Fetal intracerebral hemorrhage and *COL4A1* mutation: promise and uncertainty

The first prenatal diagnosis of fetal intracranial hemorrhage (ICH) associated with *COL4A1* gene mutation was reported recently[1]. Through an additional prenatal case, we would like to highlight several issues surrounding parental counseling and obstetric management that are raised by this diagnosis.

A 29-year-old patient was referred to our center at 25 weeks' gestation following detection on ultrasound of bilateral ventriculomegaly. Targeted neurosonography at 27 weeks' gestation showed enlarged lateral ventricles with hyperechogenic walls and intraventricular blood clots. There was no relevant family history and the patient did not report any abdominal trauma during the pregnancy. Screening for TORCH and alloimmune thrombocytopenia was negative. Recent maternal cytomegalovirus infection was also excluded. A follow-up ultrasound scan at 28 weeks showed bilateral ventricular dilatation and hemorrhage, with massive right hemorrhage involving the subependymal area and the ventricle, and extending to the adjacent basal ganglia and parietal parenchyma (Figure 1). Magnetic resonance imaging confirmed the ultrasound findings. The hemorrhage appeared T1 hyperintense, slightly T2 hyperintense and markedly hypointense on T2*-weighted imaging (Figure 2). The parents were informed of the poor neurological prognosis and elected to terminate the pregnancy at 30 weeks' gestation. There was no fetal thrombocytopenia at cordocentesis. Postmortem examination confirmed grade IV extensive ICH with the particular association of hemorrhagic lesions of different ages. Hemorrhages were also found in other organs (thymus, liver and adrenal glands).

Following termination, fetal genomic DNA was amplified by polymerase chain reaction with 42 sets of primers to investigate the 52 exons and intron–exon boundaries of the *COL4A1* gene, based on its reference sequence. A previously unreported G188E mutation of exon 10 in the *COL4A1* gene was found. The parents were informed of this result and elected to undergo genetic testing. The mother was found to carry the same *COL4A1* mutation. An ophthalmological examination revealed that she had retinal arterial tortuosity.

During the patient's subsequent pregnancy, the implications of genetic prenatal testing were discussed, including the possibility of an elective Cesarean section in case of an affected fetus. The parents opted for prenatal diagnosis. Amniocentesis was performed at 16 weeks' gestation and the fetus was found to carry the same mutation. The pregnancy was uneventful and serial fetal cerebral ultrasonographic examinations were normal. A 3350-g girl was delivered by elective Cesarean section at 39 weeks. At the time of writing the child was 9 months old with normal development.

Our case confirms that a *COL4A1* mutation should be considered in cases of ICH when no other identifiable causes are found[2]. Together with COL4A2, COL4A1 is an important component of the Type IV collagen in basement membranes, including the vascular basement membrane[3]. Gould *et al.*[4] reported that in both mice and humans a mutation in the *COL4A1* gene predisposes both newborns and adults to ICH owing to the increased fragility of the brain vessels. Recently, several cases of young patients presenting with either recent ICH or porencephalic lesions have been reported[5,6]. These lesions were sequelae of previous ICH and were related to a *COL4A1* mutation. Therefore *COL4A1* gene mutation appears to play a role in a substantial proportion of young patients with ICH, and it is likely that this mutation accounts for some cases of ICH observed in fetuses.

