Postnatal IVIG treatment for persistent anaemia in neonate due to congenital parvovirus infection

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SUMMARY

Congenital parvovirus B19 infection is a rare but serious condition that can result in hydrops fetalis and fetal death. Due to the virus' cytotoxic effect on fetal red blood cell precursors, postnatal infection can cause a neonatal viremia and secondary pure red cell aplasia. Here, we describe a case of congenital parvovirus infection in a preterm infant complicated by hydrops fetalis and chronic anaemia that responded to postnatal treatment with intravenous immunoglobulin administered on day of life 44. After treatment, the anaemia resolved as the neonate exhibited interval increases in haemoglobin, haematocrit and reticulocyte count with no subsequent need for red blood cell transfusions.

BACKGROUND

Parvovirus B19 is a small non-enveloped single-stranded DNA virus that frequently infects humans. Parvovirus B19 can cause erythema infectiosum, also known as fifth disease, characterised by self-limited fever, rash and arthropathy. The incidence of parvovirus B19 infection in pregnancy is 3.3%–3.8%.[1] Approximately 30%–50% of pregnant women are non-immune and vertical transmission is common.[2]

During pregnancy, parvovirus B19 is cytotoxic to fetal red blood cell precursors. The virus is highly trophic to human bone marrow and replicated in erythroid progenitor cells.[3 4] Most intrauterine parvovirus infections do not have adverse outcomes; however, in rare cases, transplacental transmission of parvovirus B19 in the setting of maternal viremia can result in fetal hydrops or death due to severe fetal anaemia.[4] Parameters of hydrops fetalis include scalp and skin oedema, ascites, pleural effusions and pericardial effusions.

During pregnancy, a positive parvovirus B19-specific immunoglobulin antibody can be used to diagnose acute or chronic maternal infection. PCR detection of B19 in the amniotic fluid is the method of choice for diagnosis of congenital parvovirus infection.[5] Fetal anaemia is suspected on ultrasound examination when middle cerebral artery peak systolic velocity (MCA PSV) Doppler is >1.5 multiples of the median (MoM).[6] Percutaneous umbilical cord blood sampling (PUBS) examines blood from the fetal umbilical cord and confirms the diagnosis. In severe cases of fetal anaemia, intrauterine red blood cell transfusions may be indicated to prevent fetal death.[7]

After delivery, congenital infection may result in persistent neonatal viremia with secondary pure red cell aplasia (PRCA) and chronic anaemia. The mainstay of treatment for PRCA in neonates is red cell transfusion(s). In certain patients with persistently high viral loads, intravenous immunoglobulin (IVIG) has been used successfully for the treatment of persistent parvovirus-induced anaemia, but data remains limited in neonates.[8–15] Here, we describe a case of congenital parvovirus infection in a preterm infant complicated by hydrops fetalis that responded to a postnatal treatment of IVIG.

CASE PRESENTATION

A preterm male neonate was born at 29 weeks and 2 days gestation to a 27-year old gravida 5, para 1 mother. Serologies were negative (rapid plasma reagin non-reactive, HIV antibody screen negative, hepatitis B surface antigen negative, group B streptococcal status negative). The prenatal course was complicated by ultrasound findings of polyhydramnios, with an amniotic fluid index up to 28.5 cm. Fetal ultrasound at 27 weeks and 2 days gestation showed scalp oedema, ascites, pleural and pericardial effusions, skin oedema, and elevated middle cerebral arterial Doppler's consistent with fetal hydrops. Fetal echocardiogram revealed a structurally normal heart. Serologic testing showed maternal parvovirus seroconversion (positive parovirus B19 immunoglobulin M with a previously documented negative parvovirus B19 immunoglobulin G). Maternal parvovirus PCR confirmed positive. The mother had no known sick contacts and no history of febrile illness, rashes, joint pain or other infectious symptoms during pregnancy.

In the setting of the persistent fetal anaemia and severe hydrops, the decision was made to perform a PUBs procedure with intrauterine transfusion of packed red blood cells total three times, at 27 weeks and 3 days, 28 weeks and 1 day, and 28 weeks and 3 days gestation. Red blood cell transfusion consisted of leucocyte reduced, irradiated, cytomegalovirus negative, type O negative blood. Preprocedure MCA PSV Dopplers for the three procedures were 106 cm/sec, 73.8 cm/sec and 72 cm/sec with MCA PSV MoM averaging 3.0, 1.99 and 1.92, respectively. Pretransfusion fetal haematocrit levels were 6.8%, 15% and 20%. Postprocedure haematocrits increased to >25% with normalisation of MCA Dopplers in each case. Last Doppler prior to delivery at 29 weeks and 0 days had an MCA PSV of 60 cm/sec (1.58 MoM). Fetal reticulocyte count was 2.2%. The mother also received intrauterine transfusions of platelets for thrombocytopenia, with lowest fetal platelet count 48×10^9/L.

