A rare presentation of Multisystem Inflammatory Syndrome in Neonates (MIS-N) with a cerebral haemorrhage

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Introduction

Covid-19 infection during pregnancy poses diverse challenges to the developing fetus[1]. Multisystem Inflammatory Syndrome in Children (MIS-C) usually develops around 4-8 weeks after Covid-19 infection due to immune dysregulation[2]. Pathogenesis of MIS-N is similar to MIS-C but the Covid-19 infection occurs in the mother while the multiorgan inflammation occurs in the neonate due to the transfer of maternal antibodies[3]. Gastrointestinal bleeding and thrombotic events are known associations of MIS-N[3]; however, there are only a few cases with cerebral haemorrhage[4]. We describe a case of MIS-N with cerebral haemorrhage and microangiopathic haemolytic anaemia (MAHA) that showed a good response to immunotherapy with intravenous immunoglobulin (IVIG).

Case report

A baby boy was born to healthy non-consanguineous parents in their second pregnancy at 37 weeks of gestation by an emergency caesarean section as there was absent diastolic flow and intrauterine growth restriction (IUGR). The gestational period was not complicated with pregnancy-induced hypertension but the mother had a febrile illness in the second trimester lasting for a day. The baby had a birth weight of 1.75 kg, a length of 51 cm and an occipitofrontal circumference of 33 cm (asymmetrical IUGR). Apgar scores were 9,10, and 10 at 1, 5 and 10 minutes respectively.

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Intramuscular vitamin K 1mg was given and the baby was given to mother for breastfeeding. At six hours of life, the baby had respiratory distress and hypothermia (35^{0}C) while being with the mother. There were no environmental factors contributing to hypothermia. Clinical examination revealed that the baby was pale, tachypnoeic with intercostal and subcostal recessions and there was a long systolic murmur over the left upper sternal edge. The anterior fontanelle was normal, there were no dysmorphic features and no organomegaly was found in the abdominal examination. Tables 1 and 2 show the investigations that were done.

The baby had severe anaemia, thrombocytopenia and leucopenia. Prothrombin Time (PT) and International Normalized Ratio (INR) were elevated while the blood picture showed features suggestive of MAHA. The baby was started on intravenous penicillin and cefotaxime suspecting sepsis. Even though the mother had a febrile illness in the second trimester which resolved spontaneously, it was not screened for Covid-19. There was no close contact with a Covid-19 positive patient throughout the pregnancy. She had also not been vaccinated against Covid-19. Her blood sample for Covid-19 antibodies became positive (titre >10.0 index) and the baby was investigated for MIS-N (Table 3).

The baby was transfused with red cell concentrates (20ml/kg twice), platelets (10ml/kg seven times) and fresh frozen plasma (10ml/kg twice) in the first five days of life. He was ventilated because of significant respiratory distress. Later, he developed convulsions which were treated with two anticonvulsants, phenobarbitone at 20 mg/kg/day and levetiracetam at 60 mg/kg/day. Electroencephalogram (EEG) showed a diffuse slow background without epileptiform discharges. He had hypertonia with flexed upper and lower limbs (Figure 1) and fixed constricted pupils. The baby had bleeding from the endotracheal tube and brownish gastric aspirates from the nasogastric tube in the first two days which settled afterwards. Intracranial haemorrhage did not progress. A course of oral paracetamol 15 mg/kg/6 hourly was given for five days from day-01 onwards as the treatment for patent ductus arteriosus (PDA).

