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Neonatal multisystem inflammatory syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: a single-center experience

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Abstract

Objectives Neonatal Multisystem Inflammatory Syndrome (MIS-N) is believed to result either from the transplacental transfer of maternal SARS-CoV-2 antibodies or from a delayed hyperinflammatory response triggered by the neonate's own immune reaction to SARS-CoV-2 infection. In this study we aim to explore the clinical presentation, laboratory findings, and current approaches to the diagnosis and management of MIS-N in neonates.

Material and Method A total of 15 infants with MIS-N followed in Bursa Uludag University Neonatal Intensive Care Unit between January 2022 and January 2023 were included in this retrospective study.

Results Eight mothers had a history of COVID-19 disease during pregnancy. All of neonates had cardiac involvement (supraventricular tachycardia, persistant sinusal bradycardia or AV block) and 10 infants had respiratory failure. All infants had elevated inflammatory biomarkers and received steroids or/and IVIG. Two infants died.

Conclusion The common presentation of MIS-N included cardiac aritmia and respiratory failure. Newborns with MIS-N may be at higher risk for adverse outcomes. Early diagnosis and treatment are important in these patients.

Keywords Neonate, Multisystem inflammatory syndrome, Anti SARS-CoV-2 antibodies, COVID-19

Introduction

The emergence and global dissemination of Coronavirus Disease 2019 (COVID-19) has been accompanied by a growing number of reports describing multisystem inflammatory syndrome in children (MIS-C), a hyperinflammatory condition temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. The exact pathogenesis of MIS-C is unknown. The most likely hypothesis is post-infective immune dysregulation [2].

Various studies have shown that maternal antibodies and inflammatory cytokines are transfered on to the fetus

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and these antibodies and cytokines can cause immune activation in the newborn baby [3, 4]. Recently, multisystem inflammatory syndrome in the newborn (MIS-N) has been defined.

Although MIS-C diagnosis and treatment criteria have been defined there are only case series related to MIS-N [1, 4, 5]. MIS-N may present with different clinical findings, such as cardiac arrhythmia, shock, respiratory failure or sepsis.

We present a case series of 15 neonates with multisystem involvement, hyperinflammatory syndrome and positive anti SARS-CoV-2 IgG antibodies, temporally related to maternal antenatal SARS-CoV-2 exposure.

To our knowledge, this is the first serie of MIS-N presenting in the neonatal period in Turkey.

Materials and methods

This retrospective study was performed in Uludag University Neonatal Intensive Care Units (NICU) between January 2022 and January 2023.

The study protocol was approved by the Ethics Committee of Uludag University, Faculty of Medicine. Written informed consent was obtained from the parents of all patients included in the study.

Definition of MIS-N

There is a clear definition of MIS-C in children as described by the World Health Organization (WHO) and Centers for Disease Control (CDC). But there is no agreed definition of MIS-N. We defined criteria of MIS-N according to Pawar et al.'s [4] study (Table 1).

Laboratory tests

SARS-CoV-2 antigens were tested using the real-time polymerase chain reaction (RTPCR) method in nasopharyngeal swabs. Euroimmun anti-SARS-Co-V2 ELISA Ig G and Colloidal Gold rapid test were used for detection of anti-SARS-CoV-2 Ig G in both maternal and neonatal serum samples.

In all cases, the baseline investigations included complete blood count (CBC), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, creatinine kinase (CK-MB), troponin (TropT), Pro B-type natriuretic peptide (proBNP), ferritin, lactate dehidrogenase (LDH) and coagulation profile.

In cases with suspected cardiac involvement echocardiography (ECHO) was performed. Immunomodulator therapy (intravenous immunoglobulin, IVIG) was based on the guidelines and recommendations.

Results

The median of gestational age and birth weight were 38 week and 3295 g in all of patients.

Of the 15 mothers 8 (53.3%) were symptomatic for COVID-19 during pregnancy, 7 (46.7%) were asymptomatic but serological positive for COVID-19. All of symptomatic mothers had febrile ilness and were in the second trimester. Six out of 15 mothers were not vaccinated before or during pregnancy.

