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REVIEW ARTICLE

Glanzmann's Thrombasthenia: The Spectrum of Clinical Disease

By James N. George, Jacques P. Caen, and Alan T. Nurden

GLANZMANN'S THROMBASTHENIA is a well-defined inherited disorder of platelet function.[1-11] It is caused by a deficiency or abnormality of the membrane glycoprotein (GP) IIb-IIIa complex with bleeding due to defective platelet hemostatic plug formation. Thrombasthenia has achieved much recognition for such a rare disease because it has been important in defining GP IIb-IIIa as a platelet receptor for fibrinogen and other adhesive proteins, and it has provided a model for understanding the molecular basis of platelet aggregation. Thrombasthenia is also familiar from a clinical perspective because the diagnosis must be considered in patients presenting with the common problems of purpura, a normal platelet count, abnormal platelet aggregation, and a long bleeding time.[12]

Although the membrane GP abnormalities of Glanzmann's thrombasthenia have been carefully studied[5-11] and genetic defects are being described,[13-15] the clinical aspects of the hemorrhagic disease are not well-documented. In this review the data on 177 patients are analyzed: previously published data on 113 patients are supplemented with the description of 64 patients who have been studied in Paris over the past 33 years. The opportunity to observe the nature and severity of the bleeding manifestations among these 177 patients has allowed us to define the clinical spectrum of thrombasthenia. The opportunity to follow the 64 patients in Paris for many years has provided data on the course and prognosis of the hemorrhagic disease. These observations provide a basis for discussing the management of patients with Glanzmann's thrombasthenia and other disorders of platelet function.

CLINICAL OBSERVATIONS

Patient selection. This study reviews the clinical observations on 177 patients. Data for 113 patients are reviewed from published reports: 10 studies have published concise case descriptions of 38 patients[16-25]; three other studies have discussed 75 patients, providing data on age, sex, and family background, and describing the major bleeding complications.[26-28] Sixty-four patients, representing 51 individual families, have been studied in Paris, France, during the past 33 years at the Hopital Lariboisiere under the direction of Professor Jacques Caen (Table 1). Clinical summaries on 18 of these patients have been published previously.[1,29,30] Many observations in this review were only possible because of the complete data available on the patients studied in Paris. When this group of 64 patients is discussed separately to make a particular point, they are referred to as "the Paris patients." All patients were diagnosed by the presence of a normal platelet count, normal platelet morphology, a long bleeding time, absent or severely diminished platelet aggregation by adenosine diphosphate and other agonists, normal platelet agglutination by ristocetin, and normal plasma coagulation studies. Clot retraction was absent or severely diminished in the patients classified as type I in Table 1, it was present in the patients classified as type II, and it varied from absent to normal in the patients classified as variants. These criteria allow the diagnosis of thrombasthenia to be made quickly and definitively in a routine clinical laboratory.

Occurrence of Glanzmann's thrombasthenia. The rarity of this disease and its uneven geographic distribution is demonstrated by the fact that only 12 of the 177 patients have been reported from the United States.[18,19,21,22,24] Fifty-five patients were from Israel and Jordan,[23,27,28] and 42 from South India.[26] The cause for this uneven distribution is the frequent occurrence of intermarriage in these regions, allowing expression of autosomal recessive traits and suggesting a rare occurrence of asymptomatic heterozygous subjects. The frequency of consanguinity among 84 patients from the literature, for whom data were available, was 67%. The 64 Paris patients represented a diverse genetic spectrum since only 2 of these 51 families (families 16 and 17, Table 1)[30,31] are known to be related to one another, yet the frequency of consanguinity was high (39%). The association of thrombasthenia with consanguinity is further emphasized by the observation that 10 of the families studied in Paris were of North African or Middle Eastern origin and three families were gypsies, in whom intermarriage may be an accepted custom. Therefore, although Glanzmann's thrombasthenia is typically a rare disorder, it can be almost as frequent as

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Table 1. Glanzmann's Thrombasthenia. Biographic Data, Platelet GP IIb-IIIa Content, and Clinical Observations on 64 Patients Studied in Paris, 1956 to 1989

	Patient	Age, Sex	Platelet GP IIb-IIIa	Clinical Observations	References
Type I: severe GP IIb-IIIa deficiency					
1a	A Bla	22F	<2*	No transfusions required for epistaxis. Severe bleeding only at menarche, requiring transfusions. Death from intrahepatic hemorrhage at age 22.	2,8
1b	C Bla	31F	<2†	Neonatal purpura. Severe epistaxis as a child, requiring many transfusions. Mild bleeding disorder as an adult. Normal pregnancy and delivery.	1,2,7,9,10,29,61,64,65,73
2a	Nad Ait	8F	<2†	Frequent hospitalizations and transfusions for epistaxis.	
2b	Nah Ait	4F	—	Frequent hospitalizations and transfusions for epistaxis. One episode life-threatening.	
3	E Ech	3F	<2‡	Petechiae at age 1 mo. Purpura and GI hemorrhage at age 2 years.	7,61
4	L DaC	1F	<2‡	Severe neonatal purpura. Required transfusion in infancy.	
5	J Leb	32F	<2‡	Many hospitalizations and transfusions for epistaxis as a child.	7,61
6	G Luc	61M	<2‡	Very mild, has never had epistaxis or gingival bleeding. Transfused twice for bleeding duodenal ulcer, ages 38 and 46. Isoantibody against GP IIb-IIIa persistant for 15 years.	51-57,64
7	M Zem	17M	<2‡	Transfused for recurrent epistaxis.	
8	J Rou	36F	<2*	Many transfusions for childhood epistaxis, minimal disease now.	
9	F Lat	33F	<2*	Frequent transfusion for epistaxis as a child. Normal pregnancy and delivery.	
10a	Am Bo	10F	<2†	Very mild disease. Never transfused.	
10b	As Bo	13M	—	Severe, recurrent GI hemorrhage, indication for marrow transplant at age 5. Now normal except for mild GVHD.	49
11	A Mer	33F	<2*	Many transfusions for childhood epistaxis and at menarche. No transfusions since menarche. One episode of deep venous thrombophlebitis as an adult.	
12a	A Cau	36M	<2§	Transfused three times for epistaxis, ages 6 to 10. No transfusions since.	1,2,3,29,23,56,64,66
12b	M Cau	45M	<2§	Mild disease. Transfused once for epistaxis at age 10.	1,2,29,64,66
13	B Jou	46M	<2‖	Severe epistaxis and bleeding with an appendectomy as a child. Minimal bleeding since.	1,29
14	M Teb	18M	<2†	Many transfusions for epistaxis and gingival bleeding.	10
15	M Tor	19F	<2‖	No childhood bleeding, no epistaxis. Transfused first at menarche and also after a tooth extraction.	
16a	J Haa	26F	<2¶	Many transfusions for epistaxis, GI hemorrhage at age 6, and menorrhagia. Has had two normal pregnancies and deliveries.	30,31
16b	S Haa	28F	<2¶	Neonatal purpura. Many transfusions for epistaxis and gingival hemorrhage as a child. Normal pregnancy and delivery.	30,31
17	F Wei	23F	<2¶	Recurrent GI bleeding age 1, then only minor bleeding until menarche. Persistent menorrhagia.	30,31

