Intracranial hemorrhage in patients with hemophilia

RUTH ANDREA SEEELER, M.D., AND RENATO B. IMANA, M.D.

Cook County Hospital, Hektoen Institute for Medical Research, and Abraham Lincoln School of Medicine, University of Illinois, Chicago, Illinois

Intracranial hemorrhage occurred in four patients with hemophilia following mild head trauma. Three patients had severe factor VIII (antihemophilic factor, AHF) deficiency while one had mild (5.5%) AHF deficiency. The authors stress the need for immediate AHF replacement therapy and appropriate neurosurgical work-up, and a joint effort by hematologist and neurosurgeon to minimize neurological damage. In the four patients, three subdural hematomas, one epidural and one intracerebral hematoma were safely evacuated.

KEY WORDS  intracranial hemorrhage  hemophilia  factor VIII  antihemophilic factor (AHF)

Intracranial hemorrhage is becoming more common in patients with hemophilia because of the more active lives of these patients made possible by vigorous replacement therapy for intra-articular hemorrhages. Bleeding may be subdural, intracerebral, epidural, or subarachnoidal. Hemophilia encompasses deficiencies of factor VIII (anti-hemophilic factor, AHF), factor IX (plasma thromboplastin component, PTC), and factor XI (plasma thromboplastin antecedent, PTA). AHF and PTC deficiencies comprise 98% of the genetic coagulation disorders and are inherited in an X-linked manner. The hemorrhagic diatheses are clinically classified "mild," "moderate," and "severe." Severely deficient patients have less than 1% of the coagulation factor and bleed spontaneously into joints and muscles. Moderately deficient patients have levels of 2% to 5%, while mildly affected patients have 7% to 15%. The moderate hemophilic bleeds only after trauma while the mild hemophiliac requires greater trauma, frequently surgical.

In hemophilia, the partial thromboplastin time (PTT) is prolonged. The bleeding time, prothrombin time, and clot retraction are normal. The whole blood clotting time is of doubtful value because it is normal in patients having over 2%; without replacement therapy such individuals may be exsanguinated by surgical procedures.

Diagnosis has been simplified by the commercial availability of AHF and PTC deficient plasmas. One simply mixes equal volumes of a known AHF-deficient plasma with the patient's plasma, and if the PTT remains abnormal, the diagnosis is AHF deficiency. The technically complex thromboplastin generation time (TGT) and other types of mixing experiments are no longer needed. For safe surgical procedures, however, the coagulation factor levels must be monitored.
Ruth Andrea Seeler and Renato B. Imana

The availability of concentrates coupled with frequent monitoring of the coagulation factor levels have made surgical procedures safe and practical. AHF concentrates include cryo-precipitate (cryo) either commercially available* or prepared by blood banks from individual units of plasma, and a glycine AHF precipitate.† For PTC-deficient patients, there are concentrates containing factors II, VII, IX and X.‡ Because concentrates are specific, one must determine whether the patient is AHF or PTC deficient.

Case Reports

Case 1

A 14-month-old black boy with less than 1% AHF pulled himself over the side of his playpen, landing on his right shoulder and right side of his head. That evening one bag of cryo (see discussion) was infused, and he seemed normal for 6 days before becoming lethargic, and at 10 days, unarousable.

Physical examination revealed a semicomatose child responsive to painful stimuli. The right pupil measured 4 mm, the left, 2 mm; both reacted to light. Ecchymosis was present over the right shoulder but none on the forehead.

The hematocrit was 20%, and he was immediately transfused with 120 cc of whole blood and three bags of cryo. Brain scan suggested a right parietal lesion, but bilateral subdural taps were negative. He deteriorated, developing flaccid paralysis of the left extremities, and further dilation and sluggishness of the right pupil. Carotid angiogram demonstrated midline displacement of the right anterior and posterior cerebral arteries and elevation of the middle cerebral artery. Just prior to surgery (13 hours after admission) a second infusion of cryo increased the AHF level to 125%. A subdural hematoma extending over the parietal lobe and under the temporal lobe was evacuated without difficulty. The next morning spontaneous motion returned to the left foot, and by afternoon, the pupils were equal and reactive to light. All motor deficits cleared completely. Hemostasis was maintained by infusion of one bottle of commercial cryo containing 215 to 271 units of AHF every 12 hours. During the 12 days of therapy he received a total of 29 bottles of commercial cryo equivalent to 6784 units of AHF.

