CASE STUDY

Lessons from a neonate with unusual bleeding

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Healthy, term neonates rarely encounter problems with bleeding, despite physiological differences in their levels of clotting factors, reflected in prolongation of the prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT). Their risk of bleeding, however, is significantly increased by the presence of a severe congenital bleeding disorder. Establishing such a diagnosis can present a particular challenge, given the rarity of these conditions and the difficulty in performing and interpreting laboratory assays in this age group. However, a delay in diagnosis and implementation of appropriate treatment can result in catastrophic sequelae. Therefore, the presentation of a healthy child at birth, whose condition rapidly deteriorates as a result of bleeding, should prompt the urgent investigation of a congenital haemostatic defect and involvement of expert haematological advice. We describe a very unusual presentation of a severe bleeding disorder in the first few days of life to highlight these issues.

Keywords: von Willebrand disease, bleeding

A male infant presented to his local Accident and Emergency (A&E) department on day 2 of life. He had been born at 41+2 weeks gestation by uncomplicated vaginal delivery and discharged home on day 1. He had received intramuscular vitamin K at birth. There was no significant family history. On arrival in A&E, he was unresponsive, hypotonic and making poor respiratory effort. He was found to be hypoxic and hypoglycaemic, with a severe metabolic acidosis. He was intubated, resuscitated and commenced on inotropes and antibiotics.

The haematologists contacted the paediatric team urgently with the results of his initial blood tests, which showed that he was severely anaemic (Hb 23 g/L). Congenital anaemia and haemolysis were excluded as he had been well at birth and was not jaundiced. Clinical examination and ultrasound scans performed in the resuscitation room did not identify a clear source of bleeding. However, his coagulation screen showed a disproportionately prolonged APTT (Table 1) raising the suspicion of severe occult bleeding due to haemophilia or, possibly, severe von Willebrand disease. He was treated with packed red cells (PRBC), fresh frozen plasma (FFP) and cryoprecipitate. He was then transferred to the Neonatal Intensive Care Unit (NICU) at a tertiary referral centre for further investigation and management.

On transfer, his abdomen was noted to be distended, but soft. A repeat ultrasound demonstrated echogenic material adjacent to the right lobe of the liver and within both paracolic gutters, most likely representing organising haematoma. There was also evidence of a large haemoperitoneum. Following surgical review he was managed supportively and received further PRBC, FFP, cryoprecipitate and intravenous vitamin K.

His clotting parameters normalised for 48 hours, but then became deranged again, notably with a prolonged APTT of 70 sec (29-55 sec). Factor assays showed a low Factor VIII (FVIII) of 8 IU/dL with a von Willebrand antigen (vWF:Ag) of 3 IU/dL. This confirmed a diagnosis of severe von Willebrand disease (vWD). He subsequently received doubly virally-inactivated intermediate purity FVIII/vWF concentrate (Wilate; Octapharma, AG Zurich [1]) 250 units 8-hourly with tranexamic acid (TXA) 20 mg/kg. He was extubated after 48 hours, weaned off inotropes and discharged from the NICU 24 hours later. FVIII/vWF concentrate was continued for the next 7 days, during which time, trough (pre-dose) FVIII and vWF levels were measured at 62-92 IU/dl and 38-87 IU/dl respectively. TXA was continued for a week after stopping the FVIII/vWF concentrate. There was no evidence of further intra-abdominal bleeding either during or after this period of treatment. Post-discharge (ten days after the last dose of concentrate) blood tests were repeated (see Table). Regular prophylaxis with FVIII/vWF concentrate was not considered necessary at this stage, as the presenting bleed was felt to have been precipitated by birth trauma and the risk of subsequent trauma in a non-mobile baby was likely to be very low. However, the family were given supplies of concentrate to keep at home, along with clear instructions regarding the process for rapid assessment and treatment in the event of any more bleeds in the future. A plan was also put in place to regularly review the need for prophylaxis as the child grew up.

