Multisystem Inflammatory Syndrome in Neonates Associated with COVID-19 in Neonatal ICU of a Tertiary Care Hospital

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ABSTRACT

Objective: Neonatal multisystem inflammatory syndrome (MIS-N) is a unique disease of neonates described in several case reports from all over the world with a myriad of presentations and the emergence of new cases.

Study Design: Retrospective case series.

Place and Duration of the Study: Department of Paediatrics, Fazaia Medical College, Pakistan Air Force Hospital, Islamabad, Pakistan, from December 2021 to November 2022.

Methodology: The study was conducted on neonates who were managed as MIS-N in the neonatal ICU. Data were collected and analysed on SPSS version 24.

Results: Patients in this study ranged from newborns to 13 days of age with a mean age of 3.27 ± 4.29 days and average gestational age of 35.18 ± 3.67 weeks. Among these neonates, 7 (63.6%) had bleeding diathesis, 11 (100%) had seizures, 8 (72.2%) presented with haemodynamic instability and shock, and 7 (63.3%) had signs of heart failure. All neonates (100%) had markedly raised *SARS-CoV2* IgG antibodies, CRP, ferritin, D-dimers, interleukin 6, procalcitonin, 10 (90.9%) had hypoalbuminemia, and 7 (63.3%) had deranged coagulation profile. Cardiac involvement was seen in all neonates (100%) with raised proBNP and myocardial dysfunction on echocardiography. Pulmonary hypertension was present in 6 (54.4%) neonates. High mortality was observed at 6 (54.5%) among which 4 (66.6%) were premature neonates.

Conclusion: MIS-N is a new disease entity which is still under research. There is a high propensity for cardiovascular system involvement and higher mortality among preterm neonates.

Key Words: *Neonatal multisystem inflammatory syndrome (MIS-N), Multisystem inflammatory syndrome in children (MIS-C), SARS-CoV2 infection, SARS-CoV2 spike protein, SARS-CoV2 IgG antibodies.*

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INTRODUCTION

SARS-CoV2 infection spread rapidly after its emergence and became a global pandemic in December 2019. It posed a major health crisis worldwide causing a death toll of 6.58 million since then.[1] Most children are asymptomatic or have very mild symptoms.[2] Even though mortality due to primary *SARS-CoV2* in children was 0.4%, emergence of a severe postinfectious multisystem inflammatory syndrome in children (MISC) was recognised.[3,4]

Several case reports have been reported in neonates since 2021, most of them from Asian countries. Pawar *et al.* and More *et al.* have to date, described the largest case series on neonates from India.[5,6]

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Some authors have also done meta-analyses of case reports of individual cases reported from their respective hospitals.

Neonatal MIS occurs in neonatal period with symptoms similar to sepsis. There is multisystem involvement (more than two organ systems) along with marked rise in inflammatory markers similar to MIS-C. Evidence of negative COVID real-time polymerase chain reaction (RTPCR) and presence of COVID antibodies are important diagnostic criteria for both MIS-C and MIS-N.[5,6]

As the understanding of MIS in neonates is still evolving in terms of pathophysiology, symptoms and management, and there are no separate diagnostic criteria that exist for MIS-N, it is important that cases of MIS-N are documented with details in the literature. The objective is to share the experience to further add to the existing knowledge. To the best of the authors' knowledge, so far no cases have been reported or published from Pakistan in this regard.

METHODOLOGY

The authors conducted a retrospective case series analysis from retrieved hospital charts of all cases admitted in NICU of PAF Hospital, who were managed as MIS-N from December

2021 to November 2022 after approval from the Hospital's Ethical Review Committee. Consent was taken from parents / guardians on a specially designed form to use the data for research purpose and confidentiality of data were ensured.