Now at 6 years, the patient is hyperactive and slightly retarded.

Case 2

A 5-year-old Mexican boy with mild hemophilia, 5.5% AHF, fell down four steps hitting his right forehead. Except for a small hematoma he appeared perfectly well. Nine days later he complained of right frontal headache and vomited blood-streaked material.

Physical examination revealed a sleepy child with no neurological deficit. The pulse was 84/min. Four bags of cryo were infused every 12 hours, and antacid ulcer therapy was begun. He remained alert, cooperative, and oriented, but refused to sit up because it aggravated his headache. The bradycardia persisted. Two days later, review of the initial skull films revealed a supraorbital fracture. Brain scan demonstrated an abnormal right frontal uptake, and carotid angiogram showed the right anterior cerebral artery displaced across the midline. An organizing epidural hematoma was evacuated through a right frontal craniotomy.

AHF infusions were continued every 12 hours through the 8th postoperative day. For weekend and evening infusions, commercial cryo was given; on weekday mornings he received cryo from 5 units of blood. Pre-infusion AHF levels ranged from 22% to 48%, post-infusion levels 50% to 82%. The patient received cryo from 50 units of blood (20 preoperatively) and 40 bottles of commercial cryo equivalent to 9124 cc of fresh-pooled normal plasma. During 24 months of follow-up he has been well.

*AHF concentrates are available from Abbott Laboratories, North Chicago, Illinois 60064; Armour Pharmaceutical Company, P.O. Box 1022, Chicago, Illinois 60690; and Parke Davis & Company, Detroit, Michigan 48232.
†Glycine AHF precipitate available from Hyland Laboratories, Division Travenal Laboratories, 3300 Hyland Avenue, Costa Mesa, California 92626.
‡Factor II, VII, IX, and X concentrates available from Cutter Laboratories, 4th and Parker Streets, Berkeley, California 94710, and from Hyland Laboratory.
Intracranial hemorrhage in hemophilia

Case 3
A 17-year-old black boy with < 1% AHF was admitted 8 days after an automobile accident in which he hit his head against the padded front seat. He did not consider himself injured, and no ecchymosis developed. On the morning of admission, he developed severe headache, noted some difficulty with vision, vomited several times, and became drowsy.

Physical examination revealed a lethargic, slightly confused patient without focal neurological signs. Ten bags of cryo were infused. The anteroposterior view of the brain scan was suggestive of subdural hematoma or soft tissue injury in the left frontoparietal region. The patient had a generalized convulsion and became aphasic. Bilateral carotid angiograms were initially interpreted as normal. Weakness developed in the right arm. A repeat carotid angiogram revealed a subdural hematoma over the left hemisphere. The patient had received AHF infusions every 12 hours since admission 3 days earlier. At operation, a chronic subdural hematoma was evacuated without difficulty. Postoperatively, he became alert and regained complete motor function. The AHF infusions were continued to the 11th postoperative day, consuming the cryo from 100 units of blood and 95 bottles of commercial material. Pre-infusion AHF levels ranged from 20% to 32%, while post-infusion values ranged from 92% to 154%.

The patient is now a college student with no residual problems noted during 3½ years of follow-up.

Case 4
A 16-year-old black boy with less than 1% AHF was admitted because of fever, headache, and vomiting of several days' duration. The pulse was 58/min, blood pressure 140/80, respirations 20/min, the temperature 101° F. The patient was so restless and uncooperative that the admitting service thought he was retarded. On the second hospital day, a hematoma of the left forearm was noted. The patient continued to be confused, uncooperative, and lethargic, with bradycardia and hypertension. A right hemiparesis and right facial weakness associated with paralysis of right conjugate gaze and papilledema developed. Left carotid angiogram demonstrated communicating hydrocephalus, and a right ventriculoperitoneal shunt (Denver type) was inserted. Immediately he improved with spontaneous movements of all extremities. Infusions of 10 bags of cryo every 12 hours were continued through the 10th postoperative day. He was discharged normotensive, without neurological defect; the etiology of the communicating hydrocephalus remained unexplained. During this admission he received 300 bags of cryo from B+ plasma and eight bottles of commercial cryo.