(*Continued on following page*)

hemophilia and von Willebrand disease in regions where consanguinity is common.[26]

Patient age. The average age (at the time of the latest examination or of the literature report) of the 113 patients for whom age was known was only 20. Most patients were diagnosed before age 5, many at birth or during early infancy.[16-20,22,23,26,27] Because the mortality of thrombasthenia is low, the young age reflects the recent era in which the diagnosis has been established and the minimal symptoms in most adults. It would be of interest to know if patients with thrombasthenia are protected from atherosclerotic disease, since platelets have a postulated role in the pathogenesis of atherosclerosis[32] and therapeutic inhibition of platelet GP IIb-IIIa function prevents thrombosis.[33-37] There are no reports of myocardial infarction or stroke in patients with thrombasthenia, but only 5 of these 177 patients were over 50 years old, therefore little or no thrombotic disease would be expected.

Patient sex. Among the 113 patients from the literature, 60 (53%) were female, consistent with the known autosomal inheritance. The proportion of females among the Paris patients (66%) was greater than expected, probably re-

Table 1. Glanzmann's Thrombasthenia. Biographic Data, Platelet GP IIb-IIIa Content, and Clinical Observations on 64 Patients Studied in Paris, 1956 to 1989 (Cont'd)

	Patient	Age, Sex	Platelet GP IIb-IIIa	Clinical Observations	References
18	N Adi	51F	<2¶	Moderate epistaxis and gingival bleeding.	56
19a	S Chi	10F	<2‖	Repeated platelet transfusions for epistaxis, 2 episodes of hematuria, and 1 episode of GI hemorrhage.	
19b	R Chi	6F	—	Minimal symptoms. Never transfused.	
20	S Mor	29F	2-5‡	Neonatal purpura. Multiple episodes of epistaxis requiring transfusion up to age 20. No transfusions since.	
21	E Bau	32F	2-5†	Moderate severity. Normal pregnancy and delivery.	60,61
22	S Har	17F	2-5‡	Minimal disease with epistaxis and ecchymoses. Never transfused.	7,61
23a	R Alo	26F	2-5‡	Mild disease. Transfused twice for bleeding with loss of deciduous teeth and at menarche.	6,7,8,61
23b	I Alo	33F	—	Transfused three times: minor trauma, menarche, and near-fatal postpartum hemorrhage.	
23c	M Alo	35M	2-5‡	Mild disease with no transfusions until age 35; then 10 episodes of epistaxis, each requiring transfusion, also requiring internal maxillary artery embolization to control bleeding.	6,8
24	G Car	15F	—	No significant bleeding until transfusion required at menarche. Mild disease since.	
25	J Fra	36M	—	Epistaxis as a child requiring multiple transfusions. Minimal bleeding after age 22.	
26a	A Lee	11M	—	Transfused many times for epistaxis. Required internal maxillary artery embolization three times.	
26b	C Lee	5F	—	Transfused only once, for epistaxis.	
27	L Lou	10F	—	Neonatal purpura. Moderately severe bleeding, primarily epistaxis.	
28a	M Mel	14M	—	Neonatal purpura. Transfused seven times, primarily for epistaxis, until age 7. No transfusions since.	
28b	K Mel	11M	—	Transfused only once for teeth extractions.	
28c	A Mel	7M	—	Transfused once for epistaxis.	
29	M Rei	16M	—	Many transfusions for epistaxis.	
30a	Mo Sai	30M	—	Hemoptysis at age 9 mo. Many transfusions for epistaxis, ages 2 through 4, also meningeal hemorrhage after head trauma. Less severe bleeding as an adult.	
30b	Ma Sai	24F	—	Frequent transfusions for epistaxis and melena, ages 3 through 7. Transfusions required for initial menstrual periods.	
31	V Lie	32M	—	Transfused three times for epistaxis as a child and for a bleeding ulcer at age 20. Mild disease since.	1,3
32	R Lop	18F	—	Transfused only twice: traumatic hemarthrosis at age 10 and at menarche.	
33	C Bus	41F	—	Minimal epistaxis. First transfusion at menarche.	1
34a	J Fer	11M	—	Transfused only at the time of a fatal car accident, age 11.	1
34b	L Fer	33M	—	Mild disease. Transfused only for the car accident, a tooth extraction, and an appendectomy.	1
35	S Jeu	24F	—	Neonatal purpura. Many transfusions for epistaxis and for initial menstrual periods.	1
36	A Sar	9F	—	Died of hemorrhage, unknown site, age 9.	1
37	R Win	1F	—	Lost to follow-up after initial hospitalization for epistaxis requiring transfusion.	1

(*Continued on following page*)

flecting the serious problem with menorrhagia. Four women (Paris patients 15, 24, 33, and 42) were initially diagnosed because of severe bleeding at the time of menarche, when hemorrhage is typically severe and hospitalization for transfusion usually required.

Hemorrhagic symptoms. The nature of the bleeding in Glanzmann's thrombasthenia is clearly defined in these 177 patients (Table 2). Purpura, epistaxis, gingival hemorrhage, and menorrhagia are nearly constant features.

