Clinical report

Cerebellar hemorrhage in utero associated with 'massive' fetal thrombotic vasculopathy

Mana Taweevisit

Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Background: Cerebellar hemorrhage is a rare but serious perinatal condition with various etiologies leading to fetal and neonatal death and adverse neurological complications. Complete autopsy and placental examination are essential for identification of a cause of the bleeding.
Objective: Present a case of cerebellar hemorrhage in utero associated with 'massive' fetal thrombotic vasculopathy (FTV).
Method: Autopsy of a stillborn female fetus, 26 weeks gestation, with intrauterine growth restriction, delivered by a 37-year-old woman.
Results: The fetus showed multiple recent peticheal hemorrhages along the cerebellar cortex. The placenta revealed a large thrombosed chorionic blood vessel. Microscopic findings showed multiple vascular thrombosis and massive FTV throughout the placental villi. These were recognized as two histologic patterns, 'early' stromal karryorhxis, and 'late' villous stromal involution.
Conclusion: Massive FTV was a leading cause of fetal stress due to increased resistant of downstream placental villi. This longstanding stressful environment induced auto-regulation impairment of fetal cerebral blood flow resulting in cerebellar parenchymal bleeding. Careful placental examination is beneficial for understating the mode and mechanism of fetal death.

Keywords: Cerebellar hemorrhage, fetal stroke, fetal thrombotic vasculopathy

Nowadays, accumulating medical evidences have shown that neurological complications in neonates can be attributed during fetal life, without any correlation to intrapartum events [1, 2]. Fetal stroke is the entity of brain damage due to cerebrovascular injuries whether ischemia, thrombosis, or hemorrhage in fetuses whose age are between 14 weeks of gestation and the onset of labor [3]. In addition, the condition has been proven as a leading cause of fetal demise and adverse neurological outcomes such as postnatal epilepsy, mental retardation, and cerebral palsy in the majority of cases [3]. For hemorrhagic brain injury, supratentorial hemorrhage is common whereas infratentorial, in particular, cerebellar hemorrhage is a relatively rare phenomenon. The etiologies and associated risks of intracranial hemorrhage are very variable. Underlying feto-maternal risk factors do not necessarily cause fetal stroke.

Fetal thrombotic vasculopathy (FTV) is the placental villous lesion secondary to thrombo-occlusive events of upstream chorionic or stem vessels [4]. The affected downstream villi show involution of villous stromal capillaries with formation of avascular villi [5, 6]. Moreover, placental thrombi can propagate to fetal organs such as brain, liver, and kidney as well as body extremities, leading to tissue infarction following thrombo-embolism [7, 8]. FTV has been reported to be associated with poor fetal and neonatal outcomes such as fetal growth restriction, discordant growth in twins, birth asphyxia, neurological complication, and fetal demise [5, 6]. Fetal or maternal hypercoagulability, maternal diabetes, and umbilical cord obstruction have been identified as underlying disorders in association with FTV [4, 7].

Correspondence to: Mana Taweevisit, MD, Department of Pathology, Faculty of Medicine, Chulalongkorn University, 1873 King Rama IV Street, Pathumwan, Bangkok 10330, Thailand. E-mail: dr.mana4@gmail.com

In this study, we examined a case of cerebellar hemorrhage, a rare clinical presentation of fetal stoke, in a stillborn, 26-week-gestation female fetus, whose placenta were identified as having a vascular thrombosis with 'massive' FTV. During antenatal care, the mother developed pregnancy-induced hypertension and follow-up ultrasonographic studies disclosed severe intrauterine growth restriction (IUGR). The association of cerebellar hemorrhage and FTV is discussed.

