HEREDITARY PSEUDOHEMOPHILIA

Report of 4 Cases

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ABNORMAL bleeding is a frequent clinical problem, and as a rule its diagnosis offers the clinician little difficulty. In the majority of patients with hemorrhagic diathesis the bleeding is associated with (1) an altered permeability of the capillary endothelium, allowing the escape of erythrocytes from the blood vessels, or (2) an abnormality of the clotting mechanism itself. Increased vascular permeability may be due to a platelet deficiency, as in thrombocytopenic purpura, or to impairment of the endothelial nutrition, as in vitamin C deficit. Various drugs, toxins, and possibly certain allergic states are also responsible for capillary injury and increased permeability capable of producing abnormal bleeding. Hemorrhagic diseases such as hemophilia, hypothrombinemia, and afibrinogenemia are associated with a defective clotting system.

An atypical variety of hemorrhagic diathesis occurs, however, which does not conform to the entities embraced by the usual classification of bleeding problems. Known as hereditary pseudohemophilia, this disease is characterized by excessive bleeding associated with prolonged bleeding time, normal platelets, without demonstrable defect in the clotting mechanism, and normal clot retraction.

Case Reports

Case 1. A boy, aged 6, was referred because of abnormal bleeding since infancy. He had bled profusely from minor wounds, and several times slight cuts had produced bleeding which lasted for several hours. At the age of 3 he had fallen, causing severe bleeding from the throat and mouth for twenty-four hours. This had necessitated hospitalization for four days. After this episode he was apparently asymptomatic until three weeks before admission, when he developed a sore throat which lasted for one week and was followed by continuous oozing and bleeding from the oral cavity for two weeks. For three days prior to admission the patient had epistaxis.

The past medical history was negative and he was otherwise in perfect health. Family history disclosed that the mother was a "bleeder," but other cases of bleeding in the family could not be discovered.

On physical examination the blood pressure was 88/68 and the temperature 98.6 F. There were no petechiae; however, the tourniquet test was positive. There was some dried blood present in the left nostril and several areas of petechiae over the soft palate. A small hematoma was noted on the gingival margin in the left upper molar region. There was a soft pulmonic systolic murmur. The liver and spleen were not palpable, and there was no lymphadenopathy.

Examination of the blood on June 13, 1939, revealed 9.5 Gm. of hemoglobin (Haden-Hausser) per 100 cc., 3,860,000 erythrocytes, 8750 leukocytes, and 450,000 platelets per cu. mm.; bleeding time (Duke method) was more than thirty minutes; coagulation time (Lee-White) was fifteen minutes and prothrombin time (Quick) seventeen seconds (normal

seventeen seconds). The clot retraction was normal. Examination of the blood smears revealed a normal differential count and no abnormal cells. The blood Wassermann and Kahn tests were negative.

For the next month the patient received injections of Lederle's moccasin venom, 0.5 cc. every four days, and no bleeding occurred during this time. One year later the patient felt well but was again having excessive bruising and bleeding from small cuts. In March and May, 1943, he bled from the left tonsil, and in both instances the bleeding responded to several injections of snake venom. On February 20, 1946, the patient slipped on the icy sidewalk and his left leg doubled underneath him. He developed a large ecchymotic area about the left thigh with soft tissue swelling. A roentgenogram of the leg showed no fracture, but soft tissue calcification was noted and thought to be the result of an old hemorrhage.

The blood studies on February 20, 1946, approximately eight years after his first visit revealed the hemoglobin to be 9.8 Gm. (Haden-Hausser) per 100 cc., and there were 4,100,000 erythrocytes, 7900 leukocytes and 720,000 platelets per cubic millimeter. The bleeding time (Ivy method) was stopped after twenty-five minutes, and the coagulation time (four test-tube method) was ten minutes. Clot retraction was normal, but the clot was more friable than usual.

Case 2. A woman, aged 37, mother of the first patient, submitted to an examination at our request. Though she had always regarded herself as a "bleeder" she had never sought medical advice. As a child she had suffered from severe nose bleeds, particularly about the ages of 6 and 7 and during severe colds. She had had two permanent teeth removed and the bleeding was extreme on each occasion. She bruised easily and her gums bled freely even on slight trauma. Menstruation had always been normal and she had had abnormal vaginal bleeding on only two occasions. Six years before admission and twelve days following the birth of her only son, she had developed severe vaginal bleeding. In spite of two weeks of futile effort by the attending physician to stem the blood flow, it continued and became alarming. A hysterectomy was performed without difficulty. There was no subsequent vaginal bleeding, and the incision healed without undue oozing. She had continued to bruise easily. Past history was irrelevant. No history of familial hemorrhagic disease could be elicited.