Clinical features

Clinical characteristics of 15 neonates are shown in Table 2. Individual patient characteristics.

are shown in Table 3.

Cardiac and respiratory

All of neonates had cardiac involvement (supraventricular tachycardia ($n=8$), persistant sinusal bradycardia ($n=4$), AV block ($n=1$), wide QRS complex bradycardia ($n=1$)) and 10 infants had respiratory failure. Three patients had cardiac arrest and shock. Ten patients needed invasive or non-invasive mechanical ventilation. Antiarrhythmic therapy was applied in seven patients with supraventricular tachycardia. All of newborns were

Table 1 Inclusion criteria of neonatal multisystem inflammatory syndrome

1. A neonate aged < 28 days at the time of presentation
2. Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother
   - Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy
   - Symptoms consistent with SARS CoV-2 infection during pregnancy
   - COVID-19 exposure with confirmed SARS CoV-2 infection during pregnancy
   - Serological evidence (positive IgG specific to SARS CoV-2 but not IgM) in the neonate
3. Clinical criteria
   - Severe illness necessitating hospitalization AND
   - Two or more organ systems affected [i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological, temperature instability (fever or hypothermia)] OR
   - Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without involvement of a second organ system)
4. Laboratory evidence of inflammation
   - One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
5. No alternative diagnosis (such as birth asphyxia–cord pH < 7.0 and Apgar score < 3 at 5 min; viral or bacterial sepsis–confirmed blood culture; maternal lupus resulting in neonatal AV conduction abnormalities; presence of these findings indicating an alternate diagnosis excludes MIS-N).

CRP C-reactive protein, *LDH* Lactate dehydrogenase, *ESR* Erythrocyte sedimentation rate, *IL-6* ınterleukine-6

Table 2 Clinical Characteristics

Maternal, [mean (min-max)]	
• Age	31.4 (21–42)
• Symptoms n (%)	8 (53.3)
o Asymptomatic	7 (46.7)
o Symptomatic	
• Gestatioanal week when positive or had exposure	21.37 (18–26)
• Cesarean delivery, n (%)	10 (66.7)
Neonatal, [mean (min-max)]	
• Gestational week	37.8 (36–40)
• Birth weight, (gr)	3429 (2050–5970)
• Postnatal age (day)	3.4 (1–17)
• Gender (Female/Male)	9 (60)
• Clinical findings n (%)	15 (100)
o Cardiac	10 (66.7)
o Respiratory	4 (26.7)
o Hematologic/thrombosis	3 (20)
o Gastrointestinal	4 (26.7)
o Neurological	1 (6.6)
o Cutaneous	4 (26.7)
o Renal	1 (6.6)
o Fever/temperature instability	
• Single system involvement (cardiac)	4 (26,6)
• Multipl system involvement	11 (73,3)
• Laboratory tests, [mean (min-max)]	20,495 (8690–47500)
o CBC	16.86 (9.40–21.5)
■ WBC count (mm^3)	268,253 (20000–518000)
■ Hemoglobine (gr/dl)	4.27 (2–19)
■ Platelet (mm^3)	4.99 (0.09–21.67)
o Inflamatory markers	715.2 (9.40–6564)
■ C-reactive proteine (mg/L)	1604 (101.8–5000)
■ Procalcitonin (microgr/L)	996 (74-3029)
o Cardiac markers	75.23 (2.9–232)
■ Troponine	4399 (28 -29950)
■ NT-Pro BNP	868.33 (369–2032)
■ CK (IU/L)	3.44 (2.1–5.1)
■ CK-MB (microgr/L)	7322 (363–47225)
o Others, [mean (min-max)]	
■ Ferritin (microgr/L)	
■ LDH (IU/L)	
■ Albumin (gr/dL)	
■ D-Dimer (microgr/L)	
• Therapy n (%)	3 (20)
o Steroids	14 (93.3)
o IVIG	0 (0)
o LMWH	4 (26.7)
o Inotropes	
• Outcome, [mean (min-max)]	2 (13.3)
o Mortality, n(%)	17 (5–61)
o Duration day of hospitalization, [mean (min-max)]	

sinus rhythm on discharge. Distribution of patients with cardiac involvement are shown in Table 4.