Case report

This case was a stillborn female fetus, 26 weeks of gestational age, delivered by a G1P0, 37-year-old woman who had been pregnant by intrauterine insemination (IUI). The mother attended antenatal care for seven times at a private clinic. Her blood tests included a hematocrit level of 41.8% and MCV of 90 fl. Her blood group was O$^+$. The results of serum HBsAg and Anti-HIV tests were negative as well as non-reactive VDRL test. Urinalysis was unremarkable. Chromosome analysis yielded normal 46,XX. At the gestational age of 24 weeks, she was admitted at King Chulalongkorn Memorial Hospital due to headache. Vital signs revealed a blood pressure of 170/110 mmHg, respiratory rate of 16/minute, body temperature of 37 degree Celsius and pulse rate of 78/minute. Single viable fetus with cephalic presentation was documented. No pitting edema was noted. Deep tendon reflex test was normal (2+). During admission, the patient experienced progressive headache, blurred vision, and epigastric pain. Fetal heart sound was 146/minute with regular rhythm.

The clinical diagnosis was pregnancy-induced hypertension. Fundoscopic findings showed no hypertensive retinopathy. Then, she was treated with oral methyldopa (125 mg), twice a day.

The results of basic laboratory investigation including antiphospholipid profile were within the reference ranges. No proteinuria was detected by urine examination. Fetal ultrasound revealed reverse end diastolic flow of umbilical artery with brain sparing effect. The estimate fetal weight was less than fifth percentile. These findings were compatible with severe IUGR. According to maternal history and clinical findings, the most likely cause of IUGR was maternal hypertension, pregnancy-related. Then, maternal intramuscular dexamethasone injection was started in order to enhance fetal lung maturation. However, due to the extremely low birth weight of the fetus, a poor pregnancy outcome was discussed with the couple. They accepted the prognosis. The patient's symptoms related to hypertension responded well to oral medication. At the gestational age of 26 weeks, the fetal surveillance testing disclosed pulsatile umbilical vein, indicating poor prognosis with a high possibility of death fetus in utero. Emergency cesarean section was done to remove the fetus and placenta. Unfortunately, the fetus was stillborn, weighing 600 g (normal: 739±181 g) and measuring 21 cm of crown-rump length (normal; 23.3±1.9 cm) and 28 cm of crown-heel length (normal: 32.2±2.4 cm).

Autopsy showed a female fetus with no congenital anomaly. The brain, weighing 100 g (normal: 98±37 g), showed multiple recent petechial hemorrhages of the cerebellum (**Fig. 1**).
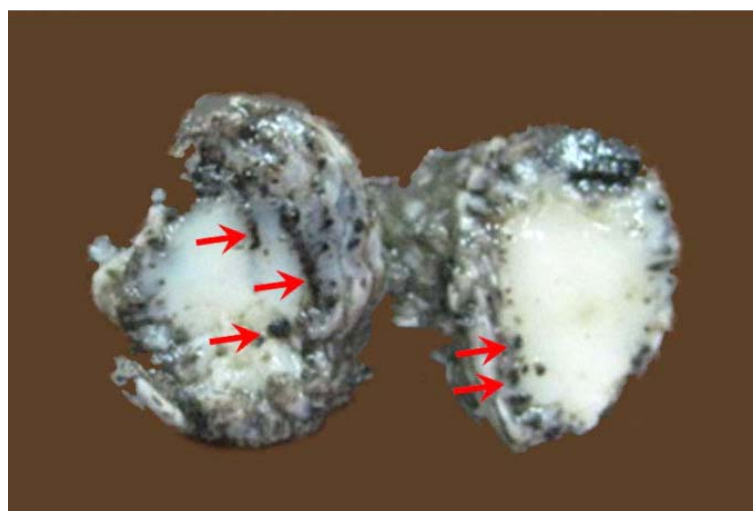

Fig. 1 Cut sections of the fetal cerebellum. Cut surfaces showed multiple dark red peticheal hemorrhages, particularly along the cortex (arrows).

