RESEARCH ARTICLE / *Araştırma Makalesi*

Evaluation of Electrocardiographic Changes and Laboratory Parameters in Pediatric COVID-19

Pediyatrik COVID-19'da Elektrokardiyografi Değişiklikleri ve Laboratuvar Parametrelerinin Değerlendirilmesi

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Abstract

Objective	Cardiac involvement of Coronavirus 19 disease (COVID-19) may be reflected by electrocardiographic (ECG) changes. ECG changes that may occur in hospital admission for COVID-19 in children have not yet been fully evaluated.
Materials and Methods	We examined 83 children admitted to our hospital with proven COVID-19. A detailed clinical examination, 12-lead ECG and laboratory tests were recorded. And then all laboratory parameters were evaluated by age.
Results	P wave amplitude was normal in 77.1% and high in 22.9% of study population. There was a significant difference in white blood cell (WBC), lymphocyte, neutrophil, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), D-dimer values between the group with P wave amplitude normal and the high group. 13.3% of patients had first degree AV block and 86.7% did not. There was a significant difference between the groups in WBC, lymphocyte, D-dimer, AST values. In our study, there was right ventricular hypertrophy (RVH) in the ECG of 17 cases. There was a significant difference in WBC, lymphocyte, D-dimer, LDH, AST values between groups with and without RVH. In addition, there were positive correlations among V1R, V6S, V1 R / S ratio and WBC, lymphocyte, D-dimer, creatinine kinase (CK), creatinine kinase isoform MB (CK-MB), LDH, AST values.
Conclusion	Pathological ECG findings were associated with laboratory values used in the course of the disease. We think that ECG is a test in the course of COVID-19 in children, which may make important contributions to clinicians to manage the patients when interpreted correctly.
Keywords	Child; COVID-19; electrocardiography

Öz

Amaç	*Koronavirüs 19 hastalığının (COVID-19) kardiyak tutulumu elektrokardiyografik (EKG) değişikliklerle yansıtılabilir. Çocuklarda COVID-19 nedeniyle hastane başvurularında meydana gelebilecek EKG değişiklikleri henüz tam olarak değerlendirilmemiştir.*
Gereç ve Yöntemler	*Kanıtlanmış COVID-19 tanısı ile hastaneye başvuran 83 çocuk değerlendirildi. Ayrıntılı klinik muayene, 12 derivasyonlu EKG ve laboratuvar testleri kaydedildi. Tüm laboratuvar değerleri yaşa göre değerlendirildi.*
Bulgular	*P dalga amplitüdü çalışma popülasyonunun % 77,1'inde normal ve % 22,9'unda yüksek bulundu. P dalga amplitüdü normal olan grup ile yüksek grup arasında beyaz kan hücresi (WBC), lenfosit, nötrofil, aspartat aminotransferaz (AST), laktat dehidrojenaz (LDH), D-dimer değerlerinde anlamlı fark vardı. Hastaların % 13,3'ünde birinci derece AV blok varken % 86,7'sinde yoktu. Birinci derece AV blok olan ve olmayan gruplar arasında WBC, lenfosit, D-dimer, AST değerlerinde anlamlı fark vardı. Çalışmamızda 17 olgunun EKG'sinde sağ ventrikül hipertrofisi (RVH) vardı. RVH olan ve olmayan gruplar arasında WBC, lenfosit, D-dimer, LDH, AST değerlerinde anlamlı farklılık vardı. Ayrıca V1R, V6S, V1 R / S oranı ile WBC, lenfosit, D-dimer, kreatinin kinaz (CK), kreatinin kinaz izoform MB (CK-MB), LDH, AST değerleri arasında pozitif korelasyon saptandı.*
Sonuç	*Patolojik EKG bulguları hastalığın seyrinde kullanılan laboratuvar değerleri ile ilişkilendirildi. EKG'nin çocuklarda COVID-19 seyrinde çok önemli bir test olduğunu ve doğru yorumlandığında klinisyenlerin hasta yönetimlerine ciddi katkılar sağlayabileceğini düşünüyoruz.*
Anahtar Kelimeler	*Çocuk; COVID-19; elektrokardiyografi*

