BRIEF COMMUNICATION

Patterns of myocardial involvement in children during COVID-19 pandemic: Early experience from northern Italy

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ABSTRACT

There is limited information about coronavirus disease 2019 (COVID-19) in the pediatric population. Preliminary data suggest a not insignificant prevalence of cardiac involvement. Here, we report our early experience with COVID-19 in the pediatric population. These patients display exceptionally high levels of acute-phase reactants. The clinical syndrome in these patients is somewhat similar to Kawasaki disease with or without myocardial involvement. In some cases, the presentation mimics typical myocarditis. Severe myocardial involvement is associated with transient electrocardiographic and echocardiographic abnormalities. These findings may be due to the cardiotropic nature of the virus or may be the result of an immunologic response to the infection.

Keywords: Coronavirus disease 2019, Kawasaki, myocarditis

INTRODUCTION

Italy is facing an overwhelming epidemic spread of coronavirus disease 2019 (COVID-19). Northern Italy is one of the most affected areas, with exponential growth in cases. Our hospital is almost converted to a COVID-19 hospital. Patients below 18 years represented a minority of COVID-19 cases in the preliminary data from China and Spain.[1,2] It was, therefore, initially thought that children are relatively immune to COVID-19 infection. This, however, is not correct, and COVID-19 infection is being increasingly reported among children and adolescents. We hereby present our experience with COVID-19 infection in patients below 18 years. We describe peculiarities in clinical presentation and challenges posed in the diagnosis.

SUBJECTS AND METHODS

All patients presenting to our hospital between March 30 and April 10, 2020, suspected to have COVID-19 were included. The provisional diagnosis was based on symptoms and history of exposure. Confirmation of COVID status was done using a rapid polymerase chain reaction (PCR) test. All patients underwent at least two rapid PCR tests on a nasopharyngeal swab. Additional samples from other biological fluids, such as cerebrospinal fluid, were also taken in selected cases. Clinical evaluation included physical examination and chest X-ray. Chest computed tomography (CT) was also performed in patients with respiratory distress and/or desaturation.

Cardiac involvement was systematically assessed by serially measured high-sensitivity troponin and transthoracic echocardiography.

RESULTS

The first six patients, including three males, presenting to the pediatric emergency were included. The median

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age was 7 (3–16) years. The clinical presentation was characterized by high fever associated with a combination of gastrointestinal symptoms, sore throat, rash, cough, conjunctivitis, and lymphadenitis [Table 1]. One female patient presented with neck stiffness and underwent lumbar puncture that turned out to be negative for COIVD-19.

All patients but one had marked leukocytosis and all had a significant increase of acute-phase reactants and liver enzymes.

Table 1 summarizes patient laboratory findings.

Three patients had two negative swabs each. Their parents were also negative, despite having reported the occurrence of mild typical symptoms, including ageusia and anosmia, in the previous weeks.

Chest X-ray showed mild retrocardiac consolidation in two cases, whereas in one, chest CT confirmed dorsal patchy interstitial and alveolar infiltrates [Figure 1]. Three patients displayed moderate respiratory distress and arterial desaturation in the range of 90% requiring low-flow oxygen. None of the patients required escalation to either noninvasive or mechanical ventilation.

Electrocardiogram (ECG) was not specific in three cases, apart from sinus tachycardia secondary to fever. In one patient, pericarditis-like changes were observed, whereas in two, QRS voltage reduction and fragmentation transiently developed [Figure 2].[3] Echocardiography revealed mild-to-severe left ventricular (LV) dysfunction associated with mild pericardial effusion in three patients, but all fully recovered in 48–72 h. The median lowest LV ejection fraction was 50% (25–60). The two patients with significant LV dysfunction needed admission in intensive care unit and inotropic support with milrinone (0.4–0.8 mcg/kg/min) in one case and milrinone plus adrenaline (0.05 mg/kg/min) in the other one. We have not seen any significant clinical sequelae, and all patients were transferred out of the intensive care unit to the pediatric ward for further observation. The median duration of the acute phase ranged between 3 and 5 days.