Purpura typically appears in areas of pressure or minor trauma. Spontaneous petechiae are uncommon and always few in number. A diffuse petechial rash, typical of severe

Table 1. Glanzmann's Thrombasthenia. Biographic Data, Platelet GP IIb-IIIa Content, and Clinical Observations on 64 Patients Studied in Paris, 1956 to 1989 (Cont'd)

	Patient	Age, Sex	Platelet GP IIb-IIIa	Clinical Observations	References
Type II: moderate GP IIb-IIIa deficiency					
38	N Cham	42F	10*	Mild disease except for severe hemorrhage postpartum and after hemorrhoid surgery.	
39	B Rot	28F	12¶	Frequent severe epistaxis beginning at age 22 and continuing to the present time requiring frequent transfusions.	7,9
40	A Dom	26F	12*	Transfused only three times: at menarche, during pregnancy, and for near-fatal postpartum hemorrhage	6,8
41	J Her	50F	12†	Continual ecchymoses and gingival bleeding. Transfused three times: at menarche, for severe postpartum hemorrhage, and after tubal ligation.	1,2,3,7,9,10,29,56,61,64,66
42	G Chat	37F	15†	Minimal disease, never transfused. Normal pregnancy and delivery.	1,7,61,64,65
43	M Pau	30F	20§	Transfusions for tonsillectomy and menorrhagia. Normal pregnancy and delivery.	9,10
44	B Hei	34M	—	Minimal disease. Transfused twice for epistaxis at ages 4 and 7. Active practicing physician.	
45	C Co	7F	—	Transfused once at age 7 for gingival bleeding. Killed in a car accident the same year.	1
46	D Le G	35M	—	Transfused once at age 10 for epistaxis. No significant bleeding problems since.	1
Variants: dysfunctional GP IIb-IIIa with no or minimal deficiency					
47	A Pav	18M	50/20†	Mild epistaxis. Never transfused.	66,72
48	C Man	29F	100§	Never transfused. Two normal pregnancies and deliveries.	7,9,10,11,71,73
49	M Sch	16F	60§	Traumatic intracerebral hematoma at age 6. Transfused at menarche.	
50	R Pel	60M	50†	Never transfused. Plays rugby. No excessive bleeding even after four wisdom teeth extracted without platelet transfusions.	7,9,10,11,66,70
51	C Gna	14F	60§	Multiple transfusions for epistaxis and menorrhagia.	

The 64 patients representing 51 families are presented who have been studied in Paris at the Hopital Lariboisiere under the direction of Professor Jacques Caen. Siblings are listed with the same number. The patient's age represents the age at the time of the latest evaluation. Platelet GP IIb-IIIa was measured by CIE, Western blot, and/or MoAb binding and the results are given as the percent of normal. The method of GP measurement on the individual patients is identified by the suprascript notation: *, CIE + WB; †, CIE + Western blot (WB) + MoAb binding (MAb); ‡, WB only; §, CIE + MoAb; ‖, MoAb only; ¶, CIE only. Two values are given for patient 47 because his platelet GP IIb-IIIa content was estimated to be 20% by MoAb binding to unstimulated platelets, but to be 50% by CIE and MoAb binding to thrombin-activated platelets.[72] Patients in whom these measurements were not performed were classified as types I or II as described in the text. Siblings were assumed to share the same degree of GP IIb-IIIa deficiency when no direct measurements were performed. Major clinical events are noted. Although many descriptions seem redundant, they emphasize the common clinical features of thrombasthenia, while other observations emphasize the discrepency between the severity of GP IIb-IIIa deficiency and the bleeding manifestations. In the clinical descriptions, transfusion refers only to the transfusion of red cells or whole blood. All patients received either red cell or platelet transfusions, given for bleeding episodes or before procedures, except patients 47 and 50. References are given where the original data from studies on each patient are reported. These patients were referred by the following physicians: Dr Bellucci, Professor Tobelem, and Professor Caen (patients 1, 10, 12, 21, 31, 41, 42, 44, 50), Drs Scrobohaci and Drouet (patients 13, 14, 43, 51), Drs Torchet and Gazengel (patients 4, 7, 26, 27, 28), Professor Alagille (patients 33, 34), Dr Conard and Professor Samama (patient 38), Drs Paty and Rodrigue (patient 2), and Professor Wautier (patient 20), all of Paris; Professor Cazenave (patients 16, 17, 49), Strasbourg; Dr Hourdille (patients 8, 9, 11, 29), Bordeaux; Professors Juhan and Orsini (patients 3, 30, 36), Marseille; Dr Parquet (patients 5, 22, 48), Lille; Dr Le Fur and Professor Castel (patient 46), Brest; Dr Saleun (patient 6), Brest; Professors Coutel and Morel (patient 35), Rennes, France; Dr Pico (patients 15, 23, 32, 40), Barcelona, Spain; Dr Bevers (patient 25), Maastricht, The Netherlands; Dr Schlegelberger (patient 39), Kiel, West Germany; Professor Hardisty (patient 47), London, England; Dr Nunes (patient 24), Lisbon, Portugal; and Drs Behnam and Al-Attar (patients 19), Baghdad, Iraq.

Abbreviations: GI, gastrointestinal; GVHD, graft-versus-host disease.

thrombocytopenic purpura, does not occur. The exception to this rule was that 7 of the 64 Paris patients presented with diffuse petechial hemorrhage at birth (patients Ib, 4, 16b, 20, 27, 28a, 35) and neonatal purpura was also described in 9 of 22 patients reported from Israel.[23] This is likely to be related to the petechial hemorrhages that can be found by careful inspection of most normal newborn infants, apparently caused by compression during vaginal delivery and the resulting increased venous pressure. Two studies found petechiae in half (173 of 348) of normal neonates.[38,39] Therefore, the neonatal purpura in thrombasthenic infants can be considered the result of greater susceptibility to birth trauma. This is consistent with the observation that purpura in older children and adults is related to minor trauma, and that spontaneous petechiae are rare.

Epistaxis is the most common cause of severe bleeding in

Table 2. Bleeding in Patients With Glanzmann's Thrombasthenia

	No. of Affected Patients	Frequency (%)
Symptoms		
Menorrhagia	54/55	98
Easy bruising, purpura	152/177	86
Epistaxis	129/177	73
Gingival bleeding	97/177	55
Gastrointestinal hemorrhage	22/177	12
Hematuria	10/177	6
Hemarthrosis	5/177	3
Intracranial hemorrhage	3/177	2
Visceral hematoma	1/177	1
Severity		
Requirement for red cell transfusions		
Patients from literature*	32/48	67
Paris patients	54/64	84

Data are from 113 patients presented in the literature,[16-28] and 64 patients presented in Table 1. The frequency of each type of bleeding in the patients reviewed from the literature was often noted only in concise comments or tables, and may represent only the more prominent symptoms. The actual occurrence of purpura, epistaxis, and gingival bleeding may be nearly universal among these patients if careful observations are performed over a long time. As discussed in the text, it is not clear if spontaneous hemarthrosis, intracranial hemorrhage, or visceral hematomas occur. When these hemorrhages were fully described, a predisposing cause was apparent or suspected.