On physical examination the blood pressure was 130/80 and the pulse 72. There were numerous bruises over her entire body, but the tourniquet test was negative. The liver and spleen were not palpable, and there was no lymphadenopathy.

Blood and hemorrhagic studies at this time disclosed 12.5 Gm. of hemoglobin (Haden-Hausser) per 100 cc., 4,610,000 erythrocytes, 7050 leukocytes, and 230,000 platelets per cubic millimeter. The bleeding time was more than one hour and forty-five minutes, the coagulation time was eleven minutes (Lee-White) and the prothrombin time (Quick) was fourteen seconds (normal nineteen seconds). The clot retracted normally. Examination of the blood smear was negative.

Case 3. A boy, aged 3, was admitted to the Cleveland Clinic Hospital on June 6, 1940, with severe epistaxis of six days' duration. He had bled to the point of extreme danger, and in spite of two blood transfusions the bleeding had remained uncontrollable. The child had experienced frequent easy bruising since infancy, and he had always bled excessively from small cuts. One year previously he had bled for twenty-four hours from a small cut on his tongue. In 1939 the patient had epistaxes lasting many days, but never with the vigor of his present one. Hemoptysis, hematuria, melena, or hemarthrosis had never been noted. However, he had vomited "almost a quart of blood" soon after onset of the present illness. He was otherwise in good health. Family history revealed that the patient's father was a "bleeder," and one of his great uncles on the paternal side was reported to have died of hemorrhage from a wound on his thigh at the age of 17.

The physical examination disclosed an acutely ill, pale, and exsanguinated child with rapid respiration. The temperature was 99 F. and pulse 124. The blood was dropping freely from both nostrils, and there were numerous dime-sized purpuric spots on the arms and legs. The tourniquet test was negative. A soft apical systolic murmur was present. The liver and spleen were not palpable, and there was no lymphadenopathy.

An examination of the blood on June 5, 1940 revealed 4.7 Gm. of hemoglobin (Haden-

Hausser) per 100 cc., 1,730,000 erythrocytes, and 450,000 platelets per cu. mm. The bleeding time (Duke method) was thirteen minutes, coagulation time (Lee-White) was five minutes; prothrombin time (Quick) was twenty seconds (normal nineteen seconds). Clot retraction was normal. The blood smear was negative. The blood Wassermann and Kahn tests were negative. Calcium was 9.3 mg. and plasma fibrinogen 269 mg. per 100 cc. of blood.

The child was admitted directly to the hospital and was given immediate transfusion. Bleeding decreased rapidly, and by the next day it had completely subsided. He was discharged after the third day and was placed on calcium carbonate, vitamin C, and occasional injections of snake venom. On October 10, 1940, the patient returned. He was continuing to have occasional epistaxis. Blood examination disclosed 10.0 Gm. hemoglobin (Haden-Hausser) per 100 cc., 10,650 leukocytes, and 500,000 platelets per cu. mm. The bleeding time (Duke) was twenty-eight minutes, clotting time (Lee-White) seven minutes, and there was normal syneresis.

The patient was not again heard of until recently, when through correspondence with his father we learned that the child had died on October 20, 1944. He had grown progressively worse and had had frequent nose bleeds, each more severe. He had developed hemarthrosis in both knees. He died following an episode of uncontrollable nasal hemorrhage that failed to respond to five blood transfusions.

Case 4. A man, aged 44, father of case 3, was examined at our request. He gave a history of severe nasal hemorrhages in earlier years. In 1921 he had had epistaxis "almost continuously" for sixteen days. He had experienced similar episodes throughout his entire childhood and at times had bled until he was quite pale and extremely weak. The epistaxis was unrelated to trauma and often began at night while he was asleep. For the past twenty-five years there had been bleeding from the gums, which upon two occasions was excessive, and which was so easily provoked that he had been unable to brush his teeth for many years. He had not had any extractions. There had been no hemoptysis, hematuria, melena, or hematemesis. He had one child aged 3 (case 3) who was a "bleeder" and another, aged 6, who was normal. One uncle on the maternal side had died at the age of 17 following uncontrollable hemorrhage from a wound on his thigh.

