Multisystem Inflammatory Syndrome In Neonates Associated With SARS-CoV2 infection- A case series.

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Abstract

Multisystem inflammatory syndrome(MIS) in children (MIS-C) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is well recognised in children, however, rarely reported in newborns. We describe a case series of 20 neonates who were diagnosed as MIS in neonates (MIS-N).

We grouped cases into three categories as Most likely MIS(5), Possible MIS(9) and Unlikely MIS(6). All neonates had high titres of SARS CoV 2 IgG antibodies and were negative for SARS CoV 2 antigens. The most common clinical findings noted in Most Likely MIS neonates were respiratory distress (4/5), shock with hypotension (4/5) and encephalopathy (4/5). Inflammatory markers like CRP (1/5), Procalcitonin (1/5), Ferritin (3/5), D-dimer (4/5) and LDH (2/5) were found to be elevated, and four of them had significantly high levels of proBNP. The majority of them (4/5) responded to immunomodulators, three discharged home and two neonates died. The most common clinical findings in Possible MIS infants were fever (6/9), respiratory distress (3/9), refusal to feeds (6/9), lethargy (5/9) and tachycardia (3/9). ProBNP as a marker of cardiac dysfunction was noted to be elevated in five infants correlating with Echocardiography in two. All infants in this group responded to immunomodulators.

MIS-N manifested as a milder disease in term neonates than preterms, where it was a more severe presentation with cardiac dysfunction. The diagnosis of MIS-N can be challenging and requires a high index of suspicion and early, proactive management. However, it is also important to be cautious of incorrect or overdiagnosis of this condition during the current pandemic.

What Is Known

Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is well recognised in children, however not so comprehensively described in the newborn population, with only few published case reports.

What Is New

Multisystem inflammatory syndrome in neonates (MIS-N) results either from potential transplacental transfer of SARS-CoV2 antibodies or following infection with SARS-CoV-2 in the neonate. MIS-N manifests with a variety of presentations causing relatively milder disease in term neonates, whereas more severe presentation with cardiac dysfunction in preterm infants.

Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) associated with multisystem inflammatory syndrome in children (MIS-C) has been increasingly reported worldwide with the spread of Coronavirus Disease 2019 (COVID-19) infection [1, 2]. The exact pathogenesis for MIS-C remains elusive. Virus-induced post-infective immune dysregulation appears to play a predominant role [3]. The neonatal immune system is immature and may not produce sufficient SARS-CoV-2 antibodies. However, a large study cohort has recently demonstrated efficient transplacental transfer of Immunoglobulins(IG)-G antibodies from mother to fetus [4]. These immunoglobulins are generally thought to be protective, but the transplacental transfer of immunoglobulins along with other inflammatory cytokines may mimic a similar process, potentially causing immune activation and manifesting as a multisystem inflammatory syndrome in neonates (MIS-N) [5]. Seroconversion response to SARS-CoV-2 infection has been seen within 2–3 weeks of symptomatic infection, with both Immunoglobulin-M (IG-M) and IG-G levels detected in plasma [6]. Newborns acquiring perinatal SARS-CoV-2 can also mount an antibody response and may manifest late with similar presentation to MIS-C seen in children [7]. This condition has been reported anecdotally in the newborn population, presenting with fever and multi-site inflammation, especially myocarditis manifesting clinically or with raised biomarkers such as Troponin and ProB-type natriuretic peptide(proBNP) [8].

MIS-C in the paediatric population is now better described; however, the spectrum of possible manifestations in neonates presenting with MIS-N has only been reported in a small number of cases [5, 9,10,11]. An increasing number of pregnant mothers are either exposed to SARS-CoV-2 during pregnancy or received a vaccination or may receive antibodies via blood product transfusion. These antibodies may cause MIS-N or MIS-C in the neonate or may result in overdiagnosis by treating clinician if incidentally detected during another illness. We describe a case series of MIS-N following potential transplacental transmission of SARS-CoV-2 antibodies, highlighting how to differentiate true disease from possible misdiagnoses.

Methods

A national Indian registry for SARS-CoV2 in newborns up to August 2020 was published recently [12]. After this, five other tertiary centres from Western India voluntarily reported on newborn infants with suspected MIS-N syndrome between October 2020 and March 2021. SARS-CoV2 antigens were tested using the Real-Time Polymerase Chain Reaction (RTPCR) method in nasopharyngeal swabs, whereas SARS-CoV2 Immunoglobulins were tested on Roche Cobas e411 by ECLIA method in both maternal and neonatal serum samples. This method detects total antibodies against SARS-CoV-2, and levels >1.00 S/CO index were considered reactive or positive. In all cases, the baseline investigations included complete blood count (CBC), C-reactive protein (CRP), procalcitonin (PCT), Ferritin, D-dimer, Creatinine Kinase (CK-MB), or Troponin (TropT), and coagulation profile. In addition, ferritin and Interleukin (IL6) levels were monitored when a cytokine storm was suspected. In cases with suspected cardiac involvement, LDH, Troponin, and Pro B-type natriuretic peptide(proBNP) were done to assess myocardial involvement/dysfunction, and also echocardiography(ECHO) was performed as feasible.

