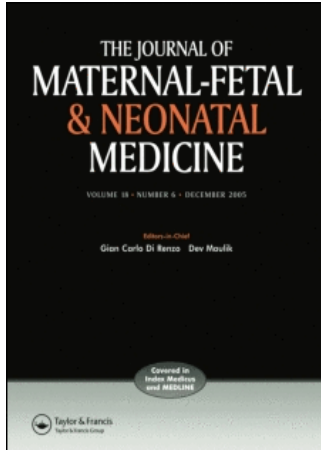


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CASE REPORT

Fetal cerebellar hemorrhage in parvovirus-associated non-immune hydrops fetalis

ORIT A. GLENN¹, KATHERINE BIANCO², A. JAMES BARKOVICH¹, PETER W. CALLEN¹, & JULIAN T. PARER²

¹Department of Radiology, and ²Department of Obstetrics and Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA

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Abstract

We report two cases of fetal cerebellar hemorrhage in the setting of parvovirus-associated hydrops fetalis and fetal blood transfusion. In both cases, the cerebellar hemorrhage was diagnosed by fetal magnetic resonance imaging after intrauterine blood transfusion. To our knowledge, this is the first report of fetal cerebellar hemorrhage in the setting of parvovirus-associated hydrops fetalis, and may be the result of cerebrovascular changes both during and after the transfusion.

Keywords: *Fetal MRI, cerebellar hemorrhage, parvovirus, hydrops fetalis*

Introduction

When *in utero* exposure to B19 parvovirus results in non-immune hydrops fetalis, intrauterine blood transfusion results in improved outcome. We report two cases of cerebellar hemorrhage in the setting of fetal parvovirus infection complicated by hydrops fetalis requiring fetal blood transfusion. We propose that the hemorrhage may be the result of cerebrovascular changes both during and after the transfusion.

Cases

Case 1

A 33-year old, G2P1 woman was exposed to parvovirus at 12 weeks gestation and tested positive for parvovirus IgG and IgM. Ultrasound (US) performed at 17^{1/7} weeks demonstrated fetal hydrops with ascites, pericardial effusion, integumentary edema, polyhydramnios, and elevated middle cerebral artery (MCA) peak systolic velocities (PSV) (45–50 cm/s). An amniocentesis was performed; and parvovirus B19 DNA was detected by PCR test of

the amniotic fluid. The sonographic findings were consistent with parvovirus infection and fetal anemia. At 18^{1/7} weeks, fetal blood sampling revealed low fetal hemoglobin (3.9 g/dl). Twenty cc of blood was transfused into the umbilical vein. Post-transfusion fetal hemoglobin was 11.5 g/dl. Post-transfusion MCA PSV was normal (25 cm/s). Six days later, US demonstrated mild improvement in hydrops, and normal intracranial anatomy. At 19^{5/7} weeks, US showed asymmetric echogenicity of the cerebellar hemispheres and increasing size of the ventricles (Figure 1). At 20^{1/7} weeks, fetal magnetic resonance imaging (MRI) performed for further evaluation showed a large hematoma in the right cerebellar hemisphere characterized by heterogeneous signal on *T*₁ and *T*₂-weighted images (Figure 1). The lateral ventricles were prominent with slightly diminished parenchyma posteriorly. The patient elected to terminate the pregnancy; autopsy was declined.