Renal

Four patients had acute renal failure and hemodiafiltration was applied to two of these patients.

Hematological

Four patients had hematological disorders that disseminated intravascular coagulation (DIC). Fresh frozen plasma was used for treatment. None of the patients had thrombosis.

Neurogical

Four newborns had encephalopathy. One of them did not cry immediately after birth, had an APGAR score of 5 at

Table 3 Clinical Features n (%)

Cardiac	15 (100)
Arrhythmia	15 (100)
Shock / cardiac dysfunction	4 (26,6)
Respiratory	10 (66,6)
Respiratory distress	
Hematological	4 (26,6)
Thrombocytopenia	2 (13,3)
Disseminated intravascular coagulation	4 (26,6)
Renal	4 (26,6)
Acute renal failure	
Neurological	4 (26,6)
Encephalopathy	4 (26,6)
Seizure	1 (6,6)
Gastrointestinal	3 (20)
Feeding intolerance	3 (20)
Cutaneous	1 (6,6)
Fever/temperature instability	1 (6,6)
Hypothermia	

Table 4 Distribution of patients with cardiac involvement n (%)

Supraventricular tachycardia	8 (53,3)
Wolf Parkinson White Sydrome	1 (6,6)
Persistent sinus bradycardia	4 (26,6)
Wide QRS bradycardia	1 (6,6)
First-degree atrioventricular block	1 (6,6)
Fetal tachycardia	1 (6,6)

Table 5 Elevated inflammatory markers n (%)

Ferritin	12 (80)
Procalcitonin	6 (40)
CRP	5 (33,3)
D dimer	12 (80)

the 5th minute, and had a seizure on the second day (case 3). He was treated with anticonvulsant medication. Other newborns were 17, 7, 1 days old (Cases 1, 4 an 11) and had severe encephalopathy.

Cutaneus

Case 4 had hemorrhagic bullous lesions and on pathological examination, the epidermis had a necrotic appearance and there was leukocytoclastic inflammation. She was treated local medication (antibiotic and epithelial ointment). These lesions resolved within 3 weeks.

Laboratory tests

Anti-SARS-CoV-2 IgM antibodies were negative in all the neonates, and IgG antibodies were positive. All infants had elevated inflammatory biomarkers and the elevated biomarkers are shown in Table 5.

Treatment

Fourteen infants were managed with supportive therapy and IVIG. Three patients were treated with methylprednisolone.

While 13 out of 15 newborns were discharged, two neonates (case 5 and case 11) died due to multi-organ failure. Detailed clinical and laboratory information of 15 patients is shown in Table 6.

Discussion

MIS-N is a clinical syndrome characterized by multisystem involvement and a hyperinflammatory state secondary to transient maternal antenatal SARS-CoV-2 infection in babies born to pregnant women with positive anti-SARS-CoV-2 IgG antibodies [4]. Diagnosis is based on clinical presentation and laboratory findings such as elevated inflammatory markers, thrombocytopenia, liver dysfunction, and coagulopathy [6]. Although the diagnostic criteria for MIS-C in childhood have been established by CDC, there is not yet consensus, even between the World Health Organization and CDC, on the diagnostic criteria for MIS-N [5]. The multisystem inflammatory response associated with SARS-CoV-2 is believed to occur through three distinct pathophysiological mechanisms and may lead to multisystem inflammatory syndrome in the neonatal period (MIS-N): (a) active

Table 6 Clinical features, treatments, and outcomes with Neonatal Inflammatory Multisystem Syndrome