There are no international guidelines for diagnosing MIS-N as yet, therefore, World Health Organisation (WHO) Guidelines for MIS-C were used as diagnostic criteria for the patients.[7] All neonates (birth to four weeks of life) presenting with hypo / hyperthermia, evidence of two or more organ system involvement (renal, cardiac, respiratory, gastrointestinal tract (GIT), nervous, dermatological, haematological, and temperature instability), neutrophilia, neutropenia, lymphopenia, thrombocytopenia, hypoalbuminemia, and raised inflammatory markers (CRP, ESR, fibrinogen, serum procalcitonin, D-dimers, serum ferritin, and IL-6) along with evidence of *SARS-CoV2* immunoglobulins (IgG) in the sera of neonates, positive RTPCR for *SARS-CoV2* antigens in nasopharyngeal swabs of mother during pregnancy or history of *SARS-CoV2* infection during pregnancy were included in the study. Multisystem involvement was confirmed by the investigations done as per the requirement of individual patients including deranged clotting profile, raised lactate dehydrogenase (LDH), and pro B-type natriuretic peptide (ProBNP) along with echocardiography, aminotransferases (ATPs), blood urea nitrogen and serum creatinine, ultrasound or CT scan brain and chest x-ray. The neonates admitted with neonatal sepsis and severe birth asphyxia with similar symptoms but no laboratory evidence of *SARS CoV2* IgG antibodies or positive RTPCR in nasopharyngeal swabs were excluded. The collected data were analysed on SPSS version 24 in the form of frequencies for numerical data and percentages of presenting clinical symptoms and signs, organ involvement, and inflammatory markers. Continuous data were expressed as means and standard deviations.

RESULTS

Patients in the case series range from newborns to 13 days of age with a mean age of 3.27 $\pm$ 4.29 days and median age was 1st day of life. Most of the babies were premature having a mean gestational age of 35.18 $\pm$ 3.67 weeks with a minimum gestational age of 28 weeks and the maximum was 40 weeks. Two full-term neonates were small for gestational age.

The mean duration of stay was 14.09 $\pm$ 10.51 days (median 13 days). Most of the neonates were males (72.7%). Most of the neonates required only routine care at delivery (45%), 4 (36.4%) needed positive pressure ventilation, and only two needed cardiopulmonary resuscitation (CPR). All had injections of Vitamin K administered as routine care.

Only 2 (18.2%) mothers had a positive RT-PCR for *SARSCoV2* at birth and 1 (9.1%) had it three weeks before delivery. The COVID 19 infection history during pregnancy was given by seven mothers, four had symptoms four weeks before delivery, 2 mothers had 2 weeks, and one had symptoms one week before delivery. However, all neonates (100%) were positive for *SARS CoV2* IgG antibodies.

The presenting symptoms and frequencies are described in Table I. All patients 100% had raised inflammatory markers with 90.9% having hypoalbuminemia (Table II). Blood and cerebrospinal fluid (CSF) cultures showed no growth in the patients. All neonates (100%) had evidence of myocardial dysfunction on echocardiography. Other manifestations were pulmonary hyper-tension in 6 (54.5%), mitral regurgitation in 2 (18.2%), and tricuspid regurgitation in 1 (9.1%).

Among the 11 neonates, 6 (54.5%) died and 5 (45.5%) were discharged. All the six neonates died of pulmonary haemorrhage and two also had gastrointestinal bleeding in spite of giving therapeutic doses of Vitamin K. Individual characteristics of all patients are shown in Table III.

Table I: Signs and symptoms.

Signs and symptoms	Present, n (%)	Absent, n (%)
Fever	6 (54.5%)	5 (45.5%)
Unconsciousness	3 (27.3%)	8 (72.7%)
Haemodynamic instability	8 (72.7%)	3 (27.3%)
Seizures	11 (100%)	
Bleeding	7 (63.6%)	4 (36.4%)
Heart failure	7 (63.6%)	4 (36.4%)
Abdominal distension	2 (18.2%)	9 (81.8%)

Table II: Lab parameters.

Parameters	Low, n (%)	Normal, n (%)	High, n (%)
Haemoglobin	4 (36.4%)	7 (63.6%)	
Total leucocyte count	1 (9.1%)	8 (72.7%)	2(18.2%)
Platelets	8 (72.7%)	3 (27.3%)	
Serum procalcitonin			11 (100%)
Serum ferritin			11 (100%)
IL6			11 (100%)
CRP			11 (100%)
D-dimers			11 (100%)
LDH			11 (100%)
CKMB		3 (27.3%)	8 (72.7%)
proBNP			11 (100%)
Urea		11(100%)	
Creatinine		11 (100%)	
ALT		5 (45.5%)	6 (54.5%)
AST		4 (36.4%)	7 (63.6%)
Albumin	10 (90.9%)	1 (9.1%)	
PT		4 (36.4%)	7 (63.6%)
APTT		4 (36.4%)	7 (63.6%)

DISCUSSION

MIS in neonates has become an established diagnosis by now as a number of case reports by various authors have been reported worldwide.

