Journal of Health and Rehabilitation Research 2791-156X JHRR

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Case Series

Investigating Neonatal Multisystem Inflammatory Syndrome Associated with Covid-19 in the Neonatal Intensive Care Unit: A Case Series

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Conflict of Interest: None.

Hassan MWU., et al. (2024). 4(1): DOI: https://doi.org/10.61919/jhrr.v4i1.567

ABSTRACT

Background: The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, has presented significant challenges to global healthcare systems, affecting individuals of all ages, including neonates. Recent studies have identified a condition similar to Multisystem Inflammatory Syndrome in Children (MIS-C) occurring in neonates, termed MIS-N (Multisystem Inflammatory Syndrome in Neonates), linked to maternal infection with SARS-CoV-2. Understanding MIS-N's clinical manifestations, laboratory findings, and treatment outcomes is crucial for improving neonatal care during the ongoing pandemic.

Objective: The objective of this study was to explore the clinical characteristics, laboratory diagnostics, and treatment outcomes of neonates diagnosed with MIS-N, aiming to contribute to better diagnostic and management approaches for this vulnerable population.

Methods: This retrospective case series analyzed neonates admitted with suspected MIS-N to the Children's Medical Center in Tehran, Iran, from March to September 2020. Inclusion criteria encompassed neonates showing clinical signs suggestive of MIS-N, elevated inflammatory markers, and positive for SARS-CoV-2 antibodies. Key data points included demographic information, clinical presentation, laboratory results (including complete blood count, inflammatory markers, and specific COVID-19 serology), treatment modalities, and patient outcomes. The effectiveness of interventions was evaluated based on symptom resolution and normalization of lab values.

Results: Two neonates were identified with MIS-N. Case I involved a 39-week-old male presenting with diarrhea, dehydration, fever, and a rash, with initial inflammatory markers showing a white blood count (WBC) of 23,000 cells/µL, C-reactive protein (CRP) of 93 mg/L, and serum IgG of 10 g/L. Following treatment with corticosteroids, the patient's condition stabilized, with a decrease in WBC to 18,000 cells/µL and CRP to 34 mg/L. Case II, a 38-week-old female, exhibited a cough, rashes, with WBC of 17,000 cells/µL, CRP of 2 mg/L, and serum IgG of 40 g/L. A single dose of hydrocortisone led to symptom resolution. Both cases had no significant adverse outcomes at a three-month follow-up.

Conclusion: Our findings illuminate the clinical and laboratory characteristics of MIS-N in neonates, emphasizing the role of maternal SARS-CoV-2 infection in its etiology. The successful resolution of symptoms with corticosteroid treatment highlights the potential efficacy of this intervention in managing MIS-N. These insights contribute to the growing understanding of MIS-N and underscore the need for ongoing research to define optimal diagnostic criteria and treatment protocols.

Keywords: Multisystem Inflammatory Syndrome in Neonates, MIS-N, COVID-19, SARS-CoV-2, Neonatal Inflammatory Response, Corticosteroid Treatment, Neonatal Care, Inflammatory Markers, Pediatric Infectious Disease, Neonatal Intensive Care

INTRODUCTION

The emergence of the novel SARS-CoV-2 strain, responsible for the COVID-19 pandemic, has significantly disrupted global health systems, manifesting primarily with respiratory symptoms, including difficulty breathing, fever, and pneumonia, that can be fatal in vulnerable populations (1). This disease has been predominantly associated with respiratory complications, which are the most

common cause of hospital admissions following infection. The pandemic has been further complicated by the discovery that asymptomatic individuals can also facilitate the virus's transmission, thereby complicating the efforts to understand and control its spread (2). Initially, the impact of COVID-19 on neonates and children was thought to be minimal, with reports suggesting a lack of significant symptoms in these populations (3). However, this perception changed dramatically with the first reported case of a life-threatening condition known as Multisystem Inflammatory Syndrome (MIS-C) in April 2020 in the United Kingdom, which occurs as a result of exposure to SARS-CoV-2 (4).

