

## PRESUMED FRESH MUTATION HEMOPHILIA A PRESENTING WITH SUBARACHNOID HEMORRHAGE IN A NEWBORN

Asindi Andrew Asindi, FRCP; Rajesh Malhotra, MD

A male Saudi infant of an uncomplicated pregnancy and labor became lethargic, cried excessively, and had a bulging fontanelle on the fourth day of life. A computerized tomography of the brain revealed an occipital subarachnoid hemorrhage. Other investigations excluded meningitis, but demonstrated a diagnosis of hemophilia A (Factor VIII 6%). The patient recovered on Factor VIII therapy. A family history of hemophilia was negative. This case is presumed to be a fresh mutation hemophilia A, and it is of interest since it was complicated with intracranial hemorrhage, a rare presentation in the newborn period.

Hemophilia A or B is an uncommon disease in most populations. These two disorders together occur in approximately one in 5000 male births.<sup>1</sup> Rarely does either of the hemophilias present with bleeding in the newborn period, even the severe type, except following surgical trauma such as circumcision to induce excessive hemorrhage. Curiously, 30% of the severe type do not bleed excessively from circumcision and most mild hemophilias completely escape excessive bleeding, even with circumcision.<sup>2</sup>

Occasionally, hemophilia may manifest in the newborn period with spontaneous intracranial hemorrhage, but this is very rare.<sup>3-5</sup> We report an infant who presented with lethargy, irritability and pallor, and was subsequently discovered to have subarachnoid hemorrhage, low Factor VIII level, but with a negative family history of a bleeding tendency or hemophilia.

### Case Report

A male Saudi infant was born at term by spontaneous vaginal delivery in Abha Maternity Hospital, Saudi Arabia, following an uncomplicated pregnancy. The Apgar scores were 9 and 10 in one and five minutes, respectively. The

birth weight was 2800 grams, length 53 cm and head circumference 36 cm. The mother and infant were discharged after 24 hours in hospital, since the postnatal period was entirely uneventful.

The infant remained well until the fourth day of life, when he became irritable, cried excessively, and was disinclined to feed. There was no fever and no history of trauma. He consequently presented for admission in the neonatal intensive care unit (NICU) of Asir Central Hospital on the fifth day of life.

During the antenatal period, the mother had remained fairly well apart from fever and an itchy rash on the face and trunk, which lasted for only two days during the 30th week of gestation. She was not on any medication throughout this pregnancy.

The infant has one sister (age three years, six months) and a brother (two years), both of whom have kept well. The brother had been circumcised without any unusual bleeding. The mother (age 30) has two sisters and a brother. The brother underwent a circumcision and an appendectomy at the ages of 12 and 40 years, respectively, without any complications. One of her sisters has two daughters and two sons and none of the latter has had any bleeding tendency. The father of the index child has five sons and three daughters from his first wife and there is nothing remarkable about them.

On admission, the infant was uncircumcised, lethargic and pale, with a temperature of 36.8°C. There were no signs of trauma or external bleeding. The heart rate was 145 per minute, BP 70/40, mean 45 (Dinamap). The head circumference was 35 cm and the anterior fontanelle was bulging but not tense. The muscle tone, deep tendon reflexes and pupils were normal. The rest of the physical examination was unremarkable.

Based on these findings, tentative differential diagnoses of intracranial hemorrhage and meningitis were entertained.

Initial laboratory investigations yielded the following results: hemoglobin 95 g/L, hematocrit 0.29, white cell count  $10.4 \times 10^9/L$  and platelet count  $182 \times 10^9/L$ , prothrombin time (PT) 13 seconds, control 12 seconds, activated partial thromboplastin time (APTT) 77 seconds,

---

From the Department of Child Health, Asir Central Hospital, Abha.

Address reprint requests and correspondence to Dr. Asindi: Department of Child Health, College of Medicine, King Saud University, P.O. Box 641, Abha, Saudi Arabia.

Accepted for publication 30 July 1996. Received 17 March 1996.



FIGURE 1. Non-contrast CT brain scan taken on day 2 of admission showing a subarachnoid hemorrhage in the posterior fossa, interhemispheric fissure and right temporoparietal region.

control 30 seconds, fibrin degradation product (FDP) 5  $\mu\text{g}/\mu\text{L}$  and fibrinogen 4 g/L. The cerebrospinal fluid (CSF) was uniformly bloodstained, with numerous red blood cells, and 8 to 10 white cells per high-power field.

Based on the initial laboratory results and the clinical suspicion, the infant received vitamin K, fresh frozen plasma, packed red cell transfusion and antibiotics (ampicillin and amikacin).