INTRODUCTION

Coronavirus 19 disease (COVID-19) is an infectious disease caused by the SARS –CoV-2 virus, which started in a certain region in China in December 2019 and affected the world in a very short time. The SARS-CoV-2 virus is an RNA virus which is a member of the same family as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) corona viruses. Although the fatality of SARS- CoV-2 is lower than SARS and MERS, it is predicted that it will affect more people and cause more deaths.[1] The clinic varies from a mild respiratory infection to shock and death. It began as a series of pneumonia cases but it was later observed that it triggered a serious inflammatory response in the body and negatively affected all systems. It has negative effects on the cardiovascular system as in other systems.

Cardiovascular involvement has been associated with the mortality of the disease.[2] Electrocardiography (ECG) is an inexpensive, simple, easy to apply and very important test that directly demonstrates the electrical activity of the heart.[3] Therefore, standard ECG has an important role in SARS-CoV-2 infection as in all serious diseases. However, one of the sides of COVID-19 research that has not been clarified yet is ECG changes. It has not been identified, especially in the acute phase of the disease. The contagiousness of the SARS- CoV-2 virus is very high. Clinicians must keep in contact with a cardiologist as soon as possible, while the most accurate evaluation of the patient. SARS- CoV-2 affects the child age group less frequently and more mildly than adults. However, as the number of infected children increase, serious clinical findings are observed more.

In this study, ECG changes in children diagnosed with COVID-19 were evaluated and their role in determining prognostic markers that could assist clinicians in the rapid triage of patients and guide the clinical decision-making process was investigated.

MATERIALS and METHODS

This study is a cross-sectional descriptive study which was performed in pediatric COVID-19 cases between the ages of 0-18 years who admitted to the Ministry of Health Sakarya University Training and Research Hospital and were followed up in the pediatrics clinic. According to the Republic of Turkey Ministry of Health to the COVID-19 Diagnosis and Treatment Guidelines patients who were matching the definition of confirmed SARS-CoV-2 infection enrolled the study.[4] A study was planned with a total of 90 patients. However, 7 patients were excluded because they refused to participate in the study. A total of 83 patients diagnosed with COVID-19 were evaluated. During the patient's admission to the hospital, a detailed clinical examination, 12-lead ECG, hematological and biochemical laboratory tests were performed. The ECG was recorded with a calibration of 25 mm/s and 1 mV/cm and a filter setting of 0.05-150 Hz. The ECG recordings were scanned and transferred to a personal computer. After 400x magnification in AdobePhotoshop, measurements of P wave amplitude, PR distance, QRS time, QRS axis, V1R, V1S, V1 R / S, V6R, V6S, V6 R / S from these ECG tracings were performed by a blinded pediatric cardiologist. P wave amplitude, PR distance, QRS time, QRS axis, V1R, V1S, V1 R / S, V6R, V6S, V6 R / S values were calculated. According to the criteria of right ventricular hypertrophy (RVH), the patients were grouped with and without RVH. In addition, the following test results from hospital admission were recorded: Complete blood count, white blood cell (WBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine kinase (CK), creatinine kinase isoform MB (CK- MB), lactate dehydrogenase (LDH), troponin-I, D-dimer. SARS-CoV-2 PCR positivity was detected in the simultaneous nasopharyngeal swabs of all patients.

An ethics committee approval from Faculty of Medicine of Sakarya University was provided for this study (Ethics Committee Number: 71522473 / 050.01.04 / 228).

Statistical Analysis

Descriptive statistics were used to compare the general features of all participants. The Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to compare the distributions of numerical variables. We calculated means ± standard deviation of variables that were normally distributed, and medians (with minima and maxima) of those that were not normally distributed. Student's t-test and the Mann-Whitney U test were used as appropriate to compare data between groups. We assessed relationships between numerical variables by calculating linear correlation coefficients using the methods of Pearson and Spearman. SPSS for Windows software (ver. 20.0; IBM SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A p-value <0.05 was considered to reflect statistical significance.