MIS-C is characterized by multi-organ dysfunction and a heightened inflammatory response, typically manifesting 4-6 weeks following SARS-CoV-2 infection. This condition bears similarities to Kawasaki disease in children and the cytokine storm observed in adults, though the pathogenesis and physiological responses differ notably. Interestingly, over 80% of children diagnosed with MIS-C possess antibodies against SARS-CoV-2, including IgG and IgM, despite less than half showing a positive PCR result for the virus (6).

The potential for vertical transmission of SARS-CoV-2 from an infected mother to her newborn has been a subject of considerable concern, though evidence was initially scarce. Recent cases, however, have highlighted neonates born to COVID-19 positive mothers presenting with symptoms such as late-onset fever, thrombocytopenia, and elevated inflammatory markers, indicative of a systemic inflammatory response akin to that observed in MIS-N (7). Moreover, these neonates have also exhibited conduction anomalies, including prolonged QT intervals and 2:1 Atrioventricular block, and in some instances, thrombosis, mirroring the complications noted in MIS-C (6).

This case series focuses on two neonates with multisystem involvement who tested positive for anti-SARS-CoV-2 IgG antibodies, attributed to prenatal exposure to the virus, in a Neonatal Intensive Care Unit setting. The cases underline the critical need for heightened vigilance and comprehensive understanding of the implications of maternal SARS-CoV-2 infection on neonates, challenging previous assumptions about the virus's impact on this vulnerable population. Through detailed examination and documentation of these cases, this study aims to contribute to the growing body of knowledge on the complex nature of SARS-CoV-2 transmission dynamics and its multifaceted effects on different age groups, particularly the most vulnerable.

MATERIAL AND METHODS

The case series study was designed to investigate unexplained symptoms in neonates admitted to the Neonatal Intensive Care Unit (NICU) at the Children Medical Center, affiliated with Tehran University of Medical Sciences, during the years 2021 and 2022. The study focused on patients who tested positive for SARS-CoV-2 via PCR and were also positive for IgG/IgM antibodies, following the exclusion of all known causes of their symptoms. The inclusion criteria were neonates referred to the emergency room (ER) more than two weeks after confirmed COVID-19 infection, with a positive PCR test for SARS-CoV-2 and the presence of IgG or IgM antibodies. Neonates who were PCR negative and lacked IgG or IgM antibodies were excluded from the study. This methodological approach allowed for a concentrated examination of MIS-N (Multisystem Inflammatory Syndrome in Neonates) cases diagnosed within the specified timeframe, without the need for recruitment strategies typically associated with prospective studies.

The study was conducted retrospectively, examining medical records for relevant clinical data, including patients' birth weight, sex, gestational age, and clinical outcomes. The collection and analysis of patient data were carried out with utmost respect for privacy and confidentiality, adhering to ethical standards in medical research. The ethical approval for this study was granted by the Ethics Committee of Tehran University of Medical Sciences, ensuring compliance with the Declaration of Helsinki principles for medical research involving human subjects.

Data collection was systematically performed, leveraging the NICU's existing medical records to gather comprehensive information on the diagnosed cases. All data were anonymized to maintain confidentiality. The statistical analysis was not performed using SPSS or any other statistical software, given the nature of a case series study, which typically does not involve hypothesis testing or comparative analysis. Instead, the study focused on descriptive analysis, providing detailed observations of the clinical presentations, treatment interventions, and outcomes for each case included in the series.

Upon completion of data collection and review, a comprehensive report was prepared, documenting the findings and insights gained from the analysis of MIS-N cases. This report contributes to the understanding of the clinical manifestations and implications of SARS-CoV-2 in neonates, emphasizing the need for ongoing vigilance and research in the face of emerging infectious diseases. The study underscores the importance of ethical considerations in conducting medical research, particularly in the context of a global pandemic, and highlights the role of case series studies in enhancing our understanding of rare but significant medical conditions affecting neonatal populations.

