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COVID19: potential cardiovascular issues in pediatric patients

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Summary. The novel severe acute respiratory syndrome coronavirus 2 (SARS-COV 2) has rapidly spread worldwide with increasing hospitalization and mortality rate. Ongoing studies and accumulated data are detailing the features and the effects of the new coronavirus disease 19 (COVID 19) in the adult population, and cardiovascular involvement is emerging as the most significant and life-threatening complication, with an increased risk of morbidity and mortality in patients with underlying cardiovascular disease. At present, though the limited data on the effects of COVID 19 in pediatric patients, children seem to count for a little proportion of SARS-COV 2 infection, and present with less severe disease and effects However infants and toddlers are at risk of developing critical course. The disease has a range of clinical presentations in children, for which the potential need for further investigation of myocardial injury and cardiovascular issues should be kept in mind to avoid misdiagnosing severe clinical entities. Overlapping with Kawasaki disease is a concern, particularly the incomplete and atypical form. We aim to summarize the initial considerations and potential cardiovascular implications of COVID-19 for children and patients with congenital heart disease. (www.actabiomedica.it)

Key words: COVID - 19, Children, Cardiovascular, Myocarditis, Kawasaki disease, Congenital heart diseases.

Introduction

Coronavirus disease 19 (COVID-19) is a severe acute respiratory syndrome for which the etiologic agent is the novel beta coronavirus SARS-CoV-2, first described in December 2019 in China in a cluster of patients presenting with pneumonia. In the past few months, the disease has spread worldwide and become a pandemic. Since the outbreak began, the virus has raised concerns among medical professionals worldwide because of the increasing rates of patient hospitalization and mortality. The main presenting clinical feature of the disease is pneumonia, ranging from asymptomatic or mildly symptomatic to severe acute respiratory distress syndrome, but cardiovascular involvement is emerging as one of the most significant and life-threatening complications of SARS-CoV-2 infection (1, 2). In addition, patients with underlying cardiovascular diseases (CVDs) may be subject to an increased risk of death (1,2,3). At present data are limited regarding the incidence and effects of COVID-19 in pediatric patients, but it seems that children present with less severe effects and disease. We aim to summarize the initial considerations and potential cardiovascular implications of COVID-19 for children and patients with congenital heart disease.

COVID – 19 and Cardiovascular Injuries

Viral infection has been widely described as one of the most common infectious causes of myo-

carditis. Some reports suggest that SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV) share similar pathogenicity with SARS-CoV-2 (1), and since the previous coronavirus epidemics (SARS-CoV and MERS-CoV), known cases of myocarditis have been caused by these viruses (4-6). Furthermore, patients with underlying heart disease (both congenital or acquired) seem to have increased morbidity and mortality related to viral infections (7).

The pathogenesis of cardiac involvement associated with SARS-CoV-2 may reflect a process of replication and dissemination of the virus through the blood and/or the lymphatic system from the respiratory tract. SARS-CoV-2 may lead to cardiac injury via several hypothetical mechanisms:

- The SARS-CoV-2 virus uses ACE2 as a receptor for entry into the cell; this enzyme is widely expressed in the lungs but also in the heart and blood vessels. It is unclear at this time, however, whether the SARS-CoV-2 binding alters ACE2 expression or causes dysregulation of the RAAS (renin-angiotensin-aldosterone system) pathway (8-11).
- Viral invasion may lead to an unbalanced response by type 1 and type 2 T helper cells, triggering an exaggerated inflammatory and immune response and a cytokine storm. The mechanism by which cytokines damage the myocardium is still unknown (12-17).
- The acute lung injury caused by the virus leads to acute respiratory damage and subsequent severe hypoxia, which may result in oxidative stress, endothelial shedding, microvascular damage, and myocardial injury due to increased myocardial oxygen demand (14, 18, 19).
- Direct viral toxicity to cardiomyocytes has been shown in other viral infections, such as Coxsackievirus or influenza-induced myocarditis, but in the setting of SARS-CoV-2 infection, though cases of myocarditis have been described (20-23), of cardiomyocytes viral invasion and direct damage have not yet been proven in pathology studies.