*Information was not available for all patients.

thrombasthenia. The common childhood habit of nose picking, combined with the vulnerability of the superficial, rich plexus of arterioles located between bone or cartilage and delicate mucosa, makes epistaxis a very common phenomenon in normal children.[40-42] In thrombasthenia, epistaxis is typically more severe in childhood, an exaggeration of the very frequent occurrence of mild epistaxis among normal children between ages 4 through 10.[41,42] Severe epistaxis is unusual in adult patients, and this may be the primary reason for the impression that the risk of bleeding in thrombasthenia decreases with age.[1,2,29] For example, Paris patients 12a, 12b, 44, and 46 had 1 to 3 episodes of severe epistaxis requiring red cell transfusions between ages 4 through 10, but they have had no significant bleeding and no transfusions in the 25 to 35 years since (Table 1). However, the inevitable exceptions are illustrated by patient 23c, who had minimal epistaxis as a child but then had 10 episodes, each requiring red cell transfusion, when he was 35 years old; and patient 39, who has had frequent severe epistaxis only since age 22 (Table 1).

Gingival bleeding is another constant feature. It is often a reflection of poor dental hygiene, and is less common in patients who have regular and thorough dental care. Gingival bleeding is rarely associated with major acute blood loss, but it is a common cause of iron deficiency.

Menorrhagia is a critical hemorrhagic problem. Bleeding at menarche represents a particular risk, and was severe enough to require transfusions in most patients. This is consistent with the prolonged proliferative estrogen stimulation of the initial anovulatory cycles, that can cause greater and more prolonged bleeding with the first menstrual periods in normal adolescent women.[43-46] More severe hemorrhage with the initial menstrual periods is another physiologic explanation for the apparent greater risk of bleeding in younger patients. Only one patient is specifically described as having normal menstrual bleeding at menarche.[17]

Hemorrhage of any other type was rare. Consistent with the mucocutaneous pattern of bleeding in thrombasthenia, gastrointestinal hemorrhage may occur, and appears to be a greater risk among young children. Hematuria has occurred in 10 of the 177 patients. Hemarthrosis has been reported in five patients: in four the circumstances were not described[23,26]; the Paris patient 32 developed hemarthrosis of her knee at age 10 after trauma while playing soccer. Only three patients have had intracranial hemorrhage: one case was not described,[26] the other two were among the Paris patients. Patient 30a had a meningeal hemorrhage after head trauma as a child, and patient 49 had an intracerebral hematoma after a fall at age 6, which required surgical evacuation. It is important to note that spontaneous deep visceral hematomas that are characteristic of disorders of coagulation, such as retroperitoneal hematomas, have not been observed except for the intrahepatic hematoma that occurred in patient 1a (described below).

Spontaneous, unprovoked bleeding is actually uncommon in Glanzmann's thrombasthenia. Severe bleeding typically occurred in association with physiologic or pathologic conditions that cause bleeding in normal subjects. Neonatal purpura, childhood epistaxis, gingival bleeding associated with poor dental hygiene, and menorrhagia at menarche could all be described as exaggerations of normal bleeding. Bleeding after trauma or surgical procedures may also be severe. In one series, 10 of 12 infants undergoing circumcision without preparative platelet transfusion had excessive bleeding,[28] and 3 of 11 patients in another series were first diagnosed because of hemorrhage at circumcision.[27] Tooth extractions without platelet transfusions are commonly associated with excessive bleeding,[28] and bleeding can be severe even with the spontaneous loss of deciduous teeth.

Pregnancy and delivery represent a particularly severe hemorrhagic risk in women with thrombasthenia. In normal women, blood flow to the placenta at term is estimated to be 600 mL/min, and this must be staunched promptly at the time of placental separation.[47] The most effective hemostatic control mechanism at delivery is uterine contraction to obliterate the lumens of the severed arterioles and veins.[47] Despite normal hemostasis, normal women lose an average of 500 mL of blood at vaginal delivery, and 900 mL at cesarian section.[48] Therefore, the risk for hemorrhage in thrombasthenia is obvious. Pregnancy itself is not a serious risk; vaginal bleeding severe enough to require transfusions occurred only once in 21 pregnancies (Table 3). Two other patients had complications of pregnancy without excessive bleeding. Delivery was complicated by severe hemorrhage on 6 of 19 occasions. All 13 uncomplicated deliveries were performed after a platelet transfusion, and platelet transfusions were commonly continued for up to 6 days postpartum. Platelet transfusion did not always prevent severe vaginal hemorrhage, which occurred as late as 13 days after delivery (Paris patient 40), and recurred up to 4 weeks later.[23] For example, one of the Paris patients (patient 40) was transfused with platelets before a normal vaginal delivery and then kept in the hospital without complications for 9 days, but life-

Table 3. Pregnancy and Delivery in Patients With Glanzmann's Thrombasthenia

Patients	16
Pregnancies	21
Complications of pregnancy	3
Vaginal hemorrhage	1
Spontaneous abortion	1
Cesarian delivery of dead fetus	1
Live births	19
Cesarian section	6
Hemorrhagic complications	0
Vaginal delivery	13
Postpartum hemorrhage	6

Twelve patients are from the Paris group and they are referred to by their number in Table 1. Four patients are from references 22, 23, and 25. Patient 40, who had vaginal bleeding during her second trimester, is the only patient who required transfusion during pregnancy. The spontaneous abortion (patient 43) and delivery of the dead fetus (patient 42) were managed with platelet transfusions without excessive bleeding. Cesarian deliveries were performed on patients 16a (twice), 16b, and 42, and patients from references 23 and 25 with both pre- and postoperative platelet transfusions without excessive bleeding. Vaginal deliveries were performed with platelet transfusions in patients 1b, 9, 21, 23b, 38, 40, 41, 43, and 48 (twice), and in patients from references 22 and 23. Severe postpartum hemorrhage occurred in patients 23b, 38, 40, and 41, and also with both deliveries in one patient from reference 23.

