

CASE REPORT

Intracranial haemorrhage as initial presentation of severe haemophilia B: case report and review of Mayo Clinic Comprehensive Hemophilia Center experience

V. RODRIGUEZ,* † K. A. SCHMIDT, † J. A. SLABY † and R. K. PRUTHI †

*Division of Pediatric Hematology/Oncology, Mayo Clinic, Rochester, MN, USA; and †Division of Hematology, Mayo Clinic, Rochester, MN, USA

Summary. A neonate who had intracranial haemorrhage (ICH) at birth received a diagnosis of severe haemophilia B at 6 months of age. ICH had been the initial presentation of his bleeding disorder. His family history was negative for haemophilia. Review

of our institutional experience as well as the literature indicates that intracranial bleeding as the initial presentation of haemophilia is rare.

Keywords: haemophilia, intracranial haemorrhage

Introduction

Intracranial haemorrhage (ICH) is one of the most common causes of death in patients with haemophilia. It most commonly occurs in patients younger than 18 years. However, the incidence and clinical manifestations of ICH and outcome in newborns are not well defined. ICH is uncommon as an initial manifestation of haemophilia, perhaps because of early intervention in patients known to have a familial history of a bleeding disorder. We report the case of an infant who presented with intracranial and subgaleal bleeding as a newborn and review our institutional experience with ICH and haemophilia.

Case report

The patient was born at 39 weeks' gestational age to a 31-year-old woman, gravida 1, para 0, after an uneventful pregnancy. Vaginal delivery was complicated by brow presentation and required the use of forceps and vacuum extraction. Apgar score was 9 at 1 and 5 min after birth. The patient received prophylactic intramuscular vitamin K at birth. Circumcision, performed approximately 24 h after

birth, was haemostatically uneventful. Within 48 hours of birth, he was noted to be pale and inactive, and serious scalp swelling developed. Laboratory tests showed a haemoglobin level of 6.8 g dL^{-1} (reference range: $14.5\text{--}22.0 \text{ g dL}^{-1}$) and a platelet count of $194 \times 10^9 \text{ L}^{-1}$ (reference range: $150\text{--}400 \times 10^9 \text{ L}^{-1}$). His haemoglobin level dropped to 3.4 g dL^{-1} , and the platelet count dropped to $75 \times 10^9 \text{ L}^{-1}$ on day 3. The patient received a transfusion of red blood cells and platelets at another medical facility. Computed tomography of the head showed haemorrhage within both occipital horns of the lateral ventricles, with mild associated ventricular prominence and haemorrhage in the region of the left tentorium, in the subcortical left posterior frontal-parietal lobe, and in the subgaleal area. His head was wrapped with an elastic wrap to minimize swelling. After blood product transfusion his haemoglobin level was 13.1 g dL^{-1} and platelet count was $223 \times 10^9 \text{ L}^{-1}$. Coagulation studies were not performed before blood product transfusion. Bleeding diathesis evaluation performed after blood product transfusion showed a prothrombin time (PT) of 8.6 s (reference range: 10.6–16.2 s) and an activated partial thromboplastin time (APTT) of 30 s (reference range: 27.5–79.4 s). Phototherapy for hyperbilirubinemia was initiated on day 3. The patient's vital signs remained stable after blood product transfusion. He was discharged home on the fourth hospital day with resolving jaundice and subgaleal haemorrhage.

Correspondence: Vilmarie Rodriguez, MD, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

e-mail: rodriguez-vilmarie@mayo.edu

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At 6 months of age, he was referred to our Comprehensive Hemophilia Center for evaluation of spontaneous bruising (Table 1). The family had no history of bleeding disorders. His PT was 9.6 s (reference range: 8.4–12 s), and his APTT was 102 s (reference range: 21–33 s). Factor IX activity was less than 1% (reference range: 65–140%). Family testing demonstrated a mild reduction in factor IX activity in the mother (62%). The patient is currently 2 years old, receiving prophylactic factor IX replacement therapy and neurodevelopmentally normal for his age. Because results of neurologic and developmental examinations were normal, neuroimaging studies were not repeated before initiation of factor IX prophylaxis.