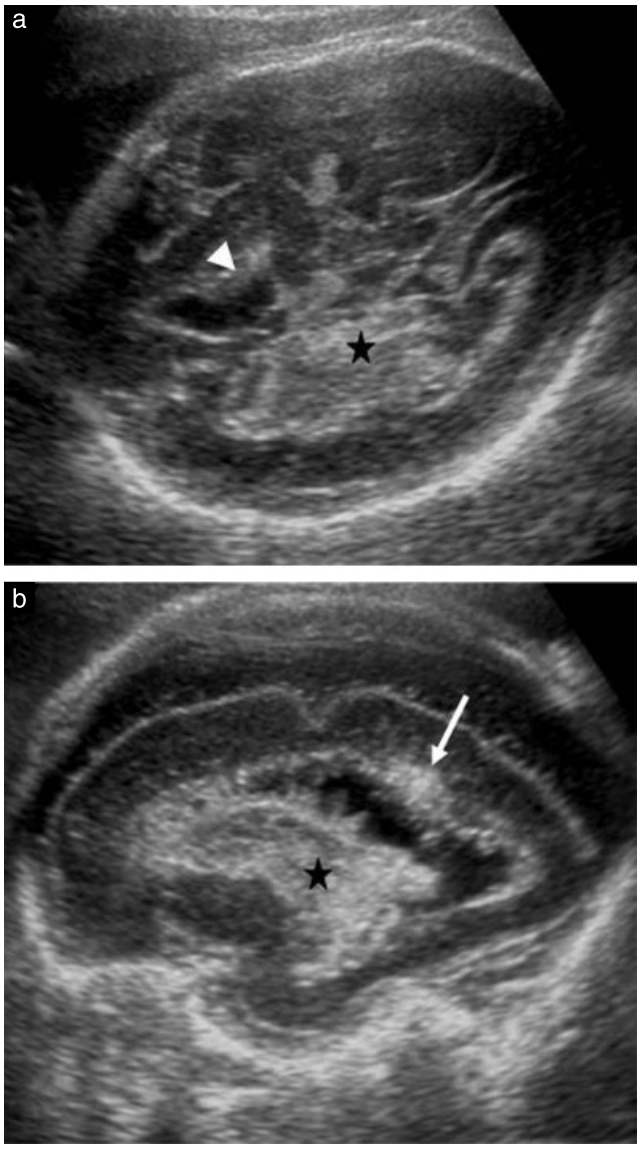

Figure 1 Ultrasound images of fetal intracranial hemorrhage at 28 weeks' gestation demonstrating enlarged lateral ventricles with intraventricular hemorrhage and hyperechoic and irregular ventricular borders. (a) Axial view, showing involvement of left subependymal area (arrowhead) and hemorrhage (star) in the right ventricle and adjacent thalamus. (b) Right parasagittal view, showing massive hemorrhage (star) involving the thalamus and extending to the adjacent parietal parenchyma (arrow) with ependymal rupture.

