Received: 25 January 2022 | Revised: 21 March 2022 | Accepted: 22 March 2022

DOI: 10.1111/apa.16345

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

BRIEF REPORT

Importance of establishing antibody specificity in multisystem inflammatory syndrome in newborn during the COVID-19 pandemic

Multisystem inflammatory syndrome in newborns (MIS-N) has increasingly been reported in patients with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] MIS-N can be secondary to immune-mediated injuries, due to transplacental maternal or neonatal antibodies produced during the infection. This process is similar to multisystem inflammatory syndrome in children.[3] Transplacental transfer of maternal SARS-CoV-2 immunoglobulin G (IgG) antibodies can be protective,[4] but sometimes in-utero transfer of these antibodies, concomitant other inflammatory cytokines, may trigger MIS-N. Increased viral transmission and mass vaccination have increased SARS-CoV-2 seroprevalence, and babies are increasingly being born with positive antibodies.[5] We describe a baby with multi-organ dysfunction, due to placental abruption, but confounded by SARS-CoV-2 antibodies consistent with MIS-N. Parental consent was provided.

A male baby weighing 2,690 kg was born at 33 + 5 weeks to a primipara mother with placenta previa. She was an unvaccinated nurse, with potential exposure to SAR-CoV-2, who tested negative before labour. The baby was born vigorous, but pale, and required intubation at 11 min. His cord gas was normal, but he had low haemoglobin (11 g/L). The initial treatment included mechanical ventilation, empirical antibiotics, fluid management, packed red blood cells (PRBC) and fresh frozen plasma (FFP) transfusions for abnormal coagulation. His renal function started to deteriorate 12 h after transfusion, with no urine output since birth and increasing hyperkalaemia. At 24 h, he was transferred to our quaternary hospital, in case he needed peritoneal dialysis. He presented with severe multi-organ dysfunction, with respiratory distress needing ventilation and cardiac compromise with low blood pressure. An echocardiogram suggested mild left ventricular dysfunction and exponential elevation of cardiac biomarkers, N-terminal-pro-B-type natriuretic peptide (>70,000 pg/ml) and troponin-T (2,046 ng/ml), suggesting myocardial injury. He had acute renal failure, with elevated serum potassium (9.5 mmol/L) and rising urea and creatinine and needed peritoneal dialysis from 3 to 11 weeks of life. Gastric bleeding, with abnormal clotting and platelet levels, required multiple vitamin K doses, PRBC, cryoprecipitate, FFP and platelet transfusions. His liver enzymes were significantly elevated on admission, but gradually declined, with extensive necrosis visible on his abdominal ultrasound.

The baby was not encephalopathic, with a discontinuous background on amplitude-integrated electroencephalogram and normal cerebral near-infrared spectroscopy. Brain magnetic resonance imaging on day 19 showed minor multifocal deep white matter abnormalities.

All his inflammatory markers were markedly elevated: Serum ferritin (3,825 mcg/L), lactate dehydrogenase (>1,200 IU/L), procalcitonin (7.21 ng/ml) and D-Dimer concentration (>7,500).

Multiple nasopharyngeal swabs, tracheal aspirate and stool samples tested negative for SARS-CoV-2, and he and his mother were negative for SARS-CoV-2 immunoglobulin M antibodies. However, he tested positive for immunoglobulin G (IgG) antibodies against SARS-CoV-2 with titres of 210 and 155 BAU/ml on days 3 and 11 of life. His mother's level was 17.9 BAU/ml.

We suspected MIS-N, as SARS-CoV-2 IgG was present, and he received immunomodulatory therapy from day 2 of life, with a single dose of intravenous immunoglobulin (1 g/kg) and daily methylprednisolone (1 mg/kg). Enzyme-linked immunosorbent assays showed that he and his mother had antibodies against the SARS-CoV-2 spike protein, but not nucleoprotein. MIS-N was thus ruled out, and immunomodulator therapy discontinued. The baby was extubated at 3 weeks of life, but his liver failure continued. His clinical condition progressively worsened, and he died 93 days after birth.