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RESULTS

In the conducted case series study, we meticulously examined the laboratory data and medical interventions for two neonates admitted to the NICU with unexplained symptoms, presenting a detailed analysis of their clinical progression and treatment outcomes. The laboratory data, crucial for understanding the clinical picture of each case, are summarized in Table 1.

Case I, at the time of admission, exhibited elevated levels of blood urea nitrogen (BUN) at 29 mg/dL, which significantly decreased to 17 mg/dL during the course of the hospital stay, indicating an improvement in renal function. The creatinine levels also showed a positive trend, reducing from 0.8 mg/dL upon admission to 0.5 mg/dL, further confirming renal recovery. However, this case experienced a notable decrease in calcium levels from 9 mg/dL to 8.5 mg/dL and an increase in phosphorous from 4.8 mg/dL to 5.8 mg/dL, highlighting potential electrolyte imbalances that required monitoring and management. Magnesium levels in Case I dropped from 2.8 mg/dL to 1.4 mg/dL, necessitating careful attention to magnesium supplementation. The initial sodium level was significantly high at 154 mmol/L but normalized to 144 mmol/L during treatment, aligning with the correction of the patient's initial hypernatremic state. Potassium levels remained within the normal range throughout the admission, changing slightly from 4.6 mmol/L to 4.2 mmol/L.

The white blood count (WBC) presented an initial high at 23,000 cells/µL, which was reduced to 18,000 cells/µL, indicating a response to the treatment for the underlying infection or inflammatory process. The differential count showed a decrease in polymorphonuclear leukocytes (PMN) from 15,900 cells/µL to 4,200 cells/µL and an increase in lymphocytes from 5,500 cells/µL to 7,400 cells/µL, suggesting a shift from an acute bacterial infection towards a resolution phase. Hemoglobin levels slightly decreased from 13.9 g/dL to 13 g/dL, and platelets remained stable at 212,000 cells/µL throughout the hospital stay. The C-reactive protein (CRP), a marker of inflammation, showed a significant decrease from 93 mg/L to 34 mg/L, indicating a reduction in systemic inflammation.

Case II's initial presentation was less severe, with a BUN of 6 mg/dL and creatinine of 0.3 mg/dL, which did not show further data during admission, suggesting stability in renal function. This case also maintained stable calcium and phosphorous levels, with no data reported during admission for magnesium, sodium, or potassium levels. The initial WBC count was lower at 17,000 cells/µL, with a significant reduction observed to 7,100 cells/µL, demonstrating effective management of the neonate's condition. The PMN and lymphocyte counts for Case II also indicated an improvement in the inflammatory status, with PMN decreasing to 1,630 cells/µL and lymphocytes to 430 cells/µL.

Both cases showed negative results for COVID PCR, indicating no active SARS-CoV-2 infection during their hospital stay. However, serology indicated past exposure with IgM and IgG antibodies detected during admission, which played a pivotal role in diagnosing and managing these patients according to the MIS-N criteria.

The treatment regimens for both cases were tailored to their specific needs, with Case I receiving ampicillin and amikacin initially, followed by vancomycin and cefotaxime. A rheumatologic consultation recommended methylprednisolone, and a cardiologic evaluation confirmed normal function. Case II required less intensive intervention, with rheumatologic and cardiologic consultations confirming no immediate concerns, and outpatient hydrocortisone was prescribed.