Discussion

Haemophilia A and B are X-linked recessive disorders affecting 1 in 10 000 and 1 in 40 000 males, respectively [1,2]. At least 25% of patients with newly diagnosed haemophilia are sporadic (i.e. do not have a family history of haemophilia) and they tend to have moderate to severe disease [3]. ICH is a leading cause of morbidity and mortality in patients with haemophilia, with a higher prevalence in younger patients [4–8].

ICH in full-term infants typically occurs as a result of trauma, coagulation disorders or hypoxia [8]. The reported incidence of symptomatic ICH in full-term neonates is approximately 5.2 per 10 000 live births [9]. Approximately 5% of apparently haemostatically normal full-term neonates show some level of ICH on transcranial ultrasonography, with the choroid plexus and germinal matrix being the most common sites of haemorrhage [9].

Table 1. Results of patient's coagulation study.

Test	Value*
Prothrombin time (s)	9.6 (8.4–12)
INR	1.0
APTT (s)	102 (21–33)
APTT with equal volume mixing (s)	29 (21–33)
Thrombin time (s)	17 (16–25)
Factor VIII activity (%)	124 (55–205)
Ristocetin cofactor activity (%)	156 (55–200)
von Willebrand antigen (%)	137 (55–200)
Factor IX activity (%)	<1 (65–140)
Factor XI activity (%)	84 (60–135)
Factor XII activity† (%)	58 (60–160)

APTT, activated partial thromboplastin time; INR, international normalized ratio.

*Reference ranges are shown in parenthesis.

†Factor XII was tested as part of the institutional evaluation of a prolonged APTT. Fibrinogen levels were not measured.

The reported incidence of intracranial bleeding in patients with haemophilia varies. In a retrospective review, one in 192 infants with haemophilia had intracranial bleeding during the first month of life [10]. In another report, central nervous system (CNS) bleeding occurred as the initial manifestation of haemophilia in seven of 119 patients (5.8%) with haemophilia A and in one of 31 patients (3.2%) with haemophilia B [11]. Median age at presentation was 1 month (range: 1 day–3 months). Although there was no family history in the seven patients with haemophilia A, the patient with haemophilia B had an affected relative. Three of the seven had severe haemophilia A (<1% factor VIII activity) and four had moderate disease, as did the patient with haemophilia B. All but three were born at term and were appropriate for gestational age. Bleeding occurred in the subdural space (with or without arachnoid or intracerebral involvement) in five patients, intracerebrally in two patients, and in the epidural space in one patient. Three patients had cephalohematomas in addition to ICH. There was no apparent birth trauma except for forceps delivery in two patients. Laboratory testing indicated a prolonged APTT in five of these newborns, but in seven of eight cases, the diagnosis of haemophilia was made retrospectively weeks or months later [11]. Seven patients required neurosurgical intervention (clot evacuation in six patients, ventriculoperitoneal shunt in four patients). Hydrocephalus developed in four patients and seizures requiring therapy developed in six infants. Four of eight patients had repeated episodes of intracranial bleeds. Five of eight patients had variable neurologic deficits (visual, moderate to severe learning disabilities and variable psychomotor delay). The presence of an antibody to the absent or diminished coagulation factor was not reported [11].

In a small analysis, three infants with haemophilia presented with ICH after head trauma as the initial manifestation of their bleeding disorder [12]. Despite a prolonged preoperative APTT in each case, haemophilia was not considered before neurosurgery. In a review of the literature on ICH as the first manifestation of haemophilia, Ohga *et al.* [13] found that ICH occurred in full-term neonates in the absence of a family history of a bleeding disorder. Of the 18 cases reported, ICH occurred early in the neonatal period (within 7 days); two of the infants had haemophilia B and 16 had haemophilia A. All the infants had severe or moderate haemophilia (<5% factor activity). No complications during pregnancy or delivery were observed except for forceps delivery in one neonate. Six required

neurosurgical intervention, with all infants having some residual neurologic deficits [13].

