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# NEONATAL MULTISYSTEM INFLAMMATORY SYNDROME (MIS-N) : A CASE SERIES FROM A TERTIARY CARE HOSPITAL IN NORTH INDIA

Neonatology

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## ABSTRACT

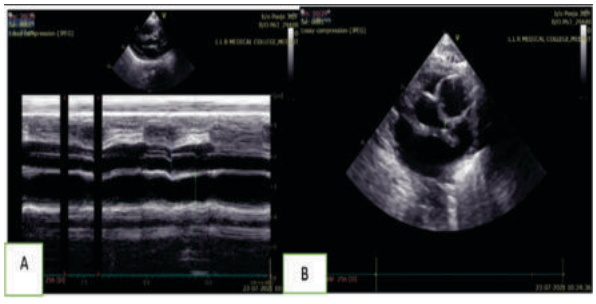
**Introduction:** Multisystem inflammatory syndrome in children is uprising issue amongst all the paediatrician in the world. It is speculated that a upregulation of immune system after being triggered by SARS COV infection is the main cause. MIS-N is an extrapolation of such symptoms in neonates which cannot be explained by any other cause. **Material & Method:** We reviewed the perinatal history, clinical features, and outcomes of 5 neonates with features consistent with MIS-C/MIS-N **Result:** Anti-SARS-CoV-2 IgG and IgM antibodies were tested in all neonates. All presented with features consistent with MIS-C within first 5 days after birth. Three out of five neonates had cardiac involvement with AV block, coronary dilatation or ventricular dysfunction. Other findings included respiratory distress, refusal to feed, thrombocytopenia. All infants had elevated inflammatory biomarkers and received steroids while only three received IVIG. **Conclusion:** We hypothesise somehow maternal SARS-CoV-2 exposure and transplacental antibodies cause multisystem inflammatory syndrome in neonates (MIS-N). Immunomodulation may be helpful to some extent, but more studies are needed.

## KEYWORDS

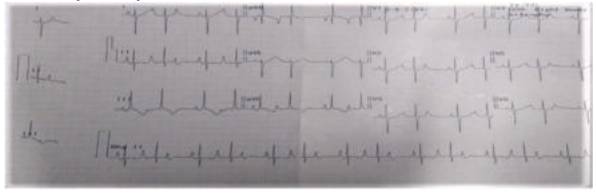
**INTRODUCTION**:
Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly spreading , which has led to a global pandemic of coronavirus disease 2019 (COVID-19). SARS-CoV-2 has infected people of all ages, but the most of paediatric cases reported have been asymptomatic, mild, or moderate [1,2]. However some children have developed severe illness needing hospitalization, intensive care support and ventilatory support. Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but serious medical state associated with COVID-19 [3]. The etiology of MIS-C is still not clear but an association with SARS-CoV-2 infection has been seen [4]. It usually presents as fever and multiorgan involvement, with blood investigations showing increased inflammatory markers weeks after exposure to SARS-CoV-2 [5,6,7]. Multisystem inflammatory syndrome in children (MIS-C) is an immune mediated condition seen usually 3–5 weeks after COVID-19 affecting all organ systems. Maternal SARS-CoV-2 may potentially cause a similar hyperinflammatory syndrome in neonates due to transplacental transfer of antibodies.

We are reporting a case series of 5 patients from a tertiary care centre in the state of Uttar Pradesh who presented with multiple inflammatory syndrome in neonate(MIS-N).