Table 1: Laboratory Data and Interventions for Case I and Case II

Lab Data	Case I In Admission	Case I During Admission	Case II In Admission	Case II During Admission
Blood Urea Nitrogen (mg/dL)	29	17	6	-
Creatinine (Cr) (mg/dL)	0.8	0.5	0.3	-
Calcium (mg/dL)	9	8.5	9	-
Phosphorous (mg/dL)	4.8	5.8	5	-
Magnesium (mg/dL)	2.8	1.4	1.9	-
Sodium (mmol/L)	154	144	137	-
Potassium (mmol/L)	4.6	4.2	4.5	-
White Blood Count (cells/µL)	23000	18000	17000	7100

Lab Data	Case I In Admission	Case I During Admission	Case II In Admission	Case II During Admission
Poly Morph Nuclear Leucocytes (PMN)	15900	4200	4000	1630
Lymphocyte (Lymph) (cells/µL)	5500	7400	3100	430
Haemoglobin (HB) (g/dL)	13.9	13	12	11.9
Platelet (PLT) (cells/µL)	212000	212000	293000	250000
C-Reactive Protein (mg/L)	93	34	2	1
CSF Culture	-	Negative	Negative	-
Stool Exam	Many Fats Droplet/ Reducing Substance: Trace	WBC=8-10	NL	-
Blood Culture	Negative	Negative	-	Negative
Urine Culture	Negative	Negative	-	Negative
COVID PCR	Negative	Negative	-	Negative
COVID Serology	-	IgM: 2, IgG: 10	-	IgM: 0.1, IgG: 40
Others	D-Dimer: 1215, Alanine Aminotransferase: 15, Aspartate Aminotransferase: 30	D-Dimer: 809, LDH: 453, Ferritin: 553, Fibrinogen: 334, CPK: 29	Alanine Aminotransferase: 10, Aspartate Aminotransferase: 17	D-Dimer: 435
Treatment Case I In Admission: Ampicillin, Amikacin During Admission: Vancomycin, Cefotaxime, Rheumatologic Consultation (Methylprednisolone), Cardiologic Consultation (Normal Function / PFO) Treatment Case II In Admission: Rheumatologic Consultation (No Intervention), Cardiologic Consultation (Normal) During Admission: Outpatient Hydrocortisone				

Figure 1 Multiform rashes observed on day 3 of hospitalization in Case 1; Cutaneous rashes identified in Case 2

In two distinct cases at the Children's Medical Center in Tehran, Iran, neonates presented with symptoms potentially indicative of Multisystem Inflammatory Syndrome in Neonates (MIS-N) associated with COVID-19, showcasing the complexity and variability of this condition. The first case involved a 39-week-old male newborn, delivered by elective cesarean section, admitted for suspected newborn sepsis presenting with diarrhea, dehydration, and fever 17 days post-delivery. Despite an initial negative COVID-19 PCR test, elevated inflammatory markers and the mother's COVID-19 exposure history led to a diagnosis of MIS-N, treated effectively with methylprednisolone and oral prednisolone, resulting in symptom resolution and stable condition three months post-discharge.

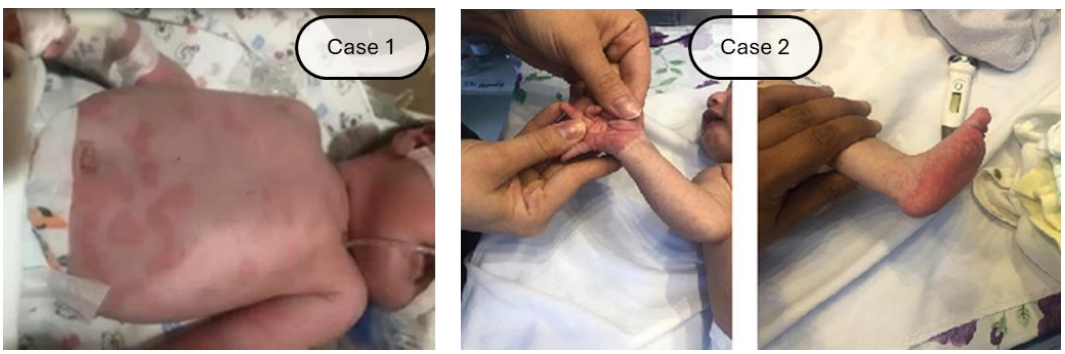

Figure 1 Multiform rashes observed on day 3 of hospitalization in Case 1; Cutaneous rashes identified in Case 2

The second case, a female newborn delivered at 38 weeks and presenting with cough and rashes 20 days post-birth, showed elevated COVID-19 antibody levels but normal physical examinations and lab results. A single dose of hydrocortisone provided relief, with a mild MIS-N diagnosis considered by the

consulting rheumatologist. Both cases, despite their initial alarming presentations, stabilized with appropriate interventions, underscoring the necessity for vigilant assessment and treatment strategies for neonates exposed to SARS-CoV-2, as well as the importance of follow-up care in the context of the ongoing pandemic.