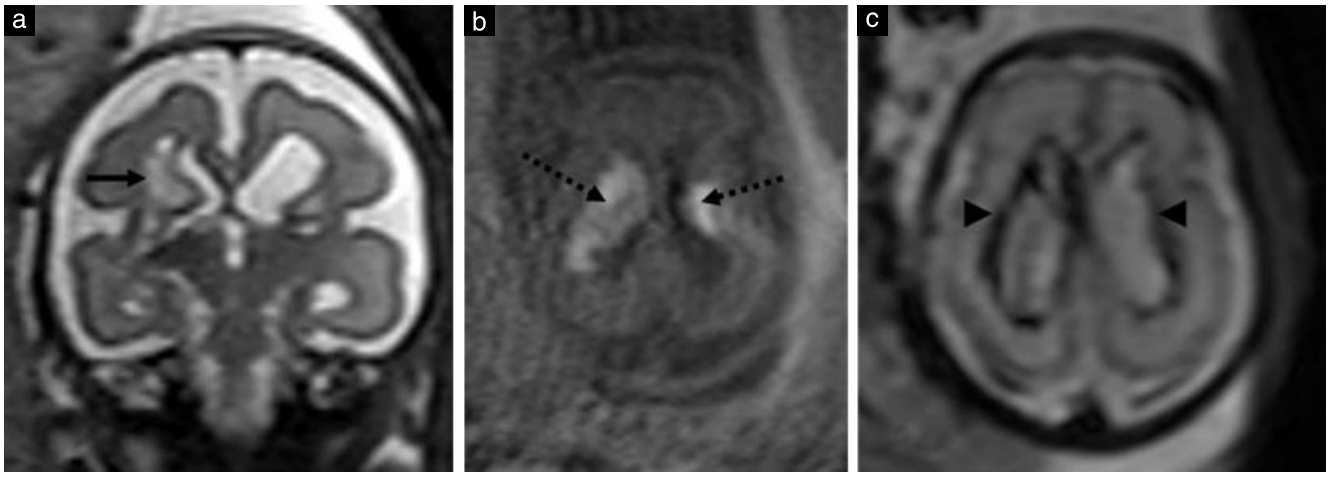

Figure 2 Magnetic resonance images of fetal intracranial hemorrhage at 28 weeks' gestation, showing enlarged lateral ventricles and pericerebral spaces. (a) T2-weighted coronal image demonstrating slight hyperintensity (arrow) in right intraventricular and parenchymal hemorrhage. (b,c) Axial images showing that bilateral intraventricular hemorrhage is hyperintense (dotted arrows) on T1-weighted imaging (b) and markedly hypointense (arrowheads) on T2*-weighted imaging (c).

Prenatal identification of this autosomal dominant genetic disease raises important issues regarding parental information (i.e. identification of the carrier and his or her own risk for stroke), genetic counseling for future pregnancies, management of delivery of an affected fetus and the provision of information for the rest of the family if the mutation is inherited from one of the parents. Indeed, identification of *COL4A1* mutation during the prenatal period raises both ethical and medical questions. First, the parents should be informed that one of them is likely to carry the same mutation (excluding *de novo* mutation). Parental consent for this predictive genetic testing requires complete and clear information. Owing to the absence of a consistent correlation between genotype and phenotype, as for the mutation found in our case, and the wide range of clinical expression of this disease, possible psychological consequences of being diagnosed with this mutation need to be anticipated. Adult carriers may be asymptomatic or present with a variable phenotype including neurological features such as migraine, epilepsy, stroke or hemiparesis[6,7]. Systemic features including ocular, renal and muscular involvement may also be observed[6,7]. Secondly, the legitimacy of a genetic prenatal diagnosis for future pregnancies is questionable, given the wide phenotypic spectrum. Besides the difficulty in predicting the long-term outcome of a fetus that carries a *COL4A1* mutation, the risk of ICH in case of vaginal delivery needs to be taken into account. Gould *et al.*[4] reported on a mouse model with a *COL4A1* mutation. They showed that cerebral hemorrhage occurred in all 20 mutated mice pups after normal delivery, whereas none of the 26 surgically delivered mutated pups had a severe cerebral hemorrhage. Nevertheless, we agree with others that Cesarean delivery would not be sufficient to prevent the occurrence of ICH in this situation[6]. However, one could readily expect that this risk would be greater in cases of vaginal delivery. In addition, the question of a possible increased risk for maternal ICH during expulsive efforts at the time of delivery must also be taken into account when the mother carries the mutation.

Recent identification of *COL4A1* mutation as an etiology for fetal ICH has uncovered issues in both genetic counseling and obstetric management. Moreover, in cases of ICH diagnosed in the neonatal period, one should consider the possibility of a *COL4A1* mutation before automatically attributing it to obstetric trauma. We hope that the reporting of further cases will increase our knowledge of the natural history of perinatal cerebral *COL4A1*-related lesions.

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Voiding dysfunction related to a vaginal hematoma after a Perigee™ procedure

About 0.9–7.8% of women develop voiding dysfunction following transobturator vaginal mesh (TVM) procedures[1–4]. Reported contributing factors include preoperative obstructive voiding or concomitant surgery[4]. We report a case of voiding dysfunction caused by a vaginal hematoma after a Perigee™ (American Medical Systems, Minnetonka, MN, USA) procedure, successfully managed with the help of ultrasonography.