threatening uterine hemorrhage, to a hematocrit of 12%, began at home on the 13th postpartum day. None of six patients delivered by cesarian section, with platelet transfusions continued until wound healing was complete, suffered from excessive bleeding. Even though normal women lose almost a liter of blood with an uncomplicated cesarian section, twice as much as with a vaginal delivery,[48] this operative procedure may avoid the complication of adherent pieces of placenta or the accumulation of large blood clots that can inhibit uterine contraction. Uterine contraction is stimulated by a rapid infusion of oxytocin as soon as the infant's shoulder is delivered, and full contraction for effective hemostasis can be directly observed.[47]

Severity of hemorrhage. In contrast to the well-defined nature of the bleeding in thrombasthenia, the severity of bleeding was not predictable. Thrombasthenia is certainly a severe hemorrhagic disease, as 54 (84%) of the Paris patients have required red cell transfusions. However, some patients have never had serious bleeding, and most have been healthy and free of bleeding complications throughout their adult lives. The unpredictability of severe hemorrhage is best illustrated by the inconsistency between siblings, who presumably share the same genetic defect. For example, patient 10a has never required a red cell transfusion and was given platelets only once, when purpura developed during varicella at age 2. In contrast, her brother (patient 10b) was the most severely affected among the Paris patients. He had recurrent severe gastrointestinal hemorrhage that was only controlled when an allogeneic bone marrow transplant at age 5 corrected his genetic defect.[49] Appreciable differences in the severity of bleeding were also noted between the siblings of families 1, 19, and 26 (Table 1).

Isoantibody formation. A possible complication of transfusion therapy is the development of an isoantibody against GP IIb-IIIa, since GP IIb-IIIa on transfused platelets is strongly immunogenic[50] and it is deficient and/or structurally abnormal in thrombasthenia. However, this has been documented only once among the Paris patients (patient 6),[51-57] even though only two patients (patients 47 and 50) have not been transfused with either red cells or platelets. Patient 6 is one of the least symptomatic patients of the Paris group. He has never required a platelet transfusion and has been transfused with red cells only twice, at ages 38 and 46 (1966 and 1974) for a bleeding duodenal ulcer. His isoantibody, presumably stimulated by the presence of platelets in the red cell transfusions, has been persistent but clinically insignificant. This isoantibody reacts with the intact GP IIb-IIIa complex on all normal platelets, and also binds to the dissociated GP IIb polypeptide.[55] Three other thrombasthenic patients have been reported who developed isoantibodies to GP IIb-IIIa, which reacted primarily with GP IIIa.[50,58,59] Two further patients may have developed similar isoantibodies.[57,60] Perhaps the presence of some residual platelet GP IIb-IIIa may protect many patients from isosensitization.

MOLECULAR ABNORMALITIES OF PLATELET GP IIB-IIIA

The measurements of GP IIb-IIIa available on the Paris patients are presented in Table 1. No comparable data are available for the patients reviewed from the literature. Patients with severe GP IIb-IIIa deficiency (less than 5% of normal) were designated type I (78% of the patients); patients with moderate GP IIb-IIIa deficiency (10% to 20% of normal) were designated type II (14%); and patients with half-normal to normal GP IIb-IIIIa, whose primary defect appeared to be in the receptor function of GP IIb-IIIa rather than a molecular deficiency, were designated as variants (8%). The classification of types I and II was originally proposed by Caen in 1972,[2] before the GP IIb-IIIa abnormality was discovered,[3] on the basis of platelet fibrinogen content and clot retraction. Because 26 of the 64 patients presented in Table 1 were not studied for their platelet content of GP IIb-IIIa, it is assumed that some of these patients may not be accurately assigned. For example, some patients classified here as type I in whom platelet GP IIb-IIIa was not measured could have a variant disorder with dysfunctional GP IIb-IIIa. Despite these possible inconsistencies, the classification of types I and II is a convenient way to describe this group of patients, and it facilitates the comparison of clinical disease with the molecular abnormalities. It is not meant to imply a universal standard for Glanzmann's thrombasthenia, or even the existence of distinct categories of this disease.

Although many type I patients studied by Western blotting demonstrate traces of residual GP IIb and GP IIIa, up to about 10% of normal,[61-63] none of the patients had more than a trace of intact platelet GP IIb-IIIa complex detectable by crossed immunoelectrophoresis (CIE) or monoclonal antibody (MoAb) binding. Platelets from all type I patients had absent or severely deficient fibrinogen and no or minimal clot retraction. Binding of exogenous fibrinogen was absent or negligible in four patients (patients 1a, 1b, 12a, 12b).[64] In contrast, type II patients had equivalent amounts of GP IIb and GP IIIa, greater than 10% of normal, present as an

intact platelet surface GP IIb-IIIa complex, and their platelets were able to bind an equivalent amount of exogenous fibrinogen (10% to 23% of normal in patients 41 and 42[64,65]). Type II patients all had normal or only moderately diminished clot retraction, and substantial amounts of platelet fibrinogen demonstrable by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and measured to be 30% to 58% of normal in patients 41 and 42.[7,66] Assuming that α-granule fibrinogen is largely acquired from plasma by megakaryocytes or platelets after surface binding to the GP IIb-IIIa receptor,[67-69] the presence of platelet fibrinogen in these patients is consistent with the intact fibrinogen receptor function of their residual plasma membrane GP IIb-IIIa. When only SDS-PAGE analysis and platelet function testing were available, patients were designated as type I (patients 24 through 32) or type II (patient 44) on the basis of clot retraction and the absence or presence of platelet fibrinogen on SDS-PAGE analyzed samples (eg, see Fig 12, reference 6 or Fig 41-1, reference 8 for a comparison of family 23, designated "GT 1-3" in the figure, and patient 40, "GT 4"). Eight patients who have not been studied since 1966[1] were designated as type I (patients 33 through 37) or type II (patients 45 and 46) on the basis of absent or present clot retraction. The GP IIb-IIIa concentration of the patients designated as variants was either normal or within the range of asymptomatic heterozygous subjects, and the platelet fibrinogen concentration and clot retraction varied from absent to normal.[70-73] Relevant data on patients 49 and 51, who have not been previously published, are discussed below.

