



COVID-19 and congenital heart disease: a case series of nine children

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Abstract

Background Coronavirus disease 2019 (COVID-19) is the current pandemic disease without any vaccine or efficient treatment to rescue the patients. Underlying diseases predispose the patients to a more severe disease and to a higher mortality rate. However, little evidence exists about COVID-19 outcomes in the pediatric population with congenital heart disease (CHD). Here, we report nine children with COVID-19 and concomitant CHD.

Methods Our study included nine children with COVID-19 and concomitant CHD who were admitted to Children Medical Center Hospital during March and April 2020. The patients were classified based on the final outcome (death), and their clinical sign and symptoms, type of CHD, and drugs administered were compared.

Results Among the nine patients, two died and we compared different characteristics, laboratory results and clinical findings of these cases based on the mortality. The deceased patients had severe types of CHD, worse arterial blood gases, severe clinical symptoms, higher mean level of partial thromboplastin time and C-reactive protein, and required more medications.

Conclusions The present study showed that the general consideration of mild COVID-19 in children does not include patients with CHD and that it is necessary to pay greater attention to children with CHD to determine guidelines for treatment of COVID-19 in these children. Owing to the scarcity of CHD and COVID-19, we reported only nine cases. However, further studies are highly required in this regard.

Keywords Congenital heart disease · Coronavirus disease 2019 · Pediatrics

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), is now an important concern and infects more patients each day with a worldwide mortality

[1]. Since SARS-CoV-2 appeared, it spread around the world quickly by human-to-human transmission [2].

Although the respiratory system is the main site of infection during COVID-19 [3], atypical presentations in children have been reported [4]. Some cases of COVID-19 may be complicated with multiple organ failure resulting in the death [5]. Patients with comorbidities have a higher risk of acquiring COVID-19 [6, 7] and experiencing poor clinical outcome [8]. One of the crucial organs affected by COVID-19 is the heart [7, 9]. In fact, it has been suggested that COVID-19 might lead to a “Kawasaki-like disease” [10].

Several biomarkers in the heart, such as brain-type natriuretic peptide and cardiac troponin I, have been associated with intensive care unit (ICU) admission and even with mortality of patients with COVID-19 [11]. Cardiac injury during COVID-19 is assumed to be caused by respiratory failure and hypoxemia, as well as systemic inflammatory response. Furthermore, COVID-19 can directly damage organs expressing angiotensin-converting enzyme (ACE2) receptor (e.g., lungs, heart, kidneys and intestines) as coronavirus enters the body's cells by binding to ACE2 receptor

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[12]. According to the significant effect of COVID-19 on the heart, patients with congenital heart disease (CHD) are considered to be at high risk for COVID-19 complications [13, 14]. However, few studies have assessed the clinical outcome of COVID-19 in adult and pediatric populations with CHD [15].

At the beginning of the disease spread, COVID-19 was reported to be less common in children [16]; however, subsequent research showed that children of all ages and sexes, especially infants, are vulnerable to COVID-19 [17]. An epidemiological study showed that the frequency of severe and critical cases was 10.6% at the age < 1 year, 7.3% at the age of 1–5 years, 4.2% at the age of 6–10 years, 4.1% at the age 11–15 years, and 3.0% for the age group > 15 years [17]. Children generally present with mild clinical manifestations with a better prognosis than adults; however, the issue of comorbidities in children with COVID-19 has rarely been evaluated [18]. A few studies have reported that children with an underlying disease were critically ill and required ICU [19, 20]. In the present study, we presented the laboratory and clinical characteristics of nine children with CHD who were admitted with COVID-19.

Methods

The present study included all children (with maximum age of 14 years) who were diagnosed with COVID-19 and concomitant CHD and were admitted to Children's Medical Center, an Iranian referral hospital, between March and April 2020. Diagnosis of COVID-19 was based on the detection of SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal samples [4]. The researcher explained the study's design and objectives to the participants' parents, and written informed consent was obtained.

Participants' information, including age and sex of the child and type of CHD, were extracted from the medical records. Type of CHD was determined by a cardiologist based on the results of cardiac echocardiography. A venous blood sample was taken from all children during admission and was sent to the laboratory for measurement of white blood cells, red blood cells, hemoglobin, platelet, creatinine, creatinine phosphokinase, lactate dehydrogenase, estimated sedimentation ratio, C-reactive protein (CRP), prothrombin time, partial thromboplastin time (PTT), and international normalized ratio. In addition, one arterial blood sample was taken from each participant to assess the arterial blood gas (ABG), which indicated the partial pressure of carbon dioxide, the partial pressure of oxygen, bicarbonate, and oxygen saturation.

