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CASE REPORT

COVID-19: report of cardiovascular manifestations in childhood

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Abstract

Coronavirus 2019 disease (COVID-19) was believed to have little effect on the pediatric population. However, over the months, it became evident that its occurrence goes beyond the oligo or asymptomatic form in childhood, being part of a vast multisystemic affection secondary to the inflammatory cytokine storm called, multisystemic inflammatory syndrome (MIS-C). This, in turn, includes cardiac involvement, which can lead to myocarditis, pericarditis and even coronary changes. We will describe two cases of children diagnosed with COVID-19, admitted to the pediatric intensive care unit (PICU), with different forms of cardiovascular involvement. Thus, through this variety of signs and symptoms associated with the virus, our goal is to be able to contribute to filling in the gaps regarding its clinical manifestations and possible therapeutic approaches aiming at a more homogeneous performance to add knowledge to future studies

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INTRODUCTION

We are living in a pandemic caused by SARS-CoV-2, a virus of predominantly airborne transmission from the coronavirus family, discovered in Wuhan, China, in December 2019[1].

Although the respiratory tract is the preferential path for the multiplication of the virus in individuals of all ages and the disease generally progresses without or with few symptoms in children, in the last few months we have observed an increase in the incidence of cases of severe non-pulmonary symptoms in pediatric patients[2,3]. Manifestations include Kawasaki-like disease[4]; gastrointestinal symptoms[5]; cardiac involvement (ranging from myocarditis to vasculitis and aneurysm); circulatory shock with potential multiple organ failure and death and multisystem inflammatory syndrome[6-8].

This report presents the cases of two children diagnosed with SARS-CoV-2 infection with different forms of severe cardiac involvement who were admitted to the PICU of a tertiary referral hospital in Rio de Janeiro. This paper aims to add to the knowledge base to be used in future studies about cardiovascular symptoms secondary to SARS-CoV-2 infection, a less explored subject lacking standardized therapy for pediatric populations.

CASE REPORT

Case 1

A previously healthy brown male child aged one year and five months, the son of parents who had been in contact with individuals with COVID-19 with mild respiratory symptoms, was admitted to the emergency unit with diffuse non-itchy purpuric urticaria-like lesions (Figure 1), extremity edema, non-bloody diarrhea, rhinorrhea, and high fever lasting for three days. At first, the IgG/IgM rapid test for SARS-CoV-2 was negative, but the polymerase chain reaction (PCR) test of the child's nasal and oropharyngeal swabs came back positive. The child was stable, but since his D-dimer indicated high risk for thrombosis, he was referred to the PICU. Increases in B-type natriuretic peptide (BNP) and cardiac enzymes, with the exception of troponin, were observed on the fourth day of disease (Table 1); peaked T wave in the electrocardiogram (ECG); left coronary artery dilation by about 2.5 mm without aneurysm and with an ejection fraction (EF) of 57% in the echocardiogram (echo); and normal findings in the venous Doppler ultrasound examination of the leg and neck vessels and in the arterial Doppler ultrasound examination of the carotid arteries.



Figure 1. Skin manifestations from COVID-19 - Diffuse cutaneous vascular lesions from the patient described in Case 1. Picture taken and published with parental consent.

Incomplete Kawasaki disease was considered after infection by arthropod-borne viruses and other community-acquired viral and bacterial diseases were ruled out, and the patient was started on human immunoglobulin (2 g/kg/day) and acetylsalicylic acid (ASA - 80 mg/kg/day, later decreased to 5 mg/kg/day). The child was kept without fever and in excellent general condition during hospitalization, and the skin lesions resolved within 72 hours of admission. Coronary artery diameter decreased to 1.8 mm and the EF increased to 70% in the control echo examination performed one week after the introduction of drug therapy. The patient was discharged on Day 12 of disease with a prescription of ASA (5 mg/kg/day).