CORRELATION OF CLINICAL DISEASE WITH THE PLATELET MOLECULAR ABNORMALITY

Most clinical observations demonstrated no correlation between the amount of platelet GP IIb-IIIa and the severity of hemorrhagic disease. This discrepancy is emphasized by the different bleeding symptoms between siblings who presumably share the same genetic defect (discussed above). Eight Paris patients did not present with their first hemorrhagic symptoms until adolescence or adulthood, and four of these patients (patients 6, 15, 24, 33) had severe GP IIb-IIIa deficiency. Patients 38, 39, 40, and 41, who have 10% to 12% of normal platelet GP IIb-IIIa that can function as a fibrinogen receptor, have had repeated episodes of extremely severe hemorrhage. In contrast, the brothers 12a and 12b are among the least affected of the 64 Paris patients, despite essentially undetectable platelet GP IIb-IIIa and absent platelet fibrinogen binding. All seven of the Paris patients who presented with neonatal purpura had severe GP IIb-IIIa deficiency (type I), suggesting the possibility that at times there may be a correlation between clinical symptoms and the degree of the platelet membrane abnormality.

The Paris patients designated as variant thrombasthenia were heterogeneous both in their molecular and clinical manifestations. Two of these five patients (patients 47 and 50) are the only ones of the Paris group who have never been transfused with either red cells or platelets. Data on these two patients have been published[70,72]: both have about half normal GP IIb-IIIa, half-normal to normal platelet fibrinogen, and normal clot retraction. Patient 48 also has mild disease, has never required a red cell transfusion, and has had two normal pregnancies and vaginal deliveries, but she has no platelet fibrinogen and absent clot retraction.[71] Data for the other two patients with variant thrombasthenia have not been published. Patient 49 has an abnormality similar to patient 48 (abnormal dissociation of the GP IIb-IIIa complex and absent platelet fibrinogen), but she has had more severe bleeding complications. Patient 51 has absent platelet fibrinogen, absent clot retraction, and severe hemorrhagic disease. In the original description of a family from San Diego with a variant type of thrombasthenia, the patients had a normal platelet content of GP IIb-IIIa, but absent platelet content and binding of fibrinogen and absent clot retraction, and severe hemorrhagic symptoms.[74]

Eighteen of the Paris patients with type I thrombasthenia have been studied by Western blot analysis: 15 had detectable GP IIIa and 7 had detectable GP IIb.[61] In the patients with only demonstrable GP IIIa, it may exist as a heterodimer complex on the platelet surface with the vitronectin receptor α-subunit.[75,76] It has been postulated that the presence of vitronectin receptor function in platelets with residual GP IIIa may partially protect the patients from hemorrhage.[75] Only two of the Paris families had a complete deficiency of both GP IIb and IIIa by Western blot analysis (families 1 and 2; see Fig 12, reference 7 for an illustration of patient 1b), and therefore would also be deficient in the platelet membrane vitronectin receptor. The two sisters of family 2 both have severe hemorrhagic symptoms. Patient 1b had severe problems with epistaxis as a child,[1] but she has had relatively mild disease as an adult and had an uncomplicated pregnancy and delivery. Her sister, patient 1a, died from complications of an intrahepatic hematoma (described below), but she had minimal bleeding symptoms as a child and did not require transfusion until hemorrhage occurred at menarche. These observations suggest that the absence of the vitronectin receptor does not increase the risk for hemorrhage.

It has been suggested that cells other than megakaryocytes and platelets may be abnormal in Glanzmann's thrombasthenia, and this could be a basis for heterogeneous bleeding symptoms. Because the GP IIIa component of the GP IIb-IIIa complex is present in many tissues as the β subunit of the vitronectin receptor,[77-79] it is possible that an abnormality in the GP IIIa gene may be expressed in cells other than megakaryocytes and platelets. Abnormalities have been reported in fibroblast[80-82] and monocyte function.[83] However, examination of one thrombasthenic patient with absent platelet GP IIb-IIIa demonstrated normal GP IIIa in vascular endothelial cells, vascular smooth muscle cells, and fibroblasts.[84,85] One report suggested that normal monocytes contained intrinsic GP IIb-IIIa, which was deficient in a patient with thrombasthenia,[86] but subsequent studies demonstrated that GP IIb-IIIa on monocytes was the result of adsorbed platelet membrane fragments or platelet contamination of the monocyte preparation.[87-89]

The critical range of GP IIb-IIIa concentration can be defined by these clinical observations and by observations on heterozygous subjects. The bleeding problems of the patients

with type II thrombasthenia demonstrate that more than 10% functional GP IIb-IIIa is required to provide adequate hemostasis for severe challenges, such as obstetrical delivery. Heterozygous subjects, who have about half the normal platelet concentration of GP IIb-IIIa, have no significant bleeding, or at most, some minor bruising that is difficult to distinguish from normal.[23,28,90,91] Because residual GP IIb-IIIa is evenly distributed among circulating platelets in thrombasthenia,[92] a 50% concentration, but not 10%, must be sufficient for normal hemostasis. Fifty percent GP IIb-IIIa may be required to provide enough fibrinogen binding sites to include the majority of platelets within a developing hemostatic plug. Fifty percent GP IIb-IIIa may also be necessary for normal platelet adhesion to subendothelium at the high shear rates of microvascular blood flow.[93-95]

The clinical observation that normal hemostasis can be preserved despite absent platelet fibrinogen binding and aggregation suggests that other platelet functions can compensate for this deficiency. The observation that severe bleeding can occur after events such as childbirth, despite substantial platelet fibrinogen-binding function, suggests that a great hemostatic contribution is required from platelets to meet serious hemostatic challenges.