The collected information was analyzed using the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp), and the results were described by actual values, range, and frequency (percentage).

Results

Clinical course of congenital heart disease cases with COVID-19

Case 1

This was a 14-year-old male patient with aortic stenosis who presented with pressure-like chest pain along with respiratory distress and cough. Chest high-resolution-computed-tomography (HRCT) scan showed diffuse ground-glass opacification in both lungs and moderate bilateral pleural effusion. Blood culture was positive for *Staphylococcus aureus*. The patient was treated with azithromycin, hydroxychloroquine (HCQ), oseltamivir, ceftriaxone, and levofloxacin. The patient's general conditions worsened, and trimethoprim/sulfamethoxazole, meropenem, and vancomycin were initiated. However, the patient passed away due to acute respiratory distress syndrome (ARDS), even after treatment with lopinavir/ritonavir and methylprednisolone.

Case 2

This was a 10-month-old male infant with hypoplastic left heart syndrome (HLHS) and patent ductus arteriosus (PDA) admitted due to cyanosis, lethargy, and decreased oxygen saturation. A chest HRCT scan showed deformed interlobular septal thickening and mosaic attenuation along with subpleural alveolar consolidation in both upper and lower lobes. Nasopharyngeal RT-PCR was positive for SARS-CoV-2, and *Pseudomonas aeruginosa* was isolated from blood culture. The patient was treated with azithromycin, HCQ, cefotaxime, and clindamycin. Unfortunately, the infant passed away due to respiratory failure.

Case 3

This was a 5-year-old boy with truncus arteriosus (TA) who was admitted due to respiratory distress, facial and limb edema, and decreased oxygen saturation. On examination, the patient had generalized edema and hepatomegaly. The chest HRCT scan showed a bilateral diffuse alveolar ground-glass pattern. Blood culture was positive for *Enterobacter* spp.. The patient was treated with azithromycin, HCQ, and cefotaxime.

Cases 4 and 5

These included two infants, an 18-month-old male and a 6-month-old female, who were diagnosed with ventricular septal defect (VSD) and situs ambiguus. These patients were admitted for emergent surgery. A nasopharyngeal RT-PCR for SARS-CoV-2, which was ordered for preoperational assessment, tested positive in both patients; subsequently, they were treated with azithromycin and survived from the surgery and the COVID-19.

Case 6

This was an 18-day-old female neonate with PDA who presented with respiratory distress at birth. The patient was intubated and referred to our center. The blood culture was positive for *P. aeruginosa*, and the urine culture was positive for *Candida* spp.. The patient was treated with cefotaxime and vancomycin. Nasopharyngeal RT-PCR for SARS-CoV-2 was positive, and azithromycin was added to the therapeutic regimen.

Case 7

This was a 2-year-old female child with tetralogy of fallot (TOF) who presented with nausea and vomiting, diarrhea, generalized rash, and shortness of breath. Nasopharyngeal RT-PCR for SARS-CoV-2 was positive, and the patient was treated with azithromycin and cefotaxime.

Case 8

This was a 5-month-old boy with VSD/total anomalous pulmonary venous connection (TAPVC) who was admitted due to failure to thrive and reconstructive surgery. The patient became febrile during hospitalization, and ceftazidime and vancomycin were initiated for the patient. Nasopharyngeal RT-PCR for SARS-CoV-2 was positive, and the patient was treated with azithromycin and HCQ. The patient had impaired renal function, and hemodialysis was conducted. In addition, blood culture of the patient was positive for *Acinetobacter baumannii*, so the patient was treated with ampicillin/sulbactam.

Case 9

This was a 4-month-old girl with pulmonary atresia-intra-ventricular septum-status post (PA-IVS-S/P) PDA stenting who presented with lip cyanosis after routine vaccination. The patient was admitted due to low ejection fraction and blood hemoglobin. Blood culture was positive for *P. aeruginosa*, and nasopharyngeal RT-PCR was positive for SARS-CoV-2. The patient was treated with cefotaxime.

Comparison of cases with and without mortality

The participants were categorized based on mortality. Among the nine patients, whose ages ranged from 18 days to 14 years [median 10 months (interquartile range 5 months–3.5 years)], two died. Both deaths were boys: one was 14 years old, and the other was ten months old. The surviving patients included 3 boys and 4 girls. The age range of this group was 18 days–5 years.