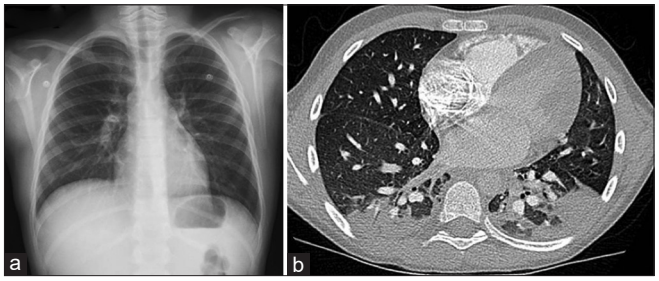

Figure 1: (a) Chest X-ray, anteroposterior projection. (b) Chest computed tomography of the same patient showing interstitial and alveolar infiltrates

DISCUSSION

Preliminary data from China and Spain suggest that the clinical impact of SARS-CoV2 infection in patients younger than 18 years is negligible in comparison with the general population. However, the true incidence of COVID-19 in pediatric patients is unknown due to the high prevalence of asymptomatic infections, atypical clinical presentation, and the low sensitivity of nasopharyngeal swab.[2,4] Instead, evidence of various degrees of myocardial injury is commonly observed among children with SARS-CoV2 infection. SARS-CoV2 is shown to be associated with a clinical syndrome like Kawasaki disease.[5-7]

The cluster of symptoms and signs that we observed could have been grouped into two main, although overlapping, groups: one fulfilling criteria for Kawasaki disease, with or without coronary or myocardial involvement, and a second one presenting with isolated myocarditis [Table 1]. A typical common laboratory finding was a significant increase in leukocyte count and inflammatory markers. Two patients also had an exceptional increase of both triglyceride and ferritin levels, as described in macrophage activation syndrome. In its complete presentation, this condition is a serious complication of different rheumatology conditions.[8]

The remaining two patients displayed a clinical course compatible with myocarditis. In both these patients, ECG was a sensitive tool in showing evolving changes characterized by ST changes and fragmentation of QRS. Despite a severe clinical presentation with markedly depressed LVEF, a rapid and complete recovery was observed. Remarkably, although COVID-19 infection was strongly suspected in all cases based on epidemiological and clinical grounds, only half the patients had a positive swab test. This is in line with preliminary reports suggesting a lower sensitivity of conventional virological

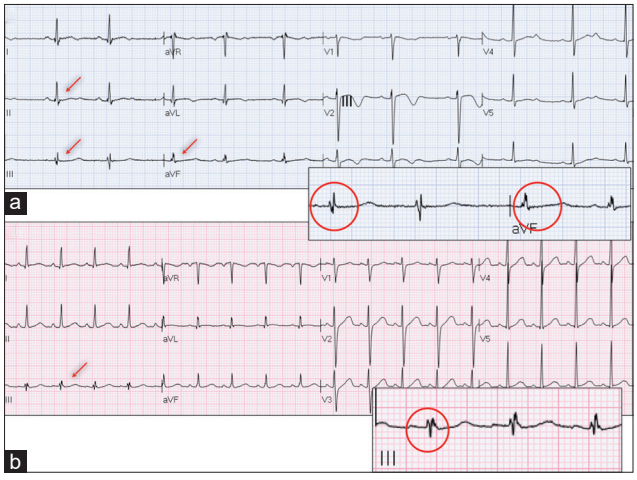

Figure 2: (a and b) Electrocardiogram tracings of two patients with typical myocarditis. Arrows and circles indicate QRS fragmentation