Upon physical examination his temperature was 99 F., pulse 84, and blood pressure 108/72. There was some bleeding from the gums and poor oral hygiene with fetor and pyorrhea. The heart had a grade 2 basal systolic murmur. The tourniquet test was negative. The spleen and liver were not palpable, and there was no lymphadenopathy.

Examination of the blood revealed 13 Gm. of hemoglobin (Haden-Hausser) per 100 cc., 4,890,000 erythrocytes, 5050 leukocytes, and 320,000 platelets per cubic millimeter. The bleeding time (Duke) was one hour and ten minutes; clotting time (Lee-White) was seven minutes. The clots retracted normally. Prothrombin time (Quick) was nineteen seconds (normal nineteen seconds). Fasting blood sugar was 106 mg. per cent. The serum calcium was 10.1 and plasma fibrinogen 292 mg. per 100 cc. The blood Wassermann and Kahn tests were negative. The blood vitamin C was 0.30 and 0.40 mg. per 100 cc.

On November 29, 1946, this patient was continuing to bleed from his gums and to bruise easily. Bleeding time (Ivy method) was still prolonged, being eighty-eight minutes; clotting time (four test-tube method) was eighteen minutes, and prothrombin time (Quick) was fourteen seconds (normal fifteen seconds). The hemoglobin (Haden-Hausser) was 11.5 Gm. per 100 cc.

Pathogenesis

The true pathogenesis of hereditary pseudohemophilia remains obscure. Glanzmann,[1] when describing his patients, speculated upon a functional deficiency in the platelets themselves as a basis for the prolonged bleeding. It was he who first named this condition "hereditary hemorrhagic thrombasthenia." Morawitz and Jürgens[2] and von Willebrand and Jürgens,[3] using an apparatus

called a capillarthrombometer, claim to have shown that the platelets in such cases do not agglutinate as rapidly as normal ones. They postulated that the disease was due to some qualitative defect in the platelets which prevented their agglutination within a normal time. Buckman,[4] however, was unable to demonstrate any abnormality in the blood platelets and found that the addition of a suspension of platelets from a patient with hereditary pseudohemophilia to hemophilic blood caused as rapid coagulation as a suspension of platelets from a normal person. Since the majority of these cases exhibit normal syneresis, it seems reasonable to conclude that the defect responsible for the abnormal bleeding may be elsewhere than in the platelets.

By means of direct visualization of the capillaries in the nail bed, MacFarlane[5] demonstrated a capillary defect in patients with pseudohemophilia. He noted the response of a normal capillary when injured by means of a glass fibre, and he compared the normal reactors with 5 cases of pseudohemophilia. He found that the platelets were of normal morphology in all 5 cases, and they could be visualized clumping actively in contact with the glass. The capillaries in the patients with pseudohemophilia, however, were distorted and displayed bizarre forms, and they did not constrict normally after injury in any instance. Perkins,[6] also studying the capillary loops in the human nail bed, was unable to demonstrate constriction of these vessels when subjected to trauma. These authors concluded that there is a functional defect in the capillaries themselves which is responsible for the excessive bleeding.

Symptomatology

Clinically, patients with pseudohemophilia are indistinguishable from those with thrombocytopenia. The bleeding tendency is as pronounced, and fatalities occur. One of our patients died from uncontrollable hemorrhage. The condition is usually noted in infancy and may be present at birth. It occurs in both sexes with almost equal frequency, being slightly greater in women in the small series so far reported. The age incidence of pathologic bleeding extends from infancy to old age, but as a general rule, as Minot[7] has pointed out, the severity tends to diminish as the patient grows older.

The paramount symptom of pseudohemophilia is the tendency to bleed severely from minor wounds. Epistaxis is present in practically all cases. Easy bruisability and the formation of large ecchymoses, sometimes spontaneously but more often post-traumatically, are next in frequency. Petechiae appear quite rarely. Bleeding from the mucous membranes is often present, especially hemorrhage from the gums and following tooth extractions. Frequently these patients are unable to brush their teeth because of the bleeding that ensues. Recurrent hemorrhage from the gastrointestinal tract, uterus, and kidneys has been reported. Hemarthrosis occurred in 1 of our patients, though its occurrence may be considered a rarity. The course of the disease is characterized by periods of apparent remission from symptoms, and there is no correlation between the bleeding time and the clinical severity.

