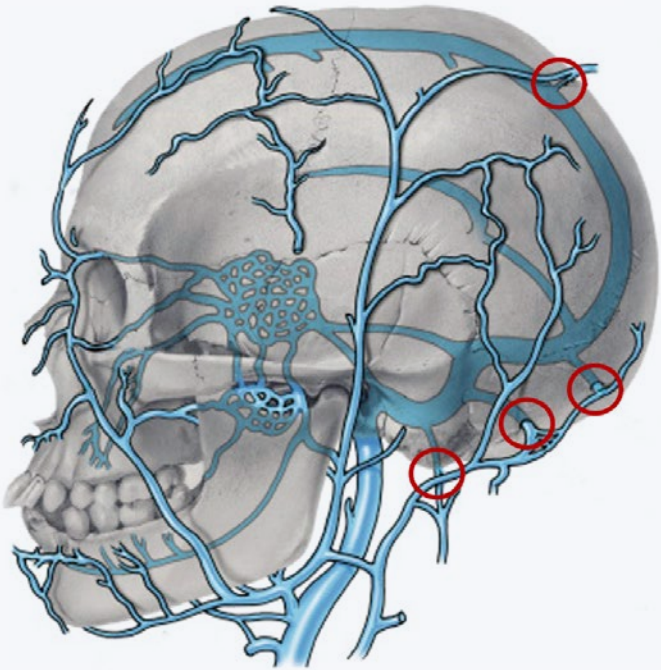
SWISS SOCIETY OF NEONATOLOGY

Sometimes,

it really is a zebra!



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Title figure:
Emissary veins (source: adapted from ScienceDirect.com)

We present the case of a male infant who was born at 40 5/7 weeks of gestation to a 34 year-old G2/P1. The baby was delivered by Cesarean section after two failed vacuum extraction attempts. He adapted well with Apgar scores of 9, 10 and 10 at 1, 5 and 10 minutes, respectively, and umbilical cord pH values of 7.21 and 7.29. Birth weight was 3960 g (P50 – 75), length 52 cm (P50 – 90), and head circumference (HC) 35 cm (P50 – 90).

Following examination by a pediatric resident, he was transferred to the obstetrical intermediate care unit for maternal reasons. During the first hours of life, the parents reported that their child was irritable with signs of pain and discomfort, but the infant was not reevaluated. At 30 hours of life, the infant was assessed by a midwife and found to be uncomfortable and pale, with a 4 cm increase in his HC.

At that time, the Neonatal Intensive Care Unit (NICU) resident was called. The newborn was extremely pale, irritable and in apparent pain. The physical exam revealed a vacuum extraction mark and a marked, hard and pitting edema over the skull, and protruding ears (Fig. 1). There was no fluctuating mass. SpO_2 was 100 % in room air, the heart rate was 135 bpm and blood pressure was 66/32 mmHg (mean 43 mmHg). The blood gas analysis showed severe metabolic acidosis with a pH of 6.84 and a lactate of 23 mmol/l; in addition, there was severe anemia with a hemoglobin concentration of 46 g/l.

