

Prenatal Diagnosis of Anoxic Cerebral Lesions Caused by Profound Fetal Anemia Secondary to Maternal Red Blood Cell Alloimmunization

Bruno Carbonne, MD, Amélie Nguyen, MD, Evelyne Cynober, MD, Vanina Castaigne, MD, Anne Cortey, MD, and Yves Brossard, MD

BACKGROUND: The long-term neurological prognosis of severe fetal anemia is usually considered favorable, especially when fetal hydrops regresses after successful in utero transfusion.

CASES: We report two cases of prenatally diagnosed fetal cerebral anoxic lesions associated with severe fetal anemia despite appropriate and successful treatment by in utero transfusion. The two pregnancies were terminated.

CONCLUSION: Profound fetal anemia may cause anoxic lesions of the fetal brain that may be diagnosed prenatally. If new onset ventriculomegaly is observed on ultrasonography after in utero transfusion for severe fetal anemia, anoxic lesions could be suspected.

(*Obstet Gynecol* 2008;112:1-1)

Maternal red blood cell alloimmunization, to RhD and K antigens in particular, is the most common cause of severe fetal anemia. Neurological prognosis after anemia is usually considered favorable if fetal hydrops regresses after in utero transfusion.¹⁻⁴ We report two cases of alloimmunization with poor outcomes: cerebral lesions were diagnosed prenatally despite successful in utero transfusion.

From Centre National de Référence en Hémiobiologie Périnatale, Hôpital Saint-Antoine, Paris, France; Service de Gynécologie Obstétrique, Hôpital Saint-Antoine, Assistance Publique – Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France.

Corresponding author: Pr. Bruno Carbonne, Service de Gynécologie-Obstétrique, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France; e-mail: bruno.carbonne@sat.aphp.fr.

Financial Disclosure

The authors have no potential conflicts of interest to disclose.

© 2008 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.

ISSN: 0029-7844/08

CASE 1

A 28-year-old woman (para 2) was referred to our center in 2005 at 21 weeks of gestation for the management of severe anti-K alloimmunization (KEL1). Her obstetric history included a term delivery in 2003 of a healthy 3,000-g baby girl. Testing for immune antibodies was negative at delivery. In the second pregnancy, an anti-K antibody titer of 256 was discovered at a gestational age of 12 weeks. Because the patient's spouse was a K (KEL1)-positive heterozygote, amniocentesis was performed to determine the K genotype of the fetus at a gestational age of 19 weeks. The same day, the Doppler measurement of the middle cerebral artery peak systolic velocity was found to be 2.5 multiples of the median (MoM). Because the operator was not familiar with this measurement and because there were no signs of fetal hydrops at this time, the patient was only referred to our center 2 weeks later. The fetal K-positive genotype was then confirmed by amniotic fluid analysis.

When she arrived in our department, fetal ultrasonography revealed fetal hydrops with predominant ascites, subcutaneous edema, moderate pericardiac effusion, and normal amniotic fluid volume. No other morphologic abnormalities were detected. The middle cerebral artery peak systolic velocity was 96 cm/second, that is, 3.6 MoM. A reversed diastolic flow in the middle cerebral artery was also present on initial examination (Fig. 1). This pattern was persistent on repeated examinations, several minutes apart, without pressure on the fetal head.

In utero transfusion was performed the same day, revealing a fetal hemoglobin level of 1.3 g/dL. A prolonged deceleration during the transfusion reduced fetal heart rate to 80 beats per minute (bpm) for 5 minutes and required that the transfusion be stopped and then begun again later, after the heart rate returned to normal. Posttransfusion fetal hemoglobin was 11.3 g/dL. A second in utero transfusion followed a rapid rise in the middle cerebral artery peak systolic velocity at 22 weeks, without reversed diastolic flow at this time. Hemoglobin had fallen again to 5.3 g/dL, rising after transfusion to 16.4 g/dL. At 23 weeks, the ascites had totally disappeared, but fetal ultrasonography then showed bilateral symmetric cerebral ventricular dilatation, measured at 12 mm. The remaining cerebral parenchyma was clearly thinned on subsequent examinations. At 25 weeks, a third transfusion took place. Magnetic resonance imaging of the fetal brain, performed at 26 weeks, confirmed cerebral atrophy with severe ventricular dilatation and left temporal hemorrhagic porencephaly, compatible with sequelae to an anoxic episode (Fig. 2).

In view of the very poor prognosis, the pregnancy was terminated at the parents' request. A fetopathologic examination of the fetal brain confirmed the data obtained by ultrasonography and magnetic resonance imaging.