The patient's severe multi-organ dysfunction was related to placental abruption, but the degree of bleeding was unclear at birth. High levels of inflammatory markers, cardiac biomarkers and mild left ventricular dysfunction on admission, during the pandemic, suggested MIS-N. He tested negative for the virus, but his mother was positive for SARS-CoV-2 IgG antibodies and his antibodies were 6 times her levels. The initial immunomodulatory treatment, due to suspected MIS-N, was stopped after we established the antigen specificity of the antibodies. The results were inconsistent with natural infection, and vaccination-derived antibodies from transfusions were suspected. The mother's serum

Abbreviations: IgG, immunoglobulin G; MIS-N, multisystem inflammatory syndrome in newborns; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

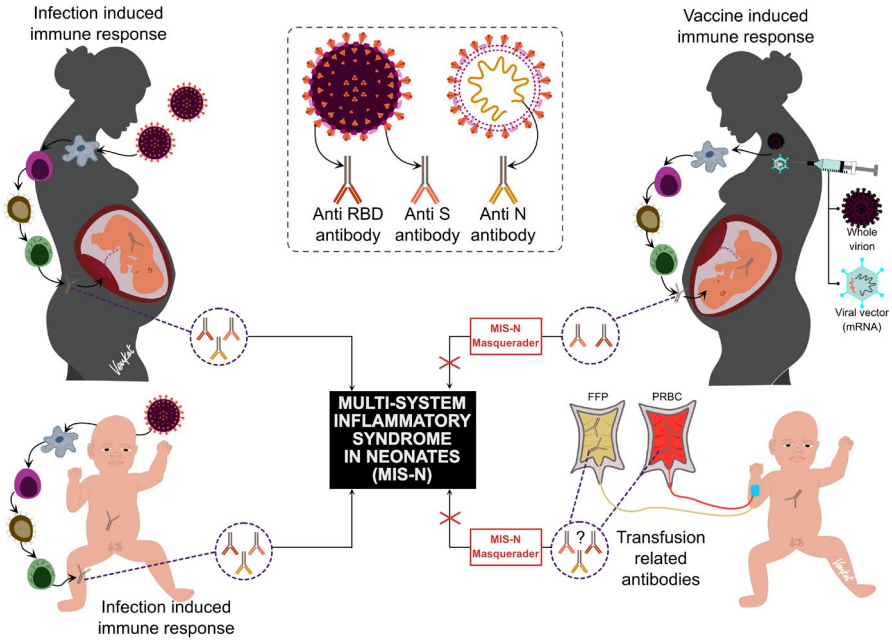

FIGURE 1 Mechanisms of exhibiting SARS-CoV-2 antibodies in newborn. *Source:* Anti-N antibody, anti-nuclear protein antibody; Anti-RBD antibody, anti-receptor-binding domain antibody; Anti-S antibody, anti-spike protein antibody; FFP, fresh frozen plasma; mRNA, messenger RNA (ribo nucleic acid); PRBC, packed red blood cells

sample was collected after three blood transfusions, and the infant had received multiple blood product transfusions before his serology sample. Both had received transfusions from vaccinated donors which were traced from blood bank. The increased prevalence of SARS-CoV-2 antibodies in blood donations has been reported.[5] Just over a quarter (28%) of Qatar residents were fully vaccinated using the Pfizer and Moderna messenger ribonucleic acid vaccines at the time of the child's hospitalisation. Detecting antibodies against the spike protein, but not nucleoprotein, argued against a natural infection.

The pandemic and the baby's critical neonatal inflammatory response made it vital to rule out MIS-N, and the antigen specificity of SARS-CoV-2 played an important role in this process. Figure 1 shows the mechanism of MIS-N and potential sources of SARS-CoV-2 antibodies.

Neonatal multi-organ dysfunction can be severe, but many conditions can masquerade as MIS-N. SARS-CoV-2 antibodies may cause MIS-N, but they could also be incidental bystanders and all possibilities must be thoroughly investigated.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None.

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