PSEUODOHEMOPHILIA:

Case Study*

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Introduction

A case of a hereditary hemorrhagic disease has been studied and is recorded primarily because the family history offers an unusually good opportunity to trace the genealogical background in this particular instance. The only persistent abnormality found has been prolongation of the bleeding time. Such a condition, which is often hereditary and is characterized chiefly by a prolonged bleeding time in the presence of normal platelets, has been previously described and referred to as 'pseudo-hemophilia,' or 'hereditary hemorrhagic thrombastHENIA.'

Report of Case

The patient, a 20-year-old white American-born male, was admitted to the hospital with a swollen, painful left knee, which had been 'twisted' 9 days previously in a baseball game. Almost immediate swelling followed the trauma. He was treated conservatively by the family physician until 3 days prior to admission, when the joint was aspirated with removal of clear, straw colored fluid. Because of recurrence of joint pain 3 days following this tap the patient was hospitalized and a second aspiration was done with removal of blood. The role of a bleeding tendency in the etiology of this hemarthrosis was suggested when the patient continued to ooze fresh blood into his dressing for at least 12 hours following this second aspiration.

Physical examination revealed a well developed and nourished young man in considerable discomfort. The temperature was 100°F; pulse rate, 90 per minute; respirations, 24 per minute; blood pressure, 136/90 mm. Hg. The skin showed ecchymoses over both deltoid areas where he had received injections of penicillin. There were no petechiae either before or after application of a tourniquet to the arm. Heart, lungs, abdomen were not abnormal. Liver and spleen were not palpable. The left knee was acutely tender and swollen. It was observed that both hands went into spontaneous intermittent carpal spasm, and that the Chvostek sign was strongly positive. There was no pedal spasm; Trousseau's sign was negative. Physical examination was otherwise negative.

Initial laboratory studies were as follows: RBC, 5,400 million; Hb., 16 Gm. per cent; WBC, 12,700 per cu. mm.; polymorphs, 82 per cent; lymphocytes, 17 per cent; monocytes, 1 per cent; platelets, 300,000 per cu. mm. Bleeding time, 15 minutes plus (not timed after 15 minutes, but still actively bleeding). Clotting time, 7 minutes (capillary tube method). Serum calcium, 7.36 mg. per 100 cc. X-ray of the knee showed evidence of increased synovial fluid.

At this time the nature of his illness was not understood. His knee appeared to have stopped bleeding 24 hours after the aspiration. The acute problem was the presence of tetany. Penicillin therapy was discontinued, and he was given calcium lactate 1 gram orally daily, and vitamin K (Synkayvite) 5.0 mg. intramuscularly daily.

Further blood studies were then made over the period of his 7 weeks' hospitalization. The serum calcium became normal. The only persistent abnormality was the prolonged bleeding time. These studies are discussed more fully below.

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PAST HISTORY

Inquiry into past illnesses revealed that the patient had been a "bleeder" since about 1 year of age. His first episode of uncontrollable bleeding occurred when he was learning to walk and fell, cutting his lip. He bled for 2 to 3 days despite medical aid. He had always bruised easily, had spontaneous epistaxis, and bled profusely when losing his deciduous teeth. Since childhood he had had 8 to 10 hospital admissions for the numerous bleeding episodes. In recent years, however, there had been a definite diminution in the severity of the abnormal bleeding. He had never been operated upon. There was no history of genito-urinary or previous joint hemorrhage. Following "several days" of vomiting with sea-sickness while in the Navy, he noticed red blood in the vomitus on one occasion. Some years ago he had had intermittent bleeding hemorrhoids, but never noticed more than occasional spotting. Other forms of gastrointestinal bleeding had not occurred. There had been no hemoptysis, even during an attack of "mild pneumonia" 5 years ago.

The presence of carpal spasm with a low serum calcium brought forth a history of several previous similar episodes, "when I get excited," and during the period of protracted vomiting with sea-sickness.

Dietary history revealed that since childhood he had been a "touchy" eater, but had subsisted mostly on milk, fruits, and meats.

FAMILY HISTORY

One of the most unusual features of this case study has been the family history, for the patient is the fifth of a direct line of males to be a "bleeder." This family
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. history can best be reviewed with reference to the genetic chart. The accessibility and cooperation of the whole family has made this study possible.

No. 1.—The patient.
No. 2.—An 18 month old boy, half brother of the patient, the son of the patient’s father and the latter’s second wife. His observed bleeding time was 1 hour 10 minutes. His parents reported that he bled for another 1/2 hours after the test had been performed. On this date his blood count was: RBC, 4,62 million, Hb. 15 Gm. WBC, 18,00, P 37, L 57, E 5, M 1. Platelets, 124,000 per cu. mm. (Other platelet counts done this same day by the same technician on controls ranged between 120,000 and 180,000.) This child underwent an uneventful circumcision a few days after birth. No history of bleeding episodes prior to this date.