Table 1: ***Haematological investigations (day 1)***

Investigation	Result
Full blood count Haemoglobin (g/dL) White blood cell count (/μL) Neutrophils % Lymphocytes % Platelet count (/μL)	 5.8 (Normal range 11-17) 5.98 $\times 10^3$ (Normal range 13-38 $\times 10^3$**)** 62.2 (Normal range 46–74) 28.9 (Normal range 13–30) 3 $\times 10^3$ (Normal range 150 - 350$\times 10^3$)
Activated partial thromboplastin time (seconds)	27.1 (Normal range 23 – 35)
Prothrombin time (seconds)	**22** (Normal range 11–14)
International normalized ratio	**2.22** (Normal range 1.0 – 1.25)
Blood group	B negative
Direct antibody test	Negative
C-reactive protein (mg/L)	2.0 (Normal range < 5)
Blood picture	Reduced red cell counts with macrocytes, spherocytes, nucleated cells, polychromatic cells, acanthocytes, and fragments. Neutrophils predominate with normal morphology, No abnormal white blood cells Markedly low platelets. Features of **microangiopathic haemolytic anaemia**

Table 2: ***Imaging studies***

Investigation	Result
2D-echocardiogram	Large patent ductus arteriosus is present. No other structural abnormalities. No evidence of heart failure or ventricular dysfunction. No coronary dilatation
Ultrasound scan of brain	**Grade I haemorrhage in left side caudo-thalamic groove**. Left sided parietal lobe haemorrhage measuring 2.3×2.4 cm seen. Prominent right lateral ventricle is seen
Ultrasound scan of abdomen	Normal

Table 3: ***Additional investigations in the baby***

Investigation	Result
Rapid antigen test for SARS-Cov-2	Negative
RT-PCR for SARS-Cov-2	Negative
Covid-19 antibody levels	**Titre > 10.0 index (positive)**
Blood culture	Negative
Ear and umbilical swab cultures	Negative
Chest x-ray	Normal
D-dimer level	**1503 ng/ml (0-335)**
Lactate dehydrogenase level	**1121 U/L (178-629)**
Ferritin level	**400.1 ng/ml (36-381)**
Albumin level	**27.9 g/L (35-54)**
Plasma fibrinogen	2 g/L (1.5-4.5)
Alanine transaminase	14.8 U/L (5-40)
Aspartate transaminase	113 U/L (5-40)
Serum creatinine	101.8 mmol/L (49-95)
Blood urea	12.6 mg/dL (10-40)
Serum sodium	136 mmol/L (135-155)
Serum potassium	5.44 mmol/L (3.5-5.1)
Corrected serum calcium	2.51 mmol/L (2.02-2.60)
HIV 1 and 2 antigens	Negative
HIV 1 and 2 antibodies	Negative
TORCH screening	Negative
Highly sensitive troponin I	**0.055 ng/ml (<0.034)**

Figure 1: ***Hypertonia***

A diagnosis of MIS-N was made based on the following:

1) Covid-19 antibody positivity in both mother and baby with a febrile illness in the second trimester
2) Severe illness and multi-organ involvement (haematological, neurological and hypothermia)
3) Laboratory evidence of inflammation (raised D-dimer, lactate dehydrogenase, ferritin, and low albumin)
4) Exclusion of alternative diagnoses such as birth asphyxia, sepsis, history of maternal lupus[3]

The baby was treated with IVIG 1g/kg/day on consecutive days (day 03 and day 04). Low Molecular Weight Heparin (LMWH) was not considered for the elevated troponin-I as the baby had a cerebral haemorrhage. Baby's imaging studies, haemoglobin, platelet count, INR, and D-dimer levels (Table 4) improved; hence, a course of methylprednisolone (MP) was not considered. Baby's pupils started to respond to light and hypertonia improved with the settling of the convulsions by end of the second week of life. A lumbar puncture was performed on day 18 of life (Table 5).