There are defined clinical criteria for MIS-C in children [13]; however, for newborns, there is no clear agreed definition. Therefore, we decided to extrapolate the definition of MIS-N from CDC criteria used in a similar case series [5].

We classified neonates into two categories:

A. Multisystem inflammatory syndrome in the newborn (MIS-N) and

B. Multisystem inflammatory syndrome in children (MIS-C)

A. MIS-N: Newborn presenting at birth or within the first two weeks of life with

i. Fever along with two or more systems involvement (Fever if present is suggestive but not mandatory for diagnosis in newborn)

ii. Some evidence of raised inflammatory markers such as CRP, PCT, D Dimer, Ferritin, IL-6 etc

iii. Supporting history or laboratory or epidemiological evidence of SARS-CoV-2 infection in mother. Newborn needs to demonstrate the presence of positive SARS-CoV-2 antibodies; SARS-CoV-2 antigen may or may not be positive.

iv. Other neonatal conditions mimicking similar presentation such as sepsis, birth asphyxia or any other possible infection should be ruled out.

B. MIS-C: Newborn presenting beyond the first two weeks of life with the above-mentioned features; however, definite evidence of perinatal SARS-CoV-2 infection at birth or in neonatal period and presence of SARS-CoV-2 antibodies.

Age-specific normal ranges were used for interpreting laboratory parameters. Abnormal values were defined as Serum Ferritin values of > 260 ng/ml in term newborn and > 200 ng/ml in preterm, [14] D-Dimer > 200 ng/ml, Pro B-type natriuretic peptide (proBNP) l > 700 pg/ml and serum lactate dehydrogenase > 450 U/l [15]. Where indicated, echocardiogram(ECHO) was performed by a paediatric cardiologist. Cardiac dysfunction or myocarditis on ECHO was defined as decreased Left Ventricular(LV) ejection fraction(EF) <55% and fractional shortening (FS) < 26% on functional echocardiography [16].

Parental consent was obtained for each case where data was shared, along with permission from local hospital authorities for data sharing. Ethics committee approval was obtained from the primary site.

Results Or Case Summaries

A total of 26 neonates were reported as diagnosed and treated for MIS-N / MIS-C. We analysed all 26 cases, excluded six and selected 20 cases which were grouped into three categories, *Most likely MIS* where clinical picture mostly meets defined criteria, *Possible MIS* where there is an unusual clinical presentation that does not meet specified criteria, *Unlikely MIS* where there may be an alternative diagnosis explaining the clinical presentation but MIS couldn't be ruled out. Of the 20 cases, five were categorised as Most likely MIS, 9 were categorised as Possible MIS, and six as Unlikely MIS. All 20 neonates had positive serology in the form of high titres of SARS CoV 2 IgG antibodies. Table 1 summarises clinical characteristics and management of all the cases.

Most likely MIS

The majority of them (4/5) presented within the first week of life, with two neonates showing on da-1, one on day-2 and another on day-5. One presented late, on day 30 of life. Figure 1 summarises the clinical and laboratory profile of all cases in this group. The most common clinical findings noted in these neonates are respiratory distress (4/5), shock with hypotension (4/5) and encephalopathy (4/5). Fever and seizures were each noted only in one neonate. All of them had cardiac dysfunction on echo, and only one neonate had dilated coronaries with pericardial effusion. Inflammatory markers were found to be elevated in these neonates with raised CRP (1/5), Procalcitonin (1/5), Ferritin (3/5), D-dimer (4/5) and LDH (2/5). Four of them had significantly high levels of proBNP, and one had high levels of Troponin T. Majority of them (4/5) required immunomodulators in the form of steroids and IVIG. All the neonates required respiratory support in the form of oxygen or ventilation and cardiac support in the form of inotropes. Three of them were discharged home, and two neonates succumbed to the illness.