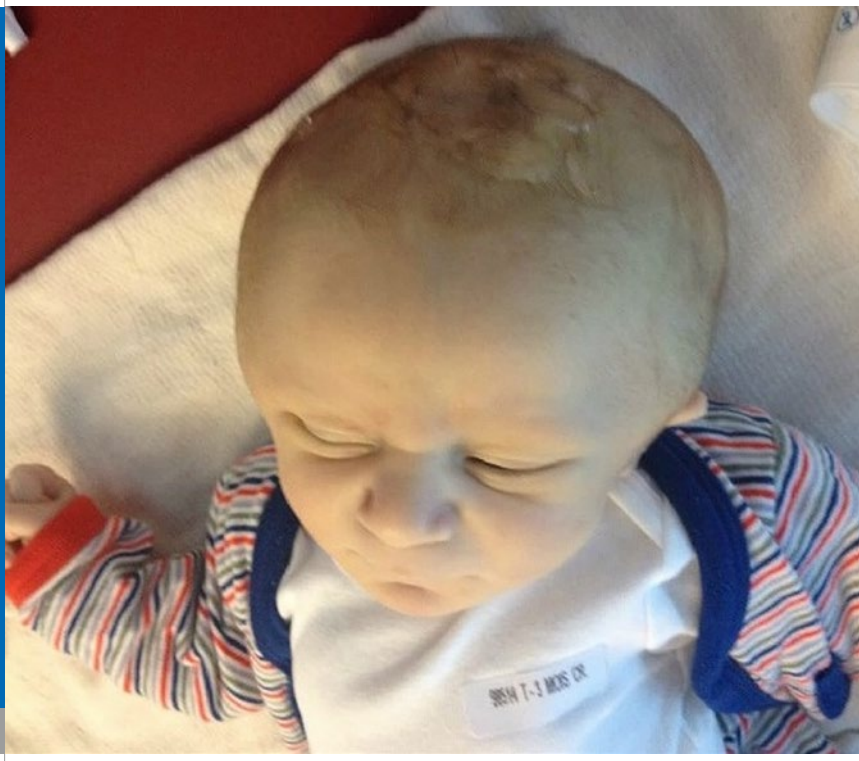

Fig. 1

Clinical presentation when first evaluated by the NICU resident.

The newborn was immediately transferred to the NICU, where he required resuscitation with bag-mask ventilation before emergency intubation. An umbilical venous catheter was inserted and 30 ml/kg of O negative red blood cells were immediately transfused, as well as fresh frozen plasma and fibrinogen concentrate. Calcium gluconate and sodium bicarbonate were also administered. During resuscitation, he was not actively warmed and therapeutic hypothermia (34°C) was induced.

Blood coagulation studies showed a prothrombin time (PT) of 35 %, an activated partial thromboplastin time (aPTT) of >160 sec, and fibrinogen level of 1.2 g/l. A head ultrasound, performed to exclude intracranial hemorrhage, showed diffuse echogenic changes in the extracranial soft tissues, without a definitive diagnosis. An emergency head CT scan suggested a subgaleal hemorrhage (Fig. 2).

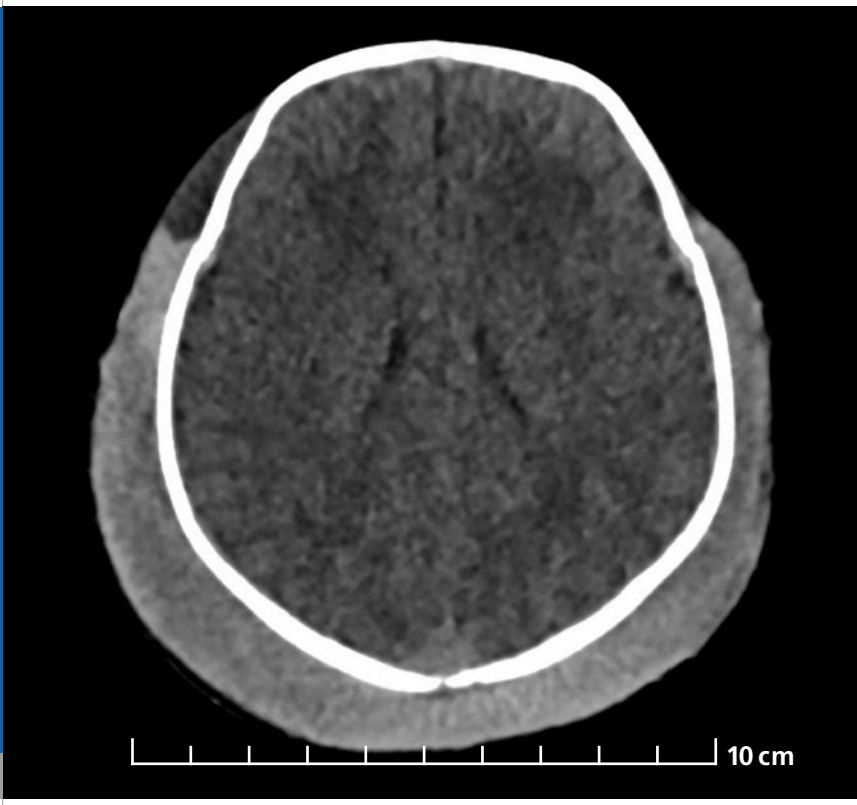

Fig. 2

CT scan: extensive subgaleal hemorrhage.

While in hypothermia, without analgesia nor sedation, the newborn's neurological status was grossly abnormal, with a Sarnat score fluctuating between 2 and 3, axial and peripheral hypotonia, absence of spontaneous movements, weak grasping and no suction reflex. Abnormal movements were also present, but the EEG was impossible to interpret due to the thick oedema around the skull.