Both kidneys and adrenal glands showed a few minute foci of extramedullary hematopoiesis. The placenta showed eccentrically inserted, trivessel umbilical cord. There was a large thrombosed vessel on the chorionic (fetal) surface (**Fig. 2A, B**). Serial cut sections showed multiple wedge-shaped pale areas with a base at the placental floor involving approximately 40% of the placental mass (**Fig. 2C**).

Microscopic examination of the pale areas revealed contiguous groups of avascular villi in different ages, ranging from early stromal karyorrhexis (**Fig. 3A**) to late stromal hyalinization (**Fig. 3B**). Avascular villi were also alternating with preserved placental villi containing patent stromal capillaries. The chorionic membrane revealed decidual vasculopathy characterized by dilated, tortuous spiral arterioles associated with fibrinoid material deposition of the vascular wall with foamy histiocyte infiltrates.

Discussion

Intracranial hemorrhage of fetuses during 14 weeks of gestational age to the onset of labor is one of the conditions of 'fetal stroke' [3]. Despite subclinical in utero, most affected cases are strongly associated with adverse perinatal outcomes, particularly neurodevelopmental handicap, fetal demise and neonatal death [1]. Multiple etiologies have been described including trauma, asphyxia, intrauterine infection, vascular malformation, bleeding tumor, blood dyscrasia, hypercoagulable state, cocaine usage, thrombocytopenia, and platelet dysfunction [3]. Intracranial hemorrhage in utero is rare. Moreover, the incidence of cerebellar hemorrhage is even rarer [9, 10].

Cerebellar hemorrhage in fetuses is an infrequent phenomenon. The condition is rarely diagnosed prenatally, but magnetic resonance imaging is claimed
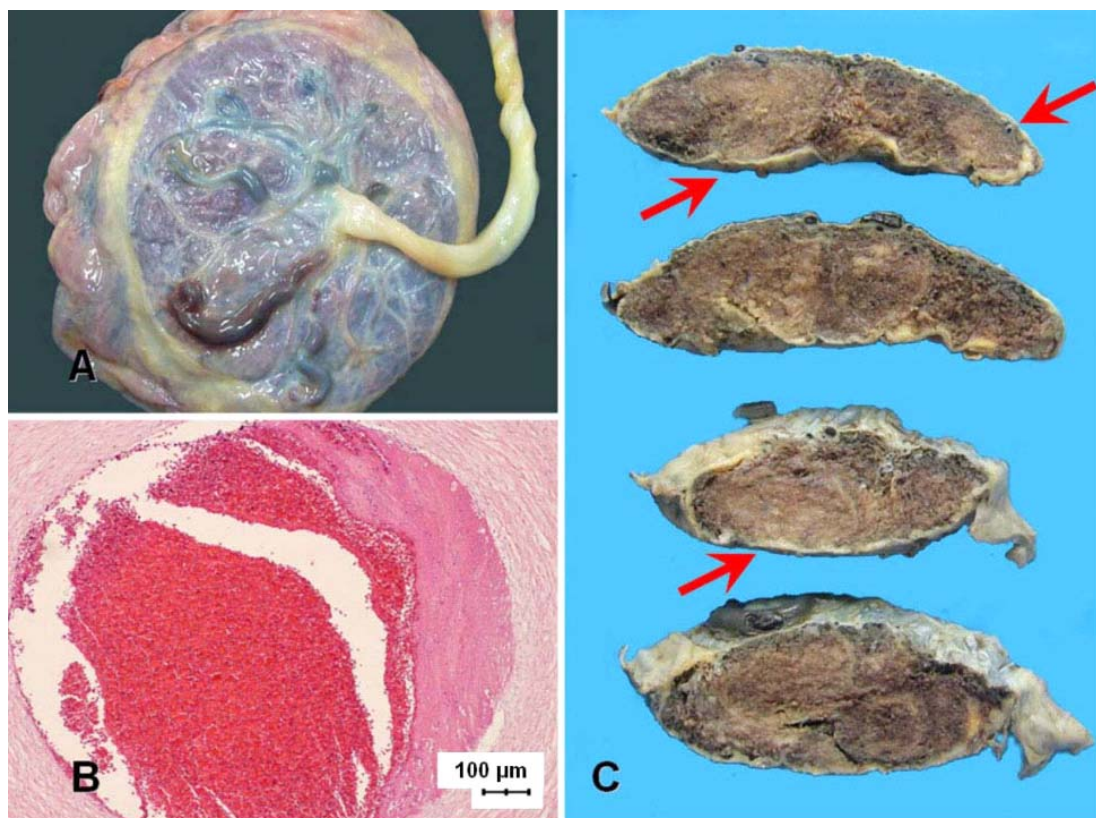