**Case Presentation**
**Case 1 :**
A female baby weighing 2000gram was delivered via LSCS at 38 week of gestation at LLRM Medical College & Hospital, Meerut. She did not require any resuscitation with APGAR score of 7 and 8 at 1 and 5 minute. Soon after birth baby developed respiratory distress so was admitted to neonatal intensive care unit(NICU). On admission baby was in distress with Silverman Anderson score of 5/10 , irregular heart rate , prolonged CRT, feeble pulses. Patient was put on CPAP support along with antibiotics. Initial investigations showed leucocytosis, neutrophilia, raised CRP and thrombocytopenia. Chest x ray was normal. ECG were suggestive of second degree heart block. Urgent ECHO was done which showed large PDA with right to left shunt, right ventricular hypertrophy with both systolic and diastolic dysfunction, small pericardial effusion with dilated left main coronary artery(Z score=3.25). ECHO findings raised suspicion of MIS-N. Thereafter, covid antibody, coagulation profile and cardiac enzymes were assessed. Results came out positive for covid 19 antibody (Ig M = 2.6), D dimer (10,000 ng/ml), serum CK MB ( 38.5 IU/L). Further, impression of myocarditis was made and IV dobutamine was started to improve ventricular function. Oral sildenafil was started in view of PPHN. On Day 3 of life diagnosis of MIS-N was made. IV methylprednisolone (@ 1mg/kg/day) for 5 days and IVIG (@ 1g/kg/day) for 2 days were given. LMWH was also started due to raised D Dimer values and stopped after 7 days. One unit of platelet were transfused on day 7 of life due to thrombocytopenia( PC <20,000). Patient's general condition gradually improved. We were able to wean off the baby from CPAP to oxygen via nasal prongs to finally room air. Gradually her haematological and biochemical parameters improved, HR became regular. Patient's feed were gradually built and shifted to mother feeds. Repeat ECHO showed no effusion with improved ventricular function. Baby was discharged successfully in stable condition after 12days of hospitalisation.

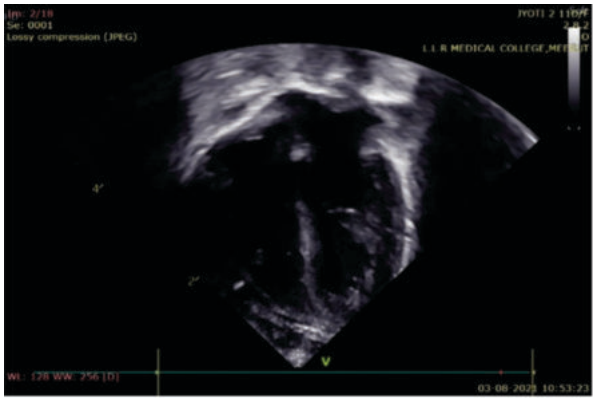


**A: M Mode shows ventricular dysfunction. B: dilated left main coronary artery**


**12 lead ECG showing sinus arrhythmia with A-V block**

**Case 2:**
At 36 weeks of gestation, female baby weighing 2000 gram was delivered via emergency LSCS due to eclampsia at LLRM medical college and hospital. Baby presented on day 3 of life with complaint of refusal to feed and lethargy with no history of perinatal asphyxia. On admission baby was hypoglycaemic(RBS-35 mg/dl), mild respiratory distress with Silverman Anderson Score of 2/10, while heart rate, pulse volume and CFT were within normal limits. Patient was given bolus of 10% dextrose after which hypoglycaemia was corrected. Supportive treatment was started with empirical IV antibiotics and intranasal oxygen. Initial investigations showed neutrophilia and increased CRP. On day 4 of life baby had 1 episode of seizure so phenobarbitone was started. On same day patient was shifted to CPAP due to shallow respiratory efforts. Subsequent investigations revealed increasing

