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REVIEW ARTICLE

COVID-19 and its manifestations in children: a literature review

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Abstract

Coronavirus disease is a global public health challenge. Due to its high rate of mutation to adapt to the host, the virus can cause serious human diseases, including in children. The article is a literature review using research on COVID-19 in children, published in the PubMed and Medline database, between November 2019 to March 2021. The clinical signs are similar to other childhood respiratory diseases, and may progress to dyspnea, vomiting, diarrhea, lethargy, cough, and fever. On pediatric chest tomography, we found multiple irregular bilateral opacities in ground glass, which can be sparse and irregular, and/or infiltrate the middle third or periphery of the lung or subpleural. Given the diversity of symptoms and most research on COVID-19 with an adult focus, health services need to improve specific treatment plans to treat pediatric patients infected with the virus.

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INTRODUCTION

The 2019 coronavirus pandemic (COVID-19) has become a global public health challenge, leading to thousands of deaths daily in the world[1]. More than 100 million people have been infected worldwide, and the disease has caused nearly 2.6 million deaths. The North American continent is the most affected area of the disease, with more than 53 million confirmed cases, followed by Europe (41 million), then Southeast Asia, Eastern Mediterranean, Africa, and Western Pacific[2]. Despite great efforts to contain the pandemic and develop an ideal vaccine, the number of infected patients and deaths are increasing every day.

Formally referred to as SARS-CoV-2 (severe acute respiratory syndrome of coronavirus 2), the virus is a unique strain of RNA that has never been identified in humans. It has a high rate of mutation to adapt to the host, can be transmitted by aerosols and has the ability to lead severe conditions in humans - including the children[3]. The disease has several main clinical manifestations that can affect the kidney, respiratory, cardiovascular, and central nervous systems[4]. The serious condition of the disease is caused by pro-inflammatory and uncontrolled "cytokine storms" such as interleukin (IL)-6, tumor necrosis factor-α (TNF-α) and IL-1β. Besides that, it was reported that SARS-CoV-2 can take advantage of the inhibition of angiotensin-converting enzyme 2 (ACE2), which is a protective tissue mediator in the process of lung injury induced by a specific interferon[4-9].

Regarding data on pediatric patients, a laboratory in the United States showed that of the 149,760 confirmed cases of COVID-19 between February 2020 and April 2020, a total of 2,572 (1.7%) occurred in children under 18 years of age[10]. People in this age group represent less than 5% of the total COVID-19 patients in the world[11]. On February 8, 2021, of 2,060 patients with multiple system inflammation syndrome (MIS-C), 30 died in the USA. The Center for Disease Control and Prevention (CDC) in the United States estimated that 1.9% of positive cases of COVID-19 were from children aged zero to four years, while 9.4% of diagnoses occurred in the age group of 5-17 years[12,13]. In addition, approximately two-thirds of patients with the syndrome resorted to intensive care unit (ICU).

According to the literature, adults, most importantly the elderly, are at a high-risk of suffering from severe acute respiratory syndrome (SARS), developing serious complications and death[14]. Children with COVID-19 appear to have a milder clinical course than adults, and there are lower reports of deaths[15,16]. However, in addition to eliminating the virus in nasal secretions, pediatric patients can also play an important role in disease transmission, including evidence of fecal elimination within weeks after diagnosis, which is challenging for infection control[17].

The World Health Organization (WHO) recommends testing for all suspicious cases, but infected children may not have the typical symptoms[16]. The reasons for the lower risk of severe coronavirus infection in children are still uncertain. One of the hypotheses is that different age groups have different immune responses[18]. Unlike babies and children with different innate immunity, once an adult is infected, it is more likely to have an unbalanced immune response, leading to a cytokine storm, which is often associated with lung damage and poor prognosis.

Another hypothesis explaining the lower severity of COVID-19 in children is related to the expression of ACE2 in type I and type II alveolar epithelial cells. ACE2 is the SARS-CoV-2 receptor and it is necessary for future replication into host cells and viruses[19]. Therefore, the limited expression of ACE2 seems to protect children from more serious diseases.