Possible MIS

Of the nine infants, four presented within the first week of life and the remaining five from the second to the fourth week. The most common clinical findings noted in these infants were fever (6/9), respiratory distress (3/9), refusal of feeds (6/9), lethargy (5/9) and tachycardia (3/9). Haematological abnormalities noted in this cohort were leucocytosis in two, thrombocytopenia in two and thrombocytosis in three infants. Elevated CRP was documented in five neonates and procalcitonin (PCT) in three infants. The inflammatory markers associated with SARS-CoV-2 infection were markedly elevated- D-dimer (6/9) and Ferritin (5/9). Interleukin-6 was measured and found to be elevated in one infant, whereas ESR levels were not measured in any patient. ProBNP as a marker of cardiac dysfunction was noted to be elevated in five infants. Echocardiography was performed in seven neonates, two of them had cardiac dysfunction, and one had PPHN. Coronary vessels were found to be normal in all of them. Immunomodulators were given to seven infants in the form of steroids (5/7) or steroids along with IVIG (2/7). All these infants were discharged home.

Unlikely MIS

All the neonates in this category had a strong alternative diagnosis in the form of sepsis, respiratory distress syndrome, necrotising enterocolitis and parotitis, which can explain the clinical condition in the infant. These newborns also had elevated inflammatory markers, with one newborn having LV dysfunction and significantly elevated ProBNP. The majority of newborns in this group were also treated with immunomodulators mainly steroids(5/6), and 2/6 were also additionally treated with IVIG.

Discussion

MIS-C in the pediatric population presents a new challenge in the COVID-19 pandemic, with few cases reported worldwide [17]. In newborns, SARS-CoV-2 infection can present either as an early-onset infection, likely due to vertical or intrapartum transmission of SARS-CoV-2 or late-onset SARS-CoV-2 infection,

mainly acquired through close contacts. MIS-N syndrome may be caused either by trans-placentally transferred SARS-CoV2 IgG or antibodies potentially produced by the neonate in response to SARS-CoV2 infection [18].

It was speculated that neonates might have less inflammation, milder COVID-19 illness, and faster recovery compared to older children and adults due to passive transfer of protective maternal IgG antibodies, immature immune system, presence of fetal haemoglobin, and lower Angiotensin-Converting Enzyme-2 (ACE-2) expression [19,20]. MIS-N is emerging as a new disease with few reported cases globally [21]. We believe this is the first case series reporting MIS-N either following transplacental transfer of SARS-CoV2 antibodies or antibodies developed in the neonate after infection with SARS-Cov-2.

Diagnosing and confirming SARS-CoV-2 infection in neonates due to vertical transmission not only requires positive SARS-CoV2 antigen in respiratory secretions for both the mother and neonate but ideally also demonstration of the virus in amniotic fluid/placenta and cord blood along with the presentation of neonatal disease attributable to COVID-19 [22]. Diagnosing MIS-N in neonates is even more challenging. MIS-N is proposed to be a disease manifestation of antibody-mediated immune activation affecting various organs (Figure 2) rather than the infection itself.[3] Hence, to differentiate neonatal SARS-CoV2 from MIS-N, the neonate should be negative for SARS-CoV2 antigen but positive for SARS-CoV2 antibodies, more likely trans-placentally transmitted from the mother or produced by self after an interval of recovery from SARS-CoV2 infection. Moreover, the clinical manifestations of MIS-N are very similar to sepsis-like illnesses and other conditions associated with prematurity, making it difficult to differentiate between them on clinical grounds alone.

In our cohort, we scrutinised the cases that were treated as MIS-C by clinicians and categorised them into Most likely and Possible MIS on the basis of defined clinical criteria and if they justified immunomodulatory therapies. Cases that were treated like MIS by their clinicians but did not fit specified criteria and had other possible explanations for the clinical presentation were classified as Unlikely MIS. We specifically included these cases to highlight how presence of antibodies and some of the biochemical parameters can be confusing, leading to a risk of overdiagnosis and potentially incorrect treatment during the pandemic.

Six of the cases (case no 5 and 10-14) presented late, beyond the second week of life, where we found positive titres of antibodies in both mother and newborn, however SARS-CoV2 RTPCR in the newborn at the time of presentation was negative but that at the time of birth was not available. We thus labelled them as Possible MIS-C based on late presentation, as early asymptomatic perinatal infection leading to this presentation couldn't be ruled out. We observed that term babies tended to have milder symptoms and presented a little later after birth. Preterm babies, however, tended to have moderate to severe disease and presented at birth or earlier in the first week. These differences could partly be due to concurrent illnesses of prematurity contributing to their sickness. Fever was a striking feature in term neonates leading to suspicion of possible MIS-N, but skin manifestations and gastrointestinal symptoms were not common, as against frequent reports in older children [23,24]. Preterm neonates tended to have severe symptoms presenting with respiratory distress, and cardiac dysfunction, similar to the observation of Lima et al [9]. We observed, in addition, few term babies also presenting with cardiac dysfunction and severe multisystem disease.