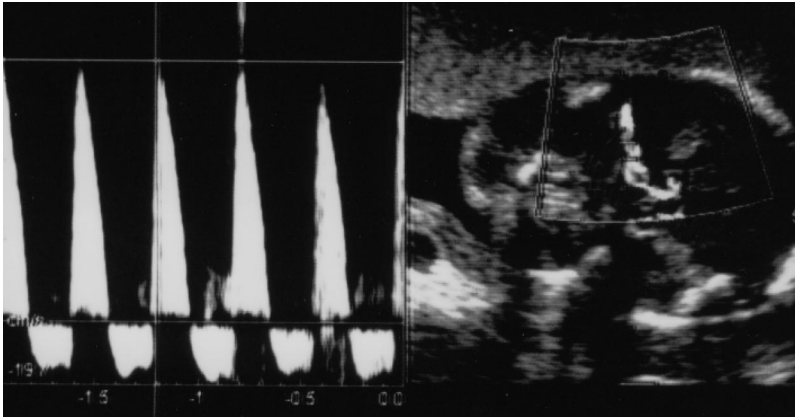


Fig. 1. Reverse flow in the middle cerebral artery before in utero transfusion. Fetal hemoglobin was 1.3 mg/dL.
Carbonne. Fetal Brain Lesions Caused by Anemia. Obstet Gynecol 2008.

CASE 2

A 31-year-old RhD-negative woman (para 4) was referred to our center at a gestational age of 25 weeks for management of severe anti-RhD alloimmunization. In 1997, she gave birth to an RhD-positive child in good health. Anti-globulin testing at delivery was negative. She did not receive a prophylactic injection of anti-RhD immunoglob-



Fig. 2. Magnetic resonance imaging of the fetal brain at 26 weeks of gestation revealing severe bilateral ventriculomegaly, a temporal porencephalic cyst (*thin arrow*), and a thinned cortical matrix (*thick arrow*).

Carbonne. Fetal Brain Lesions Caused by Anemia. Obstet Gynecol 2008.

ulin. In 1999, anti-RhD alloimmunization was diagnosed at the beginning of the second pregnancy, with antibodies stable at 2 micrograms/mL throughout the pregnancy without signs of fetal anemia. The newborn received a simple transfusion and intensive phototherapy. In 2004, the patient's third pregnancy was also normal, with stable anti-RhD antibodies. The RhD-positive child received intensive phototherapy but did not require a blood transfusion.

At the beginning of this fourth pregnancy, the anti-RhD antibody titer was 32, with a concentration of 2 micrograms/mL at 11 weeks. The detailed morphology ultrasound scan at 22 weeks found no abnormalities. Blood testing every 2 weeks was requested, but the next sample did not reach the laboratory until 4 weeks later and showed a massive reactivation, with a titer of 256 or 15 micrograms/mL.

The patient was not referred to our center until 25 weeks. Ultrasonography then showed fetal hydrops with predominant ascites and middle cerebral artery peak systolic velocity at 80 cm/second, that is 2.5 MoM. Fetal hemoglobin was 2.3 g/dL at blood sampling performed the same day and 12.1 g/dL after an uncomplicated in utero transfusion. At 26 weeks, ultrasound monitoring showed partial regression of the hydrops and cerebral ventricular dilatation of 11 mm at the posterior horn of the lateral ventricle. Two days later, the ventricular dilatation had increased to 14 mm (Fig. 3). At 27 weeks, ultrasonography showed that the hydrops had disappeared, but ventricular dilatation had increased to 18 mm with a thinned cerebral parenchyma. At the parents' request, the pregnancy was terminated. They did not agree to either a pathology examination or a fetal cerebral magnetic resonance imaging.

F3

COMMENT

In utero transfusion is the standard treatment for severe fetal anemia and results in the survival of nearly 90% of fetuses with anemia.² Several intermediate and long-term studies have followed children born after severe anemia corrected by in utero transfusion; these studies suggest neurological prognosis is



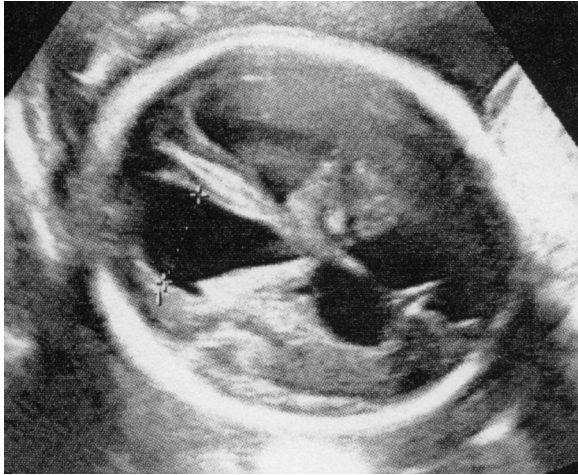


Fig. 3. Severe fetal cerebral ventricular dilatation at 27 weeks of gestation, 2 weeks after successful in utero transfusion. Fetal hemoglobin was 2.3 g/dL at the time of transfusion.

Carbonne. *Fetal Brain Lesions Caused by Anemia. Obstet Gynecol* 2008.

favorable in 92–98% of cases, even in cases of fetal hydrops.^{1–4} Among the children whose psychomotor development was described as abnormal, Janssens et al³ related three cases of cerebral motor disabilities to fetal distress during labor. Other authors describe developmental delay without identifying any clear causation. Unfortunately, none of these studies mention any pre- or postnatal imaging studies of cerebral morphology.