Hypothermia was discontinued after 72 hours, and the infant was gradually rewarmed. The neurological status progressively normalized. Cerebral magnetic resonance imaging performed on day 4 of life was normal without evidence of ischemic lesions (Fig. 3, 4).

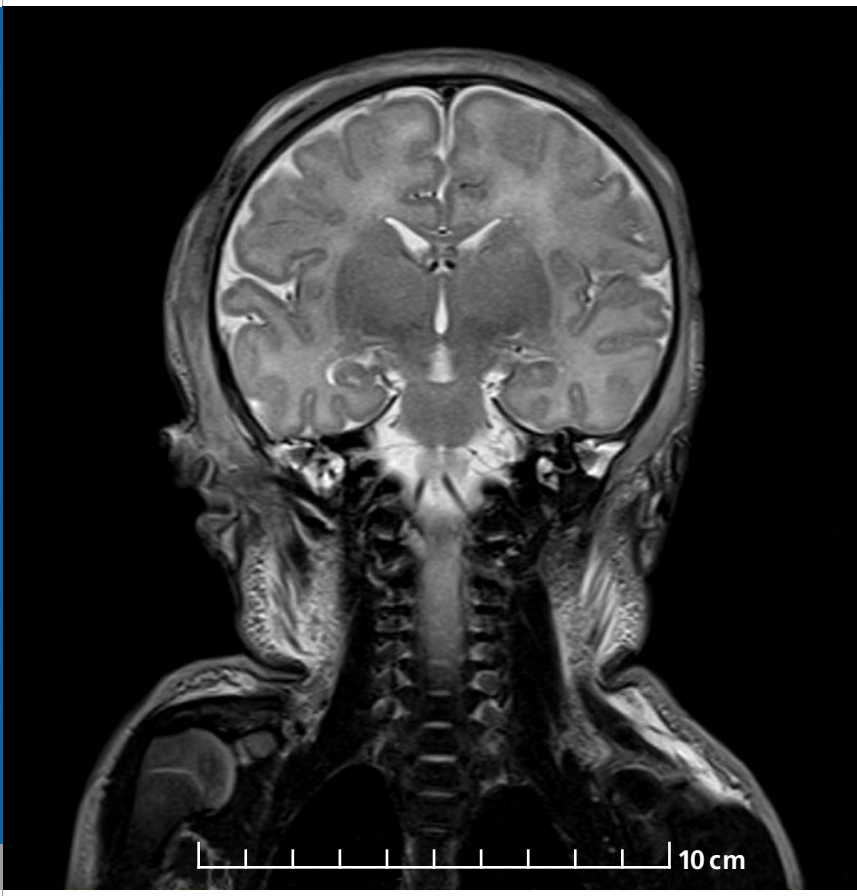

Fig. 3

MRI (T2-weighted image, coronal view): extensive subgaleal hemorrhage without signs of cerebral ischemia.