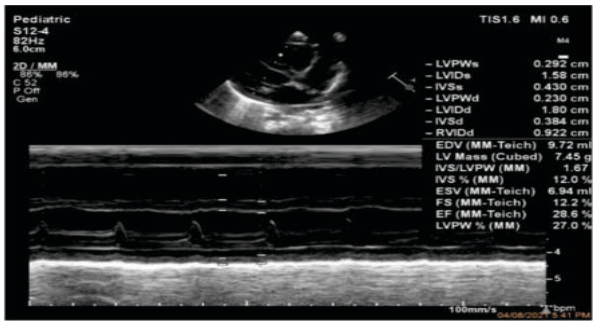
trend of TLC (neutrophilia), CRP with thrombocytopenia. Baby tested positive for SARS-CoV-2 antibody(IgG=31IU), increased D-Dimer (2750 ng/ml). ECHO showed PFO (left to right shunt), mild TR, small pericardial effusion, right ventricular hypertrophy and normal coronaries. Putting all information in same picture a diagnosis of MISN was made. Patient was given IVIG @1gm/kg/day for 2 days, IV methylprednisolone @1mg/kg/day for 7 days. Initially LMWH was given for 2 days then aspirin was started. Repeat investigations revealed improvement in both haematological and biochemical parameters. Patient was gradually weaned off from CPAP. Later feeds were started. Antibiotics were stopped after blood cultures came negative. Phenobarbitone was tapered and stopped before discharge. Baby was discharged in stable condition after 15 days.




**2D Echo: shows right ventricular hypertrophy**

**Case 3:**

Baby was delivered at private hospital at 38 weeks of gestation and were discharged in stable condition. Baby was doing apparently well but on 18th day of life baby developed fast breathing and irritability. On examination he had tachypnoea, tachycardia(HR>280bpm), hepatomegaly(2.5cms), prolonged CRT with signs of poor perfusion. ECG revealed supraventricular tachycardia. Emergency cardioversion was done with adenosine @200mcg/kg stat following which rhythm was reversed to sinus(HR =160 bpm). Clinical signs also improved. Patient was then put on amiodarone infusion for 3 days. Patient was then shifted to oral digoxin, furosemide and metoprolol. Patient was investigated for MIS-N. He tested positive for SARS CoV 2 IgG antibody(27.6), positive CRP(18.5) and elevated D Dimer(670 ng/dl ). An urgent ECHO was done which showed dilatation of both atria, moderate TR, mild PR(PG= 30mmhg), normal coronaries, mild PAH, with severe biventricular dysfunction. Patient was then put on IV methylprednisolone @2mg/kg/day for 5 days and aspirin @3mg/kg/day. After 5 days of steroid, repeat ECHO was done with showed improvement in ejection fraction of 30-35%. After 5 days, baby was discharged in asymptomatic and hemodynamically stable condition on oral cardiac medication. Baby was advised to review in high risk OPD after 1 week and repeat ECG & ECHO were planned on follow up.




**ECHO Showing biventricular dysfunction with ejection fraction of 28.6%**

**Case 4 :**

Baby delivered at 33 weeks of gestation via LSCS at LLRM medical college and hospital. At birth the Apgar Score was 6 and 8 at 1 and 5 minutes respectively. Soon after birth, baby developed respiratory distress so was admitted to NICU. On admission, baby had tachypnoea, retractions with Silverman Anderson score of 5/10, HR was 130bpm and normal BP and CRT. Initial investigation was normal. Due to distress baby was put on CPAP support and IV antibiotics were started along with other supportive care for prematurity. Baby improved and was weaned off from CPAP to oxygen. Baby was improving so OG feed was also started. But on day 4 of life baby developed feed intolerance, OG bleed and went in shock. Baby was again put on ventilator and ionotropic support for 24 hrs .Baby was investigated for sepsis which came out normal but had raised CRP and thrombocytopenia. Possibility of fungal sepsis was also ruled out. On further investigations, baby tested for positive SARS CoV 2 antibody(IgG=11.4) with elevated CRP and thrombocytopenia. ECHO was normal. Patient was given IV methylprednisolone for 5 days, platelet transfusion (PC<20,000) along with rest of the supportive treatment. Patient showed improvement and was gradually weaned off from CPAP and mother feeds were started. After 20 days of NICU stay, baby was discharged in stable condition.