RESULTS

In our study, the mean age of 83 patients was 9.5 (0.16-17.66). Pathological findings in ECG were: P wave amplitude change, first degree A-V block, ventricular conduction delay, ventricular right axis deviation, and ECG changes consistent with right ventricular hypertrophy. P wave amplitude was normal in 77.1% and high in 22.9% of study population. There was a significant difference in WBC, lymphocyte, neutrophil, hemoglobin (Hb), mean cell volume (MCV), AST, LDH, D-dimer values between the group with P wave amplitude high and normal groups. In addition, P wave amplitude was positively correlated with WBC, lymphocyte, AST, LDH and D-dimer, and negatively correlated with neutrophil count. The difference between the normal and high P wave amplitude groups, demographic characteristics, hematological and biochemical parameters are shown in Table 1.

Table 1. Comparisons of demographic and hematologic parameters between normal and high P wave groups in pediatric COVID-19

	Group with normal P wave (n:64)	Group with high P wave (n:19)	p
Age (year)	12.08 (0.33-17.66)	1.75 (0.16-15.66)	<0.001
WBC (×10^9 /L)	5.75 (3.04-15.00)	8.85(2.52-17.10)	0.009
LYM (×10^9/L)	2.07 (0.50-10.20)	4.97 (1.01- 13.80)	0.004
NEU (×10^9/L)	2.84 (0.74-9.43)	2.45 (0.86-5.84)	0.041
Hb (g/dL)	12.85±1.58	11.62±1.24	0.003
MCV (fL)	84.56 ±6.37	79.54±5.38	0.003
AST (U/L)	26 (13-69)	37 (18-96)	0.002
CK MB (U/L)	16.50 (10-43)	24 (16-55)	0.050
LDH (U/L)	241 (107-1136)	320 (141-487)	0.012
D-dimer (mcg/L FEU)	217 (31-32100)	447 (125-18200)	0.009

Abbreviations: AST, aspartate aminotransferase; CK MB, creatinine kinase isoform MB; Hb, Hemoglobin; LYM, lymphocyte count; NEU, neutrophil count; MCV, mean cell volume; LDH, lactate dehydrogenase; WBC, white blood cell Parameters were expressed as mean±SD and median (minimum-maximum). Student's t test and Mann-Whitney U test were performed and p value<0.05 was considered significance

The patients were divided into two groups according to the presence of first-degree A-V block in ECG. 13.3% of patients had first-degree A-V block and 86.7% did not. There was a significant difference between the groups for WBC, lymphocyte, D-dimer, CK-MB and AST (Table 2).

Table 2. Comparisons of hematological and biochemical parameters between the groups with and without first degree AV block in pediatric COVID-19

	Group with normal P wave (n:64)	Group with high P wave (n:19)	p
Age (year)	11.91 (0.33-17.66)	3.6 (0.16-17.58)	0.027
WBC (×10^9 /L)	6.0 (2.52-17.10)	8.95 (5.56-12.80)	0.009
LYM (×10^9/L)	2.11 (0.50-13.80)	3.80 (1.22-8.33)	0.011
AST (U/L)	27 (13-69)	36 (19-96)	0.028
CK MB (U/L)	19.50 (10-55)	30 (17-48)	0.028
D-dimer (mcg/L FEU)	1370.00 (179.00-5990.00)	219.00 (31.00-32100.00)	0.005

Abbreviations: AST, aspartate aminotransferase; CK MB, creatinine kinase isoform MB; LYM, lymphocyte count; LDH, lactate dehydrogenase; WBC, white blood cell
Parameters were expressed as median (minimum-maximum). Mann-Whitney U test was performed and p value<0.05 was considered significant

In addition, there was a positive correlation between V1R, V6S, V1 R / S ratio and WBC, lymphocyte, D-dimer, CK, CK-MB, LDH, AST and negative correlations between Hb and MCV (Table 3).