Although Ferritin and D-Dimer are acute phase reactants and levels may be elevated in sepsis-like illnesses, a diagnosis of MIS-N was made in the clinical context with other elevated relevant markers and negative blood cultures. Moreover, ProBNP, as a marker of cardiac dysfunction, was elevated significantly in all neonates with cardiac dysfunction, suggesting immune-mediated myocarditis, similar to a case report of a 24-day old neonate by Kappanayil et al [10]. Cardiac biomarker, ProBNP, can be raised in premature infants [25] with patent ductus arteriosus, but levels noted in this preterm cohort were exponentially high, suggesting myocarditis. Troponin T was done in only one case and was elevated, supporting the diagnosis. ProBNP and Troponin may act as screening tests for predicting early cardiac dysfunction in MIS-N; this, however, needs further study in larger cohorts. We did not find any coronary aneurysm as reported in paediatric population [17] except one baby who had marginally dilated coronaries. There was also no report of cardiac arrhythmia similar to reported in a published neonatal cohort [5].

SARS-CoV2 IgG antibodies were positive in all, suggesting possible transplacental transmission of IgG. However, we couldn't confirm this in some infants (labelled as MIS-C) who may have developed these antibodies due to perinatally acquired infection.

One preterm infant, born at 34 weeks (case 3), presented at birth with manifestations of severe cytokine storm, with features of severe myocardial dysfunction, severe pulmonary hypertension, and elevated biomarkers suggesting severe disease. Borkotoky et al. observed a similar presentation suggesting MIS-N [11].

Clinicians managing these cases of MIS-N in our cohort used steroids (methylprednisolone or prednisolone) either alone or in combination with IVIG. In the term group, fever in two babies responded only after commencing steroids. In the severely affected infants with associated cardiac dysfunction, most babies showed improvement in clinical and biochemical parameters after steroids and IV IG. All neonates in our cohort, except two, recovered completely, with no need for prolonged ventilation or Extracorporeal membrane oxygenation (ECMO).

Limitations: This is a small case series with self-reported data and therefore has its limitations. However, various clinical presentations are described, and this preliminary data may add to awareness about MIS-N amongst clinicians; not all currently recommended parameters and inflammatory markers were uniformly tested in all patients, leading to difficulty in confirming the diagnosis, including covid testing of infants at birth. This may be due to the fact that MISN is still evolving as a disease entity with no specific guidance on diagnosis and management, combined with a general lack of awareness amongst clinicians."

Conclusions

MIS-N manifested with varied presentations, term babies tended to have milder disease whereas preterm had relatively severe disease. A diagnosis of MIS-N can be challenging and needs a high index of suspicion. Where suspected, neonatologists should perform specific investigations such as SARS-CoV2 antigen and antibodies, CRP, PCT, Ferritin, IL6 levels, and D-dimers. Also, in symptomatic newborns, one must consider ProBNP, LDH, Troponin, and early ECHO

screening to assess myocardial dysfunction. In addition, there is a need for a more systematic process of registration of cases nationally and clear management guidelines for suspected MIS-N. Also, typing antibodies for anti-nucleoprotein antibodies suggests past infection rather than anti-spike protein antibodies suggests vaccination status should be done to avoid confusion and overtreatment, especially now when many more pregnant women are being vaccinated.

We encourage clinicians to follow proposed strict clinical criteria before concluding a diagnosis of MIS-N to avoid misdiagnosis due to other conditions masquerading as MISN. Further studies are required to identify risk factors for MIS-N and also predictors of disease severity.

Abbreviations

MIS-N: Multisystem inflammatory syndrome in neonates

SARS-CoV2: Severe acute respiratory syndrome coronavirus-2

COVID-19: Coronavirus Disease 2019

RT-PCR: Reverse transcriptase-polymerase chain reaction

CDC: Centres for Disease Control

CRP: C-reactive protein

PCT: Procalcitonin

ESR: Erythrocyte sedimentation rate

LDH: Lactate dehydrogenase

Pro-BNP: Pro B-type natriuretic peptide

IL-6: Interleukin 6

IG: Immunoglobulins

TLC: Total leucocyte count

ANC: Absolute Neutrophil Count

LMWH: Low molecular weight heparin

Declarations

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Contributor's statement page

Dr Kiran More, Dr Praveen Kumar and Dr. Roopali Soni conceptualised and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the final manuscript.

Dr. Sheila Aiyer helped to design the study, obtained local ethics committee approval, contributed, coordinated and supervised data collection and reviewed/approved the initial and final manuscript.

Dr. Ashish Goti, Dr. Manan Parikh, Dr. Samir Sheikh and Dr. Gaurav Patel were involved in designing the study; they contributed to and coordinated data collection, carried out the initial analyses, and critically reviewed and approved the final manuscript.

Dr. Venkat Kallem created Figures, carried out detailed analysis, formatted tables, and reviewed, edited and approve the initial and final draft of the manuscript.

