Evaluation of coronary artery and immunologic status in post-COVID-19 children in Sarajevo

Evaluacija koronarnih arterija i imunološkog statusa kod post-COVID-19 djece u Sarajevu

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Key words
POST-COVID-19,
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SUMMARY. Introduction: Although evidence has demonstrated that SARS-COV-2 primarily affects the upper respiratory tract, other systems are also involved such as gastrointestinal and cardiovascular system. At present, there is insufficient data on cardiovascular and immunologic involvement in COVID-19 paediatric patients.

Patients and Methods: This study evaluated 70 children previously healthy or with no pre-existing heart disease from Sarajevo with positive post-COVID history. Detailed cardiovascular examination was performed, with parameters of body weight, height, oxygen saturation, pulse, blood pressure, electrocardiogram (ECG), 24hrs Holter ECG, echocardiography. Laboratory tests included values of polymerase chain reaction (PCR) and SARS-COV-2 immunoglobulin G /IgG/ and immunoglobulin M /IgM/, CBC /complete blood count/, creatinine phosphokinase myofibrilae /CPKMB/, creatinine phosphokinase/CPK/, lactate dehydrogenase /LDH/, liver enzymes, D dimer, C reactive protein/CRP/ and urine.

Results: Majority of children (64.3%) were asymptomatic. ECG was normal in relation to patients’ age, except in eight patients (intermittent palpitations on exertion): short PR interval, so in 24hrs Holter EKG there was no significant arrhythmias except incomplete right branch block /IRBB/ in 12%, monofocal ventricular ectopic extrasystole /VES/ in 15%. Echocardiogram was normal in all patients with normal ejection fraction of the left ventricle, no pericardial effusion, vegetations or thrombus was detected. Mean diameter of coronary arteries right /RCA/ and left /LCA/ ranged from 1.98 mm to LCA 2.09 mm except in one symptomatic patient a diameter of left coronary artery /LCA/ was enlarged up to 3.8 mm. The concentration levels of COVID-19 IgG showed a statistical significance when compared between younger and older age groups in examined children (p < 0.05; p = 0.043).

Conclusion: Cardiovascular evaluation should always be an option in post-COVID patients. Immunological assessment is necessary in post-COVID patients in order to gain a further understanding of patient’s status.

SAŽETAK. Uvod: Iako su rezultati studija pokazali da SARS-COV-2 prvenstveno utiče na gornje respiratorne puteve, uključeni su i gastrointestinalni i kardio vaskularni sistem. Trenutno, nema dovoljno podataka o kardiovaskularnoj i imunološkoj zahvaćenosti kod COVID19 pedijatrijskih pacijenata. Pacijenti i metode: U studiji je učestvovalo 70 djece iz Sarajeva, koja su prethodno bila zdrava ili nisu imala srčane bolesti, s pozitivnom anamnezom nakon COVID-a. Urađen je detaljan kardio vaskularni pregled, uz parametre tjelesne težine, visine, mjerenja saturacije kiseonika, pulsa, krvnog pritiska, elektrokardiogram (EKG), 24 satni Holter EKG, ehokardiografija i laboratorijski testovi koji su uključivali vrijednosti lancane reakcije polimeraze (PCR) i SARS-COV-2 immunoglobulina G /IgG/ i immunoglobulina M /IgM/, KKS /kompletna krvna slika/, kreatinin fosfo kinaza miofibrila /CPKMB/, kreatinin fosfokinaza /CPK/, lactat dehydrogenaza /LDH/, enzimi jetre, D dimer, C reaktivni protein /CRP/ i urin. Rezultati: Većina djece (64.3%) bila je asimptomatska. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta: u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermittentne palpitacije na napor/sa kratkim PR intervalom, a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta a u 24h Holter EKG nije bilo statistički značajne arrhythmije osim kod jednog simptomatskog pacijenta.
The SARS-COV-2 (COVID19) has become a major concern due to its high death rate and its unknown nature. SARS-COV-2 continues to spread rapidly across the globe causing serious concerns. Although evidence has demonstrated that SARS-COV-2 primarily affects the upper respiratory tract followed by lower respiratory tract damage leading to severe pneumonia, other systems are also involved such as gastrointestinal and cardiovascular as well. Studies have shown that patients with cardiovascular diseases may be subject to an increased risk of death. The clinical manifestation varied among the population and the main symptoms of the infection are fever, dry cough, headache, and dyspnoea, with the progress to pneumonia. The manifestation and the behaviour of the virus infection in children are poorly defined. Severe manifestation of SARS-COV-2 in children is rear and the hospitalisation rate is significantly lower compared to adults. Similar to adults, the respiratory tract is affected most commonly. In the largest study up to date, 2143 paediatric patients, 94.1% of the children were either asymptomatic or had mild to moderate disease. The study also showed that, 5.2% of children had respiratory distress or hypoxia and 0.6% who progressed to acute respiratory distress syndrome or multiple organ dysfunctions. Most of the studies have shown that SARS-COV-2 infection is involved in cardiovascular system, however, mostly in adults. Earlier studies showed a milder clinical course for infants; few of them needed the intensive-care treatment. At present, there is insufficient data on cardiovascular and myocardial involvement in COVID-19 paediatric patients.