Table 3. The results of the correlation analyses between V1R amplitude, V1 R/S ratio, V6S amplitude and hematological and biochemical parameters in pediatric COVID-19

	V1 R amplitude		V1 R/S ratio		V6 S amplitude	
	r	p	r	p	r	p
WBC **(×10^9 /L)**	0.359	0.001	0.427	<0.001	0.402	<0.001
LYM **(×10^9 /L)**	0.550	<0.001	0.517	<0.001	0.517	<0.001
Hb (g/dL	-0.274	0.012	-0.272	0.013	-0.403	<0.001
MCV* (fL)	-0.273	0.013	-0.253	0.021	-0.216	0.049
CK* **(U/L)**	0.202	0.082	0.241	0.037	0.265	0.021
CK-MB **(U/L)**	0.545	0.002	0.455	0.013	0.384	0.040
AST **(U/L)**	0.615	<0.001	0.679	<0.001	0.578	<0.001
LDH **(U/L)**	0.245	0.028	0.286	0.010	0.292	0.008
D-dimer* **(mcg/L FEU)**	0.263	0.016	0.338	0.002	0.329	0.002

Abbreviations: AST, aspartate aminotransferase; CK, creatinine kinase; CK MB, creatinine kinase isoform MB; Hb, Hemoglobin; LYM, lymphocyte count; LDH, lactate dehydrogenase; WBC, white blood cell; MCV, Mean Cell Volume Pearson and Spearman correlation tests were performed and p value<0.05 was considered significant.
* Spearman correlation

In our study, only one case had troponin elevation. CK-MB values of 29 cases were examined. CK-MB increase was detected in 10 of them. There was a significant difference in WBC, AST, ALT between the groups with and without high CK-MB.

In our study, there was RVH in the ECG of 17 cases. There was a significant difference in WBC, lymphocyte, Hb, MCV, D-dimer, LDH, AST values between the group with and without RVH (Table 4).

Table 4. Comparisons of demographic and hematologic parameters between groups with and without RVH in pediatric COVID-19

	Group with RVH (n=66)	Group without RVH (n=17)	p
Age (year)	12.25 (0.16-17.66)	2.33 (0.33-15.66)	<0.001
WBC (×10^9 /L)	5.75 (3.04-16.60)	8.85 (2.52-17.10)	0.006
LYM (×10^9/L)	2.09 (.50-11.40)	4.97 (1.01-13.80)	0.010
NEU (×10^9/L)	2.84 (0.74-9.43)	2.45 (0.86-5.84)	0.041
Hb (g/dL)	12.77±1.58	11.81±1.41	0.026
MCV (fL)	84.20±6.81	80.35±3.77	0.028
AST (U/L)	26 (13-46)	40 (18-96)	<0.001
LDH (U/L)	340.00 (141.00-487.00)	241.00 (107.00-1136.00)	0.003
D-dimer (mcg/L FEU)	1116.50 (179.00-18200.00)	210.00 (31.00-32100.00)	<0.001

Abbreviations: AST, aspartate aminotransferase; CK MB, creatinine kinase isoform MB; Hb, Hemoglobin; LYM, lymphocyte count; NEU, neutrophil count; MCV, mean cell volume; LDH, lactate dehydrogenase; RVH, right ventricular hypertrophy; WBC, white blood cell
Parameters were expressed as mean±SD and median (minimum-maximum). Student's t test and Mann-Whitney U test were performed and p value<0.05 was considered significant

DISCUSSION

In our study, P wave amplitude was found to be high in 19 patients (22.9%). There was a significant difference for WBC, lymphocyte and neutrophil counts between the group with and without high P wave amplitude. P wave amplitude correlated positively with WBC and lymphocyte counts and negatively with neutrophil counts. Although studies show that there are leukocytosis and lymphopenia among common laboratory abnormalities in patients hospitalized with the diagnosis of COVID-19, there may be a variety of immunological responses due to multifactorial causes such as regional differences and racial variations with the spread of the pandemic.[5-7] Various laboratory results such as leukopenia / leukocytosis, lymphopenia / lymphocytosis has been reported in patients.[8-12] In our study, lymphocyte and WBC values were higher in the group with high P wave amplitude. Lymphocyte, WBC values showed statistically significant difference between the P wave amplitude normal and high groups. The amplitude of the P wave shows right atrial dilatation and is associated with a temporary right heart strain where pulmonary vascular flow is affected.[13] Although milder clinical course was mentioned in pediatric patients compared to adults, the presence of high P wave amplitude in the infantile period and the relationship between WBC, lymphocyte and neutrophils suggested that we should think about cardiac effects of COVID-19, especially in young children.