Ethics committee Approval: The study was approved by Institutional Ethics

Committee (IEC) of SSG Medical College and Hospital, Vadodara, Gujarat. (10^{th} April 2021)

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Tables

Table 1: Summary of Clinical findings and management of cases

Case no	Age of Presentation / Sex / Birth weight / Gestation	Maternal Antenatal COVID 19 status	Neonatal COVID 19 status	Neonatal serology	Clinical findings	Investigations	Treatment	Outcome	Any altern explanatic this presentati
MOST LIKELY MIS – N									
Case 1	Day 1 (At birth) / Male / 1500 gram / Preterm (32 weeks)	History of COVID absent	NA	IgG +ve (10.3)	**Respiratory distress** **Shock (Hypotension)** Encephalopathy	Leukocytopenia (1100) Thrombocytopenia (79,000) **Elevated Ddimer, Ferritin (3412), PROBNP (>35,000), LDH (4452)** Blood culture -ve **Echo – LV dysfunction**	Ventilation Cardiac support (Dobutamine, Epinephrine) Antibiotics	Death	-
Case 2	Day 5 / Male / 2520 gram / Term	History of COVID present RTPCR +ve	NA	IgG +ve (9.32)	**Respiratory distress** **Shock (Hypotension)** refusal of feeds, lethargy	**Elevated TropT (8.92), PROBNP (>30,000), LDH (588)** Blood culture -ve Echo – **Borderline LV dysfunction**, normal coronaries	Respiratory support (HFNC) Cardiac support (Epinephrine) Antibiotics (7 days) Steroids (Methylprednisolone for 7 days, Prednisolone for 28 days) IVIG Aspirin	Discharge	-
Case 3	Day 1 / Male / 2600 gram / Preterm (34 $^{1/7}$ weeks)	History of COVID absent RTPCR -ve IgG +ve (32.53)	RTPCR -ve	IgG +ve (> 1)	**Respiratory distress** **Shock (Hypotension)** Lethargy	**Elevated Procalcitonin (8.36), Ddimer (2445), Ferritin (279.67), PROBNP (34,308)** Blood culture -ve **Echo – LV dysfunction, PPHN**	Ventilation Cardiac support (Epinephrine, Milrinone) Antibiotics Steroids (Methylprednisolone for 10 days) IVIG	Discharge	-
Case 4	Day 2/ Female / 1900 gram / 37 week	History of COVID present RTPCR -ve IgG +ve (8.4)	NA	IgG +ve (3.4)	**Fever,** Refusal to feed, Apnea, Hypoglycaemia, Lethargy, Seizure	Elevated D-dimer (253), PROBNP (9541), CRP 6.0(at presentation) Blood culture -ve **Echo – Biventricular dysfunction** **Repeat CRP 125 (3 days later)** USG Brain -normal	Oxygen Antibiotics Inotrope (dobutamine and Noradrenaline) Steroids + IVIG (Methylprednisolone)	Discharge	-
Case 5	1 Month / Female / 2200 gram / Term	Covid IgM -ve IgG +ve (663)	RT PCR -ve	Covid IgG +ve (495)	**Respiratory distress, Shock** Hypoglycaemia	CRP (3.3) CBP – Normal Elevated Procalcitonin (18), D dimer (29,624), Ferritin (3,234) Echo – Severe Biventricular Dysfunction (LVEF 30%)	IV Antibiotics (Inj Meropenam, Inj Amikacin) Inotropes (Inj Noradrenaline, Inj Dobutamine, Inj Milirone, Inj Vasopressin) Inj Methylprednisolone	Death	-