Case 2

A 34-year-old G2P1 woman had fetal hydrops detected on a routine US performed at 19 weeks gestation. She was exposed to parvovirus and

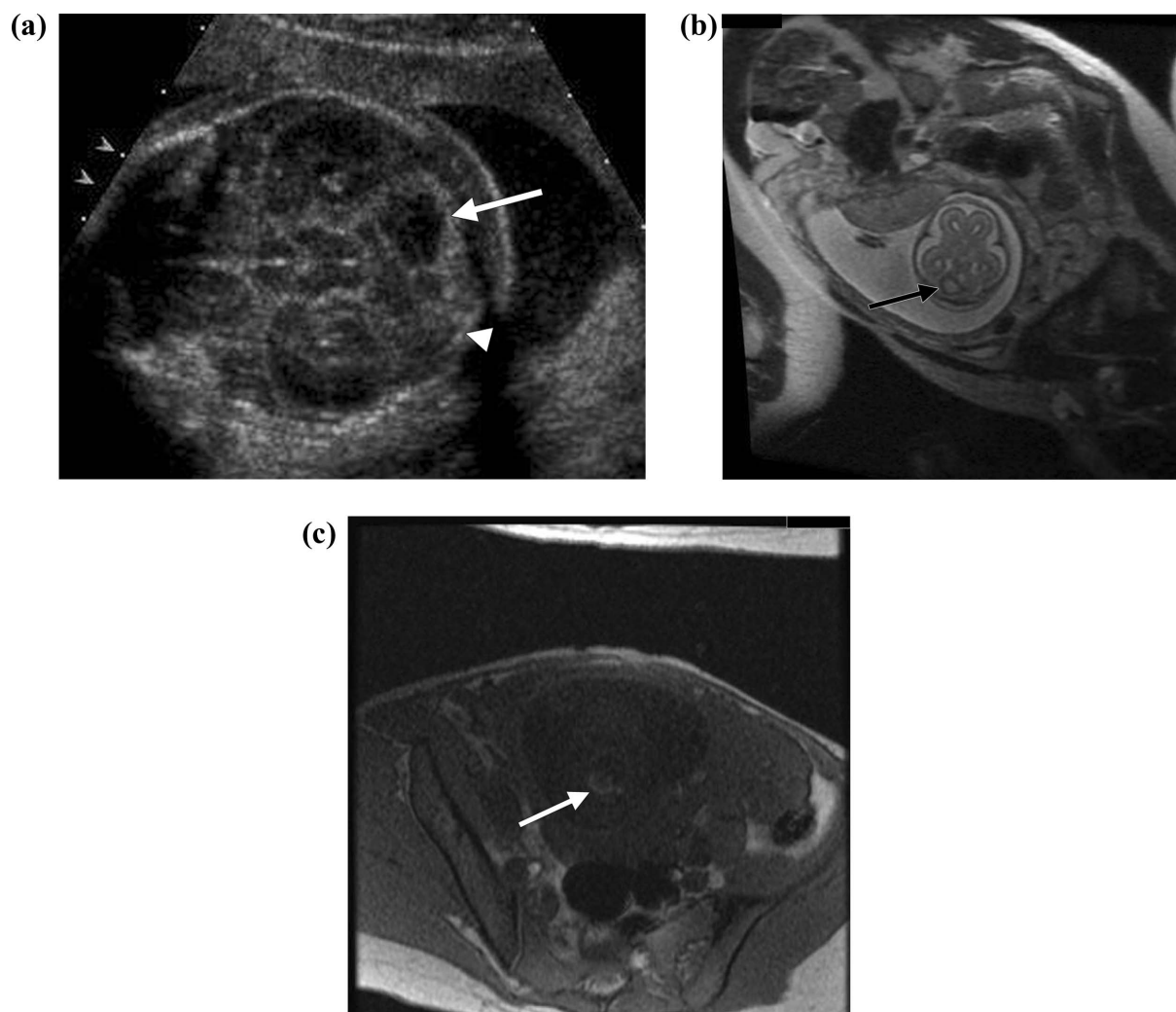


Figure 1. (a) Axial ultrasound image demonstrates asymmetry in size and echogenicity of the cerebellar hemispheres (Case 1). There is relative decreased echogenicity of the right cerebellar hemisphere (arrow) and increased echogenicity of the left cerebellar hemisphere (arrowhead). (b) Axial single-shot fast spin-echo T_2 -weighted image demonstrates an area of increased signal with peripheral decreased signal in the right cerebellar hemisphere (arrow). (c) Axial gradient-echo T_1 -weighted image at the same level as (b) shows areas of increased signal consistent with cerebellar hemorrhage (arrow). Bilobed appearance of the hematoma on both T_1 - and T_2 -weighted images suggests involvement of the cerebellar vermis.