As the data suggests, development of MIS-N seems secondary to either maternal *SARS CoV2* infection one to five weeks prior to delivery or neonatal *SARS-CoV2* infection acquired immediately after birth due to contact with an infected person.[6] Anti-spike IgG antibodies are found in the placenta and cord blood of mothers infected with *SARS-CoV2* during pregnancy.[8] Initially, it was speculated that they may be protective for the neonate against development of infection.[8]

Table III: Clinical features, investigations, treatment and outcome of suspected patients with neonatal inflammatory multisystem syndrome (MISN) associated with SARS-CoV2 infection.

Age at presentation/ gender/ weight/ gestation	Maternal COVID-19 status	Neonatal serology	Investigation	2D ECHO	Clinical features	Treatment	Outcome	Total duration of stay
Day1/male/2k/35+5	RTPCR negative, COVID symptoms before delivery	IgG >250u/ml on day1	Elevated serum Procalcitonin, ferritin, crp, IL-6, D-dimers, LDH, BNP, PT/INR, albumin low, platelets low	Severe pulmonary hypertension, myocardial dysfunction	Fever on day 1, haemodynamic instability, seizures, and distension with upper GI bleeding	Antibiotics, IVIG, steroids, clexane, inotropic support, I/v albumin	Death on 13th day of life	13 days
Day1/male/2.6kg/36 weeks	RTPCR negative, COVID symptoms 3 weeks before delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin, ferritin, CRP, IL-6, D-dimers, LDH, BNP, AST, PT/INR, thrombocytopenia	Grade 1 MR, myocardial dysfunction	Respiratory distress seizure on day 1, bleeding	Antibiotics, steroids, IVIG, I/V albumin	Death on 13th day of life	13 days
Day1/male/2kg/ 33+3 weeks	RTPCR negative, COVID symptoms before 2 weeks of delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin level, ferritin,IL-6, CRP, D-dimers, LDH, BNP, CKMB, PT/INR, thrombocytopenia, serum albumin low	Mild PDA, myocardial dysfunction	Fever, respiratory distress, haemodynamic instability seizures bleeding on the 1 day of life	Antibiotics, streroids, IVIG, inotropic support	Discharged on 31st day of life	31 days
Day10/male/4kg/38 weeks	RTPCR negative, COVID symptoms 1 week before delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin, ferritin, IL-6, CRP, D-dimers, LDH level, BNP, S. albumin low	Pulmonary hypertension, myocardial dysfunction	Fever, respiratory distress seizures on 10th day of life	Antibiotics, streroids, Ivlg, inotropic support, I/v albumin	Discharged on 18th day of life	08 days
Day13/male/3.8kg/ 38 weeks	RTPCR negative, COVID symptoms 3 weeks before delivery	IgG>250u/ml on day 1	Elevated Serum Procalcitonin, S. ferritin, IL-6, CRP, D-dimers, LDH, BNP, CKMb, albumin low	Myocardial dysfunction	Fever, seizures, respiratory Distress on 13th day of life	Antibiotics, Streroids, IVIG, I/V albumin	Discharged on 23rd day of life	10 days
Day1/female/1.6kg/40 weeks	RTPCR negative, COVID symptoms 3 weeks before delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin, S. ferritin, IL-6, CRP, D-dimers, LDH, BNP, CKMb, albumin low	Myocardial dysfunction	Fever, respiratory distress, seizures	Antibiotics, Streroids, IVIG, I/V albumin	Discharged on 18th day of life	18 days
Day1/male/2kg/37+6 weeks	RTPCR negative, COVID symptoms 3 weeks before delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin, S. ferritin, IL-6, CRP, D-dimers, LDH, BNP, CKMb, ALT/AST raised, albumin low, PT/INR raised, thrombocytopenia	Mild TR, mild EMR, myocardial dysfunction	Fever, respiratory distress, seizures	Antibiotics, steroids, IVIG, I/V albumin	Death on 4th day	04 days
Day1/male/1.3kg/31 weeks	RTPCR negative, COVID symptoms 2 weeks before delivery	IgG>250u/ml on day 1	Elevated serum Procalcitonin, S. Ferritin, IL-6, CRP, D-dimers, LDH, BNP, CKMb, ALT/AST raised, albumin low, thrombocytopenia	Mild pulmonary hypertension, myocardial dysfunction	Fever, respiratory distress, haemodynamic insatiability, seizure	Antibiotics, steroids, IVIG, IV albumin	Discharged on 24th day of life	24 days
Day5/female/1.8kg/ 38+2 weeks	RTPCR positive 4 weeks before delivery, RT PCR +ve at delivery	IgG>250u/ml on day 1 of admission	Elevated serum Procalcitonin, S. ferritin, IL-6, CRP, D-dimers. LDH, BNP, CKMB, ALT/AST raised thrombocytopenia	Small PDA, severe pulmonary hypertension, myocardial dysfunction	Fever, respiratory distress, haemodynamic insatiability, seizure, bleeding, abdomen distention	Antibiotics, steroids, IVIG	Death on 23rd day of life	18 days
Day1/female/1.5kg/ 31 weeks	RTPCR negative at delivery, RTPCR +ve 3 weeks before delivery	IgG>250u/ml on day 1 of admission	Elevated serum Procalcitonin, S. ferritin, IL-6, CRP, D-dimers, LDH, BNP, CKMB, ALT/AST raised thrombocytopenia, leucopenia, anaemia, S. albumin low	Severe pulmonary hypertension, myocardial dysfunction	Respiratory distress, haemodynamic insatiability, seizure, bleeding, heart failure	Antibiotics, steroids, IVIG, I/V albumin	Death on 3rd day	3 days
Day1/male/1.2kg/28+5 weeks	RT PCR positive before 2 weeks of delivery	IgG>250u/ml on day 1 of admission	Elevated serum Procalcitonin, S. Ferritin, IL-6, CRP, D-dimers, S. LDH, BNP, CKMB, S.ALT/AST raised thrombocytopenia, leucytosis, anaemia, S. albumin low	Mild to moderate PDA with severe pulmonary hypertension, myocardial dysfunction	Respiratory distress, haemodynamic insatiability, seizure, bleeding, heart failure	Antibiotics, steroids, IVIG, I/V albumin	Death on 30th day	30 days