Case 2

A healthy brown girl aged three years with no contact with individuals with COVID-19 was admitted after having fever for six days, abdominal pain in the right iliac fossa, vomiting, and mild maculopapular rash in her arms. Twelve hours later the patient started suffering from sensory alteration, perfusion disorder, tachycardia with abnormal heart rhythm, and oliguria. She was referred to the PICU, placed on a ventilator, and started on an inotrope for hemodynamic compensation. At first, she was positive for SARS-CoV-2 infection only in IgG testing. Her inflammatory markers and D-dimer were increased (Table 1), and the decision was made to start the patient on prophylactic anticoagulants; the patient presented with ground glass opacity with consolidations intermingled with air bronchograms in 25% to 50% of the lung parenchyma and an appendix measuring 6 mm in diameter, with minimal adjacent fat tissue density, small amounts of free fluid, and no deep enlarged lymph nodes in computed tomography (CT) scans.

She progressed with ST segment depression in leads DII, V2, and V3, increased cardiac enzyme and BNP levels (Table 1), although function was preserved with an EF of 67% (the patient was on amines), normal coronary artery diameter, and no aneurysms in echo examination. Meanwhile, her PCR test for SARS-CoV-2 infection came back positive, and she was started on methylprednisolone (2 mg/kg/day for 7 days) for suspicion of MIS-C; therapy was tapered down and discontinued in two weeks.

Table 1. Workup for Cases 1 and 2.

	Caso 1				Caso 2					
DAYS OF DISEASE	**D4**	**D6**	**D9**	**D10**	**D7**	**D8**	**D10**	**D12**	**D14**	**D19**
LYMPHOCYTES RV: 1,000 - 4,500/mm^3	5,714	5,467	4,060	5,005	689	660	2,553	1,860	4,020	2,798
PLATELETS RV: 140,000 - 400,000/ mm^3	131,000	266,000	405,000	546,000	138,000	187,000	311,000	574,000	907,000	611,000
LDH RV: 140 - 271U/l	-	-	263	280			327	338	345	259
CRP RV: up to 0.8mg/dl	3.3	< 0.8	1.1	< 0.8	29	26.7	19.4	6.87	1.63	< 0.8
ESR RV: 4 - 7 mm	22	-	50	-	56	-	64	64	28	21
FERRITIN RV: 11 - 305 Ng/ml	42.6	30.3	278.3	27.6	177.5	-	-	135.8	102.3	48.9
TRIGLYCERIDES RV: < 150mg/dl	-	123	103	2.3	-	-	-	144	108	162
CK-MB RV: up to 5ng/ml	-	10.1	6.6	5.5	2.0	7.7	5	1,1	0.7	1.1
TROPONIN RV: up to 0.018ng/ml	-	0.002	0.001	0.002	-	0.057	0.049	0.015	0.006	0.001
PRO BNP RV: < 133ng/L	-	191	127	109	-	-	6,350	1,840	390	3
FIBRINOGEN RV: 180 - 350 mg/dl	-	-	238	-	-	-	349	317	293	204
D-DIMER RV: up to 583µg/l	1,200	640	1,080	630	3,950	8,150	3,870	2,530	1,380	650
IL-6 RV: <3.4 pg/ml	-	-	-	-	-	-	26.2	-	-	-

The patient was extubated 72 hours later and therapy with vasoactive drugs was discontinued. However, she developed eyelid ptosis (without anisocoria) and myoclonic movements in the form of blinking of the left eye and involuntary lower left hemifacial contractions; she also presented orofacial dyskinesia involving her tongue and mouth and deep hyperreflexia in the legs. Head CT scans did not evince bleeding and/or ischemia, and PCR testing of the cerebrospinal fluid was negative for SARS-CoV-2 infection. The patient was suspected for epilepsia partialis continua and was empirically started on phenytoin. The neurological symptoms resolved 48 hours later and the drug was discontinued seven days after the start of treatment.