No. 3.—An 8 year old girl, true sister of No. 1, half sister of No. 1 (the patient). Bleeding time less than 3 minutes. Blood count and platelets normal. No history of abnormal bruising, epistaxis, bleeding from tooth sockets, nor excessive bleeding following tonsillectomy at age of 6 years.

No. 4.—A 3 year, 8 month old boy, first cousin of the patient. Bleeding time 2 minutes 15 seconds. No history of abnormal bleeding. Underwent an uneventful tonsillectomy at 19 months, prior to which operation the bleeding time was tested and reported normal.

No. 5.—A 10 year old girl, first cousin of the patient. Bleeding time 1 minutes. No history of pathological bleeding. Uneventful tonsillectomy at age of 4 years, prior to which operation bleeding time was tested and reported normal.

No. 6.—The patient’s mother, who is living and well. No history of abnormal bleeding at delivery, easy bruising, epistaxis, nor of bleeding after extraction of teeth. Menstrual history normal. She states there was no history of abnormal bleeding in her siblings or her parents. She and the patient’s father, No. 8, were divorced several years ago.

No. 7.—Stepmother of the patient, the father’s second wife, the mother of No. 1 and No. 3. No history of abnormal bleeding.

No. 8.—The patient’s father, aged 48, also father of No. 1 and No. 3. Definite past history of pathological bleedings; e.g., spontaneous epistaxis lasting 1 to 3 days, easy bruising, bleeding after extraction of teeth lasting 2 to 3 days. His bleeding tendency has diminished in severity in recent years. He has not had a spontaneous nosebleed in about 10 years. Bleeding time 40 minutes. Clotting time minutes (Lee-White method). Clot retraction: complete retraction from edges and bottom of test tube in 1 hour 25 minutes at room temperature. Complete blood count, including platelet count, was normal.

No. 9.—The patient’s uncle, brother of No. 8. No history of pathological bleeding. Had several teeth extracted without undue bleeding. He has no children.

No. 10.—The patient’s aunt, sister of No. 8 and No. 9, mother of No. 4 and No. 5. No history of pathological bleeding. Deliveries were uncomplicated. Uneventful tonsillectomy 2 years ago. Bleeding time 1.2 minutes.

No. 11.—The patient’s paternal grandfather. History of bleeding tendency throughout life with repeated hospitalizations for uncontrollable, spontaneous nosebleeds, bleeding from tooth sockets, and subcutaneous bleeding. Died from a fractured skull with “uncontrollable hemorrhage.”

No. 12.—The patient’s paternal grandmother, who has provided the detailed and reliable reports of the lives of those members of the family not now living. She gives no history of abnormal bleeding in herself.

No. 13.—The patient’s paternal great grandfather, personally known by the grandmother, No. 12. He was a known bleeder who suffered throughout his life with the same easy bruising and spontaneous nosebleeds as did his followers. He died at the age of 56 from a sudden pulmonary hemorrhage following a “coughing spell.” The existence of pulmonary pathology at the time of death was not determined.

No. 14.—The patient’s great grandmother, known by the grandmother, No. 12, gave no history of pathological bleeding.

No. 15.—The patient’s great great paternal grandfather, not known by the patient’s grandmother, but commonly referred to in the family folktales as having been a “bleeder” throughout his life. Cause of death unknown.
HOSPITAL COURSE

When first seen, the patient was given calcium lactate orally and vitamin K (Synkayvite) subcutaneously. Penicillin therapy was discontinued. He was given Demerol to control knee pain.

On calcium therapy the tetany and positive Chvostek sign disappeared. Blood calcium level was normal after 3 days of supplemental calcium. This produced no change in the bleeding time.

The blood pressure was measured daily because of an initial diastolic pressure of 90 mm. Hg. After about 3 weeks levels of 130/80 mm. to 120/70 mm. were maintained. Eye grounds were normal. An x-ray of the chest and an electrocardiogram showed no abnormalities. Injections of Synkayvite were discontinued after 16 days as the bleeding time continued to be prolonged despite vitamin K therapy.

The swelling of the knee joint slowly subsided over a period of 3 to 4 weeks. Motion was encouraged. He was allowed up on crutches by the fifth week, and he walked without a cane after the seventh week.

He was discharged from the hospital on the fifty-sixth day. At this time he walked with a slight limp, but had no pain nor tenderness nor swelling in the knee. X-ray of the knee was reported as normal.

THE BLOOD FINDINGS*

1. The Bleeding Time.—This was determined frequently by one of three selected technicians. With occasional exceptions, the ear lobes were the sites utilized, although finger tips were used occasionally.

It was noted that the bleeding time varied from normal on one occasion only (both ear lobes), to 1 hour and 30 minutes. The majority of bleeding times ranged between 7 and 40 minutes. Variation between 8 minutes and 1½ hours was seen within the same week when done by the same technician. Variation was also seen between the finger and ear lobe bleeding times.

