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COVID-19 and paediatric patient involvement (cardiovascular aspects)

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The majority of children with COVID-19 infections, fortunately, shows only milder symptoms. Which however has led that they are considered only for their particular transmission potential. Nevertheless, cases with Multisystem Inflammatory Syndrome in Children and Kawasaki Disease with quite specific COVID-19 involvement have been reported and should be taken seriously. In addition, there are many children with a chronic pre-existing condition such as congenital heart disease, cancer, or lung disease who may be at risk for a severe course of COVID-19 when infected. Protecting these children, and children in general, should be a top priority, as these patients will have to live the rest of their long lives with possible sequelae of COVID-19.

Introduction

While in the current coronavirus disease 2019 (COVID-19) pandemic the focus is on the geriatric population because of the high mortality rate, the paediatric target group receives less attention regarding their long-term health consequences. Since children are less susceptible to the severe development of COVID-19, they are usually considered only for their particular transmission potential.

It may be correct that the vast majority of paediatric patients are showing just mild symptoms such as mild fever, cough, rhinorrhoea, sore throat, or occasional gastrointestinal symptoms, vomit, and diarrhoea.[1] However, the clinical picture of COVID-19 is nevertheless manifold and therefore it is imperative to not lose sight of the small minority becoming severely ill specifically those with cardiac involvement in their medical history.

This is made clear by the fact that several authors around the world have reported paediatric inflammatory multisystem syndrome (PIMS) or Kawasaki syndrome like disease in connection to COVID-19 infections. In addition, acute inflammatory response similarly as seen during a cytokine storm causing cardiomyocyte injury,[2] cellular damage because of cardiomyocyte viral invasion,[3] and acute lung injury causing ischaemic injury along with severe hypoxia[4] is reported. Last but not least, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the enzyme ACE2 as a receptor for entry into the cell.[5,6] Whether this binding of the virus has an impact on ACE2 expression or leads to a dysregulation in pathways is still unclear but in the worst case, long-term cardiovascular damage could be the result of even a only mild COVID-19 infection.[7]

Multisystem inflammatory syndrome in children and Kawasaki disease

The majority of children with COVID-19 infections show milder symptoms. While few in numbers, previous reports highlight two disease conditions in particular connected to severe disease development:

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Textbox 1 Criteria for the diagnosis of Kawasaki disease according to ref.[9]
Fever for more than 5 days (4 days if treatment with intravenous immunoglobulin eradicates fever) plus at least four of the following clinical signs not explained by another disease process:

- Bilateral conjunctival injection (80–90%)*.
- Changes in the oropharyngeal mucous membranes, including one or more of injected and/or fissured lips, strawberry tongue, injected pharynx (80–90%).
- Changes in the peripheral extremities, including erythema and/or oedema of the hands and feet (acute phase) or periungual desquamation (convalescent phase) (80%).
- Polymorphous rash, primarily truncal; non-vesicular (>90%).
- Cervical lymphadenopathy with at least one node >1.5 cm (50%).

multisystem inflammatory syndrome in children (MIS-C), and Kawasaki disease (KD).

MIS-C, sometimes also referred to as PIMS is characterized by fever and laboratory inflammation conditions (such as elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin) with multisystem (>2) organ involvement (including heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs). Specific causes are still unclear.

KD is an acute febrile illness that primarily affects children younger than 5 years of age, and the leading cause of acquired heart disease in high-income countries[8] with the diagnostic criteria as shown in *Textbox 1*.[9] Symptoms such as eye redness, swelling of lymph glands in the neck, and mouth, lips or throat irritation and inflammation, lips, and throat are often similar to MIS-C. Coronary artery dilations and aneurysms can result of serious complications. KD is also sometimes seen in patients with fever and coronary artery abnormalities but who do not meet the mentioned KD symptoms and is therefore characterized as atypical or incomplete.

Since the beginning of SARS-CoV-2 epidemic, it was reported of previously healthy children with fever, multisystem inflammation and non-specific symptoms like rash, gastrointestinal symptoms, and lip swelling. Symptoms ranged to myocardial shock, development of coronary artery aneurysms and some showing characteristics that were similar to KD.[10]

An observational study in the province Bergamo, which was extensively affected by SARS-CoV-2 epidemic, reports of a high number of KD-like diseases. Since the beginning of the epidemic a monthly incidence at least 30 times greater than in the previous 5 years has occurred, with a clear starting point of the increase after first COVID-19 cases. Children affected with KD-like disease after SARS-CoV-2 epidemic were older, had higher rate of cardiac involvement and higher incidence of severer form of KD disease than children affected previously by SARS-CoV-19.[11]

Heavily affected regions by SARS-CoV-2 in Europe are also reporting of cases with MIS-C.[10,12,13] A case series of 58 children diagnosed with MIS-C in British hospitals reported of persistent fever and inflammation. 29 children developed shock and eight children developed coronary artery dilatation or aneurysm.[10] Cardiac involvement has been reported in a proportion of MIS-C patients.[14]