	Age at Presentation/ Sex/Weight/Gestation	Maternal COVID-19 Status	Maternal Serology (Ig G antibody)	Neonatal Serology	Laboratory Studies	Clinical Features	Treatment	Outcome
1	Day 17/ F 3.6 kg 39 weeks	Febrile ilness 21 weeks before delivery, no PCR validation, no vaccination	Ig G + Titer: 177 U/mL	Ig G + Titer:250 U/mL	Elevated PCT (19,41), ferritin (29950), D dimer (5551), troponin I (332.3), LDH (1675), INR (7.2), PT (100.2), aPTT (84), thrombocytopenia (123000)	Cardiac arrest on day 17, severe respiratory distres, disseminated intravascular coagulation, shock (hypotension), supraventricular tachycardia, Echo – LV dysfunction, encephalopathy, acute renal failure, feeding intolerance	Ventilation, cardiac support, antiarrhythmic treatment (esmolol, sotalol, flecainide), antibiotics, therapeutic hypothermia, IVIG (two intermittant doses, 1 gr/kg)	Discharge on PN 39th day Sinus rhytm on discharge
2	Day 2 / M 3.4 kg 39 weeks	Asymptomatic, single dose of mRNA vaccine 21 weeks before delivery	Ig G + Titer: 8798 U/mL	Ig G + Titer: 9677 U/mL	Elevated CRP (10), ferritin (273)	Respiratory distres, persistant sinus bradycardia	Ventilation, antibiotics, IVIG (single dose 1 gr/kg)	Discharge on PN 16th day Sinus rhytm on discharge
3	Day 1 / M 4 kg 40 weeks	Asymptomatic, no vaccination	Ig G + Titer: 50 U/mL	Ig G + Titer: 3120 U/mL	Elevated PCT (10,3), ferritin (466), D dimer (47225), troponin I (137), BNP (337), LDH (1530), INR (2.2), PT (23.8), aPTT (40.7), leukocytosis (31460)	Respiratory distres, disseminated intravascular coagulation, seizure, sinus bradycardia, encephalopathy	Ventilation, antibiotics IVIG (two intermittant doses, 1 gr/kg), steroids (methylprednisolone, 2 mg/kg/d), anticonvulsant	Discharge on PN 30th day

Table 6 (continued)

	Age at Presentation/ Sex/Weight/Gestation	Maternal COVID-19 Status	Maternal Serology (Ig G antibody)	Neonatal Serology	Laboratory Studies	Clinical Features	Treatment	Outcome
4	Day 7 / F 3.3 kg 39 weeks	Febrile ilness 19 weeks before delivery, COVID-19 PCR positive, no vaccination	Ig G + Titer:250 U/mL	Ig G + Titer :350 U/mL	Elevated ferritin (9067), D dimer (2951), troponin I (319), LDH (595), BNP (1678), INR (9.5), PT (120), aPTT (160), leukocytosis (33830)	Cardiac arrest on day 7, severe respiratory distres, disseminated intravascular coagulation, shock (hypotension), acute renal failure, encephalopathy, wide QRS complex bradycardia, feeding intolerance, hypothermia, hemorrhagic bullous lesions	Ventilation, cardiac support, therapeutic hypothermia, antibiotics, hemodiafiltration, IVIG (two intermittant doses, 1 gr/kg), steroids	Discharge on PN 60th day
5	Day 5 / F 4 kg 38 weeks	Asymptomatic, two doses mRNA vaccine, last dose was 6 weeks before delivery	Ig G + Titer: 1413 U/mL	Ig G + Titer: 1394 U/mL	Elevated CRP (11.1), PCT (21.67), ferritin (21995), D dimer (5604), troponin I, (3125), BNP (5000), LDH (2032), leukocytosis (47500), anemia (Hb:9.4)	Severe respiratory distres, shock (hypotension), acute renal failure, 1st degree AV block, wide QRS complex, pulmonary hypertension	Ventilation, cardiac support, antibiotics, hemodiafiltration, IVIG (two intermittant doses, 1 gr/kg), steroids (methylprednisolone, 2 mg/kg/d)	Death on day 7 -multiorgan dysfunction
6	Day 1 / M 5.9 kg 38 weeks	Febrile ilness 18 weeks before delivery, no PCR validation, no vaccination	Ig G + Titer: 6034 U/mL	Ig G + Titer: 9381 U/mL	Elevated CRP (19.1), D dimer (2128), LDH (757), BNP (879)	Respiratory distres, supraventricular tachycardia	Ventilation, antiarrhythmic treatment (esmolol, sotalol), antibiotics, IVIG (single dose 1 gr/kg)	Discharge on PN 12th day Sinus rhytm on discharge
7	Day 8/ M 3200 gr 38 weeks	Febrile ilness 14 weeks before delivery, COVID PCR positive, two doses mRNA vaccine before pregnancy	Ig G + Titer: 2036 U/mL	Ig G + Titer: 2236 U/mL	Elevated D dimer (4828), ferritin (1044), BNP (1048)	Respiratory distres, supraventricular tachycardia	Ventilation, antibiotics, IVIG (single dose 1 gr/kg)	Discharge on PN 18th day