						Dilated LMCA= 1.7mm (Z= 2.53) Moderate pericardial effusion CSF – Normal	Inj IVIG (@2g/kg/day)		
POSSIBLY MIS – N									
Case 6	Day 5 / Female / 3200 gram / Term	History of COVID present RTPCR +ve	RTPCR -ve	IgG +ve (7.89)	**Fever**, refusal of feeds, lethargy & vomiting	Thrombocytopenia (1,21,000), **Elevated CRP (9.47),** **Ddimer (570), Ferritin (519),** **IL6 (4.67)** Blood culture -ve	Antibiotics (5 days) Steroids (Prednisolone for 4 weeks)	Discharge	1. Cultu negat sepsi
Case 7	Day 1 (6 hours of life) / Male / 2340 gram / Term	History of COVID present IgM +ve IgG +ve	RTPCR -ve	IgG +ve (4.76)	Asymptomatic Cardiac murmur	**Elevated Ddimer (22,942), Ferritin (390), PROBNP (7,635), LDH (3,466)** Blood culture -ve **Echo – LV dysfunction**	Steroids (Methylprednisolone for 3 days) IVIG	Discharge	1. Trans circul – sho 2. Birth asphy (Uncl histor
Case 8	Day 1 (At birth) / Male / 2430 gram / Preterm (34 weeks)	History of COVID present RTPCR +ve	RTPCR -ve	IgM +ve (29.7) IgG +ve (1.13)	**Respiratory distress**	**Elevated Ddimer (1269), PROBNP (774), LDH (595)** **Deranged coagulation profile** Blood culture -ve **Echo – LV dysfunction**	Surfactant Ventilation Cardiac support (Epinephrine) Antibiotics (7 days) Steroids (Methylprednisolone for 7 days, Prednisolone for 7 days) IVIG Aspirin	Discharge	1. Respi Distre Syndr 2. Birth asphy (Uncl histor 3. Intrau infect with ((RTPC Neg)
Case 9	Day 1 (4 hours of life) / Male / 2500 gram / Preterm (34 $^{3/7}$ weeks)	History of COVID symptoms present RTPCR +ve	RTPCR -ve	IgG +ve (168)	**Respiratory distress**	**Elevated Ddimer (1077), PROBNP (9726)** Blood culture -ve Echo – LV normal, PPHN	Ventilation Cardiac support (Sildenafil) Antibiotics Steroids (Methylprednisolone)	Discharge	1. Respi Distre Syndr 2. Trans circul – sho 3. Early sepsi
Case 10	Day 18 / Male / 2860 gram / Term	History of COVID symptoms present RTPCR +ve	RTPCR -ve	IgG +ve (18)	**Fever,** refusal of feeds, lethargy & **Tachycardia**	Thrombocytosis (5,55,000) **Elevated CRP (180), Procalcitonin (7.1), Ferritin (1560)** **Deranged coagulation profile** Blood culture -ve Echo – normal	Antibiotics (5 days) No steroids.	Discharge	1. Late sepsi
Case 11	Day 9 / Female / 3230 gram / Term	History of COVID present IgM +ve IgG +ve	RTPCR -ve	IgG +ve (9)	**Fever**, refusal of feeds, lethargy & **Tachycardia**	Leucocytosis (28,600) Thrombocytosis (6,30,000) **Elevated CRP (38), Procalcitonin (8.2), Ferritin (1200)**	Antibiotics (5 days) Steroids (Dexamethasone for 10 days)	Discharge	1. Late sepsi

						Deranged coagulation profile Blood culture -ve Echo – normal			
Case 12	Day 28 / Male / 2950 gram / Term	History of COVID absent IgM +ve IgG +ve	RTPCR -ve	IgG +ve (177)	**Fever**, refusal of feeds & **Tachycardia**	Leucocytosis (18,700) Thrombocytosis (4,65,000) **Elevated CRP (96), Procalcitonin (3.6), Ferritin (980)** **Deranged coagulation profile** Blood culture -ve	Antibiotics (5 days)	Discharge	1. Late o sepsi
Case 13	Day 15/ Male / 2400 gram / Term	History of COVID present RTPCR -ve	NA	IgG +ve (22)	**Fever,** Refusal to feed, Apnea, ,Lethargy	**Elevated D-dimer (570), PROBNP (2469)** Blood culture -ve Echo – LV Normal CRP 0.5, Ferritin 460 LDH 3080, SGPT 110/SGOT 407, Total billi 13.59, direct 0.83, USG Brain – normal	oxygen Antibiotics Steroids (Methylprednisolone)	Discharge	1. Viral Pneu 2. Sepsi
Case 14	Day 26/ Male / 3400 gram / Term	History of COVID present RTPCR + ve	RTPCR -ve	IgG +ve (229.9)	**Respiratory distress, Fever,** Refusal to feed, Lethargy	**Elevated CRP (236), D-dimer (860), PROBNP (857)** Blood culture -ve Echo – LV normal CBC (Normal)	Oxygen Antibiotics Steroids (Methylprednisolone)	Discharge	1. Viral Pneu 2. Sepsi
UNLIKELY MIS – N									
Case 15	Day 1 / Male / 3300 gram / 37 weeks	Covid IgM +ve (1.40) IgG +ve (680.4)	RT PCR -ve	Covid IgM -ve IgG +ve (495)	Respiratory distress on admission, **Fever from day 3** of life	**Elevated CRP (71.5), Procalcitonin (173)** 2D Echo – Normal CSF – Normal Blood Culture - Negative	IV Antibiotics (Inj Meropenam, Inj Amikacin) Steroids	Discharged	1. Early sepsi
Case 16	Day 7 / Male / 1700 gram / Preterm (36 $^{4/7}$ weeks)	History of COVID absent IgM +ve IgG +ve	NA	IgG +ve (2.73)	**Respiratory distress** **Shock (Hypotension)** Ascites	Thrombocytopenia (62,000) Elevated CRP (24.95), Ddimer (1917), Ferritin (1450), PROBNP (6864) Deranged coagulation profile **Blood culture – Klebsiella** Echo – LV dysfunction	Surfactant Ventilation Cardiac support (Epinephrine) Antibiotics (7 days) Steroids (Methylprednisolone for 7 days, Prednisolone for 7 days) IVIG Aspirin	Discharge	1. Late o sepsi 2. Necro entero 3. Hepa
Case 17 (Twin I)	Day 1 Male/ 1400 gram / 28 $^{1/7}$ weeks	RTPCR + ve	RTPCR -ve	IgG +ve (27)	Respiratory distress, No fever	CBC, PCT, CRP normal	Oxygen, HFNC Antibiotics Steroids	Discharge	Preterm R