A 61-year-old woman, para 3, developed an inability to micturate and high post-void residuals upon removal of a transurethral catheter 2 days after uncomplicated pelvic reconstructive surgery consisting of total vaginal hysterectomy, Perigee procedure, posterior colporrhaphy and intraoperative cystourethroscopy for symptomatic pelvic organ prolapse. The patient's vital signs were stable. Pelvic examination and urinalysis yielded unremarkable findings. However, urination problems persisted after a 3-day voiding trial. Transvaginal ultrasound (TVS) revealed a distorted urethra and cranioventral displacement of the proximal urethra and lower urinary bladder. Following replacement of the transurethral catheter, TVS revealed an anterior vaginal hematoma, 5.7×4.8 cm in size and located between the catheterized urethra and the mesh. The mesh was dorsally deviated in a zigzag shape. Doppler angiography did not reveal a pelvic hematoma or abscess. A serial hemogram showed a decreasing hemoglobin level, from 14.4 g/dL preoperatively to 12.0 g/dL and then 10.2 g/dL on days 1 and 5 postsurgery, respectively. Given the situation of an uncomplicated vaginal hematoma with stable hemodynamic conditions, the patient was managed conservatively with serial ultrasound examinations.

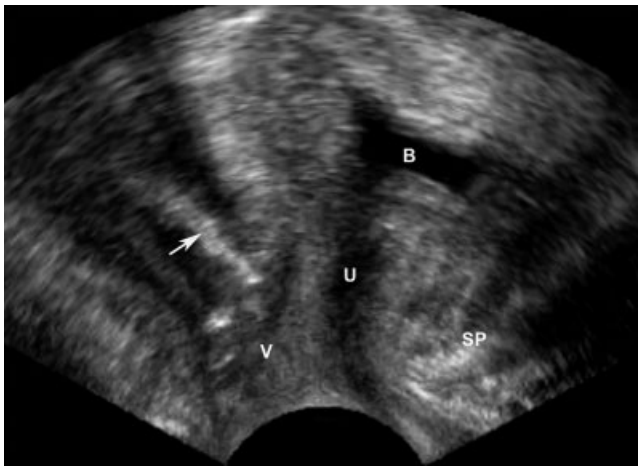

Figure 1 Transvaginal ultrasound image in a case of voiding dysfunction, showing a linear-shaped mesh (arrow) located underneath the bladder (B) and proximal urethra (U). SP, symphysis pubis; V, vagina.

On day 9 following surgery, the patient experienced unexpected vaginal bleeding. Pelvic examination identified a disrupted vaginal wound with expulsion of blood clots. TVS revealed an almost completely evacuated vaginal hematoma, a linear mesh located beneath the bladder and proximal urethra, and normal configurations of the urethra and lower bladder (Figure 1). The patient resumed normal voiding with a hemoglobin level of 10.1 g/dL, and was discharged on day 10 after surgery. At follow-up assessments on days 13 and 30 postsurgery, the patient continued to have normal voiding and the vaginal wound appeared to be well healed. TVS exhibited a properly located mesh without vaginal hematoma.

Hemorrhagic complications after Perigee procedures are rare[1,2]. The vulnerable vessels during the passage of TVM needles include the median branch of the obturator vessels and the accessory pudendal artery[5–7]. Treatment includes conservative management[5], interventional radiology with embolization[8] or surgery[5]. In this case, the hemorrhage was self limiting and uncomplicated without compromising the patient's vital signs or leading to secondary infection. Conservative treatment may allow hemostasis through external compression by the vaginal hematoma on the damaged vessels. Under such treatment, close monitoring of the patient's clinical condition, including vital signs and extent of hemorrhage and hemoglobin levels, is mandatory.

The use of ultrasound is valuable in assessing surgical outcomes after TVM procedures[3,9]. In the present patient, ultrasound identified a vaginal hematoma that compressed and distorted the lower urinary tract as the probable etiology for voiding dysfunction. Urethral distortion has been shown to be related to voiding dysfunction after suburethral tape placement[10]. Ultrasound is advantageous not only in initial evaluation but also in formulating and adjusting the management strategy in such cases.

In conclusion, vaginal hematoma should be considered as one of the differential diagnoses in patients presenting with voiding dysfunction after TVM procedures.