Table 6 (continued)

	Age at Presentation/ Sex/Weight/Gestation	Maternal COVID-19 Status	Maternal Serology (Ig G antibody)	Neonatal Serology	Laboratory Studies	Clinical Features	Treatment	Outcome
8	Day 1/M 3540 gr 40 weeks	Febrile ilness 17 weeks before delivery, COVID PCR positive	Ig G + Titer : 15,619 U/mL	Ig G + Titer :15,440 U/mL	Elevated ferritin (487), D dimer (5575), LDH (828)	Persistant sinus bradycardia	IVIG (single dose 1 gr/kg)	Discharge on PN 10 th day
9	Day 1/M 3480 gr 36 weeks	Febrile ilness 18 weeks before delivery, two doses mRNA vaccine before pregnancy	Ig G + Titer : 6652 U/mL	Ig G + Titer : 4996 U/mL	Normal	Fetal tachycardia at 33th gestation week, tachycardia was not observed in the postnatal period, feeding intolerance	Antibiotics	Discharge on PN 5 th day
10	Day 1 / F 2050 gr 36 weeks	Asymptomatic, one dose mRNA vaccine before pregnancy	Ig G + Titer : 20,457 U/mL	Ig G + Titer : 22,805 U/mL	Elevated ferritin (522), D dimer (10360), BNP (273)	Persistant sinus bradycardia	Antibiotics, IVIG (single dose 1 gr/kg)	Discharge on PN 11 th day
11	Day 1 / F 2735 gr 36 weeks	Febrile ilness 10weeks before delivery, no PCR validation, two doses mRNA vaccine before pregnancy	Ig G + Titer : 2050 U/mL	Ig G + Titer : 1745 U/mL	Elevated PCT (15.52), ferritin (601), D dimer (16711), troponin I (6564), BNP (5000), LDH (1947), INR (2,9), PT (29,5), aPTT (54), thrombocytopenia (20000)	Severe respiratory distres, disseminated intravascular coagulation, shock (hypotension), supraventricular tachycardia resistant to medical treatment and requring ECMO, Echo – LV dysfunction, encephalopathy, acute renal failure, multipl organ failure	Ventilation, cardiac support, antiarrhythmic treatment (esmolol, flecainide, propranolol), antibiotics, ECMO, IVIG (two intermittant doses, 1 gr/kg), steroids (methylprednisolone, 2 mg/kg/d)	Death on day 19 -multiorgan dysfunction
12	Day 1 / F 3230 gr 37 weeks	Asymptomatic, two doses mRNA vaccine before pregnancy	Ig G + Titer : 5199U/mL	Ig G + Titer : 6652 U/mL	Elevated ferritin (337), BNP (1564)	Wolf Parkinson White Sydrome, supraventricular tachycardia compatible with sustained and non-sustanied atrioventricular reciprocating tachycardia	Antiarrhythmic treatment (propranolol, flecainide), IVIG (single dose 1 gr/kg)	Discharge on PN 10 th day

Table 6 (continued)