Thus, as it finds a lack of information, the objective of this study is to compile the clinical, laboratory and radiological characteristics of the clinical manifestations of COVID-19 in children aged 0 to 18 years of age.

METHODS

This literature review was carried out through an active search of data in the PubMed and MEDLINE databases, SciELO, complemented with the website of the Ministry of Health of Brazil and the Pediatric Brazilian Society from November 2019 to March 2021. The search words were: "coronavirus infections"; "SARS virus"; "respiratory insufficiency"; "pediatric emergency medicine". We included publications in English and Portuguese containing information of patients from 0 to 18 years old with confirmed exams for COVID-19. There was no country limit of study or area of knowledge, and articles with no relation to the topic studied or only addressing the disease in adults were excluded.

RESULTS

Clinical manifestations

The initial signs and symptoms of COVID-19 may be similar to other respiratory infections, so diagnostic suspicion should be based on clinical manifestations related to epidemiology. Mild conditions improve as the disease progresses. In the absence of hypoxemia, in some moderate cases, it may develop into pneumonia and respiratory distress. In severe cases, blood oxygen saturation decreases, and there is drowsiness, loss of appetite, seizures associated with SARS, cardiovascular, liver, and kidney insufficiency[20]. The main characteristics and manifestations in the pediatric population are mentioned in Table 1.

A systematic review analyzed 38 studies with 1,124 cases of the disease and the most common symptom was fever, responsible for 47.5% of cases, followed by cough (41.5%), upper respiratory symptoms (11.2%), diarrhea (8.1%), nausea/vomiting (7.1 %), fatigue (5.0%), and dyspnea (3.5%), as mentioned in Table 2[1]. Although gastrointestinal (GI) manifestations are not common, they may be the only COVID-19 symptoms in children[1,3,21,22].

Table 1. Clinical symptoms, manifestations and outcome of MIS-C in the pediatric population.

Author and Date	Systematic review and meta-analysis.	Age in years (median)	MIS-C	Clinical symptoms Clinical symptoms	Outcome
March (2020)[15]	Systematic literature review.	6.7	No	Fever 41.5% (71/171); Diarrhea 8.8% (15/171); Fatigue 7.6% (13/171); Rhinorrhea 7.6% (13/171); Vomiting 6.4 (11/171) Nasal congestion 5.3% (9/171); Tachypnea on admission 28.7% (49/171); Tachycardia on admission 42.1% (72/171)	In contrast with infected adults, most infected children appear to have a milder clinical course. Asymptomatic infections were not uncommon.
June (2020)[26]	Prospective observational study.	7.9	Yes	KD shock syndrome 57% (12); myocarditis 76% (16); GI symptoms 100% (21);	High proportion of the children and adolescents had gastrointestinal symptoms, Kawasaki disease shock syndrome, and were of African ancestry.
Jul (2020)[29]	Prospective multicenter study and meta-analysis.	4	Yes	Fever 76% (59/79) Cough 51% (40/79) Tachypnea 50% (39/79) Low SpO2 (<92%) 29% (23/79) Prostration 24% (19/79) Chest retraction 23% (18/79) Runny nose 22% (17/79) Diarrhea 21% (16/79) Refusal to eat 21% (16/79) Vomiting 21% (16/79) Dehydration 17% (13/79) Nasal wing beat 10% (8/79) Moaning 9% (7/79) Cyanosis 6% (5/79) Hypotension 6% (5/79) Reddish throat 4% (3/79)	Lethality was low and chronic diseases and other comorbidities played an important role in the development of severe forms of the disease. Unlike other studies, the age of less than one year was not associated with a worse prognosis. Patients with MIS had more severe symptoms, higher levels of inflammatory biomarkers and a greater predominance of males.
Aug (2020)[52]	Systematic review.	8.6	Yes	GI symptoms 71% (553/783); abdominal pain 36% (285/783); diarrhea 27% (214/783); vomiting 25% (196/783); rashes 42% (330/783); cough 4,5%(35/783); sore throat 4% (32/783);	1,5% (12/783) were reported to have died. (The cause of death was not stated for most patients).
June (2020)[53]	Case series.	9	Yes	Vomiting 45%(26/58); Abdominal pain 53% (31/58); Diarrhea 52%(30/58); Rash 52%(30/58); Conjunctival injection 45%(26/58); Shock and required inotropic support or fluid resuscitation 50% (29/58); Coronary artery dilatation or aneurysm 14% (8/58);	PIMS-TS comparable with KD and with KD shock syndrome showed more advanced age (9 years) and higher elevation of inflammatory markers, such as C-reactive protein (229mg).
Sep (2020)[67]	Case reports and case series.	9	Yes	Fever 100% (505/502); GI symptoms 88% (442/502); Conjunctivitis or conjunctival injection 50% (184/368); Oral manifestations 57% (112/201); Edema/ erythema of feet and hands 47,5% (19/40); Cervical lymphodynia 42,5% (37/84);	MIS-C due to SARS-CoV-2 is a serious disease in school-age children and adolescents, its complication can trigger cardiac hypotension, respiratory distress, thrombosis and acute renal injury. 7/505 children died (1.4%).