With emergence of cases of MIS-N, it is postulated that in genetically susceptible neonates, anti-spike IgG antibodies acquired prenatally by the neonate or secondary to neonatal *SARS-CoV2* infection acquired perinatally, generate an antibody mediated immune dysregulation giving rise to a cytokine storm similar to MIS-C.[9]

MIS-N is characterised by two or more organ systems' involvement due to hyperinflammatory state. Symptoms reviewed mimic neonatal sepsis, respiratory distress syndrome, septic shock, seizures, Kawasaki disease, prematurity, myocarditis, and necrotising enterocolitis etc.[10] This cohort describes 11 neonates with their own characteristic clinical presentations and set of multiorgan involvement.

Majority (72.2%) of the neonates were males similar to case series by More *et al.*, while Pawar *et al.* described 50% female patients.[6,5] Most of the patients (54.4%) were premature in this series confirming greater susceptibility of the disease in premature neonates as described by More *et al.*, who reported MIS-N in 60% premature neonates in their case series.[6] Most of the neonates (72.2%) had early MIS-N as they presented at <72 hours of birth while one neonate each presented on 5th, 10th, and 13th day of life. More *et al.* and Pawar *et al.* described 50 to 80% neonates with fever within the first two days.[5,6]

Fever was the presenting symptom in the most neonates while two neonates developed fever at <72 hours of life. More *et al*. described all neonates with fever presenting after 72 hours of life,[6] while Pawar *et al*. described fever on 1st day of life in two patients only.[5] Therefore, fever may not be considered as one of the constant presenting symptoms.