Fig. 2 Chorionic plate (fetal surface) of the placenta showing a markedly dilated, dark brown chorionic vessel due to thrombotic occlusion (**A**). Cut section of the thrombosed chorionic vessel showed laminated layers of fibrinous material attaching the vascular wall. The lumen is filled with numerous red blood cells (H&E, original magnification x40) (**B**). Cut sections of the placenta showed wedge-shaped pale areas (arrows) (**C**).
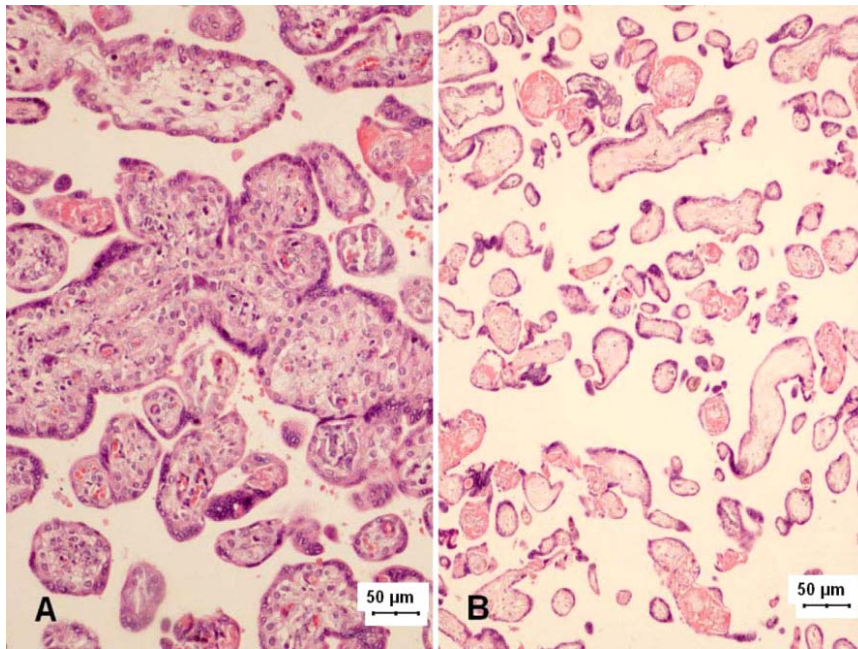
Fig. 3 Microscopic findings of fetal thrombotic vasculopathy consisting of early villous stromal karryorhexis, showing nuclear debris and small amounts of abortive blood vessels (H&E, original magnification x100) (**A**), and late villous stromal involution characterized by atrophic change associated with hyalinization of the stroma and loss of capillaries (H&E, original magnification x100) (**B**).

as an optimal tool for identification [11, 12]. Ghi et al. [10] reviewed cases of antenatally-diagnosed intracranial hemorrhage in their ultrasound unit. Ten out of 109 affected fetuses showed infratentorial hemorrhage. They identified only two cases of cerebellar hemorrhage in a 20-year period, both of which were related to anemia due to Rh alloimmunization. At our King Chulalongkorn Memorial Hospital, no cerebellar hemorrhage in utero proven by autopsy has been reported in the past 10 years. The prognosis of cerebellar hemorrhage depends on the etiology and extension of the bleeding [11]. The complications in fetuses who survived after bleeding episodes include acute bleeding compression, partial or complete loss of cerebellar mass, cystic formation, brain stem changes ranging from atrophic to absent due to previous pressure effect from adjacent hematomas, and sometimes Dandy-Walker malformation-like change, which is characterized by an absence of on vermis and fourth ventricular enlargement [9, 11, 13].