The aim of this study is to evaluate the cardiovascular status and immunological in post-COVID-19 children in Sarajevo.

**Patients and methods**

The total of 70 paediatric patients previously healthy or with no pre-existing heart disease from Sarajevo region with positive post-COVID history were evaluated. They were examined in the Eurofarm Polyclinic in Sarajevo, from October 2020 until April 2021. Patients were referred from local paediatrician or by parents concerned due to child's symptoms. The children have been previously SAR-COV-2 positive or had a previous contact with a positive person. Epidemiological data were collected, establishing the 1st day of the symptoms or the contact with SARS-COV-2 positive person, a detailed examination was performed, including parameters such as oxygen saturation, pulse, blood pressure (BP), body weight and height. Electrocardiography was performed by a paediatric cardiologist. The examination included left ventricle ejection fraction (LVEF), left ventricle end-diastolic diameter (LVEDD), left ventricle end-systolic diameter (LVESD), S (septum), LVPW (left ventricle posterior wall), diameter of RCA (right coronary artery) and LCA (left coronary artery). In addition, blood examination was performed including complete blood count (CBC), C-reactive protein (CRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), creatinine phosphokinase myofibrilae (CPKMB), creatinine phosphokinase (CPK), lactate dehydrogenase (LDH) and tests for immunological status: values of polymerase chain reaction (PCR) or serological test on corona: immunoglobulin G /IgG/ and immunoglobulin M /IgM.

**Statistical Analysis**

All data were analysed using the SPSS version (Version 26.0.0.0.2019) in this study.

**Ethical considerations**

The informed consent form was obtained from all parents following the explanation the aim of the study.

