernio (chilblains) were noted on the distal fingers, especially in children and young adults. This clinical finding is referred to as “COVID toes”. However, the association has not been clearly defined. In six patients with COVID-19, acral findings were observed days after SARS CoV- 2 symptoms onset or after testing positivity for SARS CoV-2 by PCR. Only 1% of children with acral pernio-like lesions tested positive for SARS CoV-2, indicates that skin inflammation may represent a late finding or a secondary inflammatory reaction caused by postviral change. COVID-19 causes inflammation and a dysregulated immune response and new skin changes could occur due to environmental characteristics or genetic predisposition [37].

7. Ocular involvement in children with COVID-19

Ocular involvement in adult patients with COVID-19 has been investigated in previous studies [38]. Viral replication of SARS CoV-2 was detected in the tear fluid of a patient with conjunctivitis after clinical resolution of symptoms [39].

The knowledge on ocular symptoms of children with COVID-19 is lacking. A study with the largest sample size consists of ocular manifestations in children with COVID-19, from Wuhan, China and had 216 participants. Of 216 patients, 22.7% of pediatric patients had ocular involvement. The patients showed ocular symptoms within 7 (3-10) days. Among the cases with ocular symptoms, the most common manifestation was conjunctival discharge (white mucopurulent, thin yellow-green purulent discharge) and conjunctival congestion. Other ocular manifestations included eye rubbing, eye irritation, lacrimation, and eyelid swelling. The patients with ocular symptoms were managed with observation without medication (23 participants), and the others received antibacterial/antiviral or antiallergic eye drops. In this study, the symptomatic children (e.g., fever, cough) had more ocular features than asymptomatic patients. Coughing may cause ocular infection due to the pressure of coughing may push nasopharyngeal secretions from the nasolacrimal duct into the conjunctival sac. It is suggested to observe closely the children with diagnosed COVID-19 for ocular manifestations [40].

8. Renal involvement in children with COVID-19

In a metaanalysis that included 551 children with COVID-19 from 46 studies, 5% of pediatric patients with COVID-19 had high urea and 4% had high creatinine [41].

A study by Stewart et al. showed that 29% of hospitalized patients with COVID-19, were diagnosed with acute kidney injury (AKI). Of the 15 cases with AKI, 93% were hospitalized in the pediatric intensive care unit

(PICU), and 73% had MIS-C. This study shows that AKI may be observed uncommonly in pediatric patients with COVID-19 [42].

9. Frequency of serious disease in children with COVID-19

In the retrospective study that included 1156 Turkish children, information about symptoms and severity was available for all patients. Among these, 22.7% of patients were asymptomatic, 57.7% mild, 18.1% moderate, and 1.5% severe. Two deaths were observed in the study population [7].

Deaths from SARS CoV-2 are uncommon in children and adolescents. In a recent study conducted in 7 countries (France, Germany, Italy, Spain, South Korea, the United Kingdom, and the United States), the rates of the mortality of the children with COVID-19 (0–19 years old) was 0.17 per 100,000 [43].

In a study that included 512 children with COVID-19, seven (1.4% of total) children with COVID-19 were admitted to the PICU. Supplemental oxygen was applied to all patients included in to study. High flow oxygen support via nasal cannula was used for 5 children. Four of them had noninvasive ventilation (NIV) in follow up, and 2 patients required mechanical ventilation (MV). In this study, all those seven children who had critical care were previously healthy and did not have comorbid diseases [44].

In a recent study from Turkey consisting of 1219 hospitalized children because of COVID-19, 1.64% of them (20 patients) were needed critical care in PICU. Positive airway pressure ventilation (PPV) was used for the 17 children (1.39 percent of the children) that were included in the study due to the presence of severe COVID-19 pneumonia and high-frequency oscillatory ventilation was used for 1 patient. In this study, the death rates of the patients were observed to be 0.056% (4 patients) of all cases [45].