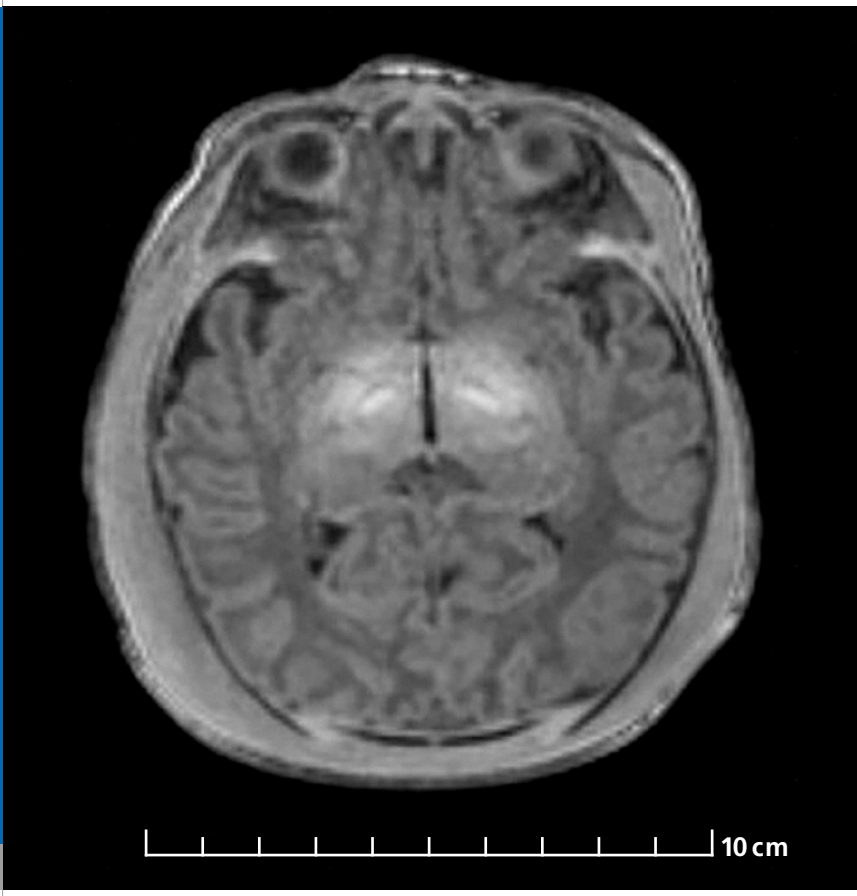

Fig. 4

MRI (T1-weighted image, axial view):
extensive subgaleal hemorrhage without intracranial abnormalities.

However, despite normalized temperature, coagulation tests remained abnormal, with the PTT increasing progressive ly to 127 seconds on the fifth day of life. Specific coagulation factors were then measured. As factor VIII activity was less than 1%, a diagnosis of severe hemophilia A was made. There was no family history of hemophilia. However, a heterozygotic mutation of the F8 gene, responsible for factor VIII production was later found in the mother.

DISCUSSION

Subgaleal hemorrhage (SGH) is a rare and potentially life-threatening event that is often under-recognized and under-diagnosed (1). It results from the rupture of emissary veins between the scalp and dural sinuses due to scalp traction during delivery (2, 3). Its general incidence is 0.2 – 3 per 1'000 live births (4, 5), and 6 to 41 per 1'000 live births after instrumental delivery (6).

The scalp consists of five distinct layers: skin, dense connective tissue, galea aponeurotica or epicranial aponeurosis, loose connective tissue and dense periosteum (2). The subgaleal space is immediately superior to the periosteum and below the tough fibrous sheath of the galea: it extends without any anatomical limits across the cranial vault from the frontalis muscle and the orbital ridges to the posterior nuchal lines and laterally to the temporalis muscle at the level of the ears. The emissary veins cross the loose connective tissue of the subgaleal space, providing drainage of the superficial veins of the scalp into the intradural venous sinuses. Due to the lack of anatomical limits, a lesion in this region can cause blood loss from 50 ml to up to 260 ml into the subgaleal space (4). This might represent 20 – 40 % of a term neonate's blood volume, with a considerable risk of hemorragic shock and death (3, 4).

The reported mortality of SGH varies from 12 to 25 % (5 – 8). Newborns who die from severe SGH usually have massive intravascular volume loss, associated

with signs of shock and acquired coagulopathy (4). Extracranial compression may be another mechanism that can jeopardize survival, by elevating intracranial pressures (3).

The main risk factor for SGH is instrumental delivery, in particular vacuum extraction (VE) more than forceps, although SGH can also occur after spontaneous delivery. Over the past three decades, increasing use of vacuum extraction to assist birth has resulted in an increased incidence of SGH in the developed world (2). Up to 5 – 10 % of all deliveries are estimated to be performed by vacuum extraction (9). Elements that may increase the risk of SGH are the type and size of the vacuum cup, location and duration of its application, the level of negative pressure, and the direction of traction. The experience of the operator is also considered an important element (6). The risk of SGH is further increased after failed vacuum extraction, for which the main risk factors are occipito-posterior position of the foetus, high birth weight, short maternal stature, induction of labor and epidural analgesia (6). SGH can also occur after spontaneous delivery; in these situations, the main risk factors are primiparous mother, prolonged second stage, male gender, dystocia, and precipitous labor (6).

Early recognition and aggressive treatment of SGH are crucial as delayed diagnosis is associated with worse outcomes (6). The differential diagnosis between

caput succedaneum, cephalhematoma and subgaleal hemorrhage might be challenging for those with less experience. Referral to a hospital with a NICU may be necessary, but this might worsen the prognosis, as the transfer itself is perilious (6).