We examined the biochemical including AST, LDH and hematological D-dimer values were found to be significantly different between the group with high P wave amplitude and the normal group. A positive correlation was found between P wave amplitude and AST, LDH and D-dimer. In studies with COVID-19 patients, AST, LDH and D-dimer values have been reported as important prognostic laboratory parameters.[10] Biochemical parameters of SARS and SARS- CoV-2 were evaluated. Both had high elevated myocardial enzymes and liver function tests.[14,15] In children infected with SARS, high LDH and higher percentage of white blood cells were positively correlated with the severity and mortality of cases.[16] Similarly, there are publications showing that LDH and D-dimer levels are related to the severity of the disease in COVID-19 in adults.[17] In our study AST, LDH and D-dimer levels showed a relationship with high P wave.

First degree A-V block was present in 11 patients. PR prolongation can be seen in COVID-19 due to A-V conduction delay secondary to possible endocardial inflammation. A significant difference was found for WBC, lymphocyte, D-dimer and AST between groups with and without PR prolongation.

In our study, RVH was detected in ECG of 17 cases. There was a significant difference in WBC, lymphocyte, Hb, MCV, D-dimer, LDH, AST values between the group with and without RVH. In addition, there was a positive correlation between V1R, V6S, V1 R / S ratio and WBC, lymphocyte, D-dimer, CK, CK-MB, LDH, AST values, while negative correlation was found in Hb and MCV values. Although currently available studies confirm the presence of myocardial damage and its association with mortality in COVID-19, there is no echocardiographic evidence to determine the characteristics of cardiac injury.[2,18] RV strain is determined by pulmonary vascular resistance. Presence of mechanical ventilation in conditions such as pneumonia or adult respiratory distress syndrome reduces venous return due to positive intra-thoracic pressure. Also, in this case, RV strain increases as a result of increased transpulmonary pressure and pulmonary vascular resistance and vasoconstriction due to hypoxemia and hypercapnia. Although the opinion that pediatric patients showed a mild clinical course during the course of COVID-19, WBC, lymphocyte, D dimer, AST, LDH levels, associated with the severity of the disease showed a significant relationship with the pathological ECG findings in our study. Accordingly, we thought that the cardiovascular systems may have been affected.

There was a significant difference in Hb and MCV values between both normal and high P wave amplitude group and between the groups with and without RVH. In addition, negative correlation was found between P wave amplitude, V1R, V6S, V1R / S ratio and Hb and MCV values. The effect of iron on the immune system is known. Anemia negatively affects the immune system, and it also occurs as a result of infections. Hb and MCV values may play an important role in the course of SARS –CoV-2, especially in childhood with rapid growth.

In our study, only one case had troponin elevation. A total of 29 patients had a CK-MB value and 10 were high. There was a significant difference in WBC, AST, ALT values between groups with and without high CK MB. A positive correlation was found between V1R, V6S, V1R / S ratio and CK-MB. In various viral infections that do not primarily show myocardial affinity such as rotavirus, dengue virus and RSV, CK-MB has been elevated. The mechanism for this is not fully known. According to our study, it may be concluded that CK is associated with WBC, ALT, AST values, which are thought to be prognostic important.

The limitations of our study can be listed as follows; we found a relationship between P wave amplitude and RVH with laboratory tests frequently used in the course of the disease. We could not answer whether the effect of the right heart was caused by lung pathology or the direct cardiac effect of the disease. We might use brain natriuretic peptide (BNP) levels to distinguish these two conditions, but patients' BNP levels were not studied.

ECG is a widely available diagnostic test that can be performed quickly without exposing large numbers of staff to SARS-CoV-2. ECG has shown an incremental prognostic value in patients with underlying cardiovascular disorders in population-based studies and therefore offers a particularly attractive method during the current pandemic. Limited data are available on what the cardiac effects of COVID-19 are in children. Especially in countries without pediatric patient data, it is important to carefully evaluate and correctly interpret ECG to define the clinical features and severity of the disease.

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Conflicts of Interest. None.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation in Turkey and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was given for this study from the Faculty of Medicine of Sakarya University (Ethics Committee Number: 71522473 / 050.01.04 / 228).

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