The mother returned with preterm premature rupture of membranes in preterm labour and

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delivered at 29 weeks and 2 days via precipitous vaginal delivery. The first course of betamethasone was given at 27 weeks gestation and a rescue dose was administered immediately prior to delivery. The neonate was intubated in the delivery room for respiratory depression and low heart rate. Apgars were 4 at 1 min and 7 at 5 min of life. Surfactant was given on day of life 0.

Initial physical examination was significant for generalised oedema and infiltrated skin with no palpable hepatosplenomegaly. Initial postnatal blood work showed white blood cell count of 10.2×10^9/L, haemoglobin of 10 g/dL, haematocrit of 29.2%, and platelet count of 65×10^6/L. Mother's blood type was A positive and newborn's blood type was O negative, Coombs negative. Postnatal echocardiography on day of life 2 showed normal segmental anatomy with qualitatively normal biventricular size and systolic function and estimated pulmonary artery pressures approximately half systemic to systemic; no pericardial effusion.

The neonate received both pack red blood cells and platelet transfusions on day of life 0. A single donor was used for iterative transfusions. Haematocrit level initially improved to 45.3%, but then continued to trend down over the following weeks. Reticulocyte count ranged from 0.9% to 1.7% during first 6 weeks of life. Subsequent red blood cell transfusions were administered on days of life 18, 32 and 46 for persistent anaemia with haematocrit ≤24.0%. Thombocytopenia resolved after the initial platelet transfusion with no subsequent need for additional platelet replacement. Iron was continued for anaemia of prematurity. Phototherapy was initiated on day of life 1 for bilirubin level 11.7 mg/dL. Liver function was monitored and showed an evolving direct hyperbilirubinaemia, with a maximum indirect bilirubin level on 11.3 mg/dL and a maximum direct bilirubin level of 4.0 mg/dL. The neonate was started on Actigall and ADEK vitamins, which were discontinued on day of life 40.

Given the transfusion dependent anaemia and poor reticulocytosis, a transient compromise in erythroblastic differentiation due to the parvovirus infection was considered. A parvovirus titre was sent on day of life 41 and confirmed a high parvovirus B19 viral load of >10 000 000 copies/mL, which exceeded level of count. Decision was made to treat the neonate with one dose of IVIG (dose: 1 g/kg) on day of life 44 for PRCA. Bloodwork within 24 hours after administration showed haemoglobin 8.0 g/dL, haematocrit 23.8% and reticulocyte count 1.3%. Within 1 week after administration, haemoglobin and haematocrit increased to 11.1 g/dL and 33.1%, and reticulocyte count increased for the first time to 3.7%. On day of life 67, haemoglobin and haematocrit remained stable at 10.1 g/dL and 31.3%, while the reticulocyte count continued to increase to 4.3%. On day of life 77, laboratory studies showed haemoglobin 10.6 g/dL, haematocrit 31.8% and reticulocyte count 3.9% with no subsequent need for transfusions. Serum parvovirus B19 PCR obtained on day of life 92 showed a significant decrease in viral load to 582 550 negative copies/mL.

OUTCOME AND FOLLOW-UP

The neonate clinically improved and remained haemodynamically stable. Extubation was performed on day of life 2 with full wean off respiratory support to room air on day of life 47. After IVIG administration, the neonate remained stable and no adverse effects were noticed throughout remainder of his inpatient hospitalisation. Hospital course was complicated by issues including apnoea of prematurity, oral feeding and weight gain; however, the neonate was safely discharged home on day of life 74 (at corrected age 39 weeks and 5 days gestation). Patient was followed outpatient up to 5 months of age with no subsequent evidence of anaemia.