In a study from Canada that included 48 children with COVID-19 admitted to the PICU, 33 cases (69%) had severe or critical disease, and 11 (23%) had failure of ≥ 2 organ systems. A total of 39 patients (81%) required respiratory support. Among these patients, 18 cases (38%) had invasive ventilation. One patient (2%) needed extracorporeal membrane oxygenation. 2 cases died [46].

In pediatric patients, deaths from COVID-19 were frequent in older children compared with younger age groups. In a previous study, 391,814 cases with COVID-19 were included, and 121 deaths (0.08% of all deaths) were recorded in people younger than 21 years of age in the United States. Pediatric deaths occurred mostly in males and the 10-to 20-year-old age group; the 18 to 20 years age group were accounted for half of all deaths in this population [47].

10. Why COVID-19 appears to be less severe in children than adults?

Cytokine release syndrome is known to play an important role in the pathogenesis of severe COVID-19 infections. Due to children have a weaker immune response to the SARS CoV-2 than adults, children have mostly mild disease [48]. Another reason could be viral interference in the airway of children, which may cause a lower SARS CoV-2 viral load. Other factors could include a different distribution of ACE2 receptors in children, preexisting cross-reactive antibodies and immunity to coronaviruses, a strong early mucosal immune response, a lower prevalence of underlying diseases associated with severe COVID-19, and children have healthier blood vessels than adults [49–51]. In addition, lower exposure to infections may play a role [52].

11. Risk factors for severe disease

Current evidence relating to specific underlying diseases with severe COVID-19 is insufficient. Considerations of each hypothesized risk factor are summarized here using case-by-case analysis [53, 54].

In a study from the USA, 121 COVID-19 related deaths in children were noted. One and more comorbid diseases were observed in 75% of those patients, and two and more comorbid diseases were found in 45% of the patients. The most common reported comorbid diseases were chronic pulmonary disease (28%), obesity (27%), neurologic diseases (22%), and cardiovascular diseases (18%) [47].

A study that included 17 Turkish children with COVID-19 pneumonia that received PPV support in PICU, 65 percent had an underlying medical condition. Thirteen patients survived (76.5%), and 4 patients died. Among the four patients who died, except one patient, three of them had comorbid diseases such as complex cardiac disease, history of hematopoietic stem cell transplantation, and chronic lung disease [45].

In a multicenter study that included 582 children with COVID-19 from 21 European countries, 48 (8%) cases were admitted to the PICU. Among these patients, 25 (4%) had mechanical ventilation, 19 (3%) had inotropic support, and one extracorporeal membrane oxygenation. 52% of PICU admissions had a comorbid disease. These diseases were chronic pulmonary disease (asthma and bronchopulmonary dysplasia), malignancy, chromosomal abnormality, chronic kidney disease, malignancy, neurological disorders. Among the four patients who died, two of them did not have the comorbid disease [55].

Down syndrome and being aged <1 year have also been found to be the risk factors for severe COVID-19 disease

in children, but this knowledge is also incompatible [3, 56–58].

In a study that included 48 children with COVID-19 admitted to the PICU, 40 (83%) cases with PICU admissions had co-morbid diseases. Eight patients (17% with PICU admission) had no comorbidities. In this study, 2 cases died and both had comorbid diseases [46].

Congenital heart disease, metabolic disease, obesity, asthma, chronic lung disease, diabetes, cancer, and or identified risk factors for other respiratory viral infections (including young age, immunosuppression) may be associated with an increased risk of severe disease in children with COVID-19³ [54].

In the previous adult studies, being obese is found to be a risk factor for critical illness of COVID-19 [59–61]. The data in the pediatric literature leads to conflicting results. In a study from New York, obesity was associated with mechanical ventilation requirements in children ≥ 2 years of age, and it was found to be the most common comorbid disease [19]. But in other pediatric case series, no significant association was documented between obesity and PICU admission [62,63]. These results may be attributed to the fact that accompanying cardiovascular disease in obese children is observed rarely compared to obese adults [64].