| Age /Sex | Clinical Presentation | CBC (Hb-gm/dl) (TLC ANC-/cumm) | PC on day 1 | PC on day 3-4 | D Dimer Ng/ ml45-500 | CRP mg/dl 0-6 | Covid Rt-Pcr | Covid Antibody | Cardiac Involvement | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1D/ F | RESPIRATORY DISTRESS | 20 20000 14000 | 0.40 | <0.20 | 10000 | 8.5 | NEG | POSITIVE IgM – 2.6 | YES | IV ANTIBIOTICS IV MPS IVIG LMWH IV DOBUTAMINE |
| 3D/F | REFUSAL TO FEED LETHARGINES SEIZURE | 16 6500 5200 | 1.7 | 0.80 | 2750 | 21 | NEG | POSITIVE Ig G - 31 | YES | IV ANTIBIOTICS IV MPS IVIG LMWH/ ASPIRIN |
| 18D/M | IRRITABLE TACHYPNEA TACHYCARDIA | 11.5 10000 4000 | 5.5 | 2.3 | 670 | 18.5 | NEG | POSITIVE IgG – 27.6 | YES | IV ANTIBIOTIC IV MPS ASPIRIN IV DOBUTAMINE |
| 1D/M | RESPIRATORY DISTRESS | 9 10500 3570 | 2.9 | 0.30 | 550 | 3.6/68 | NEG | POSITIVE IgG- 11.8 | NO | IV ANTIBIOTIC IV MPS |
| 1D/M | RESPIRATORY DISTRESS | 16.5 17000 12250 | 2.4 | 0.40 | - | 1.5/81 | NEG | POSTIVE IgG- 5.8 | NO | IV ANTIBIOTIC IV MPS |

**Case 5:**
A baby delivered at term via LSCS with birth weight of 2400g. Baby had right sided cleft lip and cleft palate along with respiratory distress but no evidence of perinatal asphyxia. Baby was put on oxygen support along with empirical antibiotics. Initial sepsis screen , blood cultures was negative and chest X ray was normal. When baby did not improve despite optimum support , he was further investigated. Investigation done on 4th day of life showed increased TLC(25000), CRP(81.4), thrombocytopenia and positive SARS CoV IgG(5.8). The ECHO was normal. IV methylprednisolone was given for 5 days. After 5 days, both clinical and haematological parameters improved. He was also screened for other congenital anomaly but all came out normal. Baby was started on oral feeds and was discharged in stable condition after15 days.

## DISCUSSION:

Multisystem inflammatory syndrome in neonates is upcoming entity and is posing a diagnostic threat to the neonatologists. It is a post infection triggered hyperinflammatory condition affecting almost all the organs including respiratory, cardiac, haematological, autonomic system etc. A high index of suspicion is needed for early diagnosis and intervention.

World health organization defines a case of paediatric MIS-C as children and adolescents 0-19 year of age with fever >3 days and 2 of the following : 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet). 2. Hypotension or shock. 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT pro BNP). 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers). 5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, Staphylococcal or Streptococcal shock syndromes. Evidence of COVID19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19[8]

Our case series comprised of 3 male and 2 female within 28 days of life with wide spectrum of symptoms which cannot be explained by other causes. Strange thing was that none of the mother had history of COVID 19 infection. SARS CoV RTPCR was negative in all patients with variable antibody levels. Blood cultures were sterile in all 5 cases. Most of them developed symptoms or worsened after 3rd of life. Most of the patients had elevated levels of inflammatory markers like CRP, neutrophilia and thrombocytopenia. Four babies had elevated D Dimer values. Three of them had abnormal echo findings. Three of them presented with respiratory distress with normal chest X rays ,2 with arrythmia and features of shock. IV methylprednisolone was given to all the patients while only 2 received IVIG, 2 patients needed ionotropic support and 2 were given LMWH. While only 1 patient was put on long term aspirin. A high index of suspicion helps in early diagnosis and treatment with good outcomes. As for now, immunomodulation seems to be the key in treatment hence IVIG and steroid hold special position. LMWH and aspirin may be needed inn LV dysfunction and coronary involvement.

## CONCLUSION:

Here we present neonates with features of MISN with variable degree of respiratory, cardiac or haematological involvement. As neonatologists we should keep ahigh index of suspicion for early diagnosis and timely intervention for favourable outcomes.

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