Neonatal Multi-System Inflammatory Syndrome Associated With Covid-19 Exposure in Two Cases From Iran

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Case Report

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Abstract

Introduction:

Immune dysregulation following exposure to Covid-19 results in MIS-N (Multi-system Inflammatory Syndrome in Neonates). MIS-N affects various systems in the body and is diagnosed with a positive history of PCR test, positive serologic test, and a history of contact with those vectors of COVID-19 infection. This case series aimed to differentiate from possible misdiagnosis about MIS-N.

Case Presentation:

Both cases are term neonates with positive serology of COVID-19 and the 2nd case with a mother’s positive history of Covid-19 PCR at 30 weeks of pregnancy. The first case was admitted with diarrhea, dehydration, fever for three days, and rash on the 3rd day of hospitalization. We admitted the 2nd case on the 22nd day of birth with a cough, rashes on the head, palms, and soles for two days. Both cases responded to corticosteroid treatment that confirmed MIS-N. Finally, we discharged them with a stable and normal condition in follow-ups.

Conclusions:

In inflammatory syndromes, especially in delayed phases of COVID cytokine storms, the mortality and morbidity caused by infections diminish with proper interventions and inhibited cytokine cascade inflammations.

Introduction

Neonatal multi-system inflammatory syndrome (MIS-N) is an inflammatory and immunologic reaction that appears three to five weeks after exposure to coronavirus (1). MIS-N affects various systems in the body and is diagnosed with a positive history of PCR test, positive serologic test, or the history of contact with those who are a vector for COVID-19 infection(1). The condition is confirmed in the case of a positive COVID-19 test result for the infant or relatives, fever that lasts three to four days, and the involvement of two or more organs (e.g., heart, lung, gastrointestinal tract, skin, kidney, joints)(2). Some mild symptoms manifest in rare cases without severe multi-organ involvement, including fever, cutaneous rashes, alterations in blood cells, blood ferritin concentration, and high C-reactive protein (CRP) levels(3). By intensity, the disease is categorized into mild, moderate, and severe conditions. In the mild type, symptoms may not appear, and the inflammatory reaction recedes with no intervention. In the intermediate class, oral corticosteroids control the disease. In severe cases with a high fever, the patient must be hospitalized in the intensive care unit and receive higher doses of corticosteroids. MIS is hard to diagnose, especially in neonates, because fever is less common in neonates.

We present two neonates with mild manifestations and variations in blood tests. They were diagnosed with MIS-N and underwent subsequent treatment and follow-up.
Case Presentation

Case I

The first case was a male neonate (GA: 39 weeks) born through elective C-section from a 23-year-old mother with G1L1 and a good APGAR score. He presented diarrhea, dehydration, and fever for three days, and we admitted him for suspicious neonatal sepsis on his 20th day after birth. Initially, considering the high CRP, we administered antibiotics and treated the dehydration. Thorax, brain, and abdominal images were normal in radiologic assessments. Due to the pandemic, we performed the COVID-19 PCR test. All the results were negative. The fever was relieved for a period but appeared again. On the fifth day of admission, multi-form rashes appeared on the trunk and limbs (Figure 1). Skin consultation results increased the probability of drug reaction and viral infection, with the possibility of alleviation straightaway. Inflammatory markers and serologic tests for COVID-19 (IgG: 5; IgM: 0.1) were requested due to high fever recurrence and elevated Fibrinogen and D Dimer levels. Rheumatologic consultation results brought up the likelihood of MIS-N. We administrated Methylprednisolone 30 mg/kg stat intravenous, followed by 1mg/kg oral prednisolone for five days because of patient limitation for staying in the hospital. The neonate became stable after corticosteroid pulse therapy. Fever did not appear during follow-ups after discharge, and the neonate ultimately regained his normal condition (Table 1).

Case II

The second case was a C-section-born female neonate (GA: 38 weeks). The neonate presented cough and rashes on the head, palms, and soles for two days (Figure 2) and was admitted on her 22nd day of birth. An outpatient center injected a single dose of hydrocortisone with the diagnosis of allergic reactions. Mother was infected with COVID-19 on her 30th week of pregnancy. Physical examination, lab data, CXR of the neonate was normal except for rash and a high level of Covid-19 antibody. The neonate was negative for the COVID-19 test. We could not confirm any infectious disease. Cutaneous conditions were relieved, and coughs were disappeared after a single dose of hydrocortisone. Rheumatologic consult confirmed mild MIS-N and recommended no aggressive intervention due to receiving a single dose of hydrocortisone and alleviating the symptoms. The case was discharged with a stable condition after two days and recommended for undergoing cardiac and cutaneous follow-ups (Table 1). In follow up the neonate had a normal state.

Discussion

MIS-C (Multisystem Inflammatory Syndrome in Children) is more prevalent in children and infants (4), but some studies report cases of MIS in newborns (5). A study further reported MIS-F during the fetal period, where the infection starts during the fetal period, and symptoms appear after birth (6), as in case 2 in this study.
The serum IgG concentration was five g/L in Case I, according to the Borderline kit results. The level could rise overtime at subsequent titrations, but we could not check it because of time limitations. Serum IgG was high level in Case II. In a study in India (1), the serologic test results were positive for 20 neonates. Since the immune system is immature and non-developed in newborns, positive IgM results are unexpected, though positive maternal IgGs and a history of positive PCR results can be a criterion for detecting MIS-N in newborns(1).