Case 18 (Twin II)	Day 1 Male/ 1400 gram / 28 $^{1/7}$ weeks	RTPCR + ve	RTPCR -ve	IgG +ve (29)	Respiratory distress, No fever	CBC, PCT, CRP normal	Oxygen, CPAP Antibiotics Steroids	Discharge	Preterm R
Case 19	Day 2 / Male / 3200 gram / Term	RTPCR + ve	RTPCR -ve	IgG +ve (39)	Fever Convulsion	Elevated D-dimer Blood culture -ve CSF-Normal Echo – LV normal CRP- elevated, CBC (Normal), Electrolytes-Normal	IV Antibiotics Methylprednisolone for 3 days IVIG X 2 doses	Discharge	Early onse sepsis Neonatal seizures
Case 20	1 Month / Male / 2600 gram / Term	Covid IgM -ve IgG +ve (4094)	RT PCR -ve	Covid IgG +ve (220.5)	Excessive crying, right sided submandibular swelling	Leucocytopenia (3,450) Thrombocytopenia (1,27,000) CRP (5.8) USG Neck (Parotitis) Echo – Prominent RCA (1.50) (Z=+1.77)	IV Antibiotics (Inj Taxim, Inj Amikacin)	Discharged	Parotitis

RTPCR – Reverse Transcriptase-Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; IG-Immunoglobulins; IgG positi
TLC- Total leucocyte count, ANC-Absolute Neutrophil Count; CRP- C reactive protein (mg/L); PCT - Procalcitonin (ng/mL); D Dimer (> 200 ng/ml); Ferritin (> 26
ng/ml in preterm); IL6 - Interleukin 6; PT – Prothrombin Time(seconds); APTT – Activated Plasma Thromboplastin Time(Seconds); PRO-BNP – Pro B-type na
of > 700 pg/ml); LDH - lactate dehydrogenase (> 450 U/l)

Left Ventricular (LV) Dysfunction - Left Ventricular(LV) ejection fraction(EF) <55% and fractional shortening (FS) < 26% on functional echocardiography