The patient was discharged 16 days after admission after her inflammatory tests and cardiac injury markers improved and the D-dimer decreased (Table 1). She was off anticoagulation and was prescribed ASA (5 mg/kg/day).

DISCUSSION

As the pandemic advanced, we saw the incidence and severity of cases of COVID-19 in pediatric populations increase. While in most publications children with severe forms of the disease were aged 5-8 years, the individuals in our series were aged 1-3 years on average[2-8].

MIS-C, a severe multi-faceted manifestation of the disease described initially in late April 2020, is diagnosed based on the criteria proposed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in the United States[9,10]. Our cases met the criteria, revealing the breadth and diversity of systemic involvement associated with COVID-19. The two individuals whose cases were described in this report belonged to the ethnic group most prevalent in literature, which comprises blacks and browns[11].

In European cohorts, a great deal of children present with manifestations consistent with Kawasaki-like or incomplete Kawasaki disease, albeit with a few specificities, which include younger age, more exuberant gastrointestinal involvement, and greater risk of shock or cardiac involvement[5,11]. As previously reported, the two individuals featured in this manuscript had fever and abdominal pain as early symptoms, with Case 2 mimicking acute abdomen[5]. With signs suggestive of vasculitis, coronary dilation, gastrointestinal symptoms, and a positive PCR test for SARS-CoV-2 infection, Case 1 resem-

bled incomplete Kawasaki disease, although accompanied by unusual signs. The overall good condition of the patient, the non-significant alterations in inflammatory activity tests, and the early cardiac involvement in the acute phase of the disease picked up in echocardiography caught our attention.

When compared with Case 1, the subject described in Case 2 had severe involvement and progressed quickly to circulatory shock. The patient was prescribed a vasoactive drug, as were 47% of the pediatric patients in an English cohort.[3] Unusual cardiac involvement was also seen in this case. Despite alterations in the electrocardiogram and increased levels of inflammatory markers and cardiac enzymes, the patient's EF was not compromised. However, the patient was on an inotrope at the time of echo examination.

Recent studies showed that children with positive markers for myocardial injury are more prone to developing poorer outcomes, including acute heart failure, when the EF reaches values close to 30%[11]. We saw that the two children described in this case report had increased cardiac enzyme and inflammatory marker levels. In Case 2, however, the increases were more significant despite the fact that the patient had a borderline EF while on amines, a finding in disagreement with current literature.

Small samples and the lack of controlled studies contribute to the little knowledge developed thus far on the best course of therapy for these patients. In Case 1, intravenous immune globulin and ASA were prescribed in regimens similar to the ones used in Kawasaki disease, with the purpose of preventing progression to aneurysmal disease[12]. Two thirds of the patients with coronary dilation of 5 mm and smaller are believed to resolve within 30 days, still in the acute phase of the disease, while 50-70 % have the condition resolved within two years. These lesions rarely become chronic after two years[13]. This fact might explain why our patient did not develop aneurysmal disease.

In Case 2, intravenous steroids played a role in controlling the patient's immune response secondary to exacerbated cytokine release from MIS-C. In agreement with recently published recommendations on the prophylactic use of heparin in children with risk factors for thrombosis, our patients were prescribed anticoagulants[14-15]. Infection, presence of a deep venous catheter, altered inflammatory markers, and cardiac involvement were decisive factors in the decision to start prophylactic care.

Our patients illustrate the clinical and workup variety of the acute phase of pediatric COVID-19 and the cardiac involvement probably caused by SARS-CoV-2, which fortunately resolved to satisfaction.

CONCLUSION

Observations made during the pandemic have made it clear that children do not develop only milder forms of COVID-19. In agreement with the literature, the two cases reported in this paper illustrate phenotypes of inflammatory involvement with severe, varied cardiovascular manifestations. Further studies with larger series are needed to enhance the knowledge about the different presentations of this disease and optimize diagnostic and therapeutic strategies.

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