GLANZMANN'S THROMBASTHENIA

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ABSTRACT

During January 1981 to June 1991, 20 patients from 16 unrelated families were detected to have Glanzmann's thrombasthenia (GT). Twelve families (75%) had history of consanguinity, with 6 first cousins and 3 uncle-niece marriages; of these 7 were Muslims, 6 Hindus and 3 Christians.

There were 12 girls and 8 boys; the mean age at diagnosis was 7.05 ± 6.03 yr (range 1 day–22 yr). All cases had initial bleeding prior to the age of 5 yr with the mean age at the initial episode of bleeding being 2.21 ± 1.34 yr (range 1 day–5 yr). Common pattern of bleeding included epistaxis, gingival bleeding, post-traumatic bruises, menorrhagia, gastrointestinal (2 cases), post-operative (2 cases) and spontaneous bleeding (2 cases). No patient showed hemarthrosis, intracranial bleeding or hemoptysis. Menorrhagia was a serious problem necessitating repeated transfusions and hormonal therapy. Twelve cases (60%) required 1-120 units of blood transfusions while five received platelet concentrates.

Key words: *Autosomal recessive, Platelet aggregation, Platelet dysfunction.*

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Glanzmann's thrombasthenia (GT) is defined as a hemorrhagic diathesis associated with prolonged bleeding time, normal platelet count and absent macroscopic platelet aggregation in response to ADP or other platelet agonists(1,2). The biochemical lesion responsible for the disorder is a deficiency or abnormality of the platelet membrane glycoprotein, IIb/IIIa complex(3-5). Although rare, GT is the commonest of inherited platelet dysfunction syndromes(6). During January 1981 to June 1991 we observed 20 patients of GT from 16 unrelated families. This forms the second largest group of cases reported from India(7).

Material and Methods

Patients referred for suspected bleeding disorders were investigated for inherited or acquired defects of coagulation system, qualitative or quantitative disorders of platelet or excessive fibrinolysis. During January 1981 to June 1991, 132 families were diagnosed to have inherited defects of which 25 (18.9%) had platelet dysfunction. The diagnosis of Glanzmann's thrombasthenia was considered in a patient with normal platelet count, normal platelet morphology, prolonged bleeding time, absent platelet aggregation with ADP and other agonists, normal platelet agglutination with ristocetin and normal plasma coagulation studies (normal prothrombin time, partial thromboplastin time and Factor XIII screen)(1,2,7-9). The degree of clot retraction was analysed as described by Diggs(10). Accordingly, patients of GT were classified as Type I GT if clot retraction was absent, Type II GT if clot retraction was decreased (<30%) and variant if clot retraction was normal (>30%)(11,12).

Bleeding time was carried out by modified "Ivy method" using a disposable

spring-loaded device, *i.e.*,"Simplate" (supplied by Organon Teknika Corpn.) to make a standardized incision(13,14). Kaolin clotting time was used for evidence of platelet Factor III availability(15). *In vivo* platelet adhesion was measured using a modification of the method described by Borchgrevink(16).

Platelet aggregation studies were carried out using 4-channel Aggregometer (Aggre-Coder PA-3210, DIC Kyoto, Japan). Adenosine 5'-diphosphate (Disodium salt, Gr. I, Sigma) was used in concentration of 1.07 μg/ml, thrombin (Sigma) in concentration of 0.5 U/ml, collagen (Hormone-Chemie, Germany) in concentration of 1 μg/ml, adrenaline acid tartrate (Sigma) in concentration of 2 μM (0.1-10), while ristocetin sulphate (Lundbeck) in concentration of 1.25 mg/ml were used.

Results

Sixteen families of GT were diagnosed during January 1981 to June 1991. Their clinical details are shown in *Table I*. Four families had 2 siblings each where diagnosis of GT was confirmed and thus 20 members had GT (*Table I*). The mean age at diagnosis was 7.05 ± 6.03 years (1 day to 22 yrs). However, first episode of bleeding had occurred prior to age of 5 years in all, mean age of onset of bleeding being 2.21 ± 1.34 yrs (1 day to 5 yrs). There were 12 females and 8 males giving a ratio of 1.5 : 1. All gave history of epistaxis, gum bleeding and post-traumatic bruises. Six females had achieved menarche and all of them had menorrhagia. Two (10%) each had GI bleeding and post-tooth extraction bleeding. No patient gave history or showed any evidence of hemarthrosis, intracranial bleeding or hemoptysis. Similarly there was no history of bleeding from umbilical stump. A newborn delivered vaginally had multiple purpuric spots and bruises all over the skin.