Although varying depths of puncture cannot be avoided in performing bleeding time tests, which may account for variations of a few minutes, the repeatedly prolonged times cannot be attributed to faulty technic when times of over 1 hour were found on more than one occasion. One can safely assume that in this condition the bleeding time was not only prolonged, but that the degree of prolongation varied.

2. Clotting Time.—On repeated tests the clotting time was between 4 and 7 minutes when done by the capillary glass method, and between 5 and 10 minutes when done by the tube method of Lee and White.

3. Clot Retraction.—Repeated tests showed good retraction from the walls and bottom of the test tube at 30 to 40 minutes. No liquefaction of the clot was observed after 18 to 24 hours.

4. Clotting Time of Hemophilic Blood Mixed with Decalcified Plasma of the Patient’s Blood.†—The blood of a hemophilic, whose clotting time by the multiple tube

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method of Lee and White at 37°C. was 2 hours and 45 minutes, was tested with the plasma of the patient (decalcified by a 5 per cent mixture of potassium and ammonium oxalate). The addition of 0.05 cc. of the patient’s decalcified plasma to 2 cc. of hemophiliac whole blood clotted the latter in 19 minutes. Normal plasma, similarly treated, clotted the hemophiliac blood in 15 minutes.

5. Formed Elements.—Repeated complete blood counts showed the patient to have normal formed elements. The red blood count ranged between 4.70 and 5.81 million, hemoglobin between 15 and 16 Gm., white count between 11,000 and 13,000 with normal differential, and platelet counts done on three occasions were 300,000, 236,000, and 156,000 respectively. The initial platelet count done when the patient’s bleeding time was over 2.5 minutes was 300,000.

6. Capillary Fragility Test.—Done with a blood pressure cuff midway between systolic and diastolic pressures, this procedure on repeated tests showed rare, scattered, minute petechiae, and was considered normal (negative). The test was done when the patient’s blood pressure was elevated as well as when it was normal.

7. Prothrombin Time.—Russell Viper Venom was employed as the source of thromboplastin. The clotting times repeatedly fell within 2 seconds of the control time.

8. Blood Chemistry.—Serum protein determination with albumin-globulin fractionation showed albumin 5.0 grams per cent, globulin 1.8 grams per cent. Plasma fibrinogen was 0.32 grams per cent.

Bromsulfalein test was normal (less than 5 per cent retention in 30 minutes using 2 mg. of the dye per kilo). Serum bilirubin was less than 0.3 mg. per cent.

Vitamin A absorption curve using Oleum Percomorph as a source of the vitamin was normal.

Vitamin C saturation test using 1000 mg. of “cevalin” (Lilly) intravenously gave a normal urinary output in 5 hours (344 mg.). The fasting vitamin C plasma level was 0.5 mg. per cent.

Serum calcium done on admission when there was clinical evidence of tetany was 7.36 mg. per cent. After 3 days of calcium lactate (15 gr. o.d.) the blood calcium was 10.1 mg. per cent, serum phosphorus 4.6 mg. per cent, alkaline phosphatase 5.7 Bodansky units, and the clinical signs of tetany were no longer present. Oral calcium therapy was discontinued after 10 days. Determinations done 1 week after discontinuing calcium therapy were: serum calcium 11.2 mg. per cent, phosphatase 3.9 Bodansky units. Clinical manifestations of hypocalcemia did not recur during the remainder of the patient’s hospital course. The cause of the initial low serum calcium cannot be readily explained. That low blood calcium is seldom if ever a factor in disturbances of the blood clotting mechanism has been indicated by Quick. X-rays of the long bones showed no evidence of demineralization.

9. Capillary Studies.—Following the work of Macfarlane and his suggestion that the intrinsic physiological disorder in this condition was related to the failure of the capillaries to constrict after trauma, studies on the status of the patient’s capillaries were undertaken. Under the microscope the capillaries at the nail bed appeared to be normal in distribution and contour. After puncturing an isolated loop no constriction of the loop was seen. This was done on a finger of each hand.
The following photographs of the patient’s nail bed capillaries, taken before and after puncture of a capillary loop, demonstrate the failure of constriction of the traumatized, punctured capillary.*

CONCLUSIONS

1. A case of hereditary pseudohemophilia is presented in which the condition was transmitted by and occurred only in the male line. The occurrence of the condition in the male offspring of the patient’s father and of the latter’s second wife irrefutably proves this point.

2. The degree of prolongation of the bleeding time varied from day to day, and was occasionally normal.

3. Except for transient hypocalcemia with tetany, no defect in the blood elements nor in clot formation was noted.

*Done with the cooperation and technical aid of Dr. A. Wilbur Duryee, Department of Medicine, New York Post-Graduate Medical School and Hospital, New York City.
4. There appears to be a failure of normal capillary constriction following trauma. This finding confirms the original observations of Macfarlane. Whether or not this physiological defect is entirely responsible for the prolonged bleeding time is not proved, but is under further investigation.

REFERENCES

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