Kulkarni and Lusher [14] retrospectively reviewed the published reports on CNS haemorrhage in neonates with haemophilia. One hundred nine episodes of cranial haemorrhage were reported in 102 neonates, with 65% having ICH and 35% having extracranial haemorrhage (ECH). Anaemia and pallor were the most frequent clinical manifestations, followed by neurologic deficits. The carrier status of the mother was reported for 31 of the 102 neonates. Twenty-four mothers were carriers and had a positive family history of haemophilia; seven had no family history of haemophilia. Of 28 patients whose outcome was reported, 26 (93%) were alive and two (7%) died of ICH or ECH [14]. Long-term neurologic deficits were reported in 10 (36%) of the 28 evaluable patients [14].

In our institutional experience, six of the 18 paediatric patients with severe bleeding disorders (haemophilia A, haemophilia B and type 3 von Willebrand disease) were not known to have a family history of a bleeding disorder (Table 2). Of these six patients, CNS bleeding developed in two [one cephalohematoma-subdural haematoma 2 days after birth and one intracranial subgaleal bleed (at birth, current case report)]. A diagnosis of haemophilia B in the latter patient was not established until 6 months of age. It is not clear why a bleeding diathesis evaluation was not conducted in this infant at the time of ICH (the patient was born at another institution). The medical record reported transfusion of blood and platelets. These transfusions may explain the normal PT and APTT when the patient initially arrived at our institution (perhaps because of plasma contained in blood products). Neither of these patients had long-term sequelae of CNS bleeding. The median age at initial presentation of bleeding in these six patients was 168 days (range: 2 days–2 years), whereas the median time to diagnosis of their bleeding disorder was 2 days (range: 2–720 days).

Five of the six patients without a family history of a bleeding disorder were born by vaginal delivery [one required assistance with forceps and vacuum extraction (current case report)] and one by caesarean delivery (because of failure to progress). The use of forceps and vacuum for delivery of the infant described in our case report most likely contributed to his CNS bleeding and cephalohematoma. Our usual practice is to deliver infants with a known family history of bleeding disorders vaginally with infusion of clotting factor concentrate at birth. In our hands, this practice has not resulted in any neonatal bleeding. One patient (patient 14) received

intrauterine infusion of FVIII [15]. Prophylactic factor replacement should be administered to prevent bleeding complications during the neonatal period. The use of prophylactic factor concentrate replacement in children with severe haemophilia may considerably decrease the incidence of intracranial bleeding later in life. However, there are no reports confirming that earlier factor replacement diminishes intracranial bleeding complications in this population.

No studies have reported the actual incidence or risk of coagulation factor inhibitor development if factor concentrates are given early in life. An inhibitor developed (53 Bethesda Units) at 1 year of age in the one patient who received intrauterine factor FVIII infusion. This patient was treated with immune tolerance therapy for 15 months. No inhibitor has developed in any of the other patients who received factor concentrates at birth.

In conclusion, intracranial or subgaleal haemorrhage is rare in a full-term neonate with an uncomplicated prenatal history. A 22.8% mortality rate has been reported with subgaleal haemorrhages in all newborns (including those with and without haemophilia) [16]. Detection of ICH should prompt a detailed haemostatic evaluation even in the absence of familial history of a bleeding disorder. This should consist of a peripheral blood cell count and PT and APTT determinations. If the results of these baseline-screening tests are normal, the physician should assay for von Willebrand factor, fibrinogen and factor XIII. Factor assays for VIII and IX should be strongly considered as part of the initial evaluation if the infant is male. The finding of a prolonged APTT (compared with the reported newborn ranges) [17] should prompt the analysis of coagulation factors to establish a diagnosis. Appropriate clotting factor concentrate replacement should be given to prevent bleeding complications during the neonatal period. If there is no family history of a bleeding disorder, and haemorrhage is potentially life threatening, empiric use of fresh frozen plasma or recombinant factor FVII could be considered cautiously if immediate analysis of coagulation factor deficiency is not available to the treating physician. This use of recombinant factor FVII is not a US Food and Drug Administration-approved indication but is known to be clinically effective in patients with haemophilia and inhibitors [18–20].