Trauma [14], post-transfusions [10, 15], cavernous hemangiomas [9], congenital cytomegalo-virus infection [16], and transformed ischemic lesions [13, 17] have been reported as causes of fetal cerebellar hemorrhage. Interestingly, hemorrhagic transformation of cerebellar ischemia (two cases documented) was strongly associated with placental thrombosis and insufficiency [13, 17].

FTV has been proven to be associated with various feto-maternal circulatory disturbances, particularly hypercoagulable state and umbilical cord abnormalities [5, 6]. The condition is related to poor pregnancy outcome, comprising IUGR, discordant growth in twins, birth asphyxia, and fetal loss. Microscopic features include villous stromal karyorrhexis and involution of villous vessels forming avascular villi reflecting early and late changes, respectively, regardless of stem vessel thrombosis, which can be demonstrated in one third of those cases [5, 6]. Massive FTV is documented when the lesion involves at least 25% of the whole placental mass suggested by Armed Forces Institute of Pathology manual [4]. In 1999, Krauss and Acheen [7] reported the association of placental thrombosis with FTV and thromboembolic phenomenon in fetal organs in 16 cases during 3-year period. Three cases showed cerebral thrombosis or infarction. FTV also complicates various degrees of neurological impairment in liveborn neonates, either preterm or term, in several studies [5, 6, 8].

In this report, the most likely etiology of cerebellar hemorrhage was stress-induced. FTV was massive enough to contribute placental vascular resistant, compatible with an ultrasonographic finding of reverse end diastolic flow of umbilical artery, leading to chronic uteroplacental insufficiency and severe IUGR [4, 18]. However, the brain-sparing effect detected in early gestation indicates the capacity of fetal auto-regulation [18]. The mechanism protects fetus during stress exposure by increased cerebral blood flow. Two weeks later, follow-up ultrasonogram showed pulsatile umbilical vein. This poor prognostic finding reflects that the fetus was not able to tolerate the stressful environment related to auto-regulation breakdown [18, 19]. In this situation, sudden changes in intracranial blood pressure can cause acute bleeding of the brain parenchyma [19-21]. The immature external granular layer of the cerebellar cortex and vascular bed may play as coexisting risk factors in this hemorrhage [21]. There has been no evidence supporting the direct association between FTV and pregnancy-induced hypertension. However, vascular thrombosis is a shared pathologic finding in both conditions [4, 6]. In this case, since thrombosis was demonstrated in both maternal (decidual vasculopathy with thrombosis) and fetal sites (chorionic vessel thrombosis with FTV), additional investigations should be done to search for the underlying feto-maternal thrombophilic disorders.

In conclusion, this rare case of stillborn, 26-week of gestational age, female fetus with cerebellar hemorrhage in association with massive FTV demonstrates the benefit of placental examination in fetal and perinatal autopsy. The findings provide necessary information to explain the appropriate mode and mechanism of death and probably use as data for counseling the mother in preparation of next pregnancies.

The author has no conflict of interest to report.

