Case Series

Atypical manifestations of MIS-N associated with asymptomatic maternal prenatal SARS COV-2 infection -A case series

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Abstract

As we know COVID-19, caused by SARS-CoV-2, is a global public health crisis. Due to the lack of viral receptors in children's lungs and placenta, children and newborns are fortunately less affected. But sometimes maternal antibodies may cause severe inflammation in neonates in the form of Multisystem inflammatory syndrome (MIS-N). Spike protein antibodies which are usually increased after immunization are protective. These antibodies cross the placenta to provide passive immunity to the newborn. Autoantibodies against endothelial, gastrointestinal, and immune cells are may potentially play a role in MIS-N. Here we are presenting atypical presentations of MIS-N. The role of genetic susceptibility in the pathogenesis of MIS-N needs further investigation.

Keywords: Neonate, Covid , MIS-N

Introduction

The global pandemic of covid 19 is caused by a novel coronavirus called SARS-COV-2. Covid -19 infections have been affecting all age groups but limited data is available in newborns[1].Covid infection in pregnant women is associated with adverse neonatal outcomes like severe respiratory disease[2]. The mode of transmission from mother to fetus could be vertical transmission but there is a risk of getting an infection by acquired rather than congenital due to the worldwide spread of covid 19[3]. Multisystem inflammatory syndrome in children (MIS-C) is a potentially life-threatening disease in children caused by post covid immune dysregulation [4]. MIS–C is characterized by fever, multi-organ damage, and raised inflammatory markers like CRP, ferritin 3-4 weeks after exposure to SARS-CoV-2[5]. More than 80% of children with MIS-C have specific IgM and IgG antibodies against SARS-CoV -2 but only about one-third are positive by RTPCR[6]. A few case reports have been showing MIS-C like inflammation in neonates (MIS-N) secondary to maternal covid infection[7]. These neonates usually present with fever and cardiac conduction abnormalities within weeks after birth [8]. Here we are presenting a case series of neonates with Multisystem inflammatory syndrome .

Materials and Methods

Access to chart reviews and publication was approved by the Institutional Ethics Committee (IEC) of the Niloufer Hospital, Osmania Medical College, Hyderabad, Telangana, India.

Neonates who met the following criteria given below (modified from CDC criteria for MIS-C and interim guidance from AAP to accommodate lack of fever in neonates and source of primary infection (mother, instead of the child) [9,10] were admitted to NICUs in Niloufer hospital between 1 September 2020 and 30 April 2021 were included.

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Table 1:Criteria for MIS-N

I.A neonate aged <28 days at the time of presentation II.Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother 1. Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy 2. Symptoms consistent with SARS CoV-2 infection during pregnancy 3. COVID-19 exposure with confirmed SARS CoV-2 infection during pregnancy Serological evidence (positive IgG specific to SARS CoV-2 but not IgM) in the neonate III.Clinical criteria 1. Severe illness necessitating hospitalization AND 2. Two or more organ systems affected [i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological,temperature instability (fever or hypothermia)] OR Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without involvement of a second organ system) IV.Laboratory evidence of inflammation One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin

Neonates with signs consistent with MIS-C, maternal history of COVID-19, and positive for anti-SARS CoV-2 antibodies were included. Common laboratory investigations required in the diagnosis of MIS-N are given below (table 2). IgG and IgM against SARS CoV-2 were detected by using SARS-COV-2 kits with ELFA (enzyme-linked fluorescent assay)

Table 2: Laboratory investigations

1.	Complete Blood Count , ESR, CRP
2.	Urinalysis
3.	Blood culture
4.	Other markers of inflammation: ferritin, LDH
5.	Coagulation panel: PT, PTT, D-dimer
6.	Mother and baby's Serology for SARS-CoV-2
7.	Mother and baby's SARS-CoV-2 PCR from nasopharyngeal swab
8.	Chest X-ray , Abdominal X-ray or ultrasound .
9.	Twelve-lead electrocardiogram (EKG) and 2D Echocardiogram

CASE 1

A 4-day old male baby was brought to our hospital with decreased acceptance of feeds, dull activity, and not passing urine for the past 2 days. No history of fever or respiratory distress in the neonate. Perinatal history was uneventful and the baby was delivered through normal vaginal delivery. On examination, the baby appeared lethargic, dull, and dehydrated with delayed skin turgor and sunken eyes. Laboratory investigations were done which revealed thrombocytopenia (platelet – 56,000 /cumm), positive CRP(>12), raised renal function tests(Blood urea – 241mg/dl and serum creatinine –8.6mg/dl) and abnormal serum electrolytes(Na – 172mmol/lit, K –5.6mmol/lit, Cl –119mmol/lit). Serum ionized calcium was normal. ABG was suggestive of partially compensated high anion gap metabolic acidosis. Ultrasound abdomen showed normal study with normal echotexture of both kidneys and no features suggestive of obstructive or post-renal pathology.