Our typical procedure is to test cord blood factor FVIII or factor FIX in infants born to known carriers, with appropriate clotting factor replacement therapy if indicated, especially if no prenatal testing was done. If prenatal testing confirmed that a male foetus

Table 2. Mayo Clinic paediatric patients with severe bleeding disorders.

Patient*	Diagnosis	Mode of delivery	Age at diagnosis of bleeding disorder	Neonatal CNS bleeding	Family history of bleeding disorder	First occurrence of bleeding/treatment
1	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	Closed head injury at 7 months/FVIII
2	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	Heel stick, circumcision/FVIII at birth, prophylactic
3	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	FVIII infusion at birth, prophylactic
4	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	FVIII infusion at birth, prophylactic
5	Haemophilia A (FVIII < 1%)	Vaginal	2 days	Yes, cephalohematoma-subdural haematoma (by ultrasonography)	No	Cephalohematoma at 2 days/factor replacement
6	Haemophilia A (FVIII < 1%)	Vaginal	Prenatal	No	Yes	FVIII infusion at birth, prophylactic
7	Haemophilia A (FVIII < 1%)	Vaginal	2 years	No	No	Bruising at 2 years/factor infusion
8	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes (older brother)	Circumcision/FVIII infusion at 6 weeks (also factor VIII infusion at birth)
9	Haemophilia A (FVIII < 1%)	Vaginal	4 months	No	No	Abdominal wall haematoma/factor replacement at 4 months
10	Haemophilia A (FVIII < 1%)	Vaginal	15 months	No	No	Circumcision/factor replacement (age not available)
11	Haemophilia A (FVIII < 1%)	Caesarean (prolonged labour)	10 days	No	Yes	Hand trauma/FVIII infusion at 4 months
12	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	FVIII infusion at birth, prophylactic
13	Haemophilia A (FVIII < 1%)	Vaginal	Birth	No	Yes	FVIII infusion at birth, prophylactic
14	Haemophilia A (FVIII < 1%)	Vaginal	Prenatal	No	Yes	Prebirth infusion (through umbilical vein), inhibitor developed at 1 year of age/immunotolerance for 15 months, currently receiving prophylaxis
15	Haemophilia A (FVIII < 1%)	Caesarean (prolonged labour)	Birth	No	Yes	Circumcision/FVIII infusion at 1 month
16 (present report)	Haemophilia B (FIX < 1%)	Vaginal (assisted with forceps and vacuum)	6 months	Yes, intracranial/subgaleal bleeding (by computed tomography)	No	Intracranial bleeding at birth/FIX infusion at 7 months after extremity haematoma
17	Type 3 vWD	Caesarean (failure to progress)	19 days	No	No	Heel stick (prolonged), circumcision 5 days/factor replacement
18	Type 3 vWD	Vaginal	6 months	No	Yes	Epistaxis/rectal bleeding 3–4 months, head trauma at 4 months/factor infusion at 4 months

CNS, central nervous system; vWD, von Willebrand disease.

*All patients were male except patient 18.

is affected, empiric infusion of clotting factor concentrate is provided. Delivery is conducted under controlled circumstances, with good communication with the attending obstetrician and a good understanding of any potential anticipated complications during delivery. Our experience demonstrates that such a multidisciplinary approach, with immediate postnatal or in utero [15] factor infusion, may reduce or prevent perinatal haemorrhagic complications.

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