In a multicenter study of 17 children from ten PICUs, 71% of children had one or more comorbid conditions [65]. Centers for Disease Control and Prevention (CDC) data described the distribution of comorbidities in hospitalized children according to age. Of infected children hospitalized by the end of July 2020 in 14 states, 42% had one or more comorbid conditions, and the most common comorbidities were obesity, chronic lung disease, and prematurity [53].

Although some case series have reported immunosuppression as an underlying condition in children with severe COVID-19, the relationship between immunosuppression and severe COVID-19 remains to be explained [66]. Currently available data do not indicate whether immunosuppressed children are at greater risk for severe COVID-19 disease than healthy children [54].

12. Multisystemic inflammatory syndrome in children with COVID-19

On April 27, 2020, the United Kingdom National Health Service first issued a warning indicating a multisystemic inflammatory syndrome associated with COVID-19 [67]. On May 6, 2020, authors from London, England described the clinical and laboratory features of eight children with hyperinflammatory shock, who had SARS CoV-2

³ United States Centers for Disease Control and Prevention. People with certain medical conditions. Available at: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (Accessed on May 20, 2021).

antibodies⁴. Finally, the WHO published a health note for this syndrome and named it Multisystemic Inflammatory Syndrome in Children (MIS-C)⁵.

The case definition of MIS-C depends on clinical and laboratory features to identify suspected or confirmed cases. There are minor differences in the case definitions of CDC and WHO. There are common characteristics in both definitions such as fever (duration varies), elevated inflammatory markers, at least two signs of multisystem organ involvement, evidence of SARS CoV-2 infection or SARS CoV-2 exposure, and exclusion of other potential causes of inflammation. Additionally, for the CDC case definition, the child should have severe clinical findings requiring hospitalization⁶.

Recent case series report this disorder as a clinical entity that may begin as a consequence of an impaired immunologic response following SARS CoV-2 infection [68]. The clinical features of MIS-C, including fever, shock, rash, edema, and conjunctivitis, have similarities to toxic shock syndrome, Kawasaki disease (KD), and Kawasaki disease shock syndrome (KDSS) [67]. Laboratory findings are associated with persistent fever, hypotension, gastrointestinal symptoms, rash, myocarditis, and increased inflammation [68].

Common symptoms in the available case series include persistent fever (four to six days), gastrointestinal symptoms (abdominal pain, vomiting, diarrhea), rash, conjunctivitis, mucosal involvement (red or swollen lips, strawberry-colored tongue), neurocognitive symptoms (headache, lethargy, confusion, irritability), respiratory symptoms (tachypnea, increased respiratory effort), sore throat, myalgia, swollen hands/feet, and lymphadenopathy⁷[66-71].

Common clinical findings reported in the available case series include shock, mucosal findings (red or swollen lips, strawberry-colored tongue), myocardial dysfunction (by echocardiogram and/or elevated troponin or brain natriuretic peptide (BNP)), arrhythmia, acute respiratory failure requiring noninvasive or invasive ventilation, acute renal failure, serositis (pleural, pericardial effusions),

⁴ Paediatric Intensive Care Society. PICS Statement: increased number of reported cases of novel presentation of multisystem inflammatory disease. April 27, 2020. <https://picsociety.uk/wpcontent/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf> (Accessed May 16, 2021).

⁵ WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. <https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19> (Accessed July 16, 2021).

⁶ Health Alert Network [HAN]: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). <https://emergency.cdc.gov/han/2020/han00432.asp> (Accessed on May 15, 2021).

⁷ Center for Disease Control and Prevention, Center for Preparedness and Response: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 [COVID-19], Clinician Outreach and Communication [COCA] Webinar. Available at: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp?deliveryName=USCDC_1052-DM28623 (Accessed on May 19, 2021).

⁸ Royal College of Paediatrics and Child Health Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: <https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf> (Accessed on May 17, 2021).

hepatitis or hepatomegaly, encephalopathy, seizures, coma, or meningoencephalitis⁸ [69-72].

Despite similar features between MIS-C and KD, the manifestations of MIS-C that differ from those of KD are summarized here.