Diagnosis is mostly clinical. Chang et al. found in their series that patients with early increase in head circumference had a better outcome, as the diagnosis was made earlier, usually because of abnormal vital signs (6). If in doubt, hemoglobin level should be measured as soon as possible (10), keeping in mind that it takes time for hemoglobin to drop, as the initial bleeding event caused a loss of both hemoglobin and volume. Therefore, a low hemoglobin is the result of hemodilution, which takes time (extravascular to intravascular shift, decreased urine output) (8, 11). Head circumference, blood pressure and heart rate should be closely monitored as initial signs may be insidious and treatment should not be delayed. Once signs of shock appear, the patient can worsen rapidly (10, 12).

Therapy includes management of hypovolemic shock with volume, ideally with red blood cells and fresh frozen plasma to correct coagulation abnormalities. Some authors have suggested a tight wrap of the head to prevent blood accumulation in the subgaleal space (13), but this is difficult to apply and its efficacy has not been proven. It may even be harmful, as this procedure might increase intracranial pressure and

decrease cerebral perfusion (6). Some authors have reported favorable outcomes after drainage with a Jackson Pratt drain to relieve extracranial pressure (8).

The usual onset of symptoms is within the first hour after birth, but some have reported up to 4 days of life in less severe cases (8). For these reasons, close surveillance is advisable after instrumental delivery. In doubtful cases, admission to the NICU for close surveillance is appropriate (2).

Coagulation disorders in the newborn can cause atypical and more severe manifestations of traumatic birth complications. Most hemorrhagic manifestations observed in the newborn are caused by acquired disorders, but inherited coagulation disorders, such as hemophilia, can also present in the neonatal period. Classically, the former occurs in a sick neonate, the latter presents with abnormal bleeding in an otherwise healthy term newborn.

Hemophilia is an inherited X-linked coagulation disorder, whose gene is located at the tip of the long arm of chromosome X (14). Depending on the deficiency of factor VIII or IX, it can be classified as hemophilia A or B, respectively. It is the most common hereditary coagulation disorder to present during the neonatal period. In two thirds of the cases, there is a positive family history, while the others are due to sporadic mutations in the gene for factor VIII. The

severity of hemophilia can be classified according to the plasma factor activity: severe (<1 %), moderate (1 to 5 %), or mild (>5 to 40 %).

Hemophilia A is the most common type, as it accounts for about 85 % of the cases, with an incidence of 1 per 5'000 male births; hemophilia B is less frequent (1 per 20'000 males) (14). In 1966, only 10 % were diagnosed in the neonatal period, but this proportion increased over time: in the nineties, the proportion of neonatal diagnoses was between 38 % and 54 % (17, 18), usually based on a bleeding event. In 2016, Jaffray reported that almost 70 % of affected children were diagnosed in the first month of life (19).

Clinical suspicion of hemophilia is usually made following an unexpected bleeding event with an isolated prolonged activated partial thromboplastin time (aPTT) in a male infant (20). The diagnosis is confirmed by a decreased level of factor VIII (hemophilia A) or IX (hemophilia B) activity, while other coagulation factors, including von Willebrand factor, are normal. As factors VIII and IX do not cross the placenta, laboratory diagnosis of hemophilia is possible at birth, even for children of hemophilia-carrier mothers. Clotting factor assays should be performed in cord blood (from a vein on the fetal side of the placenta) in all newborn males of known hemophilia-carrier mothers. When cord blood is not available, this test

should be performed on a peripheral blood sample (21).

Evaluating coagulation disorders in the newborn is particularly challenging because physiologic levels of coagulation factors in the neonatal period are lower than adult values, except for factors V, VII, and XIII (22). By 6 months of age, all coagulation factors reach the normal adult range (14). Therefore, results must be interpreted with caution (19). Newborns have slightly prolonged PT (mean 13.0 seconds; range 10.1 – 15.9 seconds) because of physiologically low levels of vitamin K-dependent clotting factors (Factor II, VII, IX and X) and also prolonged aPTT (mean 42.9 seconds; range 31.3 – 54.5 s) due to low levels of contact factors (Factor XI and XII) (21).

The severity of the coagulation disorder depends on the factor's activity level, and correlates with the clinical outcomes. The severity of hemophilia A can be diagnosed at birth, as factor VIII does not cross the placenta. In addition, levels of factor VIII at birth in term and preterm infants are similar to adult values (50 – 150 IU/dl). In contrast, hemophilia B, particularly mild forms, may be difficult to exclude in newborns. Plasma levels of factor IX are physiologically at only 15 – 50 % of adult values, ranging between 15 and 81 IU/ml, with a mean of 51 – 53 IU/ml and may even be lower in preterm infants (19). Factor IX usually reaches adult values by 3 months of age (21).