Cardiovascular system was the most frequently involved among the patients developing signs of heart failure

(63.6%) or haemodynamic instability (72.7%). Similarly, More *et al.* described 80% MIS-N cases with respiratory distress and shock with hypotension.[6] Others have reported skin lesions, renal failure, and aortic thrombosis also which were not seen in the presently reported patients.[11-13]

In this Cohort, only 2 (18.2%) neonates had abdominal distension with no evidence of necrotising enterocolitis and majority (63.6%) had developed co-agulopathy with deranged coagulation profile. Multiple researchers from India reported MIS-N cases presenting with necrotising enterocolitis, myocarditis, cardiogenic shock, and coagulopathy.[5,14-16]

Although only 3 (27.3%) patients presented with unconsciousness, all the neonates had seizures during their course of illness but none had any evidence of meningoencephalitis on imaging. Charlesworth *et al.* and Amulya *et al.* reported 2 cases with signs of meningoencephalitis with seizures contrary to the observations of this study.[17,18]

SARS-CoV2 IgG antibodies were significantly higher in all the neonates presented in this study. Two mothers also had *SARS-CoV2* RTPCR positive and nine had history of *SARS-CoV2* infection during pregnancy. *SARS-CoV2* IgG antibodies were not seen in any of the mothers.

All patients in this Cohort had markedly raised inflammatory markers including procalcitonin, ferritin, interleukin 6, CRP, D-dimers, and LDH. Hypoalbuminemia was reported in 90.9% patients and 63.6% patients had deranged PT, aPTT, and INR. Arun *et al.* and Shaiba *et al.* have reported similar observations in their patients from Kerala, India, and Saudi Arabia, respectively.[13,19] However, other authors have reported variable results considering derangement of inflammatory markers.

Agarwal *et al.* have reported a neonate from Haryana, India, presenting with abdominal distension with raised procalcitonin, CRP, liver enzymes, D-dimers, and proBNP with normal myocardial function.[20] Malek *et al.* reported from Bangladesh, a neonate with pulmonary hypertension and renal involvement with lymphopenia, thrombocytopenia, and normal procalcitonin and ferritin.[21] In the case series by Pawar *et al.* 95% neonates had raised D-dimers, 45% had raised proBNP, while LDH, procalcitonin, ferritin, and IL-6 were raised in 40%, 30%, 20%, and 5% each, respectively.

All neonates in this series had markedly raised proBNP with evidence of myocardial dysfunction. Pulmonary hypertension was also a predominant finding in this series (54.5%), with a few (3) neonates developing valvular insufficiency. In contrast, More *et al*. also documented 30% neonates with pulmonary hypertension, 20% with dilated coronary arteries, and 10% with pericardial effusion.[6] Pawar *et al.* first reported the largest Cohort with observation of predominant cardiac involvement in 90% neonates with 60% having atrioventricular (AV) conduction abnormalities and prolonged QTc interval.[5] None of the patients had any conduction abnormalities.

All neonates were managed with antibiotics along with methylprednisolone and intravenous immunoglobulin (IVIG) as specific treatment as per the recommendations for MIS-C as well as the standards of management provided by clinicians in other case reports of MIS-N reviewed by Hantoushzadeh *et al.* [10]

Six (54.5%) neonates died confirming the high mortality caused by MIS-N; most of them (66.6%) who died were premature neonates similar to observation by More *et al*.[6] All neonates who were expired, had pulmonary hypertension and haemorrhage but the NICU was not equipped with administration of nitric oxide, high frequency ventilation, and extracorporeal membrane oxygenation for advance management.

CONCLUSION

MIS-N is a unique disease among neonates which is associated with a high morbidity and mortality. The cardiovascular system seems to be the most frequently involved. With re-emergence of the disease, there is a high probability of appearance of MIS-N among the neonatal population and therefore a need to develop a better understanding of the disease patterns.

ETHICAL APPROVAL:
An ethical approval was obtained from the Ethical Committee of the PAF Hospital, Islamabad, Pakistan.

PATIENTS' CONSENT:
Consent was taken from the parents / guardians of the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AS: Concept and design of the study, data interpretation, and drafting the manuscript into the final shape.
HK: Designing the final proforma and making improvements, data collection, and data analysis.
IM: Data analysis and interpretation along with draft writing.
All authors approved the final version of the manuscript to be published.

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