Continued **Table 1.**

Jul (2020)[68]	Systematic review.	6	Yes	Fever 64,2% (72/119); Cough 34,8% (39/112); Diarrhea 13,4% (15/112); Vomiting 6.3% (7/12); Dyspnea 10.7% (12/112);	Rapid confirmation of COVID-19 in children with mild symptoms or even any symptoms is essential to prevent further spread, complications and the development of a severe inflammatory state.
Jan (2021)[69]	Systematic review and meta-analysis.	9,3	Yes	fever 99,3% (804/809); GI 87,3% (564/653); respiratory symptoms 40,7% (259/488); neurological symptoms 36,00% (98/459);	MIS-C patients had a higher incidence of organ failure, GI symptoms and CD when compared to KD.

Legends: 1: Kawasaki disease (KD); 2: Multisystem inflammatory syndrome in children (MIS-C); 3: Gastrointestinal manifestations (GI); 4: Cardiac dysfunctions.

Table 2. Signs and symptoms in the child patients.

Clinical presentation and symptoms	Number of patients
Fever	(47,5)
Cough	(41,5)
Nasal symptoms	(11,2)
Diarrhea	(8,1)
Nauseous	(7,1)
Vomiting	(7.1)
Fatigue	(5%)
Dyspnea	(3.5)

In a controlled case study, 126 pediatric patients were identified, which 33 were infected with COVID-19[1]. In the questionnaire, 15% of infected children (all over 11 years old) reported insomnia and/or GI symptoms[1]. Another symptom reported by other author is dyspnea, especially in people under one year old[1]. Dyspnea is common in patients with the moderate to severe stages of the disease[1].

In another study, babies under six months of age were reported to have GI symptoms, such as vomiting, diarrhea and abdominal pain, data similar to the study we cited earlier[10,11]. In addition to lethargy, stuffy nose and coughing may occur as well[10,11]. In studies retrospective studies on dermatological manifestations of COVID-19, cutaneous findings have been reported infrequently and are not well characterized, which included: maculopapular rashes, urticarial, vesicular lesions, and transient livedo reticularis[23-25].

There is a group of patients with an average age of ten years who develop hyperinflammatory syndrome involving multiple organs and are classified as pediatric multiple system inflammation syndrome (MIS-C). These MIS-C patients usually present fever, GI symptoms, shock and Kawasaki Disease (KD) symptoms, including skin rash, conjunctivitis, swelling of the limbs, changes in the oral mucosa and cervical lymphadenopathy[2,26,27]. According to the epidemiological bulletin of the Brazilian Ministry of Health, from April 1, 2020 to January 2, 2021, 646 cases of pediatric MIS-C associated with COVID-19 were confirmed in children and adolescents up to 19 years of age. Among these, 41 patients died, of which 51.2% were children up to four years of age[22].