Thirty-four days later, the patient awoke with headache and vomiting. He was dull, but responsive to pain. A nonreactive left pupil measured 8 mm, while the right pupil was 3 mm and reacted sluggishly. Bilateral papilledema, right facial weakness, and right-sided hemiparesis were present. He was immediately transfused with 10 bags of B+ cryo. Left carotid angiogram revealed a mass within the left temporal lobe. A left temporoparietal craniotomy was performed and a small subdural hematoma evacuated. Then, at a depth of 3 cm, a well-organized intracerebral hematoma was found and evacuated. Pre-infusion AHF levels ranged from 25% to 36%, and post-infusion values ranged from 56% to 75%.

The patient still has dysphasia and severe motor impairment despite physical therapy accompanied by AHF replacement.

Discussion
In hemophilia, intracranial hemorrhage may follow slight trauma. The initial trauma was quite mild in three of our patients. In the fourth patient, trauma was suspected, due to the presence of the hematoma on the forearm, but unconfirmed; the communicating hydrocephalus in this case may have resulted from the bleeding of the unrecognized head trauma.12

Intracranial hemorrhage in patients with hemophilia cannot be stopped by adequate replacement therapy only. In Case 2, the patient was admitted as an “acute ulcer” case and received 2½ days of intensive replacement therapy. In Case 3, the patient was admitted with the presumptive diagnosis of subdural hematoma and received regular 12-hour AHF infusions; he continued to

J. Neurosurg. / Volume 39 / August, 1973
deteriorate because the initial angiogram was interpreted as "normal." In Case 4, the patient certainly was not helped by delaying surgery; he had received multiple doses of cryo for the forearm hematoma.

Nothing is to be gained by adopting a "wait and watch" attitude in patients with hemophilia complaining of headache, or who have neurological signs. The hemostatic defect should be corrected and appropriate neurosurgical work-up immediately instituted.

Concentrated AHF and PTC must always be readily available. One unit is equal to the activity of 1 cc of fresh-pooled normal plasma. Infusion of 1 unit of AHF/kg will be diluted by the patient's plasma volume (50 cc/kg), and this results in a 0.02 unit rise, or 2% increase. The half-life of AHF is approximately 10 to 12 hours. To prevent intra- and postoperative hemorrhage, it is necessary to maintain a minimum level of approximately 20% AHF until the wound is healed. The initial recommended dose is 30 to 40 units of AHF/kg followed by 20 units/kg every 12 hours. The label of each bottle of commercial cryo gives the number of AHF units.

Cryo prepared by blood banks is an effective source of AHF. A bag of cryo from 250 ml of plasma contains 50 to 100 units of AHF. Infusion of one bag of cryo/6 to 8 kg usually results in a 35% AHF level. Higher values can be achieved by giving more cryo. Because individual bags of cryo vary considerably in AHF content, the actual AHF levels must be monitored frequently in the patient. It is our practice to use commercial materials for the night and weekend infusions and blood-bank cryo for our morning infusions.

Infusing excessive amounts of AHF is wasteful and creates unnecessary expense. A sufficient margin of safety is achieved by a 60% to 80% post-infusion level of AHF, so that 12 hours later the level ranges from 30% to 40%; this allows for the variability inherent in any biological system.

Although our patients were AHF-deficient, intracranial hemorrhage also occurs in PTC hemophilia. Therapy is similar to that used for AHF, but PTC concentrates are given insted of cryo which has no PTC.

Hemolysis may result from anti-A and anti-B present in all AHF preparations. One patient (Case 4) was blood group B, and we were fortunate in being able to obtain a large supply of B+ cryo. When the recipient is of blood group A, B, or AB, a Coombs-positive hemolytic anemia may result from intensive replacement therapy. It is preferable to use type-specific cryo if it is available.

References

Intracranial hemorrhage in hemophilia


Address reprint requests to: Ruth Andrea Seeler, M.D., Pediatric Hematologist, Cook County Hospital, 1825 West Harrison St., Chicago, Illinois 60612.