MIS-C showed overlapping clinical features as well as substantial differences with KD disease. MIS-C has some of the clinical features of KD like fever, rash, redness of the oropharynx.[15] MIS-C was shown to affect an older age group and shows higher prevalence of gastrointestinal symptoms than KD.[16] MIS-C appears to be a rare complication of SARS-CoV-2 infections with some estimations that MIS-C occurs in two out of 200 000 individuals under the age of 21 years.[17] Until now it has yet to be determined that SARS-CoV-2 is the cause of MIS-C or KD.[15]

As KD and MIS-C have shown us new and quite specific COVID-19 involvement, reported experience is described in more detail in *Table 1*.

COVID-19 in patients with CHD and other chronical disease

With a prevalence of one in 100 live births congenital heart defects (CHDs) are the most common congenital abnormality.[18] However, reports of children with CHD infected with COVID-19 are sparse, and therefore the specific impact on this specific patient population has yet to be fully determined.[7] As the risk for severe COVID-19 infections is reduced in younger populations and incidents of cardiovascular complication rates have been low, we can be hopeful that children and adolescents with CHD are not facing an increased risk.[19] However, although infections are less common and milder in children, a cardiac medical history seems to be not without risk, as severe cardiac development of COVID-19 can include myocarditis, arrhythmia, and myocardial infarction.[4] In addition, experiences with previous viral diseases such as influenza and respiratory syncytial virus have shown a more rigorous impact on children with complex CHD than on otherwise healthy children.[4]

Severe COVID-19 clinical course in children has been linked to a complex previous medical history. Paediatric patients with underlying conditions, including those with a history of CHD surgery[20,21] chronic lung disease, cirrhosis, renal disease,[4] or who showed a developmental delay, a genetic anomaly, or who were dependent on technological support for survival (tracheostomy) have been reported with more severe COVID-19 course.[14] Paediatric oncological patients might also deserve particular protection as

Table 1 Studies reporting experience with KD and MIS-C and COVID-19 involvement

Study	*n*	Participants	Clinical symptoms	Echocardiography	Laboratory results	Clinical course following admission
Childhood multisystem inflammatory disorders						
Whittaker *et al.*, 2020	58	• Age: 9 years (3 months-17 years) • Male ($n=38$) • 40 Black or Asian 51: Previously healthy 7: Comorbidities • 3 Asthma • 1 Neurodysability • 1 Epilepsy • 1 Sickle cell trait • 1 Alopecia 45/58 had evidence of current or prior SARS-CoC-2 infection	• Persistent fever 3-19 days ($n=58$) • Sore throat ($n=6$) • Headache ($n=15$) • Abdominal pain ($n=31$) • Esythematous rashes ($n=30$) • Conjunctival injection ($n=26$) • Lymphadenopathy ($n=9$) • Mucus membrane changes and red cracked lips ($n=17$) • Swollen hands and feet ($n=9$)	• Left ventricular dysfunction ($n=18$, 29 tested) • Abnormally dilated coronary arteries (z score >2), including 7 with z scores greater than 2.5 ($n=8$) • Giant coronary artery aneurysms (z score >10) ($n=2$) • Coronary artery aneurysms ($n=8$)	• ↑ troponin ($n=19$, 29 tested) • ↑ NT-proBNP ($n=11$, 1 tested)	• Developed shock ($n=29$) • Admission to paediatric critical care units ($n=29$) • Mechanical ventilation for respiratory support ($n=25$) • Persistent fever and elevated inflammatory markers ($n=23$) • Met the criteria for KD when coronary artery aneurysms were included ($n=13$) • Acute kidney injury ($n=13$) • Developed arrhythmia ($n=4$)
Dufort *et al.*, 2020	95	• Male ($n=53$) • 31 Black • 31% 0-5 years • 42% 6-12 years • 26% 13-20 years 100% had evidence of recent SARS-CoV-2 infection	• Subjective fever or chills ($n=95$) • Tachycardia ($n=92$) • Gastrointestinal symptoms ($n=76$) • Rash ($n=57$) • Conjunctival injection ($n=53$) • Mucosal changes ($n=27$) • Tachypnoea ($n=74$) • Hypotension ($n=30$)	• Some degree of ventricular dysfunction ($n=51$) • Pericardial effusion ($n=32$) • Coronary-artery aneurysm ($n=9$)	• ↑ C-reactive protein ($n=95$) • ↑ d-dimer ($n=86$) • ↑ troponin ($n=63$) • ↑ proBNP levels ($n=74$)	• Admitted to an intensive care unit ($n=76$) • Vasopressor support ($n=59$) • Myocarditis ($n=50$) • KD or incomplete KD ($n=36$) • One or more of the following: hypotension or shock, severe cardiac illness, or other severe end-organ illness ($n=29$) • Mechanical ventilation ($n=10$) • Died ($n=2$) • Lymphopenia ($n=89$)