developed a characteristic rash at about 12 weeks gestation, and tested positive for parvovirus IgM. At 20^{1/7} weeks, US showed nuchal thickening, ascites, polyhydramnios, and elevated MCA PSV (61.7 cm/s). Fetal blood sampling at 20^{1/7} weeks revealed low hemoglobin (3.3 g/dL). 43 cc of blood was transfused into the umbilical vein. Post-transfusion fetal hemoglobin was 14.9 g/dL and MCA PSV was normal (35 cm/s). Five days later, US showed minimal ascites, increased liver and bowel echogenicity, and normal intracranial anatomy. At 22^{1/7} weeks, US was normal. US at 23^{6/7} weeks showed inferior atrophy of the cerebellum with cysts. At 24 weeks, fetal MRI demonstrated small cerebellar hemispheres with heterogeneity on T_2 -weighted images and increased signal on T_1 -weighted images consistent with

hemorrhage (Figure 2). The patient elected to terminate the pregnancy; autopsy was declined.

Discussion

Although fetal cerebellar hemorrhage is rare, it has been reported following intrauterine blood transfusions in cases of hydrops fetalis secondary to severe red blood cell alloimmunization [1]. When *in utero* exposure to human (B19) parvovirus fetal infection occurs during the first 20 weeks of gestation, it can result in non-immune hydrops fetalis. Treatment with early intrauterine transfusion in parvovirus-associated hydrops fetalis usually results in a favorable outcome [2]. To date, there have been no descriptions of fetal cerebellar hemorrhage in the setting of human parvovirus infection.

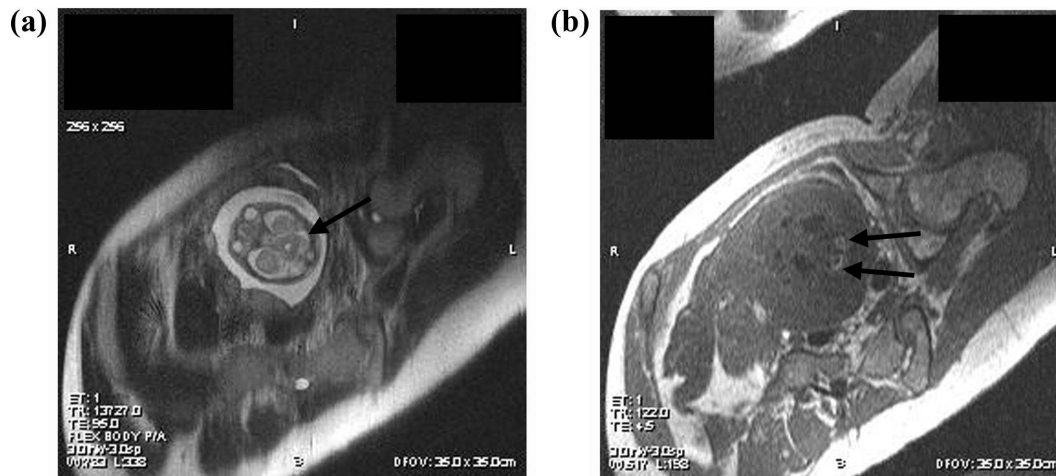


Figure 2. (a) Axial T_2 -weighted image from fetal MRI performed by an outside hospital (Case 2) demonstrates heterogeneity of the cerebellar hemispheres (arrow). (b) Axial T_1 -weighted image at the same level as (a) shows heterogeneous signal with peripheral area of increased signal in both cerebellar hemispheres consistent with cerebellar hemorrhage (arrows).