Twelve out of 20 (60%) patients had severe bleeding necessitating 1 to 120 blood transfusions. Seven cases needed it repeatedly for severe epistaxis, 4 for menorrhagia and 1 to control post-tooth extraction bleeding. Only 5 patients received platelet concentrates probably because of lack of availability.

The results of laboratory investigations are shown in *Table II*. The cases were classified as type I GT in 75%, type II in 15% and variant in 10%.

Discussion

Glanzmann's thrombasthenia (GT) is a rare hereditary disorder of platelet function of which only 177 families have been reported in the world literature till 1990. The geographical distribution of cases has been grossly uneven with 55 families (31.1%) belonging to Israel and Jordan alone. Interestingly, the second biggest geographical region has been south India from where Khanduri *et al.* have reported 42 cases(7). Most of the other previous reports from India are of 1-3 cases(17-20).

In this series, hereditary platelet dysfunction syndrome accounted for 25 out of 132 families (18.9%) with inherited bleeding disorders seen by us during last 10½ years. Out of these 25 families, GT was seen in 16 families, Bernard Soulier syndrome in 4 and Hermansky Pudlak syndrome in 1 family; in 4 families the platelet dysfunction was not characterized. A high incidence of consanguinity (75% cases) was an expected finding for a rare disorder like GT. Khanduri *et al.* from Vellore found consanguinity in 71% cases(7). Although the mean age of presentation in our group was 7.05 ± 6.03 yr, the onset of bleeding was quite early, the mean age

TABLE I—*Major Clinical Features in Patients of Glanzmann's Thrombasthenia*

Family	Case No. Sex	Age at onset of bleeding (yr)	State of origin	Consanguinity	Clinical problems
1	1F	4.5	Goa	O	Men, EP, GI bleeding, ovarian irradiation
1	2F	3.5	Goa	O	Men, Ep
2	3F	1.5	Maharashtra	C	Ep, Men
2	4F	1.5	Maharashtra	C	Men
3	5F	3.5	Gujarat	C	Ep, GB
3	6F	1.0	Gujarat	C	Ep, Br.
4	7F	4.0	Andhra Pradesh	C	Men, Ep, GB
4	8F	2.0	Andhra Pradesh	C	Br, Ep
5	9F	2.5	Tamil Nadu	U-N	Ep, Br
6	10M	3.0	Tamil Nadu	U-N	Ep, Br, GI hemorrhage
7	11M	1.7	Kerala	C	Ep, Br
8	12M	1.0	Maharashtra	C	Ep, GB
9	13M	5.0	Tamil Nadu	U-N	Ep, GB
10	14M	2.0	Uttar pradesh	C	Br, Ep
11	15 F	2.0	Karnataka	O	Br
12	16M	2.0	Gujarat	O	Ep
13	17M	2.0	Goa	Nil	GB, Ep
14	18 F	1.0	Maharashtra	Nil	Men, Ep, Br
15	19M	1 day	Andhra Pradesh	Nil	Br, Neonatal purpura
16	20 F	0.5	Gujarat	Nil	Ep

F : Female; M : Male; U-N : Uncle Niece; C : First cousin; O : others; Men : Menorrhagia; Ep : epistaxis; Br : easy bruising; GB : gum bleeding.

being 2.21 ± 1.34 yr. In autosomal recessive disease, one expects almost equal number of male and female patients. The female preponderance (ratio 1.5 : 1) noted in present series was probably due to menorrhagia being a major presenting symptom in female. The severity of bleeding was not usually predictable; cases with normal clot retration often presented with significant bleeds. The severity also differed within 2 siblings of the same family (Family No. 1 to 4) (*Table I*). Severe epistaxis needing transfusion was found chiefly under the age of 10 years. This may be due to children damaging the nasal mucosa with finger nails or pencil. Menstrual bleeding was manageable in 5 out of 6 patients with oral contraceptive pills, but artificial menopause by ovarian irradiation had to be induced in one case (*Case 1*).

The exact biochemical defect in GT is deficiency or abnormality of platelet membrane glycoprotein IIb/IIIa complex(3-5). This protein acts as the fibrinogen

TABLE II–*Laboratory Investigations*

Investigation	Number (n = 20)
Bleeding time >15 min	20
Absence of platelet clumps in blood film	20
Clot retraction*	
Absent (GT Type I)	15
Impaired (GT Type II)	3
Normal (GT-variant)	2
Impaired (*in vitro*) platelet adhesion	17
Poor platelet factor 3 availability*	12
Absent platelet aggregation with ADP, thrombin, collagen and adrenaline	20

*Technique used as described in text.

receptor(4,5,21,22). Rarely, cases of acquired thrombasthenia have been reported(23,24).