(continued)

Table 1 Continued

Study	*n*	Participants	Clinical symptoms	Echocardiography	Laboratory results	Clinical course following admission
						• Median length of hospital stay: 6 days
Feldstein *et al.*, 2020	186	• Age: median 8.3 years (IQR 3.3-12.5) • Male ($n=115$) 135: previously healthy (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing	• Fever for five or more days ($n=131$ of 167) • Gastrointestinal ($n=171$) • Cardiovascular ($n=149$) • Haematologic ($n=142$) • Mucocutaneous ($n=137$) • Respiratory ($n=131$) systems	• Coronary-artery aneurysms identified on the basis of a z score of 2.5 or higher ($n=15$ of 186) and with echocardiograms ($n=15$ of 170)	• ↑ level of BNP($n=94$, of 128) • ↑ troponin levels ($n=77$)	• Intensive care unit ($n=148$) • Respiratory insufficiency or failure occurred ($n=109$) • Vasoactive support ($n=90$) • KD-like symptoms ($n=74$) • Invasive mechanical ventilation ($n=37$) • Non-invasive mechanical ventilation ($n=32$) • Extracorporeal membrane oxygenation support ($n=8$) • Died ($n=4$) • Median duration of hospitalization: 7 days (IQR 4-10)
Cheung *et al.*, 2020 Research letter	17	• Age: 8 years (2.8-16) • Male ($n=8$) • White ($n=12$) 14: Previously healthy 3: Mild asthma 100% had evidence of recent SARS-CoV-2 infection	• Fever (median duration 5 days) ($n=17$) • Gastrointestinal symptoms ($n=14$) • Rash ($n=12$) • Conjunctivitis ($n=11$) • Lip redness/swelling ($n=9$) • Hypoxic (3) • Abnormal chest radiograph findings (14)	• Mildly decreased left ventricular function ($n=11$) • Moderate or more ventricular dysfunction ($n=6$) • Coronary arteries prominent or echogenic ($n=7$) • Medium-sized aneurysm (z score, 5.2) of the left anterior descending coronary artery ($n=1$)	• ↑ levels of inflammatory markers ($n=17$) • Lymphopenia ($n=12$) • Bandemia ($n=1$) • ↑ troponin T ($n=14$) • ↑ NT-proBNP level ($n=15$)	• Paediatric intensive care unit admission ($n=15$) • Shock ($n=13$) • Vasoactive support ($n=10$) • Hypoxia ($n=9$) • KD ($n=8$) or incomplete KD ($n=5$) • Non-specific ST/T-wave abnormalities ($n=10$) • Attenuated QRS voltage ($n=1$) • Dysrhythmias ($n=3$) • Median length of hospital stay of 7.1 days (range,

(continued)

Table 1 Continued

Study	*n*	Participants	Clinical symptoms	Echocardiography	Laboratory results	Clinical course following admission
						3-18), all discharged home with no fatalities
Kawasaki disease Verdoni *et al.*, 2020	10	• Age: 7.5 years (SD 3.5) • Male ($n=7$) 100% SARS-CoV-2 positive	50% complete KD, 50% incomplete KD: • Non-exudative conjunctivitis ($n=7$) • Hand and feet anomalies ($n=5$) • Polymorphic rash ($n=6$) • Associated changes of the lips or oral cavity, or both ($n=6$)	• Abnormal echocardiogram ($n=6$) • Left coronary aneurysm (>4 mm), reduced ejection fraction and mitral valve regurgitation ($n=2$) • Mitral valve regurgitation ($n=4$) • Pericardial effusion ($n=4$)	• ↑ proBNP ($n=10$) • Intravenous immunoglobulin-resistance ($n=7$) • Macrophage activation syndrome ($n=5$) • ↑ troponin I ($n=5$) • ↑ creatine phosphokinase ($n=1$)	• KD shock ($n=5$) syndrome • Pneumonia ($n=5$) • Meningeal signs ($n=4$)

BNP, B-type natriuretic peptide; KD, Kawasaki disease; proBNP, ↑, elevation.

they also possibly develop cardiac complications through treatment.[22] Aside from these, early reports experienced further predisposing factors for increased disease severity such as bronchopulmonary hypoplasia, respiratory tract abnormalities, haemoglobinopathies, severe malnutrition, and immune system deficiency.[23]

Conclusion

Most infections in children with COVID-19 appear to be mild. However, children with chronic diseases and complex medical histories require specific attention. Their clinical course during COVID-19 infection can be severe and we do not have any idea about the long-term (cardiovascular) consequences yet. Children always deserve special protection because they are our future and will have to live the longest with possible medical consequences.

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