Table 4: ***Haematological investigations and imaging studies on day 5***

Investigation	Result
Full blood count Haemoglobin (g/dL) White blood cell count (/µL) Neutrophils % Lymphocytes % Platelet count (/µL)	 **15.1 (Normal range 11-17)** 7.1×10^3 (Normal range 13 - 38 $\times10^3$) 42% (Normal range 46–74 %) 28% (Normal range 13–30 %) **197 $\times10^3$ (Normal range 150 - 350$\times10^3$)**
Activated partial thromboplastin time (seconds)	28 (23-35)
Prothrombin time (seconds)	14.7 (11-14)
International normalized ratio	**1.433 (1-1.25)**
D-dimer	**751 (0-335)**
2D-echocardiogram	**No patent ductus arteriosus.** No other structural abnormalities. No evidence of heart failure or ventricular dysfunction. No coronary dilatation
Ultrasound scan of brain	**The size of the haemorrhage is reduced in the left parietal lobe (1.7cm × 1.5 cm). No sagittal sinus venous thrombosis. The right-side lateral ventricle is prominent**

Table 5: ***Analysis of the cerebrospinal fluid (CSF) on day 18***

Investigation	Result
Morphology	Xanthochromic
CSF full report Red cells Polymorphs Lymphocytes	 15-20 / high power field Nil / high power field 0-1 / high power field
CSF protein (mg/dl)	**706**
CSF sugar (mg/dl)	***22 (random blood sugar – 64, 34%)***
CSF Covid-19 antibody level	**Covid-19 antibody titre – positive (>10.0 index)**
CSF culture	Negative

The baby's guarded prognosis was explained to the mother and measures to prevent further neuronal damage such as minimal handling, low-level lighting and less noise around the incubator were ensured. The baby was discharged home on day 35 of life after teaching his mother about early

interventions for improving neurodevelopmental outcomes. He will be followed up fortnightly with monitoring of occipitofrontal circumference.

Discussion

This is a case of MIS-N born to a mother who was not vaccinated against Covid-19 and has evidence of past infection possibly in the second trimester. Antibodies produced following acute infection, as well as vaccination, can cross the placenta. However, MIS-N appearing following vaccination is unlikely, because those antibodies are only against the spike protein. Multiple antibodies against autoantigens (endothelial, gastrointestinal, and immune cells) produced during natural infection are responsible for immune-dysregulation[3]. Hence, this case highlights the importance of vaccinating mothers against Covid-19.

Gastrointestinal bleeding and brownish gastric aspirates with MIS-N have been reported but their association with thrombocytopenia and coagulopathy are not described[3]. Cerebral haemorrhage and bleeding in this baby could be due to severe thrombocytopenia and coagulopathy, as they settled with correction of those abnormalities. Leucopenia, anaemia and thrombocytopenia are known complications of MIS-C[5]. Haemophagocytosis in the bone marrow, transient bone marrow stress response, and immune damage are suggested mechanisms of cytopenia in MIS-C[3,6,7]. The same mechanisms could have caused pancytopenia in our patient. MAHA and raised D-dimer levels are suggestive of disseminated intravascular coagulation but there was no evidence of thrombosis. MAHA was not reported previously with MIS-N.

Troponin-I, a described indicator of cardiac involvement in MIS-C was elevated raising the possibility of myocardial ischaemia, despite the electrocardiogram, echocardiogram, and haemodynamic parameters being normal[8]. However, troponin-I was normalized with the treatment of MIS-N. Treating MIS-N with multiple medications (IVIG, MP, LMWH) simultaneously has resulted in unnecessary over-treatment[3]. Our approach was to give IVIG and consider other medications if there was no response. There was the possibility of cerebral haemorrhage worsening with LMWH.

Neurologic involvement, convulsions, status epilepticus, altered mental status, strokes, headaches, and cerebral oedema are associated with MIS-C but the neurological involvement in MIS-N is less[3,9]. Convulsions in this baby can be due to two reasons, brain involvement of MIS-N and/or secondary to intracerebral haemorrhage[10]. However, diffuse slowing in the EEG rather than focal changes, which are expected with left parietal haemorrhage, and the generalized neurological manifestations such as hypertonia, and convulsions are suggestive of extensive brain involvement with MIS-N. The hypoglycorrhachia can be attributed to the cerebral haemorrhage[11] but could be a manifestation of MIS-N as well. Our case report widens the spectrum of neurological manifestations of MIS-N and highlights the importance of maternal Covid-19 vaccination.

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