	Age at Presentation/ Sex/Weight/Gestation	Maternal COVID-19 Status	Maternal Serology (Ig G antibody)	Neonatal Serology	Laboratory Studies	Clinical Features	Treatment	Outcome
13	Day 1 / F 3780 gr 38 weeks	Asymptomatic, two doses mRNA vaccine, before pregnancy	Ig G + Titer : 12,480/mL	Ig G + Titer : 15,804 U/mL	Elevated D dimer (796), ferritin (530)	Supraventricular tachycardia	Antiarrhythmic treatment (propranolol, flecainide), IVIG (single dose 1 gr/kg)	Discharge on PN 10 th day
14	Day 3 / M 2520 gr 38 weeks	Asymptomatic, two doses inactive vaccine, before pregnancy	Ig G + Titer : 10,313/mL	Ig G + Titer : 7011/mL	Elevated ferritin (328), D dimer (1598), LDH (532),	Respiratory distres, supraventricular tachycardia, Echo – large VSD, large ASD	Antiarrhythmic treatment (propranolol, captopril, furosemide), IVIG (single dose 1 gr/kg)	Discharge on PN 33 th day
15	Day 1 / M 3295 gr 36 weeks	Febrile ilness 14weeks before delivery, two doses mRNA vaccine before pregnancy	Ig G + Titer : 20,853/mL	Ig G + Titer : 13,730/mL	Normal	Respiratory distres, supraventricular tachycardia	Antiarrhythmic treatment (propranolol, flecainide), IVIG (single dose 1 gr/kg)	Discharge on PN 7 th day

F Female, *M* Male, *COVID-19* Corona virus disease 2019, *PCR* Polymerase chain reaction, *Ig G* Immunoglobulin G antibody. Normal ranges and units for lab values, PCT: 0–0.05 µg/L, CRP:0–10 mg/L, serum amiloid A: 0–8 mg/L, ferritin = 25–200 µg/L, D-Dimer 0–550 µg/L, BNP: 0-100 ng/L, LDH 290–775 U/L, INR:0-1.6, PT: 10–16 s, aPTT: 31–55 s, CK: mg/dL. *PCT* Procalcitonin, *LDH* Lactate dehydrogenase, *INR* International normalized ratio, *PT* Protrombin time, *aPTT* Activated partial thromboplastin time, *LV* left ventricule, *IVIG* Intravenous immunoglobulin, *PN* Postnatal, *mRNA* Messenger ribonucleic acid, *CRP* C-reactive protein, *HIE* Hypoxic ischemic encephalopathy, *AV* Atrioventricular, *CK* Creatinin kinase, *VSD* Ventricular septal defect, *ASD* Atrial septal defect

infection of the neonate following maternal SARS-CoV-2 infection — a mechanism unique to neonates and distinct from the CDC definition of MIS-C; (b) neonatal extrapulmonary multisystem inflammation resulting from active SARS-CoV-2 infection; and (c) a delayed hyperinflammatory response triggered by early or late neonatal SARS-CoV-2 infection [7]. Furthermore, the immunological mechanisms are not yet fully understood. Although activation of monocytes and increase in proinflammatory cytokines and complement have been demonstrated in MIS -C, this immunologic mechanism has not been demonstrated in MIS -N because complement does not cross the placenta [8]. Therefore, this case series presents 15 newborns diagnosed MIS -N based on the revised CDC criteria using information from various case series and systematic reviews. MIS-N diagnostic criteria are listed in Table 1 [4, 7]. The first case was reported in August 2020 by Magboul et al. [6]. There are no case series from our country in the literature.

The incidence of MIS -N was reported to be 0.1% in one review [9]. The incidence of MIS -N was 24.6% in the patients we observed in our department (Early MIS -N (within the first 72 h of life) is probably by transplacental transmission of maternal SARS-CoV-2 antibody. Late MIS -N (after 72 h of life)-presumably due to antibodies produced secondary to neonatal SARS-CoV-2 infection or transplacental transmission of maternal SARS-CoV-2 antibodies [10]. In our study, 11 patients were diagnosed with early MIS-N. It is believed that early MIS -N is caused by vertical transmission, whereas MIS -N in the late stage is caused by horizontal transmission. None of our patients diagnosed with early or late MIS -N had a COVID – 19 history of disease in their parents or caregivers. It can be presumed that MIS-N developed in our patients because of the vertical transition. In addition, the literature has revealed that maternal SARS-CoV-2 infection or exposure to COVID-19 can potentially cause multisystem inflammation in the early neonatal period. In our study, 8 mothers (53.3%) had COVID – 19 symptoms during pregnancy, and 7 mothers (37.5%) were asymptomatic but serologically positive for COVID-19. All symptomatic mothers had febrile illness and symptoms occurred in the second trimester. The serologic response in mother and neonate was confirmed by examination of serum Anti-SARS-CoV-2 Ig G from both mother and neonate.