As shown in Table 1, the two patients who died had aortic valve stenosis (AVS) and HLHS plus PDA, whereas the other seven had other types of CHD (four had a VSD with or without other CHDs, one had PDA, one had TOF, and one had PA-IVS-S/P PDA stenting). None of the participants had headache, abdominal pain, lymphadenitis, myositis, or rash. Both of the deceased patients had tachypnea, respiratory distress, and chest pain; one had cough and the other had fever. Among the surviving patients, three had no symptoms, one had only rhinorrhea, and one other had rhinorrhea and diarrhea. Fever, like cough, was only observed in one patient in this group.

Azithromycin was prescribed to all patients in both groups (deceased or survived). Chloroquine was administered to both children that died and to only one of the surviving children.

Table 1 demonstrates the length of hospital stay, clinical signs/symptoms, the administered drugs, echocardiographic findings, and HRCT findings for each patient. Tachypnea, chest pain, and respiratory distress were the most common signs in the deceased group. Furthermore, the deceased group received a wider range of drugs compared to the surviving group. The results of each patient's ABG and other laboratory findings are shown in Table 2.

Discussion

In the present study, we described the clinical and laboratory findings of nine pediatric patients with different forms of CHD and with COVID-19. As this disease is newly emerging, research continues to find different aspects of the disease in different populations. Data considering comorbidities [18], including acute lymphoblastic leukemia and lacrimal sac dredge [20], are scarce. In the present study, two of the nine children with CHD ended in death by COVID-19 infection, illustrating the importance of CHD in children with COVID-19. However, despite previous reports of a higher case-fatality rate among patients with cardiovascular comorbidities (as in our study), evidence of a mild COVID-19 clinical course exists in CHD patients [21].

It has previously been shown that COVID-19 results in myocardial injury and that adult patients with an underlying cardiac disease, particularly CHD, are a higher risk of

Table 1 Clinical and paraclinical findings for patients with congenital heart disease

Case no.	Hospital stay (d)	Outcomes	Type of congenital heart disease	Signs and symptoms	Administered drugs	Main findings of echocardiography	Chest CT scan reports
1	27	Death	AVS	Cough, tachypnea, chest pain, respiratory distress, myalgia	Azithromycin, hydroxychloroquine, vancomycin, ritonavir, corticosteroid, IVIG, trimethoprim/sulfamethoxazole	None	Diffuse ground-glass opacification in both lungs Moderate bilateral pleural effusion
2	16	Death	HLHS + PDA	Fever, tachypnea, vomiting, respiratory distress, chest pain	Azithromycin, hydroxychloroquine, ceftazidime, clindamycin	None	Deformed interlobular septal thickening and mosaic attenuation Subpleural alveolar consolidation in both upper and lower lobes
3	11	Alive	VSD+truncus arteriosus	Cough, tachypnea, chest pain, respiratory distress	Azithromycin, hydroxychloroquine, amikacin, cefepime	ASD and VSD closure at the age of 2.5 months Small residual VSD Severe TR Mild to moderate PR Moderate PS LVEF: 40–45%	Bilateral diffuse alveolar ground-glass pattern
4	6	Alive	VSD + PH	None	Azithromycin	SDS Large VSD (bilateral shunt) Mild to moderate MR Mild TR Patent LVOT Small PDA Systemic PH Patent LVOT	None
5	6	Alive	VSD	None	Azithromycin	Situs ambiguous Transverse liver D loop ventricles Complete AVSD VSD Severe PH Common atrium with small remnant of IAS Mild AVVR Double SVC	None
6	18	Alive	PDA	None	Azithromycin, ribavirin, trimethoprim/sulfamethoxazole	None	None
7	1	Alive	TOF	Fever, rhinorrhea, hepatomegaly, diarrhea	Azithromycin	None	None
8	47	Alive	TAPVC+ VSD	Rhinorrhea, diarrhea	Ribavirin, trimethoprim/sulfamethoxazole, azithromycin	SDS Mild TR Trivial PR ASD (shunt left to right) VSD (shunt left to right) Supracardiac TAPVC	None

Table 1 (continued)

Case no.	Hospital stay (d)	Outcomes	Type of congenital heart disease	Signs and symptoms	Administered drugs	Main findings of echocardiography	Chest CT scan reports
9	28	Alive	PA-IVS-S/P PDA stenting	Rhinorrhea	Azithromycin	SDS Patent ASD stent Bipartite RV Near arterial PUV (membranous pulmonary atresia) Severe TR Thick TV leaflets TAV Stretched PFO	None