In the presence of a positive family history, prenatal diagnosis is possible (21). Fetal sex determination, which can be performed by maternal blood testing aroud 10 weeks of gestation or by fetal ultrasound between 18 and 20 weeks, is part of prenatal diagnosis as it can help the management of pregnancy and delivery. Chorionic villus sampling performed at 11 – 13 weeks of gestation is the most widely used method to determine if a male fetus is affected by hemophilia (21). In the second trimester, two diagnostic methods are available: around 16 weeks, DNA analysis can be performed on amniotic fluid and around 18 – 20 weeks cordocentesis may allow analysis of fetal blood blood (21, 24). Finally, to avoid the risk of first trimester miscarriage due to prenatal diagnosis, third trimester amniocentesis is an option, carrying about a 1 % risk of early delivery (24).

Pattern of bleeding in newborns is different than in older children with hemophilia, where muscle and joint bleedings are the typical manifestations (as soon as they move, stand and walk). In neonates, the main sources of bleeding is 'iatrogenic': e.g venipuncture, intramuscular vitamin K administration or heel sticks (23). Postoperative bleeding after circumcision is common in the United States, where this procedure is highly prevalent and performed early in the neonatal period. Umbilical stump bleeding, a frequent manifestation in fibrinogen and factor XIII deficiencies, is rare in hemophilia. Gastrointestinal bleeding can

be serious but it is infrequent (< 5 % of cases) (15, 21).

The most severe hemophilia complications in newborns are intracranial hemorrhage (ICH) and extracranial hemorrhage (ECH), including SGH and cephalohematoma. The latter are usually related to birth trauma and may occur irrespective of the mode of delivery. Although ICH has been reported in 1 – 4 % of hemophilic newborns (16), the precise incidence is unknown due to underreporting, misdiagnosis and lack of cohort studies.

In Kulkarni and Lusher's review published in 1999 (20), the clinical presentation of ICH and ECH was often non-specific and subtle, similar to neonatal meningitis, sepsis or disseminated intravascular coagulation. In both ICH and ECH, common signs included anemia, lethargy, hypotension and shock. Signs of ICH can be more specific with seizures, bulging fontanel and alteration of the neurological status. The reported cumulative incidence of ICH and SGH in newborns with hemophilia A or B was 3.6 %, and the mean age at diagnosis was 4.5 days (29). More recent studies are consistent with these data and show a cumulative incidence of ICH and ECH of 3.5 – 5 % (25). ICH, and in particular subdural hemorrhage, are reported more commonly than ECH (21). Some studies suggested that the risk of symptomatic intracranial hemorrhage was 44 times higher in newborns with hemophilia (25).

While ECH has clearly been associated with vacuum extraction, this association was not unequivocally reported for ICH (24). In 11 out of 27 patients with hemophilia and ICH, bleeding was diagnosed at birth (26). The precise anatomical location of the ICH remains often unspecified in publications (21).

For suspected or confirmed cases, optimal perinatal management should reduce the risk of both neonatal and maternal bleeding and implies delivery in a perinatal centre with hematologic expertise (24). Instrumental delivery should be avoided. The role of elective Cesarean section is still controversial, as some studies have reported improved outcomes (27), whereas others have not. In one study of 87 patients, the overall hemorrhagic risk was 10 % for vaginal delivery, 64 % for vacuum extraction and 23 % for Cesarean section (28). Optimal management of breech presentation at term in infants with hemophilia still remains unclear due to lack of data (24). While the ideal mode of delivery remains unclear (29, 30), some precautions seem reasonable: vacuum extraction, rotational and mid cavity forceps should be circumvented (24). Blood samples should not be taken from the fetal scalp, and any other action that could lead to bleeding, including intramuscular injection of vitamin K, should be avoided (15).

CONCLUSION

In conclusion, hemophilia A explained the subacute but massive SGH in our patient. Most likely, small vessel injuries continued to bleed slowly due to inappropriate clotting, leading to progressive hypovolemic shock. Our patient had a rare presentation of a rare pathology, but unusual diagnoses should be kept in mind. Sometimes, it really is a zebra.

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