A provisional diagnosis of Sepsis with prerenal Acute Kidney injury with hypernatremia was considered. The baby was started on empirical antibiotics after a sample for blood culture was drawn. Fluid correction for hypernatremia was initiated. Peritoneal dialysis was started in view of Acute Kidney Injury. The baby developed two episodes of seizures which were well controlled with an antiepileptic drug (Levetiracetam). The dull activity was consistent. The probable etiology considered for seizures was meningitis and uremic encephalopathy. The antibiotics were upgraded to meningitic dose.Cerebrospinal fluid analysis was normal. The electroencephalogram was normal. Blood culture was sterile. Clinically baby developed dependent edema and sclerema along with features of feed intolerance. The baby was planned to receive Fresh frozen plasma transfusions and it was decided to continue the meningitic dose of antibiotics. Hypernatremia resolved over three days along with renal parameters which normalized in 5 days and the peritoneal dialysis catheter was removed on the 9th day of life. Urine output was normalized. The sensorium of the baby had improved by the 10th day and the feeds were restarted with better tolerance from the baby. Within 3 days baby reached full feeds and the fluids were gradually tapered and stopped. On the 17th day of life, the baby developed high-grade continuous fever, responding intermittently to antipyretic(iv paracetamol). The baby developed firm hepatomegaly. CRP was positive and blood culture showed Candida tropicalis sensitivity to fluconazole. A complete haemogram was suggestive of bicytopenia (leukopenia and thrombocytopenia). In view of persistent fever and bicytopenia for more than 3 days, bone marrow examination for haemophagocytes was carried out which showed a normal study. However, Serum ferritin was >2000 ng/ml, Serum triglycerides were 584.1 mg/dl, Serum LDH was 5258 U/L. D-dimers levels were 6900 mg/l. Plasma fibrinogen was decreased (112 mg/dl). Soluble marker CD25 was negative. RT PCR for COVID19 was negative. Covid antibodies(IgG and IgM)were positive for mother and IgG was positive for the baby. Interleukin 6 levels were raised (45.9 pg/ml). 2D Echocardiogram was suggestive of mild dilation of coronaries without any aneurysms. Left coronary artery– 2(z score 2.85), left anterior descending artery – 1.8 (z score 3.3), and right coronary artery – 1.8(z score 2.8).

A diagnosis of multisystemic inflammatory response syndrome in neonates (MIS-N) associated with Kawasaki was considered (Kawa-covid). The baby was started on iv immunoglobulin(IVIG) at 1gm/kg/day for 2 days.This was followed up with a dose of methylprednisolone 3mg/kg over 5 days. Thereafter, oral dexamethasone was started at 10mg/m²/day. Simultaneously high dose Aspirin was started at 100mg/kg/day in four divided doses which were continued till 14 days. Low-dose aspirin at 5mg/kg/day was continued after 2 weeks. The neonate had become afebrile following the above-mentioned treatment. A complete haemogram was monitored through the course of treatment which showed an improvement in bicytopenia. Repeat 2D Echocardiogram after 3 weeks was suggestive of a decrease in the size of coronaries to normal. Repeat D-dimers, serum LDH, triglycerides, and ferritin after 6weeks are normal. The neonate after 6 weeks of initiating treatment is currently on low dose aspirin and a tapering dose of dexamethasone.

CASE 2

A 21-day old male term neonate was brought to the hospital with chief complaints of dull activity and respiratory distress for 5 days. It was associated with intermittent high-grade fever subsiding with oral paracetamol. The baby required CPAP as a mode of ventilatory support in view of respiratory distress with a Down score of 5. Perinatal history was uneventful. Laboratory investigations revealed a positive sepsis screen with CRP - 24. A complete haemogram was suggestive of moderate thrombocytopenia with a platelet count of 43,000/mm³. Chest X-ray was normal. Blood culture showed a normal report. Urine culture was negative. However, considering a case of clinical sepsis, and with no response to empirical antibiotics in the initial 5 days of illness, baby was started on Meropenem providing gram-positive, gram-negative, and anaerobic coverage.Subsequently, after further questioning, it was revealed by patient attenders that the mother was an asymptomatic contact of COVID 19 patient in their family.RT PCR for COVID19 of mother and baby was negative. However, Covid antibodies for IgG and IgM in mother and IgG in baby were significantly elevated in both (>10 times). Serum ferritin was raised (1200ng/ml), Serum LDH was elevated (864U/L) and D-dimers were significantly high (1720mg/l).Echocardiogram was normal.The baby has been diagnosed with a multi systemic inflammatory response syndrome in neonates (MIS-N). The neonate received two doses of iv immunoglobulin at 1 g/kg/day for 2 days followed by steroids with injection dexamethasone at 4mg/m²/day.The baby showed improvement in both clinical and laboratory parameters within 1 week of commencing the treatment. The steroids were tapered and stopped over 2 weeks.