In a prospective multicenter study, carried out in 19 ICUs in Brazil, 79 pediatric patients with COVID-19 were evaluated. In which ten of them presented with MIS-C. The mean age was four years, 54% were male (80% MIS-C) and 41% (20% MIS-C) had previous comorbidities such as neuromuscular diseases (mainly non-progressive encephalopathy)[28]. A total of 60% had a condition similar to patients with KD, and 60% also had respiratory symptoms. In the MIS-C group, the symptoms were more severe, such as tachypnea (60%), low blood $SatO_2$ (40%), prostration (60%), groaning (30%), hypotension (20%), nasal wing beat (20%), and cyanosis (10%), as well as GI symptoms (40-60%) - more frequent than in the non-MIS-C group. The non-MIS-C group was the majority (87%) and presented the following symptoms: respiratory condition (68%) manifested with pneumonia (n=23); bronchiolitis (n=10); other causes (n=14). Besides, these they presented fever (75%), cough (53%), tachypnea (49%), low SpO_2 (<92%) (28%), prostration (19%), chest retraction (25%), runny nose (24%), diarrhea 12 (18%), vomiting (15%), dehydration (13%), nasal enlargement (9%), groaning (6%), cyanosis (6%), hypotension (4%), and red throat (3%)[28]. Non-MIS-C patients presented the same classic symptoms of COVID-19 during the disease as those with MIS-C, except for the classic manifestations of MIS-C: KD, cardiac dysfunction (CD), toxic shock syndrome, macrophage activation syndrome (MAS)[28].

Laboratorial

The initial laboratory data may present a normal blood count or mild leukopenia related to lymphopenia[7,22,29]. Certain inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may also be related to the increase of procalcitonin[29]. In more serious cases, there might be an increase in D-dimer, lactate dehydrogenase (LDH), liver enzymes (ALT, AST), and serum creatinine[3,7,26,27]. The expression of viral antigens in infected cells and the peak formation of IgG immune complexes can also activate and cause inflammation, SARS and multiple organ failure[26,28-30].

Diagnosis

The molecular reverse transcription and polymerase chain reaction test (RT-PCR) involves the polymerase chain

reaction in real time after obtaining the reverse transcription of RNA. Considered the gold standard, its collection is done with a cotton swab into the nose to nasopharynx. When a child is infected with a large number of viruses, they should be checked for in the first week of symptoms. The antigen can be detected by the rapid test, indicated for asymptomatic patients who was in contact with infected patient. The ideal collect is about five days after the contact with the patient or in the first week of symptoms. Finally, through the identification of serum antibodies, serological tests can be performed, indicated for patients who have already had the disease[19,31,32].

Imaging exams

The lung radiological characteristics of pediatric COVID-19 patients were compared with findings from two recently published systematic reviews and meta-analysis[33-35]. This comparison showed that pediatric patients were about three times more likely to have a normal CT scan compared to adults with COVID-19 (35.7% of children vs. 8.4%-10.24%)[32-34]. Bilateral damage during COVID-19 is more common in adults than in children. The most common finding in children was ground-glass opacity (37.2%), followed by consolidations or pneumonic infiltrates (22.3%)[33-35].

Early chest CT is important for symptomatic patients. Some negative tested patients are treated as suspected cases according to the typical lesions shown on chest CT. Tomographic findings provide evidence not only for early diagnosis, but also for the isolation of the infected patient. The most common findings of chest CT found were unilateral or bilateral subpleural ground-glass opacities (GGO) and consolidations with adjacent halo signs. Consolidations with surrounding halo signs represent up to 50% of cases and therefore should be considered as typical signs in this population[36]. In children, there is less diversity in chest CT findings compared to adults, with only a small number of pediatric patients presented multiple affected lobes. Chest CT may also show ground-glass opacities and segmental consolidation in both lungs. In severe cases, children may have bilateral involvement[37-39].