AVS aortic valve stenosis, HLHS hypoplastic left heart syndrome, PDA patent ductus arteriosus, VSD ventricular septal defect, PH pulmonary hypertension, TOF tetralogy of Fallot, TAPVC total anomalous venous connections, PA pulmonary atresia, IVS intraventricular septum, S/P status post, SDS S situs viscerio-atrialis solitus, D D-loop of the ventricles, S solitus, normally related great arteries, LVOT left ventricular outflow tract, AVSD atrioventricular septal defects, AVVR atrioventricular valve regurgitation, IAS interatrial septation, TAPVC total anomalous pulmonary venous, PFO patent foramen ovale, TAV tricuspid annular velocity, IVIG intravenous immunoglobulin, TR tricuspid regurgitation, PR pulmonary regurgitation, PS pulmonary stenosis, LVEF left ventricle ejection fraction, MR mitral regurgitation, SVC superior vena cave, RV right ventricle, PUV pulmonary valve, TV tricuspid valve

poor outcome of COVID-19 [8, 13, 19]. From a pathophysiological perspective, it is suggested that COVID-19 infection in children with CHD results in poorer outcomes for the following reasons: the destructive effect of COVID-19 on the heart [8, 13, 19], the poorer outcomes of influenza and other viral respiratory diseases in children with CHD [22], and the fact that many of these patients may have concomitant anomalies in other organs, such as lungs and kidneys [23]. One important factor in the prediction of the COVID-19 outcome in children with CHD is the severity of CHD. Patients with a severe CHD have hypoxemia and refractory end-organ dysfunction, and these patients are more vulnerable to the effects of COVID-19 [15]. In the current study, the type of CHD in the deceased cases included AVS in one case and HLHS plus PDA in the other case. The other seven cases that survived had other types of CHD, including VSD (one alone, one with pulmonary hypertension, one with TA, another with TAPVC), PDA, TOF, and PA-IVS-S/P PDA stenting.

Septal defects, such as PDA and VSD, are generally considered mild and simple cardiac defects, and aortic or mitral valve diseases are considered of moderate complexity. Based on the classification by Alsaied et al., these are considered less vulnerable for COVID-19; whereas, those with cyanotic CHD, cardiomyopathy, or depressed cardiac function may be at increased risk for COVID-19 [15].

Paying attention to the clinical presentations of the patients is another important issue, especially in children with CHD, because worsening of the cardiac conditions, such as shortness of breath, palpitations and fever, mimic that of COVID-19 [15, 24]. In the present study, two children who passed away had respiratory distress, chest pain and tachypnea, whereas three of the children who survived had no symptoms. One of the dead children had cough, and another had vomiting. These signs were not observed among the children that survived. Myalgia was observed only in one patient, who died.

Previous studies have reported the common clinical symptoms of COVID-19 in children [17, 25], but these results cannot be compared to ours because our patients had special conditions due to CHD. Although children are generally considered to have mild COVID-19 symptoms [17], our study showed that this is less common in children with comorbidities, especially severe CHD. Other studies have reported also that children with other comorbidities had severe symptoms and required ICU admission [18, 20]. Assessing the laboratory test results of the children in our study showed abnormal ABG results in the deceased patients. These results confirmed the effect of the CHD type on hypoxemia, which aggravated the effect of COVID-19 on the child’s heart and systemic condition.

Medications used for the patients in the present study also showed that the deceased children required a wide range

Table 2 The laboratory findings of COVID-19 patients with congenital heart disease