Platelet transfusion forms the only effective therapy to control serious bleeding episodes. This should be used judiciously so as to avoid problems of allo-immunization. Management of menorrhagia is usually carried out successfully by administration of oral contraceptives. Bone marrow transplantation has ben tried in occasional cases of GT(25). However, most cases can be managed conservatively.

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REFERENCES

1. George JN, Nurden AT, Phillips DR. Molecular defects in interaction of platelets with the vessel wall. N Engl J Med 1984, 311: 1084-1082.
2. Nurden AT. Glycoprotein defects responsible for abnormal platelet functions in inherited platelet disorders. *In:* Platelet Membrane Glycoproteins. Eds George JN, Nurden AT, Phillips DR. New York, Plenum 1985, pp 357-371.
3. Nurden AT, Caen JP. An abnormal platelet glycoprotein pattern in three cases of Glanzmann's thrombasthenia. Br J Hematol 1974, 28: 233-240.
4. Phillips DR, Jenkins CSP, Luscher EF. Molecular differences of exposed surface proteins on thrombasthenic platelet plasma membranes. Nature 1975, 257: 599-605.
5. Phillips DR, Agin PP. Platelet membrane defects in Glanzmann's thrombasthenia. J Clin Invest 1977, 66: 535-539.
6. Reichert N, Seligsohn U, Ramot B. Clinical and genetic aspects of Glanzmann's thrombasthenia in Israel. Thromb Diath Hemorrh 1975, 34: 806-811.
7. Khanduri U, Pulimood R, Sudarsanam A. Glanzmann's thrombasthenia: a review and report of 42 cases from South India. Thromb Hemost 1981, 46: 717-722.
8. Caen JP, Castaldi PA, Leclerc JC. Congenital bleeding time and normal platelet count. Am J Med 1966, 41: 4-11.
9. Hardisty RM, Dormand KM, Hutton RA. Thrombasthenia: Studies of three cases. Br J Hematol 1964, 10: 371-377.
10. Diggs LW. Observation of the clot. Memphis Mid-south Med J 1962, 37: 381-388.

11. Holahan JR, White GC II. Heterogeneity of membrane surface proteins in Glanzmann's thrombasthenia. Blood 1981, 57: 174-179.

12. Lee H, Nurden AT, Thomaidia A, Caen JP. Relationship between fibrinogen binding and platelet glycoprotein deficiencies in Glanzmann's thrombasthenia Type I and Type II. Br J Hematol 1981, 48: 47-52.

13. Ivy AC, Shapiro PR, Melnick P. The bleeding tendency in jaundice. Surg Gynecol Obstet 1935, 60: 781-785.

14. Kumar R, Ansell JE, Canuso RT, Deykin D. Clinical trial of a new bleeding time device. Am J Clin Pathol 1978, 70: 642-646.

15. Hardisty RM, Hutton RA. The kaolin clotting time of platelet rich plasma: A test of platelet factor III availability. Br J Hematol 1965, 11: 258-262.

16. Borchgrevink CF. Platelet adhesion in patients with bleeding disorders. Acta Med Scand 1961, 170: 231-243.

17. Mehta BC, Agarwal MB, Bhanobe PC. Glanzmann's thrombasthenia. J Postgrad Med 1980, 26: 210-212.

18. Lokeshwar MR, Shah VJ, Avasthi BS, Prabhu SV, Agarwal MB. Glanzmann's thrombasthenia. Indian Pract 1984, 37: 1033-1038.

19. Saraya AK, Kasturi J, Kishan R. Platelet Factor III in Glanzmann's thrombasthenia. Acta Hematol 1972, 48: 116-124.

20. Mehta MN, Paseleh SJ, Kumta NB, Shah MD, Kirtane M. Glanzmann's Familial thrombasthenia. Indian Pediatr 1974, 11: 245-247.

21. Degos L, Dautigny A, Brouet JC. A molecular defect in thrombasthenic platelets. J Clin Invest 1975, 56: 236-240.

22. Hagen I, Nurden A, Bjerrum OJ. Immunochemical evidence for protein abnormalities in platelets from patients with Glanzmann's thrombasthenia and Bernard-Soulier Syndrome. J Clin Invest 1980, 65: 722-736.

23. Niessner H, Clemetson KJ, Panzer S. Acquired thrombasthenia due to GPIIb/IIa–specific platelet autoantibodies. Blood 1986, 68: 571-576.

24. DiMinno G, Coraggio F, Cerbone AM. A myeloma paraprotein with specificity for platelet glycoprotein IIa in a patient with a fatal bleeding disorder. J Clin Invest 1986, 77: 157-163.

25. Bellucci S, Devergie A, Gluckman E. Complete correction of Glanzmann's thrombasthenia by allogenic born marrow transplantation. Br J Hematol 1985, 59: 635-639.