SARS-CoV-2 infection in neonates is asymptomatic in 40–45% [11]. Less than 15% of neonates develop moderate to severe symptoms of respiratory distress, lethargy, poor feeding, vomiting, diarrhea, and hemodynamic instability [12]. In a review of neonates diagnosed with MIS -N, the cardiovascular system [67%], was found to be most commonly affected, followed by the respiratory system [64%], fever [52%], central nervous system [22%], gastrointestinal system [11%], persistent pulmonary hypertension of the newborn (PPHN) [8%], skin

involvement [4%] and hematological system [6%], respectively [9]. In our study, all patients had cardiac conduction abnormalities and/or arrhythmias. Involvement of the respiratory system was observed second most frequently. A case series found that maternal SARS-CoV-2 infection may be associated with multisystem inflammation in the neonatal period, as well as thrombosis and AV excitation conduction abnormalities [1]. Four patients presented only when cardiac involvement was present in our study; we did not have any patient with thrombosis. Two patients were found to have cardiac arrhythmias in the fetal period (case 9, case 11). Fetal tachycardia was detected at 33 weeks' gestation in the first patient and at 22 weeks' gestation in the second patient and they were followed up at another health center during the prenatal period without treatment. There is no evidence in the literature that the findings of MIS-N begin in the prenatal period. However, one case report describes two cases of fetal supraventricular tachycardia after administration of *Pfizer-BioNTech's* vaccine COVID – 19 during pregnancy [13]. To confirm the diagnosis MIS-N, additional inflammatory markers such as CRP, procalcitonin, and ferritin should be elevated, we found a large number of positive markers such as ferritin, CRP, and procalcitonin [4]. Altough, a systematic review reported that D-dimer elevation was most common and ferritin elevation was observed in only 45% of patients; in our study, the most frequently elevated inflammatory markers were ferritin and D-dimer.

IVIG, steroids, anticoagulants, and anticytokines may be preferred as specific treatment options, with the first treatment step consisting of supportive therapies (such as respiratory support, perfusion, antibiotic therapy) [4, 7, 14]. The most commonly used specific treatment was IVIG (93.3%) among patients who participated in our study, and steroids (26%) were the second most commonly used.

A review in the literature reported that 4.2% of patients developed multiple organ failure and the mortality rate was 9–11% [9, 14]. In our study, 2 patients died due to multiorgan failure, and the mortality rate was 13%, similar to the literature. Both dead patients were late preterm infants with a history of 36 weeks' gestation.

This study has several limitations. It is retrospective, and the small sample size may limit the generalizability of the findings.

Conclusion

Inadequate recognition of MIS-N can lead to underreporting of cases and under-diagnosis. The most common systemic findings in MIS-N are cardiac arrhythmias and respiratory failure. Neonates diagnosed with MIS-N have a high mortality and morbidity rate, and the prognosis of these infants can be poor. MIS-N neonates in whom two or more systems are affected, infection should be considered if SARS-CoV2 antibodies and elevated inflammatory markers are present. In these patients, early diagnosis and an appropriate treatment regimen are important.

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Authors' contributions
This study was performed in collaboration with all the authors. OH and KN designed the study. SYC, UEK, KF, CCS, CS, HM, UF, BOM collected and analyzed the data. OH and SYC drafted the manuscript. OH, KN, CCS and SYC reviewed and edited the draft. All authors approved the final version of the manuscript.

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Data availability
The authors confirm that the data supporting the findings of this study are available within the article and as additional supporting files.

Declerations

Ethics approval and consent to participate
Ethical approval for the study was obtained before the commencement of the study from the Ethics Committee of Uludag University, Faculty of Medicine. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents of all patients included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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