Figures

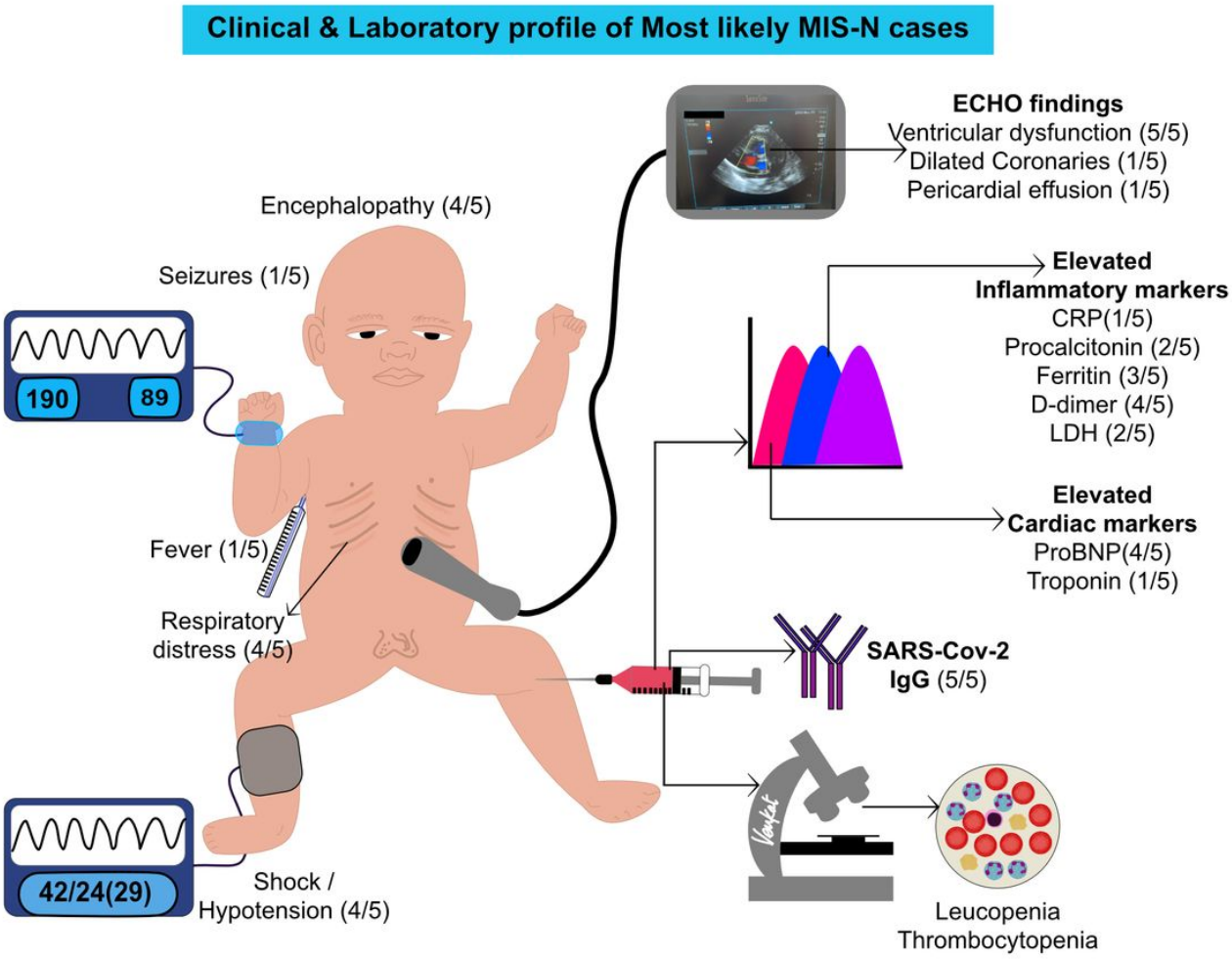

Figure 1

Summary of clinical and laboratory findings

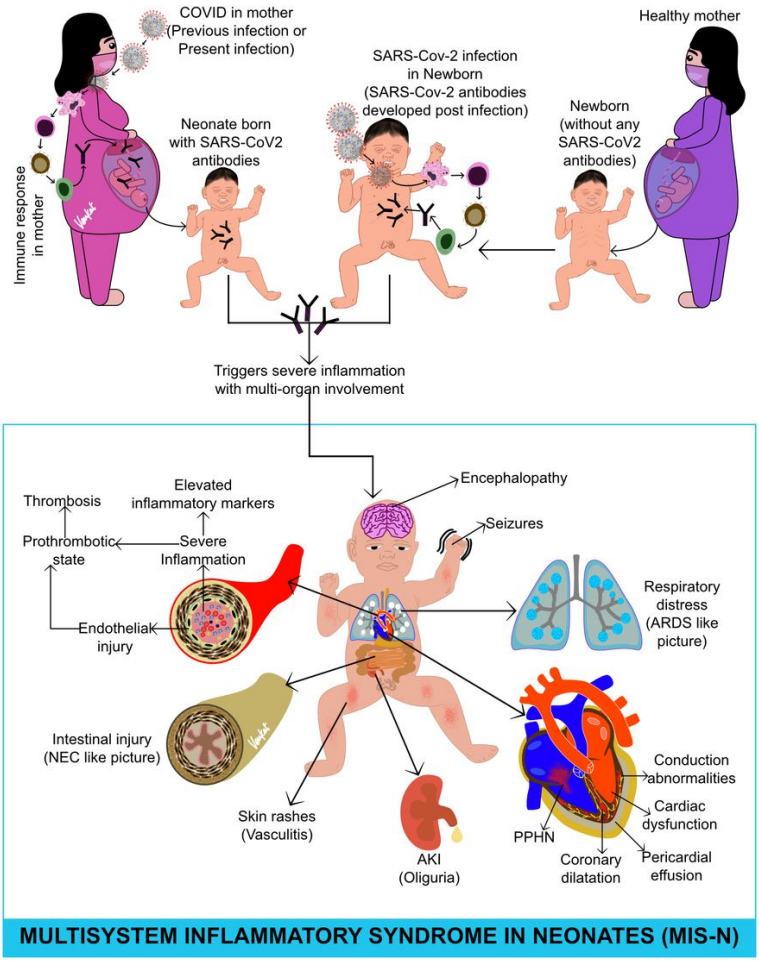

Figure 2

Proposed pathogenesis of MIS-N