Table 1: Summary of clinical presentation and laboratory findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Reference range	Median (range)
Gender, age (years)	Male, 7	Female, 3	Male, 9	Female, 7	Female, 7	Male, 16		
Prodromic symptoms	Fever, gastrointestinal, sore throat, rash, nuchal stiffness	Fever, sore throat, rash, conjunctivitis, lymphadenitis	Fever, gastrointestinal, sore throat, rash, conjunctivitis, lymphadenitis	Fever, gastrointestinal, sore throat, cough, nuchal stiffness	Fever, gastrointestinal, sore throat, cough	Fever, gastrointestinal, rash		
Laboratory findings								
Leukocyte (10^9/L)	32.84	20.74	9.00	19.04	10.26	20.00	<11.00	17.7 (9.0-32.84)
CRP (mg/L)	35.3	12.02	257	48	52.5	7.1	<1	41.65 (7.1-257)
Procalcitonin (ng/mL)	59.8	6.06	0.45	193.25	7.57	NA	<0.05	7.57 (0.45-193.25)
PLT (10^9/L)	113	116	672	145	105	250	150-400	130.5 (105-672)
Troponin I-HS (ng/L)	188	112	100	200	3557	1200	<53	194 (100-3557)
BNP (ng/L)	952	1519	1800	2072	444	103	<100	1235 (103-2072)
D-dimer (ng/mL)	NA	NA	7180	3285	4788	4700	<500	4774 (3285-7180)
Fibrinogen (mg/dL)	NA	NA	640	924	730	370	150-450	685 (370-924)
Ferritin (ng/mL)	1183	893	NA	1972	3213	2027	20-250	1972 (893-3213)
Triglyceride (mg/dL)	538	538	452	263	NA	320	40-170	452 (263-538)
Transaminase	++	+	++	++	++	+		
Chest X-ray	Normal	Mild retrocardiac consolidation	Mild retrocardiac consolidation	Normal	Normal	Normal		
Chest CT	NA	NA	Interstitial pneumonia	NA	NA	NA		
ECG	Sinus tachycardia	Sinus tachycardia	fQRS	ST elevation	fQRS	Sinus tachycardia		
Lowest LVEF (%)	60.0	60.0	45	25	30.0	55		
Echocardiographic findings	Normal	Coronary involvement	Pericardial effusion + coronary involvement	Pericardial effusion	Pericardial effusion	Pericardial effusion		
Oxygen therapy	Yes	No	Yes	Yes	Yes	No		
ICU	No	No	No	Yes	Yes	Yes		
Specific therapy	IVIG, antibiotics, ASA, methylprednisolone	IVIG, antibiotics, ASA, methylprednisolone	IVIG, antibiotics, ASA, methylprednisolone	IVIG, antibiotics, hydrocortisone	IVIG, antibiotics, ASA, methylprednisolone	IVIG, antibiotics, methylprednisolone		
Inotropic support	No	No	No	Yes	Yes	Yes		
COVID-19 swab	Positive	Negative (parents with typical symptoms)	Negative (parents with typical symptoms)	Negative (parents with typical symptoms)	Positive	Positive		
Clinical diagnosis	Kawasaki	Kawasaki	Kawasaki like, Myocarditis	Myocarditis	Myocarditis	Kawasaki		
LVEF normalization	Yes	Yes	Yes	Yes	Yes	Yes		

CRP: C-reactive protein, PLT: Platelet, BNP: Brain natriuretic peptide, CT: Computed tomography, ECG: Electrocardiogram, LVEF: Left ventricular ejection fraction, ICU: Intensive care unit, NA: Not available, IVIG: Intravenous immunoglobulin, ASA: Acetylsalicylic acid, COVID-19: Coronavirus disease 2019, fQRS: fragmented QRS, +: Two times the upper limit, ++: Three times the upper limit

investigations in children as compared with adults. It is worth noting that we are observing an unusual peak of Kawasaki-like syndromes and myocarditis in the pediatric population which is closely following the epidemiological peak of COVID-19 in our area. We might, therefore, speculate that this novel coronavirus could have acted as an immunological trigger after a few weeks from the initial infection that might have gone almost unrecognized in this population.[9]

We also noted that unlike the "adult-type COVID-19," lung involvement may be unrecognized in the chest X-ray even in more severe clinical presentation in children, warranting a low threshold for proceeding with chest CT.[4,10] Furthermore, this initial cohort showed some unique humoral hallmarks of macrophage activation syndrome. This is a novel finding worth actively looking for, as this condition may carry a poor prognosis and need early aggressive treatment.

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Conflicts of interest

There are no conflicts of interest.

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