**Results**

In the group of 70 children (40 boys and 30 girls) there were: infants <1 (n =10), 1–5 years (n = 20); 6–10 years (n=12); 11–15 years (n=21) and 16–18 years (n= 7) (Table 1.). All children were in relation to percentile scale within the average height and weight range from 25p-97p. The mean body temperature at the time of examination was: 36.6°C (34.3–37.6°C), mean oxygen saturation was 97.6% (94–99%). Pulse rate was within a normal range for age as was BP for age, height, and sex. Before referral to paediatric cardiologists, 24 patients were seen by local paediatrician. The period from contact with COVID-19 through a family member or at school, until referral to paediatrician was 7.5 days (1–21 days). Symptoms differed depending on age group; younger children had no or mild symptoms in comparison to the older group of children (Table 1). Majority of children (64.3%) were asymptomatic, except two 14-year-old boys, with pallitation on exertion, shortness of breath, including ECG changes: derelivation of ST segment in lead II, V5 and V6, lower oxygen saturation 91% and 94%, elevated CPKMB (38 and 45), with mildly enlarged in one patient a diameter of left coronary artery (LCA) up to 3.8 mm, no aneurysm, no skin changes, and with normal EF of LV. They were on short period (10–15 days) nonsteroids treatment, including low doses of Aspirin and vitamins (C and D), rest and no physical activity. Following the treatment and non-activity regime, they were fully recovered, free of symptoms, with normal oxygen saturation and normal values of CPKMB and CBC, diameter of LCA was within the normal range according to patients' age and body...
weight. CBC, including platelets and white blood count, were within normal range, as well as urine, D-dimer, CRP, LDH, liver enzymes, CPK, CPKMB except as mentioned earlier (Table 2). ECG was normal, corresponding to patients’ age, except in eight patients (intermittent palpitations on exertion) who had short PR interval 0.120–0.140 ms, with no delta wave, so 24 h ECG Holter was performed without any significant arrhythmias, except incomplete right branch block / IRBB/ that has been documented in 12%, and monofocal ventricular extrasystole in 15% (Table 2). The concentration of SARS-COV-2 IgG showed a statistical significance when compared between age groups (p < 0.05; p = 0.043). Echocardiogram was normal in all patients with normal ejection fraction of left ventricle (Table 3). No pericardial effusion, vegetations or thrombus was detected. Mean diameter of coronary arteries right (RCA) and left (LCA) ranged 1.98 mm to LCA 2.09 mm. Z score calculation for coronary arteries including: body weight, height and gender of every patient, was within normal values for RCA and LCA (21,22). No anomalies were detected in their flow and diameter, with no aneurisms, except stated earlier in the text.

Discussion

The present study was conducted to evaluate the cardiovascular and immunological status in post-COVID-19 children in Sarajevo. Cardiovascular system complications such as heart failure, myocardial infarction, and arrhythmia, are not uncommon among adult patients infected with COVID-1910. However, the proportion of severe and critical cases in children was 10.6% under 1 year of age, and 3.0% among the 1–5, 6–10, 11–15, and >15 years’ subsets, suggesting that infants may be at higher risk of severe respiratory failure than firstly thought 8. Most commonly, the COVID-19 infection is manifested as mild disease in children according to the literature and data in our study.

Analysing the symptoms in children, fever is present in 40–60% of children, cough occurs in 40–50% of children, whereas headache, myalgia, and sore throat are more common than shortness of breath. After 7–10 days19, children usually recover, whereas more severe forms are characterized by dyspnoea, hypoxia, cyanosis, dehydration with signs of respiratory distress syndrome, shock, myocardial lesions, or multiorgan failure (27–29). In our study group, fever was present in 15 (70), cough 21 (70), shortness of breath 8 (70) patients, and majority were asymptomatic, which is the case with most of reported paediatric patients in post-COVID period. Identical changes have been reported by An-
is characterized by fever, skin rash, lymphadenopathy, manifestation in Kawasaki disease in children <5 years is verified by ultrasound colour Doppler examination. The possibility of myocardial infarction in children, which spreads, causing a coronary artery aneurysm with the arteries occurs in severe cases of Kawasaki disease that causes mucocutaneous changes, elevated markers of inflammation, lymphopenia, thrombocytopenia. Multisystem inflammatory response to SARS-CoV-2 could be associated with altered cardiac parameters, however, in the series of patients evaluated in the current study, none of them fulfilled the MISC, typical or atypical Kawasaki disease criteria. All the patients were evaluated for coronary artery involvement, which was negative for all of them except as stated earlier.

Studies have shown that adults are more susceptible to severe infections and even severe forms of COVID-19 due to the large release of cytokines (cytokine storm) from macrophages, monocytes, and lymphocytes, leading to lung tissue damage and multiorgan failure. In our study, the values of immunoglobulin G were significantly higher in the older group of children which indicates that with age the immune system is getting more responsive to the virus.

Conclusion
Cardiovascular evaluation should always be an option in post-COVID patients. Immunological assessment is necessary in post-COVID patients in order to gain a further understanding of patient’s status.

Conflict of interest
The authors declare no conflict of interest.

The paper has been revised and proofread by Samra Mušija, certified translator/interpreter for English with an extensive experience in translation, revision and proofreading of medical-related papers and documents.

Reference