MANAGEMENT

Management can be described simply as supportive care. The most important measures are to anticipate risks and attempt to prevent bleeding with the judicious use of platelet transfusions. In contrast to normal subjects, in whom the risk of bleeding is best anticipated by the history,[96] bleeding in thrombasthenia can be so unpredictable that platelet transfusions before an invasive procedure appear indicated even in patients with minimal past hemorrhagic symptoms. Platelet transfusions should be continued until wound healing is complete. The potential risk of alloimmunization by HLA antigens is the same as in any transfused patient; the special risk of isoantibody formation against GP IIb-IIIa appears to be very rare and not a reason to withhold platelet transfusion. Antifibrinolytic drugs, epsilon aminocaproic acid (EACA) and tranexamic acid,[97] have been reported to be effective in controlling hemorrhage in thrombocytopenic patients,[98] but their efficacy in thrombasthenia remains uncertain. Their use is more clearly indicated in the management of teeth extractions (see below). Desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) has been tried in some patients with Glanzmann's thrombasthenia without published evidence of efficacy.[99,100]

Local bleeding can almost always be controlled by local measures. For example, epistaxis and gingival bleeding are successfully controlled in most patients by conventional conservative measures with application of gel foam soaked in topical thrombin, or nasal packing.[101] However, two of the Paris patients (patients 23c and 26a) with recurrent, severe nasal hemorrhage required embolic occlusion of the internal maxillary artery.[102,103] Regular dental care to carefully clean the teeth and remove plaque is essential to prevent gingival bleeding. Local anesthesia for dental procedures with pericemental injections of lidocaine with 1:100,000 epinephrine can be given without risk of serious bleeding. For teeth extractions, or for hemorrhage accompanying the loss of deciduous teeth, hemostasis can be significantly improved by the application of individually prepared plastic splints that fit snugly over the teeth and gums and provide physical support for hemostasis. Systemic EACA administration has become conventional therapy for managing teeth extractions in patients with hemophilia,[104,105] and it should be used as an adjunct to platelet transfusions in patients with thrombasthenia. A dose of 40 mg/kg four times daily is given, and EACA syrup (25 g/dL) is a convenient form.

Control of menstrual bleeding is a major problem. Severe menorrhagia, usually associated with an excessively proliferative endometrium caused by estrogen dominance, can be effectively treated by a high dose of a 19-norprogesterone, such as norethindrone acetate, 5 mg every 4 hours. Bleeding usually stops within 24 hours, then the dose can be decreased to 5 mg twice a day and continued for 3 weeks. Menstrual bleeding will occur on withdrawal but it should not be severe. Maintenance treatment with birth control pills, such as a combination of 2.5 mg norethindrone acetate and 0.05 mg ethinyl estradiol, should then begin.[44,46] More than one pill daily may be required to prevent breakthrough bleeding. Birth control pills control menorrhagia by causing progressively more atrophic endometrium during the initial cycles. In normal women who take birth control pills, menstrual blood loss is typically reduced by half.[46] The initiation of birth control pill treatment before the first menstrual period, which predictably causes severe hemorrhage in thrombasthenia, has been suggested but not substantiated as efficacious treatment. Menarche is a late event of puberty, preceded by the adolescent growth spurt and the appearance of breast development and pubic and axillary hair. Therefore, the initial menstrual bleeding could be anticipated and birth control pills started without risk of premature epiphyseal closure.

Finally, the frequent occurrence of iron deficiency anemia must be emphasized. Because as little as 5 mL of blood loss per day, containing 2.5 mg of iron, matches the ability of the intestine to absorb iron,[106] iron deficiency can develop insiduously with only minor bleeding, such as gingival oozing. During periods of rapid growth in infants and adolescents when iron requirements are greater, iron deficiency is expected. Maintenance therapy with oral iron is good practice.

PROGNOSIS

Although thrombasthenia can be a severe hemorrhagic disease, the prognosis should be excellent with careful supportive care. Bleeding problems may be critical, recurrent, and even intractable for periods of time, but when bleeding is controlled and anemia corrected, the patients are normal. Only 2 of the 64 Paris patients (patients 1a and 36) have died of hemorrhage. Patient 1a was healthy and active until she developed an intrahepatic hematoma. Surgical drainage was required when the hematoma recurred after platelet transfusion therapy, and death followed a complicated hospital course. It is possible that this fatal hemorrhage was related to a hepatic complication of oral contraceptive use: vascular focal nodular hyperplasia, peliosis hepatis, or periportal sinusoidal dilatation.[107] Patient 36 was said to have

died of hemorrhage at age 9 in 1963. Her records are not now available and the cause of death cannot be determined. Only one other hemorrhagic death has occurred among the 113 patients reviewed from the literature: a 2-year-old girl who died of gastrointestinal bleeding in 1949.[18] Six of the Paris patients (patients 8, 13, 30, 31, 41, and 46) and seven patients from the literature[23,24,28] had siblings who were thought to have died of hemorrhage. All of these deaths were in children less than 7 years old, four were in infants. The site of hemorrhage was known in nine patients: gastrointestinal bleeding was the cause of death in three patients, and other causes were epistaxis, tongue laceration, hemorrhagic measles, hemorrhage after splenectomy, and hemorrhage after circumcision. However, it is difficult to evaluate the significance of these deaths, as at least five occurred more than 40 years ago and nothing can be determined about the medical care.

The most objective assessment of prognosis is provided by the follow-up of the 15 patients originally described from Paris 23 years ago.[1] One patient was promptly lost to follow-up and three have died: one from hemorrhage (patient 36) and two in automobile accidents many years ago. The other 11 are well and their disease has minimal effect on their normal daily lives.

LESSONS FROM THROMBASTHENIA FOR OTHER DISORDERS OF HEMOSTASIS

Inherited disorders of platelet function. The clinical bleeding problems of Bernard-Soulier syndrome, an inherited defect of platelet membrane GP Ib-IX and GP V,[4-9] appear to be identical to thrombasthenia.[108] Bleeding may be severe but it is sporadic and often unpredictable. Distinctly different severity of bleeding symptoms between siblings has also been observed in Bernard-Soulier syndrome.[8] Only three occurrences of hemarthrosis were reported among 54 patients, and two were said to be posttraumatic.[108] Intracerebral hemorrhage occurred only twice in these 54 patients, and in the one patient in whom the circumstances were described, it was the result of severe trauma.[108] Whether the bleeding may be more severe in Bernard-Soulier syndrome than in thrombasthenia because thrombocytopenia regularly occurs, with platelet counts as low as 20,000/μL,[108,109] is not clear. The gray platelet syndrome is an inherited defect in α-granule formation with deficiencies of regulated secretory proteins, such as fibrinogen, von Willebrand factor, and thrombospondin.[4,5,7] It is a rare disorder and the clinical features are not well-described; however, the bleeding symptoms would be expected to be similar to thrombasthenia. The principals of management described for patients with thrombasthenia should be fully applicable to patients with other congenital disorders of platelet function.