In both of our cases, the cerebellum was normal prior to intrauterine fetal blood transfusion, with the abnormality detected 1–3 weeks after the transfusion. We speculate that hemodynamic changes related to the severe anemia and subsequent intrauterine blood transfusion may have led to the cerebellar hemorrhages in our cases, as has been theorized in cases following intrauterine transfusion for immune fetal hydrops and anemia.

In premature newborns, hemodynamic changes such as alterations of cerebral blood flow, particularly in the setting of decreased oxygenation, can result in injury to the delicate capillary blood supply in the germinal matrix and lead to germinal matrix hemorrhage [3]. In our two cases, the severe anemia likely caused increased cerebral blood flow combined with decreased blood oxygen delivery with consequent injury to the thin-walled capillaries of the cerebellar germinal matrix. An increase in blood volume and viscosity resulting from the subsequent blood transfusion could then have led to hemorrhagic reperfusion injury of the cerebellar germinal zones (ventricular zone and/or external granular layer). It is also possible that the increase in blood volume due to the blood transfusion could have led to acute venous congestion and subsequent germinal matrix hemorrhage, although Doppler indices to evaluate for venous congestion were not obtained in these cases. The absence of detectable hemorrhage in the cerebral germinal matrix could, perhaps, be seen because the cells in the cerebellar germinal zones are more susceptible to these vascular changes, possibly because they remain active longer than the cerebral germinal zones. Another possible explanation is that the cells in the cerebellar germinal matrix are more susceptible to direct viral infection. This is supported

by the observation that, in animals, species-specific parvovirus infections cause destruction of the external granular layer, cerebellar hemorrhage, and hypoplasia from a combination of direct infection and vascular damage [4]. In addition, parvovirus has been found in brain tissue in human cases of fetal parvovirus infection [5–7]. Either way, our observations suggest that blood transfusion may put the fetus at risk for cerebellar hemorrhage.

Reports of intracranial abnormalities associated with congenital parvovirus infection in the absence of intrauterine transfusions are rare, but include ventricular enlargement, subependymal gliosis, calcifications, and encephalomalacia [7–9]. Hemorrhagic venous infarction has been reported in a newborn with factor V Leiden mutation and late third trimester parvovirus infection [10]. Encephalitis has also been reported in two neonates with congenital parvovirus [11]. Although the mechanism for brain abnormalities observed in humans with congenital parvovirus infection is unknown, hypoxia or ischemia have been considered likely factors [8–10]. It is possible that other mechanisms, such as venous hemorrhagic infarction, may account for the observed findings in our cases. However, it is difficult to ignore the temporal relationship to the blood transfusions in both cases.

Our experience supports prior studies showing that fetal MRI is helpful in evaluating posterior fossa lesions [12]. In both our cases, a cerebellar abnormality was detected by sonography, however it was difficult to characterize further. Fetal MRI was able to identify hemorrhage as the cause of the abnormal appearance on ultrasound.

A recent study by Nagel et al. [13] on survivors of parvovirus-associated hydrops fetalis and

intrauterine blood transfusion suggests that neurodevelopmental disabilities are more common than previously thought. One-third of survivors were found to have neurodevelopmental disabilities in childhood [13]. Interestingly, postnatal MRI in one child with severe disability demonstrated atrophy of the cerebellar vermis [13], which can result from preterm vermian hemorrhage. These findings emphasize the importance of prenatal identification of brain abnormalities in fetal parvovirus infection.

In conclusion, these two cases of cerebellar hemorrhage associated with parvovirus infection and hydrops fetalis requiring fetal blood transfusion may be the result of cerebrovascular changes both during and after the transfusion. The cerebellum should be carefully evaluated in fetuses with suspected parvovirus infection, particularly after *in utero* blood transfusion. Fetal MRI should be performed if any abnormality is suspected, especially in light of the high incidence of neurodevelopmental disabilities in these children.

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