DISCUSSION

In relation to clinical manifestations, children may have present less typical symptoms than adults[23,24]. A systematic review carried out from January 2020 to March 2020 showed that children represented up to 5% of the cases diagnosed with COVID-19 in 45 reported articles[40]. Therefore, although severe cases have been reported, COVID-19 in children appears to be less severe than in adults[24,41].

MIS-C is a combination of typical/atypical KD, Kawasaki shock syndrome, toxic shock syndrome and MAS/hemophagocytic lymphohistiocytosis[2]. Kawasaki disease is a type of primary acute systemic vasculitis, of unknown etiology, most common in childhood[25,42]. The typical presentation of KD as defined by the American Heart Association (AHA) is characterized by persistent fever for more than five days associated with at least four more clinical indicators: fever for five days or more, non-purulent conjunctivitis, raspberry-like tongue, oropharyngeal erythema, cleft lip, erythema and hands edema and feet with periungual desquamation and enlargement of cervical lymph nodes[43-46]. Atypical or incomplete KD should be considered in all children with unexplained fever for over than five days associated with two or three of the main clinical findings of KD[47]. Kawasaki disease shock syndrome is a rare form, often associated with myocarditis and requires intensive care during its early course[48,49]. Lastly, MAS is a life-threatening condition, and it is a subset of hemophagocytic lymphohistiocytosis (HLH). The clinical features include persistent high-grade fever, hepatosplenomegaly, lymphadenopathy, hemorrhagic manifestations, and a sepsis-like condition[50].

Literature data point to different clinical features of MIS-C patients, including fever with inflammation, MIS-C shock with myocarditis, and classic KD[27,30,42,43,51]. A study about case series included 58 hospitalized children with definition criteria for pediatric MIS-C temporally associated with SARS, including fever, systemic inflammation, and organ dysfunction. Of these, all presented with fever and nonspecific symptoms, such as abdominal pain (53%), rash cutaneous (52%), and conjunctival infection (45%); 29 (50%) developed shock and required inotropic support or fluid resuscitation; 13 (22%) met diagnostic criteria for KD; and 8 (14%) presented coronary artery dilatation or aneurysms[52]. The MIS-C development is related to antibody production in the immune response caused by the virus, and is not directly related to virus replication. In addition, specific ethnic groups (Hispanic and African descent) confirmed the role of genetic locus associated with the most severe cases. Given these data, it is notable that patients with MIS-C usually require special care and active treatment[27,30].

Compared to serological testing, the detection sensitivity of RT-PCR reaction is low, and it is affected by many external factors, such as sampling time, collection type and kit performance. The sensitivity of serological testing ranges from 72.7 to 100%. However, serological testing can be negative in patients in the early stage of infection[53-55]. It is worth noting that the research involving antibodies was conducted in adults, so caution should be taken when applying these results to children and teenagers[56,57]. In addition to nasal secretions, prolonged removal of the virus from feces increases the possibility of transmission in children[58]. In a retrospective study, conducted in four Chinese hospitals between January and March 2020, even after nasal swabs were negative, eight out of ten children with COVID-19 had positive rectal swabs, indicating a chain of fecal-oral transmission[59].

In the early stages of the disease or in patients with mild symptoms, chest X-rays may not show relevant findings. Only 20% of the X-rays of patients with COVID-19 showed no changes[60]. Therefore, chest X-rays are not recommended as the first option for patient management because of its low sensitivity to GGO. The American College of Radiology (ACR) recommends chest CT for screening or diagnosing COVID-19[61].

