American Journal of Clinical Microbiology and Antimicrobials

Research Article
Published: 21 Jun, 2021

Tertiary Pandemic Center Experience: Characteristics, Clinical Course, Complications and Treatment of Newborns with COVID-19 and their Cardiac Manifestations

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Abstract

Objective: Despite the increased number of newborns with COVID-19, data on newborns are still scant, and new symptoms and complications continue to be reported. We want to share our own data regarding newborns with COVID-19.

Methods: This retrospective single center study was performed in a tertiary pandemic center in Istanbul. The medical records of hospitalized newborns due to COVID-19 from March 17th to December 31st, 2020 were reviewed. The demographic characteristic, the clinical course, complications, and the treatment were recorded. The babies were divided into two groups according to the presence or absence of cardiac complications. The two groups were compared. Short-term follow-up results were presented.

Results: 18 newborns were hospitalized during the study period. Most of the newborns had a mild disease. Cardiac complications developed in 3 newborns (16.6%). Two newborns who had clinically suspected myocarditis and myocardial injury were treated with intravenous immunoglobulin and ibuprofen. Baby with SVT developed adenosine-resistant arrhythmia that was controlled only with dual prophylactic medications. All 3 babies were hemodynamically stable. In follow-up the baby with SVT become 8 months old and no attack was observed. Increased troponin levels in babies with myocardial injury gradually returned to normal range for age in 3 and 4 months. When the two groups were compared, it was seen that the nasopharyngeal positive SARS-CoV-2 PCR test became negative in a longer time (days) in patients with cardiac complications (22.3 ± 5.5 vs. 7.87 ± 0.92, p=0.007).

Conclusion: Most newborns had a mild disease. In this study, it was observed that newborns with COVID-19 may also have cardiac arrhythmia and myocardial damage. A long-term positive PCR test may be related to the complicated clinical course in newborns. The long-term consequences are unknown and outpatient follow-up is necessary.

Keywords: Newborns, Cardiac manifestations, Follow up, Coronavirus infections, COVID-19

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Received Date: *07 May 2021*
Accepted Date: *18 Jun 2021*
Published Date: *21 Jun 2021*

Citation:
Coskun S, Guzel B, Imdadoglu T, Tuncer T, Ozdil A, Guven S. Tertiary Pandemic Center Experience: Characteristics, Clinical Course, Complications and Treatment of Newborns with COVID-19 and their Cardiac Manifestations. Am J Clin Microbiol Antimicrob. 2021; 4(1): 1050.

Introduction

Over the past few months, new symptoms and complications of COVID-19 that need to be understood have been reported [1-3]. It has been found that 97% of pediatric cases with COVID-19 suffer from asymptomatic to moderate illness. However, it has been reported that 1/3 of critically ill patients are small infants and the risk of serious illness is disproportionately high in this group [4]. Close monitoring of clinical symptoms and signs in newborns with COVID-19 are very important for early diagnosis and management of serious complications. We report our experience about babies with COVID-19 and their demographic characteristics, clinical signs, and laboratory findings. Although it is known that COVID-19 may have different cardiac involvement, as far as we know, cardiac involvement has not been reported in newborns. We report cardiac complications such as Supraventricular Tachycardia (SVT), myocardial injury and clinically suspected myocarditis

in newborns with COVID-19 and their short-term follow-up. With long-term follow-up of successfully treated newborns, our knowledge about the outcomes of the disease will continues to increase.