SARS-CoV-2 infection facilitates the induction of endotheliitis as a direct consequence of viral involvement and of the host's inflammatory response. Endothelial dysfunction is the main determinant of microvascular dysfunction because it shifts the vascular equilibrium toward more vasoconstriction, inflammation with associated tissue edema, and a procoagulant state, contributing to vessel thrombosis and subsequent organ ischemia (18, 19, 24).

Studies have shown that a significant percentage of patients affected with COVID-19 displayed evidence of myocardial injury (2, 3, 7, 13, 14, 17, 18). SARS-CoV-2 cardiac involvement mainly manifested as an increase in the levels of biomarkers of myocardial injury: high-sensitivity cardiac troponin I, N-terminal pro B-type natriuretic peptide, and CK-MB (1, 2, 7, 24, 25, 26). Patients with COVID-19 can present with chest pain, dyspnea, palpitations, dysrhythmia, and acute left ventricular dysfunction (1, 2, 18, 21, 28). Dysrhythmias may occur in the setting of viral illness due to hypoxia, inflammatory stress, and abnormal metabolism, but no specific ECG changes have been described in patients with SARS-CoV2 infection.

Myocardial injury may be drug-related. Although currently no specific effective therapies for COVID-19 exist, various pharmacologic agents are under active investigation, mainly antivirals (remdesivir, lopinavir/ritonavir, Favilavir), antimalarials (chloroquine, hydroxychloroquine), corticosteroids, monoclonal antibodies and antibiotics (azithromycin) (29-33). Many antiviral drugs can cause cardiac insufficiency, arrhythmia, or other cardiovascular disorders (1, 2, 17, 34, 35). Antimalarials and some antibiotics can cause QT interval prolongation and malignant arrhythmias (35, 36).

Pediatric Patients

Children do not seem to count for a large proportion of COVID-19 disease infections. Numbers gathered from different studies suggest a great deal of variation in incidence, 2% in the largest series from China, 1.2% in the pediatric cohort from Italy, 4.8% in Korea, and 1.7% in the United States (37, 38, 39, 40). It is possible that protective measures, especially social distancing from children and community closure, have impacted the incidence in pediatric patients. Only limited data detail the effects of COVID-19 on the pediatric population. Preliminary evidence suggests children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be sympto-

matic or develop severe symptoms. In the largest series published to date, 94.1% of the children were either asymptomatic or had mild to moderate disease (37, 41-44). Information about pediatric patients requiring intensive care is scarce. The largest pediatric series showed 5.2% of children with respiratory distress or hypoxia and 0.6% who progressed to acute respiratory distress syndrome or multiple organ dysfunction (37). Children under 5 years of age are at risk of developing severe disease, with infants presenting the highest risk (37, 42, 45, 46). Laboratory findings do not show a tendency toward immune dysregulation and blood count and pro-inflammatory markers may be normal, but altered liver function test results are common, as are D-dimers, especially in severe cases (38, 43, 44, 46).

Children with SARS-CoV-2 may present with flu-like features, fever, cough, and shortness of breath, as the most frequent symptoms (38, 42, 43, 47). Chest pain may be present in some cases, while others may show vomiting, abdominal pain, and diarrhea as the only symptoms (48). Infants and children with severe forms may present looking very ill, with cold extremities, weak peripheral pulses, and hepatomegaly (45, 46, 48). Tachycardia is seen as a result of multiple, simultaneous causes (fever, dyspnea, pain, anxiety, etc.) and is usually sinus tachycardia without any other significant signs on an ECG (48).

Myocardial injury

Acute myocardial injury is rare in children and adolescents. It is usually associated with either an acute inflammatory condition of the myocardium or the coronary arteries, or an anomalous origin in the left coronary artery.