In the cases we present here, cerebral lesions suggestive of diffuse anoxia were observed in utero, soon after correction of anemia and despite complete regression of hydrops. The hypothesis that seems to us most likely to explain the onset of this cerebral atrophy and porencephaly is cerebral anoxia due to profound and prolonged fetal anemia (2.1 and 1.3 g/dL). In both cases, the history suggests a delayed referral before the first in utero transfusion.

Fetal cerebral anoxia may also be caused or worsened by technical difficulties during the transfusion. Dildy et al⁵ reported a case of a porencephalic cyst related to a difficult in utero transfusion. In the first case here, a prolonged deceleration occurred for 5 minutes during the first transfusion, and it could be responsible for cerebral anoxia. Nonetheless, it is probable that cerebral lesions were not yet visible on ultrasonography but predated the transfusion, in view of the reversed diastolic flow already present in the middle cerebral artery before transfusion. This observation is consistently associated with a catastrophic neurological prognosis in reported cases.^{6,7} This first

observation of cerebral reversed diastolic flow in a context of severe fetal anemia could be due to fetal brain edema. Recently, Ghi et al⁷ also reported one case of periventricular leukomalacia and one transient mild ventriculomegaly associated with marked brain edema before fetal transfusion.

Radunovic et al⁸ reported that a more than fourfold increase in hematocrit after fetal transfusion could be responsible for fetal demise in the hydropic and severely anemic fetus. The increased blood viscosity could also cause a decrease in cerebral blood flow after transfusion. However, this threshold was indicated to prevent fetal death, and little is known about nonlethal complications. In our experience of more than a hundred blood transfusions over the last 5 years, no fetal brain lesions were observed previously, even in fetuses that had a more than fourfold increase in hematocrit.

The brain injuries that we describe seem very similar to those observed in the surviving twin after death of a sibling in case of monochorionic twin gestation. Although dedicated neurosonography seems effective in identifying fetal brain injury, magnetic resonance imaging is also widely accepted in this situation.

In conclusion, severe prolonged fetal anemia with fetal hydrops can lead to anoxic cerebral lesions, even in the case of appropriate treatment by in utero transfusion. We suggest that repeated ultrasound examinations of the fetal brain should be performed after in utero transfusion for severe fetal anemia. If new-onset ventriculomegaly is observed, then anoxic lesions could be suspected and magnetic resonance imaging examination should be discussed.

REFERENCES

1. Grab D, Paulus WE, Bommer A, Buck G, Terinde R. Treatment of fetal erythroblastosis by intravascular transfusions: outcome at 6 years. *Obstet Gynecol* 1999;93:165–8.
2. van Kamp IL, Klumper FJCM, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FPHA, et al. Complications of intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. *Am J Obstet Gynecol* 2005;192:171–7.
3. Janssens HM, de Haan MJJ, van Kamp IL, Brand R, Kanhai HH, Veen S. Outcome for children treated with fetal intravascular transfusions because of severe blood group antagonism. *J Pediatr* 1997;131:373–80.
4. Harper DC, Swingle HM, Weiner CP, Bonthius DJ, Aylward GP, Widness JA. Long-term neurodevelopmental outcome and brain volume after treatment for hydrops fetalis by in utero intravascular transfusion. *Am J Obstet Gynecol* 2006;195:192–200.
5. Dildy GA 3rd, Smith LG, Moise KJ, Cano LE, Hesketh DE. Porencephalic cyst: a complication of fetal intravascular transfusion. *Am J Obstet Gynecol* 1991;165:76–8.



6. Sepulveda W, Shennan AH, Peek MJ. Reverse end-diastolic flow in the middle cerebral artery: an agonal pattern in the human fetus. *Am J Obstet Gynecol* 1996;174:1645-7.
7. Ghi T, Brondelli L, Simonazzi G, Valeri B, Santini D, Sandri F, et al. Sonographic demonstration of brain injury in fetuses with severe red blood cell alloimmunization undergoing intrauterine transfusions. *Ultrasound Obstet Gynecol* 2004; 23:428-31.
8. Radunovic N, Lockwood CJ, Alvarez M, Plecas D, Chitkara U, Berkowitz RL. The severely anemic and hydropic isoimmune fetus: changes in fetal hematocrit associated with intrauterine death. *Obstet Gynecol* 1992;79:390-3.



000 Prenatal Diagnosis of Anoxic Cerebral Lesions Caused by Profound Fetal Anemia Secondary to Maternal Red Blood Cell Alloimmunization

Profound fetal anemia may cause anoxic lesions of the fetal brain that may be diagnosed prenatally.

Bruno Carbonne, Amélie Nguyen, Evelyne Cynober, Vanina Castaigne, Anne Cortey, Yves Brossard



AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