Materials and Methods

Medical records of newborns with COVID-19 hospitalized in Sancaktepe Training and Research Hospital Neonatal Intensive Care Unit (NICU) between March 17th, 2020 and December 31st, 2020 were evaluated retrospectively. This study was approved by the Ethics Committee of Sancaktepe Prof. Dr Ilhan Varank Training and Research Hospital, under number 2021/113. While the treatment of newborns with COVID-19 at the beginning of the pandemic is carried out at Sancaktepe Training and Research Hospital, their treatment has been continuing at the pandemic Feriha Öz Emergency Hospital since October. Written consent was obtained from their families before the babies were admitted to the hospital. The diagnosis of COVID-19 was made with positive SARS-CoV-2 PCR test on the nasopharyngeal swab sample. Babies had history of contact with SARS-CoV-2 virus infected individual (usually mother) within the last few days. The general condition of the hospitalized babies was evaluated and placed in special isolation rooms reserved for COVID-19. Blood was drawn from the babies for initial laboratory evaluations and empirical antibiotic therapy was initiated. Laboratory assessments consisted of complete blood cell count, C-Reactive Protein (CRP), Procalcitonin PCT), Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN), creatinine, albumin, coagulation tests, fibrinogen, ferritin, Lactate Dehydrogenase (LDH). Clinical signs and symptoms such as fever, cough, nasal secretions, tachypnea, tachycardia, diarrhea, vomiting and exanthema were recorded at hospitalization and follow-up. Infants were closely monitored for the clinical course and development of COVID-19 complications. Complications due to COVID and their management were recorded. Nasopharyngeal swab samples COVID-19 PCR test were taken daily from SARS-CoV-2 PCR positive babies. Babies with negative nasopharyngeal PCR test results on two consecutive days were considered COVID-19 negative. Postnatal age at hospitalization, nutrition before admission, was recorded. Duration of hospitalization, the time for the positive COVID-19 PCR test to become negative were calculated. The babies were divided into two groups according to the presence or absence of cardiac manifestation of COVID-19. Laboratory test results, demographic and clinical characteristics were compared between the two groups. Outpatient follow-up and treatment of babies with heart complications continued after they were discharged from the hospital.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0. Continuous variables were represented as mean ± Standard Deviation (SD) or median (minimum–maximum) according to the homogeneity of the distribution. Categorical data were shown as frequency and percentage. Continuous variables in two groups which did not exhibit a normal distribution were compared using Mann-Whitney U-test and $p<0.05$ was considered statistically significant.

Results

Eighteen newborns diagnosed with COVID-19 were enrolled in the study. One (5.5%) baby was late preterm; the remaining neonates (94.4%) were full term. The mean (minimum to maximum) gestational age of babies as 38 (36 to 41) weeks. The gender of the babies were 9 girls (50%) and 9 boys (50%) and their mean (min to max) birth weight was 3800 (2340 to 3880) g. All neonates were born with 5 min AGPAR above 9. Routine supportive care (supplemental oxygen therapy, fluid and electrolyte support, empiric antibiotic therapy) were provided for all hospitalized babies. Fever (14/18, 77%) was the most frequently observed symptom. Other symptoms and findings detected during hospitalization in order of frequency were nasal secretion (7/18, 38%). tachycardia, diarrhea, vomiting (4/18, 22.22%), and cough, tachypnea, skin rash (3/18, 16.66%). Abnormal radiologic findings were found in 6 (33.3%) of cases. There was only one (1/18, 5.5%) asymptomatic case. Mostly, only breast milk was used in infant feeding (10/18, 55%), after that, mixed (breast milk and formula) nutrition (7/18, 38%) was used, exclusively formula was used in only one baby. 11 (61.1%) of the babies were born by cesarean section and 7 (38.8%) were born by vaginal delivery. The median (min to max) age of the babies diagnosed and hospitalized was 17 (3 to 26) days. The demographic and clinical characteristics of the babies are shown in Table 1. AST (max to 487 U/L) and ALT (max to 518 U/L) elevation was observed in 4 (22.2%) patients and normalized on mean (min to max) within 3 (2 to 5) days. The laboratory characteristics of the babies are shown in Table 2. CRP was high in 4 (22.2%) of infants and PCT was high in 7 (38.8%) of infants. 5 (27.7%) babies had neutropenia and 4 (22.2%) had leucopenia. Median (min to max) time required for positive PCR test to turn to negative was 10 (1 to 28) days. Median (min to max) length of hospital stay was 17.3 (9 to 50) days.

Tables 1: Clinical characteristics of newborns with COVID-19.