Myocardial injury may derive from myocarditis, an inflammatory disease of the myocardium, or pericarditis, irritation or inflammation of the pericardial layers, with viral infection as the most commonly identified cause (Epstein-Barr virus, adenovirus, parvovirus B19, Coxsackievirus, influenza virus, enterovirus, and echovirus) (49-51). Children with SARS-CoV-2 may present with another viral agent coinfection (48). The clinical manifestations of myocarditis and pericarditis can range from mild nonspecific symptoms to chest pain to cardiogenic shock. Myocarditis in children may present with flu-like symptoms, shortness of breath, tachycardia, dyspnea, nausea, and decreased appetite, or poor feeding and tachypnea in infants (50, 51). In the fulminant form, the children are critically ill with cold extremities, weak peripheral pulses, a gallop rhythm, and hepatomegaly more commonly than rales and edema. Pericarditis, most common in adolescents, classically presents with chest pain exacerbated when supine, when coughing, or with inspiration and relieved by the sitting position (50, 51). Elevated cardiac biomarkers such as creatine kinase muscle-brain isoenzyme, troponin I, and troponin T (reported to have specificity of 86% and sensitivity of 71% in children) (51) and ECG anomalies (ST segment and T wave changes, QRS complex voltage) confirm the diagnosis of cardiac injury. Troponin I and T levels are more frequently elevated in acute myocarditis than are creatine kinase muscle-brain levels (50, 51). However, normal biomarker levels do not completely exclude myocarditis.

COVID – 19 and Kawasaki disease

COVID-19 may sometimes present with the clinical features of vasculitis, mimicking characteristics of Kawasaki disease, an acute febrile illness with cardiac involvement and a predilection for the coronary arteries, for which we can distinguish a typical, atypical and an incomplete form. In the typical form, Kawasaki disease is characterized by enanthem (mucous membrane rash), bulbar conjunctivitis, rash, lymphadenopathy, and extremity changes (52, 53). The incomplete form is diagnosed when the patient presents with typical fever, two or three of the principal clinical features, and suggestive laboratory findings such as elevated erythrocyte sedimentation rate, elevated C-reactive protein, hypoalbuminemia, anemia, elevated alanine aminotransferase, thrombocytosis, or leukocytosis (52, 53). Atypical form is characterized by typical fever and clinical features different from the main signs and symptoms of Kawasaki disease (pneumonia, acute abdomen, central nervous, system involvement, nephritis, myositis, etc.…) (52, 53). Although decades of investigation, and some evidence suggesting for an infectious trigger, etiology of Kawasaki disease remain unknown. Association of Kawasaki disease with viral respiratory infections have been described in several studies, including human coronavirus (54-57). Initial hypothesis of Dr Tomisaku Kawasaki was that a coro-

navirus was the etiologic cause of the mucocutaneous lymph node syndrome he was describing. Several clinical signs of Kawasaki disease providing important diagnostic clues have not been included in the diagnostic criteria, myocarditis, sterile pyuria, peripheral arthritis, and may also present with COVID-19 confounding furthermore the diagnosis. The cytokine storm present in a phase of SARS-COV 2 disease recall the role of inflammatory biomarkers in Kawasaki disease, particularly interleukine 6. In some cases, COVID-19 presentation may raise doubts, mainly related to incomplete or atypical Kawasaki disease, and differentiating the entities may be challenging but fundamental because of the potential serious cardiac sequelae.

Pre-existing cardiovascular diseases and congenital heart diseases

We learn from the adult cohort that patients with preexisting cardiovascular diseases have increased morbidity and mortality. According to a morbidity/mortality report by the Centers for Disease Control of the United States, among the pediatric cases with information on underlying conditions, the most common underlying condition after chronic lung disease was cardiovascular disease (58, 59). Up to now, no studies detail the risk of individual cardiovascular complications in patients with underlying cardiovascular disease who are infected with SARS-CoV-2, neither have any studies included patients with congenital heart disease Standing on what is known some patients with congenital heart disease are at high risk, depending on the complexity of the lesion and their clinical and surgical status. Syndromic patients, especially those with reduced immunity, including heterotaxy syndrome, Down syndrome, DiGeorge syndrome, and asplenia, may be at even higher risk (7, 60). Children with congenital heart disease who may be at higher risk for serious illness from SARS-COV 2 include:

- Patients with single heart physiology: hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia, unbalanced atrioventricular canal, Glenn anastomosis, Fontan procedure
- Patients with surgical aorto-pulmonary connection, modified Blalock-taussig shunt, Waterson anastomosis, Potts anastomosis, pulmonary artery banding
- Patients with pulmonary hypertension
- Patients who are due to have surgery in the near future, large ventricular septal defect, atrioventricular septal defect, tetralogy of Fallot, total anomalous pulmonary venous return.

