NEONATAL MULTISYSTEM INFLAMMATORY SYNDROME (MIS-N): DIVE INTO THE UNKNOWN

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ABSTRACT:
Background: The coronavirus pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has swept across the globe like an indiscriminating Tsunami. Pregnant women and neonates are at serious risk to this infection, posing unique challenges in their management. Worldwide, thousands of cases of neonatal multisystem inflammatory syndrome (MIS-N) have already been reported. The lack of high-quality data has led to considerable heterogeneity in management of MIS-N.
Materials and Methods: This was a prospective observational single center study carried out in the Department of Paediatrics, Krishna Institute of Medical Sciences, Karad, Maharashtra, India, for over one year. Twenty critically ill neonates of pregnant mothers who were symptomatic or asymptomatic but previously positive or exposed to SARS-COV-2 virus during current pregnancy were studied.
Results: The average neonatal age of presentation was 2.3 days. 16 neonates were Covid antibody IgG positive, 1 neonate was IgM positive, and 3 neonates had both antibodies in circulation. 30% neonates had respiratory system involvement, followed by cardiac (30%), neurological (15%), gastrointestinal (10%). All neonates had elevated inflammatory biomarkers and were administered IVIG and steroid therapy. Three infant mortalities were observed.
Conclusion:COVID-19 associated MIS-C like disease has not been well described in neonates. There is high suspicion that transplacental antibodies from mothers with SARS-COV-2 may cause neonatal multisystem inflammatory syndrome (MIS-N). Immunomodulation therapy may be beneficial, but further large number of studies are needed. A high index of suspicion is needed in critically ill neonates born to mothers with COVID-19.

KEYWORDS: Neonatal Multisystem Inflammatory Syndrome (MIS-N)

1. INTRODUCTION

Onset of the year 2022 and we are in the 3rd COVID-19 wave, with INDIA being a major contributor to the burden of the disease.
MIS-C is a newer disease in the paediatric population, the exact mechanism still being unclear, but assumed to be postinfectious immune dysregulation after exposure to SARS- CoV-2 (1). The presentation of the disease mimics Kawasaki disease clinically and serologically ranging from fever to multiorgan dysfunction and raised inflammatory markers weeks after exposure to SARS-CoV-2(2). However, its pathophysiology and immunological response is different, and may be mediated by autoantibodies. Majority of the children with MIS-C have specific IgM and IgG antibodies against SARS-CoV-2(3).
Unlike MIS-C in older children, where infection and multisystem inflammation occur in the same child, some case reports suggest multisystem inflammation in neonates occuring secondary to maternal SARS-CoV-2 exposure(4, 5). Maternal infection may trigger a hyperinflammatory syndrome in neonates secondary to transplacental transfer of antibodies (6-8).

2. MATERIALS AND METHODS:

This was a prospective observational single center study carried out in the Department of Paediatrics, Krishna Institute of Medical Sciences, Karad, Maharashtra, India, for over one year. Twenty ill neonates admitted to NICU, of pregnant mothers who were symptomatic or asymptomatic but previously positive or exposed to SARS-COV-2 virus during current pregnancy were studied.

INCLUSION FACTORS:

a) MATERNAL FACTORS:

- Symptomatic for COVID-19 during pregnancy
- Asymptomatic but RT-PCR positive for COVID-19
- Asymptomatic but history of close contact with COVID-19 case

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b) NEONATAL FACTORS:
(1) A neonate aged <7days at the time of presentation
(2) Clinical criteria: Severe illness necessitating hospital admissionwith two or more organ systems affected
(3) Laboratory evidence of inflammation
(4) Diagnosis of exclusion

3. OBSERVATIONS AND RESULTS:

MATERNAL CHARACTERISTICS:

The average age of presentation of mothers was 24.3 years. Out of the 20 mothers 12 were asymptomatic (Table 1) with 5 mothers having history of close contact with a covid positive family member and 7 mothers being RT-PCR positive at some time during the course of pregnancy.
8 mothers were symptomatic (Table 1) in accordance to COVID-19 symptoms with 6 mothers being RT-PCR positive and 2 mothers untested during the course of the pregnancy.