Demographic characteristics	
Sex (F/M) (%)	9/9 (50/50)
APGAR (5. Min) min.-max	9-10
Delivery mode (vaginal/C/S) (%)	7/11 (38.8/61.1)
Birth weight(g) min-max	2340 -3880
Gestational age (weeks)min - max	37-41
Mothers age, (min - max)	20-39
Mothers parity (min - max)	1-4
Symptoms and findings n (%)	
Fever	15 (%83.3)
Nasal secretions	7 (% 38.8)
Cough	3 (% 16.6)
Tachycardia	4 (% 22.2)
Tachypnea	3 (% 16.6)
Poor feeding	2 (% 11.1)
Diarrhea/ vomiting	5 (%27.7)
Dermatologic manifestations	4 (% 22.2)

Cardiac manifestations of COVID-19 developed in 3 infants (16.6%) who were consulted with pediatric cardiology. Supraventricular Tachycardia (SVT) developed in one baby. He was born at 40 gestation weeks waiting 3480 g. At postnatal 6th day, he was hospitalized due to positive PCR test and fever. Physical examination was normal except that he had fever (38.1°C). Lymphopenia (1700/mm^3) was detected in laboratory tests. After 12 h of hospitalization, his heart rate suddenly raised to 295 beat per minute. The ECG findings of the baby were consistent with supraventricular tachycardia. Pediatric cardiology consultation was performed

Table 2: Lab characteristics of newborns with COVID-19.

Parameter,	n (%)	Mean ± SD or Median (Mini-Max)	Normal Value
WBC, /µl	18(%100)	8500 ± 2600	(9100 to 34000)
ANC/µl	18(%100)	2000 ± 1070	(2500 to5800)
ALC/µl	18(%100)	5120 ± 2600	(1500 to 3000)
PLT × 100/µl	18(%100)	346 ± 165	(150 to 400)
Hematocrit, %	18(%100)	13.4 ± 2.78	(35 to 65)
Hemoglobin, gr/dl	18(%100)	39.5 ± 8.31	(11.1 to 17.4)
CRP, mg/L	18(%100)	0.25 ± 0.21	(0 to 5)
PCT, ng/mL	17(%100)	0.06 (0–1.37)	(0 to 0.05)
AST, U/L	18(%100)	45 (25–478)	(22 to 71)
ALT, U/L	18(%100)	28 (12–518)	(10 to 40)
BUN mg/dl	18(%100)	6.61 ± 3.6	(3 to 12)
Creatinine, mg/dl	18(%100)	0.47 ± 0.06	(0.03 to 0.50)
Albumin, g/dl	18(%100)	3.76 ± 0.19	(1.9 to 4.9)
Troponin, pg/ml	18(%100)	44.6 (12.8–2557)	(0 to126)
LDH, U/L	18(%100)	479 ± 9.1	(170 to 580)
Ferritin, ng/ml	18(%100)	467 (174–2942)	(0 to 310)
PT, sec	17(%94.4)	13.5 ± 1.79	(11 to 14)
PTT, sec	17(%94.4)	33.1 ± 3.88	(33.0–47.8)
INR	17(%94.4)	1.03 ± 0.15	(0.86–1.22)
Fibrinogen, mg/dl	17(%94.4)	345 ± 103	(82–383)
d-Dimer, mg/L	14(%55.5)	3.64 ± 2.91	(0.11–0.42)

to the baby and there was no structural abnormality (echo) in echocardiography. The baby remained hemodynamically stable and heart rate returned to normal after 0.35 mg (0.1 mg/kg) adenosine was administered. Propranolol prophylaxis (0.5 mg/kg/dose every 8 h) and continuous ECG monitoring was initiated. On the 7th day of his hospitalization, SVT attack developed that responded only to the maximum dose (0.25 mg/kg) of adenosine. The prophylactic dose of propranolol was increased and follow-up was continued. On the 15th day of hospitalization, SVT attack refractory to adenosine developed. Thereupon, a 60-min intravenous infusion of 17 mg (5 mg/kg) amiodarone was administered to the baby. As SVT attack developed again after 4 h, the second loading dose of amiodarone (10 mg/kg) was administered. The next day, oral flecainide (5 mg/kg/day) was added to the oral propranolol prophylaxis. The baby who did not have any other SVT attack during his hospitalization was discharged with propranolol and flecainide prophylaxis on the 30th day of hospitalization. Outpatient follow-up and treatment of the baby continued. At the time of this writing, the baby was 7 months old and no SVT episode was observed.