DISCUSSION

Parvovirus B19 infection during pregnancy is associated with adverse fetal outcomes, including non-immune fetal hydrops, fetal myocarditis and fetal death. Fetal anaemia due to parvovirus infection in combination with the shorter half-life of fetal red blood cells can lead to severe anaemia, hypoxia and fetal hydrops associated with high-output cardiac failure. Other proposed mechanisms for fetal hydrops in the setting of parvovirus B19 include fetal viral myocarditis that leads to cardiac failure and direct damage to hepatocytes that results in hepatic dysfunction.[8] While parvovirus has a stronger affinity for haematopoietic system cells, including erythroid progenitor cells, it can also affect leucocyte and megakaryocyte cell lines. Thrombocytopenia is reported in up to 97% of hydropic fetuses.[9] The risk of anaemia and fetal hydrops appears to be greater when women are infected with parvovirus B19 in the first half of pregnancy.

The treatment for parvovirus-related hydrops fetalis and chronic neonatal anaemia depends on the gestational age of the infant, other associated conditions and severity of the illness. Many hydropic infants require mechanical ventilation due to pulmonary hypoplasia or pulmonary oedema, abdominal paracentesis for ascites and thoracentesis for pleural effusions. The mainstay of treatment for chronic anaemia secondary to PRCA is red blood cell transfusions. However, neonates are especially susceptible to the effects of parvovirus B19 and their immature immune systems make it difficult to control the infection. In severely persistent cases, alternative therapies, such as IVIG, can be considered.

IVIG is an immunomodulator that was initially used to treat primary immunodeficiencies, but is now being used as primary or adjuvant treatment for various autoimmune and inflammatory diseases, including acute infection. At this time, data about administration of IVIG for persistent parvovirus B19 infections is limited to case reports. IVIG administration in utero to a mother at 24 weeks gestation with parvovirus B19-induced preeclampsia and fetal hydrops showed favourable maternal and fetal outcomes, with normalisation of maternal blood pressures and normal infant development.[10] Postnatal IVIG was also shown to improve congenital parvovirus valvular myocarditis.[11] Reports of patients with PRCA due to parvovirus B19 infection treated with IVIG show variable outcomes. Postnatal IVIG treatment of PRCA due to parvovirus B19 infection in preterm dizygotic twins born at 29 weeks 5 days gestation effectively reduced viral remission and normalised erythropoiesis.[12] Postnatal IVIG was also shown to decrease parvovirus B19 viral load in preterm infant born at 26 weeks and 6 days gestation with fetal hydrops and chronic postnatal anaemia when given at age 3 months.[13] In another case report, IVIG resulted in a marked reduction in viral load and stabilisation of haemoglobin level in a patient with persistently high parvovirus B19 viremia when given at 5 months of age.[14] The mechanism of its action of IVIG in the setting of parvovirus B19 remains unclear. A possible explanation for successful treatment is that IVIG preparations contain specific neutralising antibodies, leading to a reduction of the viral load.[15]

Based on the persistent, transfusion-dependent parvovirus B19-induced anaemia in our patient, we elected to give IVIG in an attempt to reduce viral load and decrease the need for red blood cell transfusions. Following treatment, we noted a significant decrease in viral burden and stabilisation of the haemoglobin level over the following 4–6 weeks with no adverse

Learning points

- Red blood cell aplasia is a potential outcome for neonates with congenital parvovirus B19 infection.
- Intravenous immunoglobulin (IVIG) is a potential treatment option for neonates with red blood cell aplasia secondary to congenital parvovirus B19 infection.
- Treatment with IVIG in our patient with red blood cell aplasia secondary to congenital parvovirus B19 infection had an improvement in haematocrit and reticulocyte count with no adverse reactions and no need for subsequent red blood cell transfusions.
- Larger studies are needed to assess the benefits of IVIG in the treatment of red blood cell aplasia secondary to congenital parvovirus B19 infection.

reactions. This successfully decreased the need for frequent red blood cell transfusions throughout the remainder of his inpatient hospitalisation. No additional red blood cell transfusions were required in outpatient follow-up to date.

Successful cases of postnatal IVIG administration to decrease parvovirus B19 viral load and aid in treatment of parvovirus B19-induced neonatal anaemia and red cell aplasia have been reported in case series. We present another favourable neonatal response to IVIG in the setting of congenital parvovirus B19 viremia, but this form of treatment is still experimental. Strong recommendations for use of IVIG in neonatal parvovirus B19 infections cannot be made at this time. Future studies will be needed to determine possible mechanisms of action as well as long-term effects.

Contributors OJ was a fellow physician who participated in the patient's care during his NICU stay. She helped make medical decisions regarding his treatment and overall management. After his discharge, the case was reviewed and the case report was written. Consent was obtained from mother. JL was a attending physician who participated in the patient's care. He oversaw medical decisions and overall management. He helped review and edit the case report write up.

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