Acquired disorders of platelet function. With the enormous consumption of aspirin, the frequent hospital use of parenteral β-lactam antibiotics, the ability of many drugs and foods to diminish platelet function, and the occurrence of abnormal platelet function in hematologic and other systemic diseases, acquired abnormalities of platelet function are probably the most common hematologic disorder.[110] When significant hemorrhage occurs in these patients, it is often assumed to be related to abnormal platelet function because the bleeding time is prolonged and platelet aggregation is abnormal. However, the contribution of these disorders to clinical bleeding is uncertain, and only with aspirin has an increased risk for significant bleeding been definitively demonstrated.[111] The clinical experience with thrombasthenia demonstrates that absent platelet aggregation and a prolonged bleeding time are not good predictors of clinical bleeding, and the inability of the bleeding time to predict clinical bleeding was also documented in a recent extensive analysis.[112] The abnormality of platelet function is typically much more severe in thrombasthenia than in the acquired disorders of platelet function, yet bleeding in thrombasthenia is unpredictable and can be minimal. Therefore, the acquired platelet function defects may often have no or negligible clinical significance.

The etiology of bleeding in systemic diseases that has been postulated to result from abnormal platelet function can be more clearly understood by comparison to the bleeding symptoms in thrombasthenia. For example, patients with chronic renal failure can have bleeding suggestive of abnormal platelet function, such as purpura, epistaxis, and menorrhagia, but other bleeding complications reported in uremic patients do not occur in thrombasthenia: retroperitoneal hematomas, mediastinal hematomas, and hemorrhagic pleural and pericardial effusions.[110] Therefore, these visceral hemorrhages should be attributed to other hemostatic abnormalities, such as the mucosal lesions of uremia and complications of heparin anticoagulation used for dialysis.

Three patients have been reported with an acquired thrombasthenia caused by autoantibodies against GP IIb-IIIa that blocked platelet fibrinogen binding and aggregation.[113-115] The clinical bleeding symptoms of these patients were identical to the symptoms described here. One patient, who had multiple myeloma and a monoclonal paraprotein with antibody specificity for GP IIIa, died of gastrointestinal hemorrhage.[113]

The therapeutic use of MoAbs against platelet membrane GP IIb-IIIa to prevent thrombosis[33-37] creates a new acquired disorder of platelet function analogous to thrombasthenia. Studies on the infusion of these MoAbs have demonstrated the occupation of most platelet GP IIb-IIIa, and the expected inhibition of platelet aggregation.[33,34,36,116] Significant hemorrhagic complications have not been observed. The infrequency of spontaneous hemorrhage in patients with Glanzmann's thrombasthenia, particularly the apparent absence of intracranial hemorrhage without trauma, support the potential safety of this therapy for acute situations of limited duration. However, the therapeutic use of MoAbs to GP IIb-IIIa in conjunction with thrombolytic agents may increase the risk for hemorrhagic complications.

Coagulation disorders. Thombasthenia and hemophilia (congenital factor VIII or IX deficiency), a model for coagulation disorders, share some clinical features. Epistaxis in children is nearly universal in both diseases, gingival bleeding and purpura with minor trauma are very common, and bleeding into the central nervous system is very rare in both disorders, even before the era of effective transfusion treatment for hemophilia.[117] Gastrointestinal hemorrhage and

hematuria occur in both disorders with approximately the same frequency.[117] But the clinical contrasts are more striking. Bleeding in hemophilia is typically delayed in onset, due to initially effective platelet hemostasis, but then oozing can continue for many days.[105,117,118] In contrast, bleeding in thrombasthenia is manifested promptly after trauma. Hemarthrosis occurs in all patients with severe hemophilia, and recurrent hemarthroses cause joint deformities and chronic arthritis,[105,117] while spontaneous hemarthrosis probably does not occur in thrombasthenia. Intramuscular hematomas occurred in 97 of 98 patients in Birch's 1937 series[117]; these have not been reported in thrombasthenia. Perhaps because of tissue damage from recurrent hemarthroses and other deep tissue hemorrhage, bleeding in hemophilia often appears to be unprovoked, while in thrombasthenia bleeding most often occurs as an exaggeration of a physiologic or traumatic event.

The risk for serious hemorrhage in hemophilia is directly related to the plasma activity of residual factor VIII or IX.[118] Patients with severe deficiencies predictably have a severe bleeding disorder; patients with only 5% factor VIII or IX have a significantly milder disease.[105,118,119] No such correlation between severity of bleeding and the level of functional platelet GP IIb-IIIa can be demonstrated among patients with thrombasthenia. Patients with nearly undetectable GP IIb-IIIa can have mild disease, while patients with platelet GP IIb-IIIa function that is 10% to 12% of normal can have recurrent, severe hemorrhagic episodes.

CONCLUSIONS

The nature of the bleeding symptoms is consistent in all patients with Glanzmann's thrombasthenia, and these symptoms can be used as a basis for understanding the clinical manifestations of platelet function disorders. The bleeding problems of thrombasthenia are distinct from the problems of patients with inherited disorders of blood coagulation. Based on these distinctions, a clinical assessment of patients who have acquired disorders of hemostasis, such as uremia, should assist the clinician in distinguishing bleeding due to defective platelet function from bleeding due to abnormal coagulation.

In contrast to the clearly defined nature of bleeding in thrombasthenia, the severity of bleeding is unpredictable. Truly spontaneous bleeding is uncommon, as most serious hemorrhagic episodes are the result of trauma or an exaggeration of physiologic bleeding. The severity of bleeding in thrombasthenia, in contrast to the experience in hemophilia, does not correlate with the severity of the platelet GP IIb-IIIa abnormality. Some patients with nearly absent GP IIb-IIIa have minimal bleeding problems, while severe and recurrent hemorrhage can occur in some patients who have substantial amounts of functional platelet GP IIb-IIIa. However, the importance of platelet GP IIb-IIIa for normal hemostasis is clear: patients with thrombasthenia can have serious hemorrhage while heterozygous subjects who have half normal levels of GP IIb-IIIa have no clinically significant bleeding. These clinical observations provide insight into the critical platelet concentration of GP IIb-IIIa required for normal platelet function.

With careful supportive care of patients with Glanzmann's thrombasthenia, many episodes of serious hemorrhage can be prevented, periods of recurrent bleeding can be controlled, and the prognosis for normal survival and an active life is excellent.

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