Myocardial damage was observed in the other two patients and myocarditis was suspected clinically. These two patients were consulted with pediatric cardiology specialist because of unexplained tachycardia (heart rate was 160 to 190 per min). There was no significant abnormality in the echo in either of the two patients, only one of the patients had pericardial effusion. Sinus tachycardia was detected on ECG and troponin level was measured. Cardiac troponin levels (max level of 2557 in one baby and 2418 pg/ml in other baby) were found to be above the 99th percentile (664 pg/ml) for this age group [5]. Our institution's reference range for troponin was 0 to 13.8 pg/ml. Troponin value was followed-up and it was observed that

Table 3: values are given as Mean ± SD (standard deviation) or Median (min-max).
PTT: Partial Thromboplastin Time; PT: Prothrombin Time; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen; LDH: Lactate Dehydrogenase; INR: International Normalized Ratio; CRP: C-Reactive Protein; PCT: Procalcitonin; WBC: White Blood Cells; ANC: Absolute Neutrophil Count; ALC: Absolute Lymphocyte Count; PLT: Platelet Count

Parameter,	Group 1	Group 2	p value
	Mean ± SD or Median (min to max)	Mean ± SD or Median (min-max)	
WBC /µL	7580 ± 3560	8680 ± 2480	p=0.522
ANC /µL	2750 ± 390	1850 ± 111	p=0.194
ALC /µL	1700 (1410-7940)	5500 (740 to 8950)	p=0.309
PLT× 10^3 /µL	319 ± 89	351 ± 178	p=0.772
Hematocrit %	47.6 ± 1.43	37.9 ± 8.1	p=0.064
Hemoglobin g/dl	15.8 ± 0.39	12.9 ± 2.78	p=0.094
CRP mg/L	0.12 ± 0.1	0.27 ± 0.21	p=0.041
PCT ng/ml	0.05 ± 0.1	0.22 ± 0.37	p=0.439
AST U/L	41.3 ± 4.0	111 ± 125	p=0.360
ALT U/L	26.3 ± 10.5	103 ± 148	p=0.396
BUN mg/dl	4.0 ± 1.0	7.13 ± 3.72	p=0.176
Creatinine mg/dl	0.49 ± 0.7	0.46 ± 0.03	p=0.218
Albumin g/dl	3.74 ± 0.15	3.76 ± 0.20	p=0.853
LDH U/L	410 ± 21.8	493 ± 93.9	p=0.038
PT sec	12.7 ± 1.04	13.7 ± 1.88	p=0.393
PTT sec	31.9 ± 3.81	33.3 ± 3.97	p=0.572
INR	0.95 ± 0.75	1.04 ± 0.16	p=0.394

increase gradually. Intravenous Immunoglobulin G (IVIG) (1g/kg/dose, 1 dose) was administered and oral ibuprofen (30 mg/kg/day) was started. Cardiac findings were followed-up and it was seen that the tachycardia resolved approximately 10 days after the initiation of treatment. After discharge, troponin continued to be monitored and returned to normal levels for that age after about 3 months. Clinical follow-up was continued because the long-term effects were not known.

Finally, COVID-19 babies were divided into two groups. Group 1 babies (n:3) had cardiac involvement of COVID-19. Group 2 (n:15) consisted of infants without cardiac involvement. When laboratory values were compared between the two groups, there was no significant difference except CRP and LDH levels. When the clinical characteristics were compared, the duration of hospitalization (38 ± 10.3 *vs.* 13 ± 3.3, p=0.007) and the time of positive PCR test to turn negative (22.3 ± 5.5 day *vs.* 7.87 ± 0.92 day, p=0.007) were significantly longer in group 1 than group 2. Comparison of clinical and laboratory characteristics between two groups is given in (Table 3).