References

1. Marchetti D, Belviso M, Fulcheri E. A case of stillbirth: the importance of placental investigation in medico-legal practice. Am J Forensic Med Pathol. 2009; 30: 64-8.
2. Hadi H, Finley J, Mallette JQ, Strickland D. Prenatal diagnosis of cerebellar hemorrhage: medicolegal implications. Am J Obstet Gynecol. 1994; 170:1392-5.
3. Ozduman K, Pober BR, Barnes P, Copel JA, Ogle EA, Duncan CC, et al. Fetal stroke. Pediatr Neurol. 2004; 30:151-62.
4. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM. Fetal circulation: thrombi and hematomas. In: Redline RW. Kraus FT, Gersell DJ, Nelson DM, Dicke JM, editor. Atlas of Nontumor Pathology: Placental Pathology. American Registry of Pathology. Washington DC:Armed Forces Institute of Pathology. 2004; p. 141-51.
5. Redline RW. Clinical and pathological umbilical cord abnormalities in fetal thrombotic vasculopathy. Hum Pathol. 2004; 35:1494-8.
6. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol. 1995; 26:80-5.
7. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Hum Pathol. 1999; 30:759-69.
8. Dahms BB, Boyd T, Redline RW. Severe perinatal liver disease associated with fetal thrombotic vasculopathy. Pediatr Dev Pathol. 2002; 5:80-5.
9. Sharony R, Kidron D, Aviram R, Beyth Y, Tepper R. Prenatal diagnosis of fetal cerebellar lesions: a case report and review of the literature. Prenat Diagn. 1999; 19:1077-80.
10. Ghi T, Simonazzi G, Perolo A, Savelli L, Sandri F, Bernardi B, et al. Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. Ultrasound Obstet Gynecol. 2003; 22:121-30.
11. Hiller Lt, McGahan JP, Bijan B, Melendres G, Towner D. Sonographic detection of in utero isolated cerebellar hemorrhage. J Ultrasound Med. 2003; 22:649-52.
12. Ranzini AC, Shen-Schwarz S, Guzman ER, Fisher AJ, White M, Vintzileos AM. Prenatal sonographic appearance of hemorrhagic cerebellar infarction. J Ultrasound Med. 1998; 17:725-7.
13. Yuksel A, Batukan C. Fetal cerebellar hemorrhage in a severely growth-restricted fetus: natural history and differential diagnosis from Dandy-Walker malformation. Ultrasound Obstet Gynecol. 2003; 22:178-81.
14. Breysem L, Cossey V, Mussen E, Demaerel P, Van de Voorde W, Smet M. Fetal trauma: brain imaging in four neonates. Eur Radiol. 2004; 14:1609-14.
15. Glenn OA, Cossey V, Mussen E, Demaerel P, Van de Voorde W, Smet M. Fetal cerebellar hemorrhage in parvovirus-associated non-immune hydrops fetalis. J Matern Fetal Neonatal Med. 2007; 20:769-72.
16. Ortiz JU, Ostermayer E, Fischer T, Kuschel B, Rudelius M, Schneider KT. Severe fetal cytomegalovirus infection associated with cerebellar hemorrhage.

Ultrasound Obstet Gynecol. 2004; 23:402-6.

17. Malinger G, Zahalka N, Kidron D, Ben-Sira L, Lev D, Lerman-Sagie T. Fatal outcome following foetal cerebellar haemorrhage associated with placental thrombosis. Eur J Paediatr Neurol. 2006; 10:93-6.

18. Takahashi Y, Kawabata I, Tamaya T. Characterization of growth-restricted fetuses with breakdown of the brain-sparing effect diagnosed by spectral Doppler. J Matern Fetal Med. 2001; 10:122-6.

19. Dubiel M, Breborowicz GH, Gudmundsson S, Evaluation of fetal circulation redistribution in pregnancies with absent or reversed diastolic flow in the umbilical artery. Early Hum Dev. 2003; 71:149-56.

20. Baschat AA, Gembruch U, Viscardi RM, Gortner L, Harman CR. Antenatal prediction of intraventricular hemorrhage in fetal growth restriction: what is the role of Doppler? Ultrasound Obstet Gynecol. 2002 19: 334-9.

21. Rorke-Adams L, Larroche JC, de Vries L. Fetal and neonatal brain damage. In: Gilbert-Barness E, Kapur RP, Oligny LL, Siebert JR, editors. Potter's Pathology of the Fetus, Infant and Child. Philadelphia:Mosby Elsevier. 2007; p. 2027-58.