In Case II, the mother confirmed infection with COVID-19 on her 30th week of pregnancy. This history is essential, especially during the last trimester of pregnancy (1). In cases with no history of maternal infections, mothers must undergo serologic tests to find any clue of infection in newborns. In these cases, positive IgM and IgG results are a criterion for MIS-N diagnosis. As clinically established, the neonate's infection can occur two months from their relatives' infections (7). When there is no evidence of the history of disease and/or positive serologic test results while the infant develops symptoms in the second or third week, then infection through carriers who are in contact with the infant can be expected.

Diagnosis criteria for MIS-C are not considerably different in studies. In general, MIS-C is diagnosed with positive PCR test results, positive serologic test results, and a history of contact with those infected or carrying infections.

Various case series show the involvement of multiple systems (e.g., skin involvements), spanning children from multi-form to maculopapular rashes and severe lesions such as allergic lesions, urticaria, and even gangrene infection(4). In both cases, lesions were mild and disappeared after corticosteroid treatment. There are some criteria for MIS in children (9). However, we cannot use MIS-C criteria for neonates as fever is less common compared to children. We suggest combination criteria as exposure to COVID-19, systemic symptoms with increased inflammatory lab data are enough in neonates.

MIS-C does not occur in the active phase of the coronavirus disease. Symptoms of inflamed systems usually appear two to three weeks after cytokine storm (8) (severe cytokine release syndrome (CRS)). The first-line treatment for this case is corticosteroid pulse therapy (e.g., using methylprednisolone). This technique has been successful in older babies (9) and, thereby, can treat newborns. In Case I, we did not start treatment because of alleviated fever and CRP concentrations, but inflammation was not efficiently controlled given the fever recurrence and increased CRP level. The corticosteroid pulse therapy was, therefore, started for suppressing the inflammation. Advantages of using corticosteroid pulse therapy are diminished hospitalization period, rapid inflammatory reaction alleviation in the inflammatory phase, and no need for the simultaneous use of non-steroidal anti-inflammatory drugs. In this condition, methylprednisolone is a potent medication for suppressing inflammation (10).

Intravenous Immunoglobulin Therapy (IVIG) (11), used for cardiogenic shocks in patients infected with COVID, is not well accepted due to high expenses, limited availability, and fluid restriction during shocks. The standard dose for methylprednisolone in children is 10 to 30 mg/kg as a 2-to-3-hour infusion for three days (and five days in severe cases) (9). In case I, 30 mg/kg was administrated one day and
followed by 1mg/kg oral prednisolone for five days because of patient limitation for staying in the hospital.

Studies have reported up to 90% cardiac involvement, particularly myocardial involvement as cardiac block or even cardiogenic shock, in patients with MIS-C. For this, both cases underwent echocardiography. In the case of cardiac involvement, proper interventions and regular cardiac follow-ups are required, especially at lower ages (12). Establishing at least two follow-up sessions and checking inflammatory markers within two weeks to two months (1).

In case I, the neonate had a high D-Dimer level for thrombosis, though it decreased in subsequent tests without using anticoagulant medication. Anticoagulants, such as enoxaparin (in urgent cases for patients admitted to the intensive care unit) and aspirin (dosage: 3-5 mg per kg of weight, for less severe conditions and patients not admitted to the intensive care unit), have been advised for COVID infection with a high risk of thrombosis and coagulopathy. Such medications are administrated depending on the infant's conditions because the risk of thrombosis is low at lower ages and newborns (1).

Mc Carty et al. (6) reported MIS-N manifestations as Persistent Pulmonary Hypertension in the Neonate (PPHN), which are alleviated using dexamethasone. Some studies have rarely worked with the DART (Dexamethasone: A Randomized Trial) (13) protocol for dexamethasone. Dexamethasone varies from methylprednisolone in the drug's efficacy. The former is a long-action drug, while the latter is a short-action medication. High doses of methylprednisolone suppress and restart the immune system by rapid and short-term operating, while dexamethasone’s half-life in blood is longer and can cause long-term immune system suppression implications (14).

**Conclusion**

In inflammatory syndromes, especially in delayed phases of COVID cytokine storms, considering clinical manifestations in newborns, if we consider appropriate and on-time interventions to inhibit cytokine cascade inflammations, mortality and morbidity caused by inflammation and relative complications can diminish. Furthermore, using corticosteroids in newborns to cope with such reactions demands additional trials.

**Abbreviations**

MIS-N: Multi-system Inflammatory Syndrome in Neonates

MIS-C: Multi-system Inflammatory Syndrome in Children

PCR: Polymerase chain reaction

COVID-19: Corona Virus Disease-2019

CRP: C-reactive protein
Declarations

- Ethical Approval: This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS). Ethical code IR.TUMS.VCR.REC.1399.109. Informed consent to participate in the study obtained from their parents.

- Consent for publication: We get parental consent for publication

- Availability of supporting data: Our data are available

- Competing interests: The authors declare no competing interest.

- Funding: No funding was received for the study

- Authors' contributions: Study concept and design: 'RS'. Analysis and interpretation of data: 'KM'. Drafting of the manuscript: 'ZJM'. Critical revision of the manuscript for important intellectual content: 'MS'. Developed the original idea: 'VZ'.

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References


**Table**

**Table 1.** Experimental findings and interventions required Case I, II
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<th>Lab data</th>
<th>Case I In admission</th>
<th>Case I During admission</th>
<th>Case II In admission</th>
<th>Case II During admission</th>
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**Figures**
Figure 1

Multi-form rashes on the 3rd day of admission for Case I
Figure 2

Cutaneous rashes in Case II