A systematic literature review analyzed 45 articles published between 2019 and 2020, and the diagnostic findings in children were similar to those in adults, with fever and respiratory distress as prevalent symptoms, but fewer children appear to have developed pneumonia[62]. Elevated inflammatory markers were less common in children and lymphocytopenia appeared to be rare[62]. It is suggested that ACE2 is a cell receptor for the virus and that children are less sensitive to COVID-19 than adults, due to the lower maturity and function (ex.: binding capacity) of ACE2[40,63,64]. In addition, children often have respiratory infections during the winter, and thus may present more antibodies along with the fact that a child's immune system is still developing and can respond to pathogens differently than adults[65,66].

In a study with 505 children with an average age of nine years, fever was used as a mandatory symptom for inclusion in the report. Among them, (82.2%) survived and seven (1.4%) children died; the rest remained hospitalized[67]. Symptoms such as abdominal pain, vomiting and/or diarrhea were present in 442 of 502 children (88.0%). Clinical signs of KD have frequently occurred: cutaneous rash (59.2%), conjunctivitis or conjunctival infection (50.0%), oral changes defined as cheilitis and/or "strawberry tongue" (55.7%), edema or erythema of hands and feet (47.5%), and cervical lymphadenopathy (42.5%). Family contact with suspected or confirmed SARS-CoV-2 was reported in 83 of 252 (32.9%) children (Table 3)[67].

In a survey of 917 patients with an average age of 9.3 years, with MIS-C and infection confirmed by COVID-19, high values of inflammatory markers, D-dimer and cardiac markers were found. In addition, MIS-C patients had a higher incidence of myocardial dysfunction, coronary artery dilation or aneurysm and gastrointestinal symptoms when compared to KD (Table 3)[67,68]. Therefore, the mechanisms in clinical manifestations between children and adults still need to be determined.

Table 3. Spectrum of signs and symptoms between COVID-19, MIS-C and KD.

Type of disease	Clinical characteristics
Classic COVID-19	Asymptomatic; Fever; Respiratory symptoms; Gastrointestinal symptoms.
MIS-C	Fever; Higher gastrointestinal symptoms when compared to KD; Respiratory symptoms; Systemic inflammation; Elevation of inflammatory markers; Myocardial dysfunction, coronary artery dilation or aneurysm; Organ failure.
KD	Fever; Skin rash; Conjunctivitis or conjunctival infection; Oral changes (strawberry tongue); Edema or erythema of hands and feet; Cervical lymphadenopathy.

Corroborating these data, the Brazilian study cited in our results compared patients with MIS-C (12%) and non-MIS-C (87%)[28]. It is noteworthy that the classic symptoms of COVID-19 are present in both groups; however, the common manifestations of MIS-C (KD, CD, toxic shock syndrome, MAS) are presented only by this group, which, therefore, makes it different. Interestingly, previous comorbidities (obesity, chronic respiratory disease, onco hematological disease, undernutrition, diabetes, prematurity, and chronic liver disease) are reported only in non-MIS-C patients[28]. This study has some limitations, mainly due to the small size of the subgroups and because it involves only Brazilian patients. Despite these limitations, it is believed that this study may have contributed to a better understanding of COVID-19, since it describes the first large series of patients admitted to the UTI in the southern hemisphere.

CONCLUSION

Most children have a favorable arc upon being diagnosed with COVID-19, and their clinical manifestations may be different from adults. In addition, regarding fever and respiratory symptoms, we can also consider skin and GI manifestations as part of the disease in children. Changes in chest CT may result in opacity of the subpleural glass membrane with surrounding halos, which makes this examination an effective method for identifying lung manifestations. As many hospitals are aware of such conditions, it is very important to develop a specific treatment plan for pediatric patients with COVID-19. Although children do not appear to have severe symptoms, the prognosis of children with underlying diseases may be worse, with the development of pediatric MIS-C that shares clinical and laboratory characteristics of KD (typical or atypical), staphylococcal and streptococcal toxic shock syndrome, bacterial sepsis and MAS. Research on the forms of transmission can help prevent further changes and future cardiac and respiratory complications. Finally, further studies are required to develop a better diagnosis and treatment of MIS-C.

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