Any child with a cardiopathy requiring medication for heart failure, may experience a worsening of their clinical status because of the hemodynamic impact of the lung involvement and/or myocardial injury of SARS-CoV-2 infection. Children who have had previous heart surgery without sequelae and are not taking any heart medications may follow basic preventive indications.

Arrhythmias and drug related issues

COVID-19-related issues such as fever, electrolyte disturbance, and current treatment may have a pro-arrhythmic effect, making it challenging to manage the illness in children with inherited (long QT syndrome, Brugada syndrome, short QT syndrome and catecholaminergic polymorphic ventricular tachycardia) or acquired arrhythmias, sometimes associated with repaired or unrepaired congenital structural heat lesions. Active studies are evaluating different agents to determine the best treatment, most of which may have serious undesired cardiovascular effects (2, 7, 34-36). Very few of these studies involve children, so data will have to be extrapolated from adult studies. Actual ongoing trials include (see Table 1)

- antivirals, especially lopinavir, ritonavir, and ribavirin;
- antimalarials, namely chloroquine and hydroxychloroquine;

Table 1. COVID 19 present medications and cardiovascular system

Medications	Cardiovascular effects
Antivirals	Direct myocardial toxicity; Prolonged QTc, AV blocks, Torsades de pointes, Interaction with antiarrhythmics
Chloroquine and Hydroxychloroquine	Direct myocardial toxicity; Worsen cardiomyopathy; Bundle branch block; AV block; Ventricular arrhythmias; Torsades de pointes; Prolonged QTc
Azithromycin	Dysrhythmias; Prolonged QTc; Torsades de pointes
Corticosteroids	Fluid retention; Hypertension, Electrolyte changes
Tocilizumab	Hypertension

- azithromycin;
- corticosteroids, particularly methylprednisolone;
- biologics with tocilizumab.

ACE inhibitors and angiotensin receptor blockers (ARBs) are commonly used in various settings in pediatric cardiology. Some study authors stated that their use may have affected the course of COVID-19 (1); they suggested that ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) may upregulate ACE2, thereby increasing susceptibility to the virus. Other studies, in contrast, show that ACEis/ARBs may potentiate the lung-protective function of ACE2, which is an angiotensin II inhibitor (61, 62). It remains controversial whether patients with COVID-19 under treatment with an ACE inhibitor or angiotensin-receptor blocker should switch to another drug, and further evidences are required. As such, the Heart Failure Society of America, American College of Cardiology, American Heart Association, and European Society of Cardiology released a statement recommending continuation of renin-angiotensin-aldosterone system inhibitors for patients currently taking them for "indications for which these agents are known to be beneficial".

Conclusion

Cardiovascular issues are emerging as one of the most significant and life-threatening complications of SARS-CoV-2 infection in adult patients. Though pediatric critically ill COVID-19 patients remain rare, the disease has a range of clinical presentations in children, for which the potential need for further investigation of myocardial injury and cardiovascular issues should be kept in mind to avoid misdiagnosing severe clinical entities. Data are lacking for COVID-19 in some pediatric subpopulations, including in patients with underlying conditions, but some reports indicate that these populations are at increased risk of morbidity and mortality. Children with preexisting complex cardiovascular conditions may be at higher risk. If they require careful monitoring and follow-up in case of infection, extensive preventive measures must be taken with these patients. Frequent handwashing, social distancing measures, proper and appropriate use of masks and other personal protective equipment, and the use of technology should be prominent in their management to minimize the risk of nosocomial infections.

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