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Table 1: Patient blood results

	Neonatal ranges	Presentation	2 days after blood products	Post discharge
PT	8.2 - 14.1 sec	25 sec	10.7 sec	10.9 sec
APTT	29 - 51.5 sec	169 sec	70.3 sec	106.8 sec
TT	9.2 - 15 sec	15.2 sec	12.8 sec	16.3 sec
Fibrinogen	1.7 - 4 g/dL	1.3 g/dL	3.0 g/dL	2.8 g/dL
Platelets	150 - 450 x109/l	104 x109/l	153 x109/l	272 x109/l
FVIII	50 - 178 IU/dL	-	8 IU/dL	1 IU/dL
vWF:Ag	50 - 287 IU/dL	-	3 IU/dL	1 IU/d
vWF:RiCof	50 - 287 IU/dL	-	1 IU/dL	1 IU/dL
vWF:CB	50 - 287 IU/dL	-	1 IU/dL	1 IU/dL

(vWF:RiCoF = Ristocetin Cofactor Assay; vWF:CB = Collagen Binding Assay; both markers of vWF function)

Discussion

The normal ranges for coagulation assays in the neonate differ from those of the older child and are due to a combination of vitamin K deficiency and immature synthetic function of the neonatal liver [2]. These cause low levels of the majority of clotting factors, reflected in relatively prolonged PT and APTT assays. These normal ranges are further prolonged in babies born prematurely. The TT can also be prolonged by the presence of foetal fibrinogen, with increased levels of sialic acid interfering with the assay. It is important to note however, that in spite of these differences, the healthy neonate does not normally experience problems with bleeding. This is because the findings described are balanced by concurrent low levels of natural anticoagulants (antithrombin, protein C and protein S), a relatively hypofibrinolytic state (due to low plasminogen levels) and raised concentrations of FVIII and vWF. Therefore, paediatricians are very familiar encountering neonates with apparently abnormal clotting screens but in whom bleeding is not a concern.

There were a number of early pointers that this infant's deteriorating clinical state was due to an inherited bleeding disorder, even though a source of bleeding was not immediately apparent. Firstly, he was well at birth. A baby presenting with severe congenital anaemia would have been profoundly anaemic on day 1 and this would have been obvious at, or shortly after, the birth. Therefore, there must have been a sudden fall in the haemoglobin level. The potential causes were haemolysis and bleeding. It is inconceivable that neonatal haemolytic disease could cause such a rapidly severe anaemia without leading to a marked unconjugated hyperbilirubinaemia. As this was not present, his anaemia must have been due to bleeding. Furthermore, the APTT was disproportionately prolonged in comparison to the other coagulation assays and the platelet count was relatively preserved. This makes a sampling error or an acquired coagulopathy (due to DIC, liver disease or vitamin K deficiency) highly unlikely.

These early observations were crucial in terms of the immediate management of the case. Although the baby clearly needed resuscitation with urgent blood transfusion, this would only have provided temporary relief in the setting of ongoing occult bleeding. He therefore also required specific treatment of the underlying cause. This was addressed by administering both FFP and cryoprecipitate. Bleeding in the context of a disproportionately prolonged APTT is likely to be due to a deficiency of Factors VIII, IX or XI and administration of FFP may improve levels of these sufficiently to provide haemostasis. Importantly, however, a prolonged APTT can also indirectly be due to vWD. This is because vWF, as well as enabling platelets to adhere and aggregate at sites of injury, protects FVIII from proteolytic degradation, thus markedly prolonging its half-life in the circulation. Cryoprecipitate (most commonly given to correct low fibrinogen levels) contains much higher concentrations of vWF:FVIII than FFP and it is likely that, in this case, it was administration of cryoprecipitate that caused the cessation of bleeding in A&E.

Severe vWD has previously been known to present rarely at birth [3], although this is the first description of abdominal bleeding in this condition as a probable result of birth trauma. Other severe congenital bleeding disorders can also present in the neonatal period. This can be in the form of mild, but abnormal bleeding (such as prolonged bleeding from heel pricks, bleeding from the umbilical cord and severe bruising following intramuscular injections) or, as in our case, the first presentation can be life-threatening. The best-described group of patients are those with haemophilia (FVIII/IX deficiency), with a reported 3.5% experiencing head bleeds within the first 28 days of life [4]. Many of these can be prevented by minimising the trauma of delivery in cases where the family history is already known [5]. However, a significant proportion of babies with haemophilia are born to mothers who are not known to be carriers of the disease. In addition, there will often be no relevant family history for bleeding disorders with autosomal recessive inheritance, as is the case in type 3 vWD. Such presentations, therefore, will continue to occur unexpectedly and a good understanding

of the significance of abnormal coagulation results is vital.

Conclusion

A high level of suspicion of a congenital bleeding disorder should be adopted in the case of a neonate with unexplained bleeding. Prompt supportive management of severe bleeding is key, with the use of PRBC, FFP and cryoprecipitate. Our case illustrates that early involvement of haematologists who can liaise with the neonatologists and the laboratory, help interpret results and advise on immediate treatment is crucial. Such close working relationships should be developed and fostered, both within a particular hospital, as well as between the local hospital and the specialist centre.

Disclosures

The authors have advised that there are no interests that might be perceived as posing a conflict or bias.

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