Discussion

In this study, 83% of the babies with COVID-19 had mild illnesses in accordance with the literature [6]. Neonate can become infected vertically or horizontally, but vertical transmission probability of COVID-19 has been found to be extremely low [7]. We think that babies have acquired diseases postpartum from their mothers because mothers do not have COVID-19 symptoms and diagnosis at birth. It has been reported that a significant portion of COVID-19 infections in newborns may be asymptomatic [8]. In other studies, most COVID-19-positive newborns has been found to be symptomatic

[9,10]. In accordance with later studies, most of the patients in our study were symptomatic. The reason why only 1 (5.55%) patient was asymptomatic in our study may be referral of patients with medical complexity to us. Although respiratory system involvement is the main form of COVID-19, cardiovascular system involvement has also been reported. According to a recently published review, children with acute COVID-19 requiring hospitalization should undergo a cardiac evaluation and close cardiovascular monitoring to detect and treat life-threatening cardiac complications in a timely manner [11].

Cardiac arrhythmias are often observed in patients with COVID-19, especially in severe cases, and more likely contribute to the high risk of adverse outcomes [12]. One of the COVID-19 positive newborn developed adenosine resistant and difficult to control arrhythmia. The baby who required dual prophylactic drugs was discharged in good and stable condition. His outpatient follow-up continues. As far as we know, no newborn with SVT due to COVID-19 has been reported. Increased cardiac troponin, indicative of myocardial damage, is common in COVID-19 patients and is associated with adverse outcomes such as arrhythmia and death [13]. Troponin has been found to have a prognostic value in hospitalized patients for COVID-19 [14]. We think it is important to look at troponin levels in babies with unexplained tachycardia and a structurally normal heart. Troponin levels were high in two infants with myocardial injury or clinically suspected myocarditis. Myocarditis is a difficult diagnosis due to the heterogeneity of the clinical picture ranging from mild symptoms to sudden death. Although end myocardial biopsy is the gold standard for definitive diagnosis, the diagnosis is often made base on combination of clinical and laboratory findings [15]. It is difficult to be certain that the SARS-CoV-2 infection is causing the reported symptoms and morbidity. We believe that the history of COVID-19 exposure and the presence of a positive nasopharyngeal PCR test indicate that cardiac pathologies may be associated with COVID-19.

Isolation of infectious virus from upper respiratory specimens more than 10 days after illness onset has only rarely been documented in patients who had non-severe infection and whose symptoms have resolved [16]. The time for PCR to become negative in 3 babies with cardiac complications was 28, 22, 17 days respectively, according to the order of hospitalization. When we compared babies with cardiac involvement (Group 1) with babies without cardiac involvement (Group 2), we observed that it took longer for SARS-CoV-2 RNA PCR test to turn negative in babies with cardiac complications than babies without cardiac complications. Prolonged viral RNA detection does not necessarily indicate the presence of infectious virus [17,18]. The duration of viral RNA shedding is variable and may increase with severity of illness [19]. Maybe these babies have a higher viral RNA load that takes more time to clear the virus. We believe that a prolonged positive nasopharyngeal COVID-19 PCR test may be associated with complicated clinical course in our patients. Myocarditis in our babies was mild, but the long-term outcome is unknown. IVIG and anti-inflammatory therapy may have a positive impact in patient with myocardial injury, but we cannot know this for sure. More studies of larger size are needed.

Conclusion

Most newborns had a mild disease with good outcomes. This study, it was observed that newborns with COVID-19 may have cardiac arrhythmia and myocardial damage like adults. Although these results are of uncertain significance, the long-term outcome is unknown. Long-term follow-up of successfully treated newborns will increase our understanding of the disease.

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