CASE 3

A 4-day old term male newborn weighing 2.9kg was brought to the hospital with chief complaints of decreased acceptance of feeds since 2 days, inconsolable cry since 2 days, and dull activity since 1 day. Mother had a history of COVID19 infection in the 7th month of gestation. Natal and postnatal history were uneventful. The baby was born through LSCS in view of post-term.On examination, a baby had icterus up to the level of thighs and CNS examination revealed full anterior fontanelle with normal tone and reflexes. Head circumference was 37cm. Other system examinations were normal. The baby was started on empirical antibiotics in view of clinical sepsis and laboratory investigations were sent. Complete haemogram was normal and CRP was elevated. Blood culture sensitivity showed Candidautilis sensitive to fluconazole and amphotericin B.Neurosonogram revealed dilated bilateral lateral ventricles and 3rd ventricles. Evidence of echogenic material noted in right ventricle (14.5 mm), left ventricle(15 mm) and 3rd ventricle(8mm). Impression was given as bilateral intraventricular hemorrhage with hydrocephalus. CECT Brain was suggestive of moderate dilation of supraventricular tentorial system with intraventricular hemorrhage in lateral ventricles. Mild ependymal enhancement noted in ventricles was suggestive of ventriculitis. Cerebrospinal fluid analysis revealed decreased sugars (11mg/dl) and increased proteins (145mg/dl). Gram stain showed few pus cells with no organisms noted.D-dimers were elevated with 4.48mg/l. LDH was high with 505 U/L. Serum ferritin was significantly raised with 1401 ng/ml. Diagnosis of multisystemic inflammatory response syndrome in neonates (MIS-N) was considered in this case. The baby was started on injection dexamethasone at 4mg/m²/day along with a meningitic dose of

Meropenem and amphotericin B. Antibiotics were continued for 3 weeks and the following Cerebrospinal fluid analysis showed a decreasing trend of meningitis. Antibiotics were continued for another 3weeks and stopped following clinical improvement and normal cerebrospinal fluid analysis. Steroids were tapered and stopped over 1 week. Repeat neurosonogram showed a decrease in the size of ventricles. In this case Covid antibodies for IgG and IgM were significantly elevated in mother and IgG in baby (>10 times).

Discussion

We are presenting a case series of neonates born to mothers with a history of covid 19 infections or exposure to a COVID-19 patient during pregnancy and presenting with unusual features suspecting "multisystem inflammatory syndrome. This case series was done to increase awareness of this possibility amongst all care providers. It also shows atypical systemic presentations of MIS-N.The first case had a presentation similar to Haemophagocytic lymphocytosis histiocytosis (HLH) and kawasaki disease.The second case presented with pneumonia not responding to antibiotics and associated with thrombocytopenia. The third case presented with intraventricular haemorrhage with hydrocephalus.

The common complaints in my study are dull activity and decreased feeding as seen in sepsis and one baby had dehydration signs. Fever was seen in two cases. In neonates, the MIS-N is differentiated from MIS-C by early presentation in neonates and presence of infection in the mother.

The majority of infants were delivered at term gestation in our case series. According to The NICHD Maternal-Fetal Medicine Units (MFMU) network, preterm labor and deliveries are high in COVID-19 positive mothers [11]. Thrombocytopenia was seen in two cases.CRP, LDH, and D-dimers are elevated in all cases. Covid RT PCR were negative in both mother and neonate but covid antibodies were significantly elevated in both. One case had a covid infection in the mother during 7 the month of gestation. None of the mothers in our case series had received vaccination against COVID- 19.SARS CoV-2 infection in the mother stimulates the production of IgG antibodies that cross the placenta to provide passive immunity to the newborn [12]. But in some children, these autoantibodies activate and secretion of pro-inflammatory cytokines (cytokine storm) that leads to MIS-C [13].

Multiple studies have reported the transplacental transfer of anti-SARS-CoV-2 IgG antibodies to neonates. 2D echo had shown cardiac abnormalities in 2 cases and reversed after IVIG and steroids. However, the unusual Cardiac abnormalities and response to immunomodulatory therapy with intravenous immunoglobulin (IVIG) and steroids point towards "multisystem inflammatory syndrome in the neonate (MIS-N)" deserve further study .Children with MIS-C have higher SARS-CoV-2 IgG titers than those with severe COVID-19 [14], however, this trend is transient in MIS-C .Symptomatic Therapy was the main therapy for MIS-N. All patients in our case series received intravenous immunoglobulin-IVIG and steroids, in addition, one case was received anti-platelet agents (aspirin). But further studies are important to know the benefits and risks of these therapies in MIS-N .While some cases, especially those with cardiac conduction abnormalities responded well to IVIG and steroid therapy, we need randomized trials to evaluate the efficacy of these therapies in MIS-C. Overuse of these agents usually associated with adverse effects like IVIG carries the risk of necrotizing enterocolitis so should be avoided.

Conclusion

Based on our case series, we recommend that any neonate presenting with features of sepsis and mothers with a history of COVID-19, neonatal MIS-N be considered in the differential diagnosis. Any unusual systemic manifestations not responding to routine course of medication (antibiotics) should be considered for the diagnosis of MIS-N.However, it is needed to rule out other common etiologies manifesting with unusual signs of multisystem inflammation. Maternal history of Covid 19 infection or exposure is not mandatory to establish the diagnosis of MIS-N, as in our case series maternal exposure was established only with the presence of Covid IgG and IgM antibodies.

Conflict of Interest: Nil

Source of support: Nil

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