Coagulation battery repeated on the second day of admission produced the following results: PT 13 seconds, control 12 seconds; APTT 60 seconds, control 30 seconds; FDP 5  $\mu\text{g}/\mu\text{L}$ ; fibrinogen 5 g/L; Factor VIII 13% and Factor IX 50%. Computed tomography (CT) brain scan demonstrated a subarachnoid hemorrhage involving the posterior fossa, interhemispheric fissure and the right temporoparietal region (Figure 1). Sepsis workup (blood, CSF and urine cultures) results were all negative.

The infant was subsequently treated with Factor VIII (human antihemophilic factor, Koate HP) 20 units/kg/dose every eight hours. With this regime, which was administered for 16 days, the infant's serial Factor VIII levels rapidly rose and were maintained between 56% and 40% during the period of medication. Following cessation of therapy, the level gradually declined and stabilized at 6% (three consecutive estimations) in the last week of hospitalization. On discharge at the age of 30 days, the infant showed no detectable neurologic sequelae; the head circumference was 35.5 cm, PT 12 seconds (control 12 seconds), Factor VIII 6% and APTT 42 seconds (control 30 seconds). A repeat CT brain scan showed a remarkable and satisfactory resorption of the hematoma (Figure 2).



FIGURE 2. Non-contrast CT brain scan of the same infant repeated after three weeks in hospital. It shows a marked resolution of the hematoma.

The mother was not available for any blood tests and the hospital has no laboratory facilities for determining the carrier status of the disease. The infant was lost to follow-up after discharge.

### Discussion

The presentation of lethargy, pallor and bulging fontanelle in a newborn fits the clinical diagnosis of either meningitis or intracranial hemorrhage. In the present case, the uniformly blood-stained CSF and the CT brain scan findings confirmed the latter impression. Subsequent laboratory tests yielded results (normal PT, platelet count, FDP and Factor IX, but prolonged APTT and low level of Factor VIII) consistent with hemophilia A being the most probable underlying cause of the hemorrhage.

It commonly stimulates interest when a new mutation of an inherited disease emerges in a family. A thorough and detailed historical survey of the pedigree of this infant was negative for any bleeding disorder. The proband, therefore, most probably carries a new mutation gene for hemophilia A disease. About 50% of hemophiliacs have a negative family history of any bleeding disorder,<sup>2</sup> 80% have a positive history of the disease, while up to 20% are sporadic cases presenting as a fresh mutation.<sup>5</sup> The carrier status of a mother can be determined by estimating the plasma ratio of Factor VIII activity to von Willebrand protein; female carriers have a ratio of less than one. Recently, carrier detection has become more precise by measuring restriction fragment length polymorphism using DNA probes or markers.<sup>3</sup>

Since the serial Factor VIII levels of this infant stabilized at 6% for a period of one week after stopping the replacement therapy (half-life 8 to 12 hours), he was presumably born with this level and therefore, most likely has the mild type of the disease. Clinically mild cases have Factor VIII 6% to 30% of normal activity; moderate cases have 1% to 5%, and severe cases have less than 1%. Perhaps a level of 6% in the present case is low enough to permit a spontaneous intracranial bleed. It may also be assumed that in a newborn with this level, the process of even a normal labor may be perilous enough to induce such a bleed. Perhaps the hemorrhage had occurred at birth but was initially silent until it gradually increased in size to become symptomatic from the fourth day of life. It is well recognized that a good number of small intracranial hemorrhages in the newborn can be silent. It may therefore be worth recommending a routine brain ultrasonography on all male offspring of female carriers of hemophilia in the first days of life to exclude a possible silent intracranial hemorrhage and, if positive, to institute Factor VIII therapy to limit the bleeding before it becomes catastrophic, as in the case presented.

Since the carrier status of the mother could not be tested, we would not dogmatically lay a strong claim on fresh mutation by historical evidence alone. Her subsequent male offspring need to be monitored. The parents were appropriately advised to avoid circumcision and intramuscular injection without medical supervision.

### References

1. Buchanan GR. Coagulation disorders in the newborn. *Pediatr Clin N Am* 1986;33:203-220.
2. Baehner RL, Strauss HS. Hemophilia in the first year of life. *N Engl J Med* 1966;275:524-31.
3. Corrigan JJ Jr. Diseases of the blood: hemorrhagic and thrombotic diseases. In: Nelson I, Waldo E, Behrman RE and Kliegman RM, editors. *Nelson Textbook of Pediatrics*. 14th ed. Philadelphia: WB Saunders Co, 1992:1275-86.
4. Buchanan GR. Neonatal Hematology: Hemorrhagic Diseases. In: DG Nathan, FA Oski, eds. *Hematology of infancy and childhood*. 3rd ed. Philadelphia: W B Saunders Co, 1987:118-9.
5. Mosijczuk AD, Ellis-Vaiani C. Hematologic diseases. In: Merenstein GB, Gardner SL, editors. *Handbook of Neonatal Intensive Care*. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers, 1990:287-317.