NEONATAL CHARACTERISTICS:

The mode of delivery was 11 and 9 for normal vaginal delivery and Lower section caesarean section respectively, with average gestational age being 35 weeks of gestation. Out of the 20 neonates 13 were males and 7 were females. The average birth weight of the neonates came out to be 2.35 kg. On an average the symptomatic neonate was admitted at 2.3 day of life. (Table 1)

INFANT'S SEROLOGY:

Out of the 20 neonates, all tested positive for anti SARS-COV-2 antibodies. 16 neonates had IgG antibody positive, 1 neonate had IgM antibody positive, while remaining 3 neonate had a combined serology for IgG and IgM antibodies. (Table 2)

CLINICAL PRESENTATION:

The most common systemic involvement was respiratory system with presentation being respiratory distress associated with prematurity, shock (Table 3). 4 neonates required CPAP for two to three days while 2 babies required mechanical ventilation for five to seven days. The neonates were administered surfactant for distress followed by IVIG and steroids for immunomodulation (Table 4). A total of 6 neonates had cardiovascular system involvement, presenting with shock, tachycardia, decreased perfusion to the extremities. A 2D-echocardiography was suggestive of decreased ejection fractions, decreased left ventricular function, and was suggestive of signs of myocarditis. 1 neonate presented with intracardiac thrombus in LPA.
None of the neonates had typical dilated coronaries. Neonates presenting with cardiovascular system involvement showed dramatic response to steroids and IVIG, with no mortality in this group (Table 4).
3 neonates presented with convulsions and were admitted on day of life 5, 5 and 6 respectively. One neonate from this group succumbed due to multiorgan failure. Feed intolerance, abdominal distension and gastric aspirates were the presentation of 2 neonates (Table 4). One neonate died due to gastrointestinal bleed and bowel perforation on day 12 of life. A total of 3 deaths involving respiratory, neurological and gastro intestinal systems were one each were reported (Table 5).
The other babies presented with a mild febrile illness lasting for a duration for 3 to 4 days responding beautifully to IVIG therapy.

LABORATORY INVESTIGATION:

Routine investigations including cbc, esr, crp, lft ,rft , s.electrolytes , coagulation studies, blood culture, chest x-ray, urine and stool were sent for each of these critically ill children admitted to the NICU. The cbc showed a trend of lymphocytic leukopenia with thrombocytopenia, hypoalbuminemia, raised esr and crp. All blood cultures showed no growth in this study ruling out sepsis component. After positive covid antibody serology inflammatory markers and cardiac markers were sent which were elevated (Table 6). Repeat markers after 5 days of treatment with IVIG and steroids showed normalisation or decreasing trends.

4. DISCUSSION

We presume that maternal infection with SARS CoV-2 results in production of IgG antibodies against spike protein of the virus, which cross the placenta, to provide passive immunity to the neonate(9). In few susceptible neonates, autoantibodies triggered by SARS CoV-2 infection may cause activation and secretion of pro-inflammatory cytokines resulting in development of MIS-N. There is a difference between MIS-C in the neonatal period due to early-onset SARS-CoV-2 infection from MIS-N, where the mother is infected, and the neonates present early(1).

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MIS-N management is mainly supportive. All patients received immunomodulatory therapies (intravenous immunoglobulin-IVIG and steroids), others received anti-platelet agents (aspirin), and anticoagulants (unfractionated heparin or LMWH), inotropes, surfactant as per need basis corelating lab findings and clinical judgement. Extensive studies are required to prove the risk to benefits of these therapies in MIS-N(10, 11). Some cases, especially those with cardiac dysfunction responded well to IVIG and steroid therapy. Unregulated use of these agents should be avoided and we should come to a common consensus regarding the protocols to be followed. Specific targeted therapy with these agents based on further research is warranted.

5. CONCLUSION

- The causation of neonatal multisystem inflammatory syndrome (MIS-N) may potentially be associated with maternal SARS-COV-2 infection or exposure during pregnancy.
- Although rare, MIS-N should be considered in the differential diagnosis after ruling out common causes of multisystem inflammation, as a diagnosis of exclusion.
- Echocardiography may provide critical diagnostic information and narrow the differential diagnosis.
- IVIG and steroid therapy have a dramatic response in immunomodulation and reversal of multiorgan inflammation.
- Strict screening of neonates of SARS-COV-2 infected or exposed mothers should be carried out, at least until the pandemic subsides.

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