Diagnosis

The principal and only consistently abnormal hematologic feature of pseudohemophilia is the prolonged bleeding time. This is an extremely variable factor, however, and it fluctuates in any given case from nearly normal to greatly prolonged. The coagulation time is normal, the platelets are normal and in some cases are increased. The prothrombin time, plasma fibrinogen, and blood calcium are not altered. The clot retraction is consistently normal in pseudohemophilia. The tourniquet test (Rumpel-Leede) is variable, being mildly positive in less than half of the cases and much less frequently positive than in true thrombocytopenia.

The disease must be differentiated from true hemophilia, in which the tendency to hemorrhage is accompanied by a prolonged coagulation time and a normal bleeding time, the antithesis of pseudohemophilia. The coagulation time of recalcified plasma, a test considered pathognomonic for hemophilia, is prolonged in that disease and normal in pseudohemophilia. In addition the characteristic hereditary pattern of hemophilia serves to distinguish the two diseases. The thrombocytopenic purpuras must also be excluded before the diagnosis of pseudohemophilia can be made. In this disorder the tendency to bleed is associated with a pronounced decrease in the number of circulating blood platelets which are normal in pseudohemophilia. The bleeding is usually of a chronic nature, though it may be acute. In thrombocytopenia the coagulation time is normal, the bleeding time prolonged, and the clot retraction poor or absent. The tourniquet test (Rumpel-Leede) is almost always positive in thrombocytopenic purpura. Hereditary pseudohemophilia may be distinguished from the so-called vascular purpuras by the presence of petechiae, a positive tourniquet test, and a normal bleeding time in the latter disease.

Treatment

The treatment of this disease is nonspecific and generally unsatisfactory. Various measures such as large doses of calcium, vitamin K, and ascorbic acid have been employed and have proved ineffectual. No real improvement has been obtained by the use of moccasin venom. Since the spleen is not involved in the pathogenesis of this disease, splenectomy is not indicated and may indeed be hazardous. Blood transfusions are useful in combating the anemia, but they are of little value in controlling the hemorrhage itself. Treatment with pressure bandages applied locally and the application of topical thrombin and fibrin foam are the most helpful measures of controlling bleeding.

Prognosis

Though the prognosis is exceedingly good in patients with pseudohemophilia, it is important to recognize the presence of the disease and to be cognizant of the fact that certain serious consequences may follow surgical procedures. Unlike hemophilia, in which blood transfusions or plasma will shorten

the coagulation time and control hemorrhage, or thrombocytopenic purpura in which splenectomy assures control of bleeding in most cases, there is no successful method of combating hemorrhage in pseudohemophilia. Patients, therefore, should not be subjected to elective operation.

Discussion

Though Glanzmann[1] in 1918 has been credited as the first to recognize this atypical hemorrhagic diathesis as a disease entity, it is doubtful that his cases represent true examples of pseudohemophilia. His patients were unusual in that they had a normal coagulation time and a normal platelet count, with the defect lying in the retraction of the clot, which was abnormal or completely absent, rather than in a prolonged bleeding time, which was normal. It is more likely that von Willebrand[8] in 1926 should be considered the first to have described this unusual form of bleeding, since he reported it among 16 women and 7 men in four generations of a family of 58 members. The characteristic factor about those cases was the occurrence of a prolonged bleeding time in the presence of a normal number of platelets and a normal coagulation time. Von Willebrand[8,9] first suggested the term "hereditary pseudohemophilia" as applied to this type of bleeding disorder.

Additional reports of hereditary pseudohemophilia have since appeared in the literature. Buckman[4] observed a family in which the disease was transmitted by the males and had occurred in four generations. Minot[7] also reported the transmission of the disease through the male in four generations of a family in which it affected both sexes. Fowler[10] observed two families in which the disease was transmitted by both males and females through several generations. On the other hand, Giffin[11] reported a case in which the disease was transmitted directly by the women through four generations. It has been observed in a Negro by Bailey and McAlpin[12] and appears to be inherited as a dominant Mendelian character residing on the X chromosome. A recent comprehensive review of the literature on pseudohemophilia has been made by Estrin, Sanchez Medal, and Dameshek,[13] who added 11 cases of their own to 62 cases found in the literature in which there was sufficient data to warrant the diagnosis of hereditary pseudohemophilia.

Summary

1. Patients with hereditary pseudohemophilia present the same clinical picture as those having idiopathic thrombocytopenic purpura.

2. The pathogenesis appears to be a defective retraction of the capillaries in response to injury.

3. The hemorrhagic studies show a normal coagulation time, normal platelets, normal clot retraction, and a considerably prolonged bleeding time.

4. There is no successful treatment for this disease, and surgical procedures of an elective nature are contraindicated.

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