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Normal range
White blood cells ($\times 10^9$ cells/L)	11.1	13.3	11.1	6.6	15.3	4.6	4.9	7.7	12.8	4–10
Red blood cells ($\times 10^9$ cells/L)	3.5	7.4	4.6	4.4	5.2	3.8	5.1	3.9	5.7	3.5–5.5
Hemoglobin (g/dL)	9.5	20.6	11.4	13.0	13.5	11.7	12.3	11.1	15.3	10–16
Platelet ($\times 10^9$ cells/L)	355	86	411	254	321	140	221	45	356	150–450
Neutrophil ($\times 10^9$ cells/L)	9.6	4.3	6.8	2.5	2.1	2.4	3.6	7.2	5.7	2–7
Lymphocyte ($\times 10^9$ cells/L)	1.0	8.1	3.3	3.2	11.6	1.9	0.8	0.4	6.3	0.8–4.0
Blood urea nitrogen (mg/dL)	17	30	16	–	14	9	3	63	5	5–20
Creatinine ($\mu\text{mol/L}$)	1.0	0.5	0.6	–	0.5	0.8	0.3	2.9	0.3	0.3–0.7
Creatinine phosphokinase (U/L)	252	51	60	–	–	–	27	–	43	24–172
Lactate dehydrogenase (U/L)	816	1568	791	–	–	–	616	–	738	5–746
Sodium (mmol/L)	133	130	136	–	134	146	138	134	134	135–145
Potassium (mmol/L)	4.6	4.6	4.8	–	4.6	3.6	4.0	3.7	4.7	3.7–5.9
Erythrocyte sedimentation rate (mm/h)	49	1	3	–	6	–	12	–	2	0–10
C-reactive protein (mg/L)	520	88	10	–	5	2	18	–	2	<6
Prothrombin time (s)	14.8	21.3	17.6	–	14.0	14.0	13.5	13.7	12.5	9.5–13.5
Partial thromboplastin time (s)	75	58	33	–	34	33	31	37	33	<65 (<2 mon), 30–45 (>2 mon)
International normalized ratio	1.3	2.3	1.7	–	1.2	1.2	1.1	1.2	1.0	<1.3
PCO ₂	26.4	44.3	43.2	47.5	31.2	35.2	23.7	39.3	14.8	38–42
PO ₂	46.0	29.9	36.0	96.0	41.0	169.3	27.2	83.9	50.5	75–100
HCO ₃	16.3	24.1	23.2	21.1	16.1	24.6	13.3	24.8	8.1	22–28
O ₂ saturation	82.8	53.8	65.1	96.3	73.3	99.2	50.2	96.3	85.6	94–100

PCO₂ partial pressure of carbon dioxide, PO₂ partial pressure of oxygen, HCO₃ bicarbonate, “–” none

of drugs for the treatment of their severe symptoms and conditions. These medications failed to save two children's lives. To date, no efficient treatment has been suggested for patients with COVID-19, including adults or pediatric patients with or without comorbidities. Some have claimed that hydroxychloroquine with azithromycin resulted in virologic clearance in six patients [26], whereas others have doubted such efficacy in patients with severe COVID-19 [27]. We also used hydroxychloroquine with azithromycin in three patients, among whom two died and one survived. Azithromycin was used for all of the patients in our study owing to the presence of pneumonia in all patients. Azithromycin alone seemed sufficient for treatment of four cases but was given in combination with other drugs in three patients that survived. The significant point in this regard is the severity of the underlying cardiac condition that results in worsening of the child's conditions and holds back the effect of drugs. Moreover, immune dysregulation during the severe phase of COVID-19 following inflammatory cascade and cytokine production may result in increased risk of vascular hyperpermeability and multi-organ failure [28].

Considering the laboratory results of serum parameters, the significant difference in terms of PTT and CRP between the deceased and survived groups are of note. CRP is one of

the biomarkers related to inflammation in COVID-19 patients and is associated with disease severity, admission to ICU, use of mechanical ventilation, and death [29, 30]. In another study, cox regression analysis showed that CRP > 5 was associated with ARDS. The deceased COVID-19 patients in the study by Deng et al. also showed higher levels of CRP [31], which confirm the results of the present study; however, none of the above-mentioned studies focused on the pediatric population [29–31]. The difference in PTT between the groups of our study can also be attributed to the coagulopathy and hemostasis disorders in COVID-19 patients [32]. As shown previously, COVID-19 can result in excessive activation of the coagulation cascade and platelets [33] and to increased risk of coagulation disorders associated with a higher risk of death [29, 34]. This confirms the results of the present study, although it was not focused on the pediatric population.

Due to the scarcity of CHD and COVID-19, we reported only nine cases. Further studies are required in this regard. The main strength of the present study is its reporting of clinical and laboratory findings in the rare concomitance of COVID-19 in children with CHD and the significance of this condition. However, the study has some limitations. The present study has relatively few participants, which was due to the scarcity of the concomitance of COVID-19 in children

with CHD. Also, the discharged patients were not followed and the long-term results were not evaluated.

In conclusion, the present study showed that the general consideration of mild COVID-19 in children did not include patients with CHD. Treatment of these children resulted in the death of two of nine patients. Therefore, it is necessary to pay greater attention to patients with CHD and to determine guidelines for treatment of COVID-19 in these children.

Author contributions EHEM and MS (Shima Mahmoudi) contributed equally to this work. EHEM contributed to the statistical analysis and writing of the draft of the manuscript. MS (Shima Mahmoudi) designed the study and had full access to all data in the study and take responsibility for the integrity of the data. NA contributed to data acquisition and data interpretation. MS (Setareh Mamishi) provided critical revision of the article. All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version.

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Compliance with ethical standards

Ethical approval This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1399.060).

Conflict of interest All authors declare no conflict of interest.

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