DISCUSSION

In this descriptive review, our investigation into neonatal cases presenting with multisystem inflammatory syndrome (MIS-N) associated with COVID-19 at the Children's Medical Center in Tehran, Iran, adds to the growing body of evidence on the impact of SARS-CoV-2 across different age groups. While Multisystem Inflammatory Syndrome in Children (MIS-C) has been more commonly reported (4), our study highlights the occurrence of MIS-N, aligning with limited research indicating the possibility of MIS manifestations in neonates (5). This is further corroborated by studies identifying MIS-F, where the infection is initiated in the fetal phase, with symptoms manifesting post-delivery (6), suggesting a broader spectrum of SARS-CoV-2 induced inflammatory responses across developmental stages.

The elevated serum IgG concentrations observed in the two cases from our study, with levels of 10 g/L and 40 g/L respectively, significantly exceed the normal limit of 5 g/L, indicating a pronounced immune response possibly linked to maternal transmission of antibodies. This finding is consistent with research from India, where twenty neonates exhibited positive serologic test results (3), suggesting that maternal IgG and a history of positive PCR results in mothers can serve as a criterion for MIS-N diagnosis in neonates. The relevance of maternal infection, particularly in the late stages of pregnancy as noted in Case II, emphasizes the need for serologic testing to uncover potential infections in neonates, even when maternal history of infection is absent (3).

Our study's alignment with the diagnostic standards for MIS-C, which rely on positive PCR and/or serologic test results and a history of contact with infected individuals, does not deviate significantly from existing literature (4). The skin involvements observed in our cases, which ranged from maculo-papular to multiform rashes, mirror those reported in numerous case series, reinforcing the systemic nature of MIS-C and its neonatal counterpart, MIS-N (4). Notably, the neonatal cases exhibited milder symptoms and less frequent fevers compared to older children, suggesting the need for adapted diagnostic criteria for MIS-N.

The treatment approach in our cases, particularly the use of corticosteroid pulse therapy, aligns with interventions for severe cytokine release syndrome (CRS), a condition that manifests two to three weeks post-infection (9). The efficacy of methylprednisolone in reducing inflammation corroborates existing literature advocating for corticosteroid use in managing MIS-C (10), with our study extending this recommendation to MIS-N. The consideration of intravenous immunoglobulin therapy (IVIG) (11) highlights the challenges of managing severe cases, balanced against the limitations of cost, availability, and clinical applicability in a neonatal context.

Our study contributes to the understanding of MIS-N, underscoring the critical role of early diagnosis and intervention. However, it is not without limitations. The small sample size and the retrospective nature of our review constrain the generalizability of our findings. Furthermore, the absence of long-term follow-up data limits our understanding of the potential lasting impacts of MIS-N. Future research should focus on larger cohorts and include longitudinal studies to better understand the long-term outcomes of neonates affected by MIS-N.

CONCLUSION

In conclusion, our study highlights the significance of recognizing MIS-N as a distinct clinical entity, necessitating vigilance and a multidisciplinary approach to diagnosis and treatment. The findings underscore the importance of maternal history and serologic testing in identifying potential MIS-N cases. Additionally, our research advocates for the adaptation of MIS-C treatment protocols to suit neonatal needs, considering the unique physiological responses of this age group. Moving forward, it is imperative that guidelines for the diagnosis and management of MIS-N be developed, informed by ongoing research and clinical observations, to enhance outcomes for this vulnerable population.

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