MIS-C is observed to be in older children and adolescents, but young age groups such as infants and young children are mostly affected by KD. MIS-C commonly affects black and Hispanic children, but KD affects mostly East Asian children [68].

Gastrointestinal symptoms (enteropathy) are very common in MIS-C, but these symptoms are rare in classic KD [68,72]. Cardiac dysfunction (e.g., myocardial dysfunction, shock) with extremely elevated troponin, and BNP levels are frequently seen in MIS-C cases [69].

Absolute lymphocyte and platelet counts are lower in MIS-C than KD but inflammatory markers are observed to be more elevated in MIS-C cases [68, 72]. The patients with KDSS seem to have more risk of coronary artery (CA) involvement compared to children with classic KD. There is insufficient information on whether MIS-C patients have a higher risk of CA involvement or not compared to those with KDSS [69].

The prognosis of MIS-C depends on early diagnosis and intervention [72]. The disease course in MIS-C can be severe. Many children with MIS-C require intensive medical care. Most children suffer, but deaths have also been documented. For example, in a study that included 58 children with MIS-C, shock (with myocardial dysfunction) was observed in 29 patients. Those patients needed inotropic support and fluid replacement therapy. Cardiac complications such as CA dilatation was detected in 8 patients (14%). Among all those patients, 1 patient (2%) died [73].

In another study that reported 570 MIS-C patients from the USA, 364 patients [63. 9%] were admitted to PICU, and 10 patients (1. 8%) died [69].

In a review of 16 case series involving 655 patients with MIS-C, 68% of patients admitted PICU, 40% received inotrope treatment and 15% had mechanical ventilation, there were 11 (1.7%) deaths [74].

13. Clinical follow up of children with COVID-19

There is insufficient information about long-term consequences in children with COVID-19 [55]. Studies in adults show that even mild COVID-19 can have long-term complications [75].

In three to six months follow up of 151 children with COVID-19, 12 children who were symptomatic during diagnosis, developed postacute COVID-19 symptoms. Two children developed acute postinflammatory conditions (e.g., MIS-C). Post-COVID-19 symptoms resolved in 10 children within eight weeks. The most common acute postinflammatory COVID-19 symptoms were mild postviral cough (sustained cough associated SARS CoV-2 infection) (6 of 151 children), weakness (three children), or both postviral cough and weakness (one child). The duration of postviral cough ranged from 3 weeks to 8 weeks [76].

The mechanism underlying the pathogenesis of persistent cough after SARS CoV-2 infection has been investigated. One of the hypothesized factors that SARS CoV-2 infects the sensory nerves that play important role in mediating cough, and this causes neuroinflammation and neuroimmune interactions such as cough hypersensitivity. SARS CoV-2 has neurotrophic effects. These effects could cause the post-COVID syndrome. SARS CoV-2 may cause sensory dysfunction such as cough, and loss of taste. These

symptoms might also be caused by the neuroinflammatory effects of the virus in the brain. Sustained cough after COVID-19 has been related to changed central processing of sensory input and cough reflex [77].

More comprehensive studies are needed to define long-term outcomes in children with COVID-19 [75].

14. Conclusion

In summary, a wide range of clinical manifestations of SARS CoV-2 infection can be observed in children according to the current literature. Most studies suggest that infected children remain asymptomatic or have a mild clinical course [3,6]. In addition to fever and respiratory manifestations, SARS CoV-2 infection frequently causes extrapulmonary manifestations (e.g., GI, renal, cardiovascular, neurologic, cutaneous, hepatic) [6]. The primary potential pathophysiological mechanisms for these manifestations are the direct cytopathic effects of tissues expressing the SARS CoV-2 receptor (ACE2) and immune-mediated inflammatory responses [5]. The current findings in this review highlight the priority of life-threatening clinical presentations of COVID-19 especially MIS-C. The children with COVID-19 should be carefully evaluated to describe the different clinical manifestations of the disease and to prevent adverse consequences.

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