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Pattern of bleeding and response to therapy in Glanzmann thrombasthenia

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Glanzmann Thrombasthenia (GT) is a rare autosomal recessive bleeding disorder affecting the megakaryocyte lineage. The incidence of this disorder is higher in communities where consanguinity is prevalent like Jordan, Iran, South India and Iraqi Jews [1,2]. The molecular basis shows the quantitative and/or qualitative abnormalities of the platelet fibrinogen receptor, the αIIbβ3 integrin (glycoprotein (GP) IIb/IIIa, CD41/CD61) which mediates the incorporation of platelets into an aggregate or thrombus at the sites of vessel injury [3]. Clinical manifestations in GT usually start in childhood and have clinical variability; ranging from minimal bruising to severe and potentially fatal haemorrhages. Diagnosis is associated with mucocutaneous bleeding with no platelet aggregation in response to all physiologic stimuli, a normal platelet count and morphology. Deficient or non-functional platelet αIIbβ3 should be confirmed using flow cytometry. Genetic studies reveal multiple mutations that can affect the GPIIb/IIIa complex assembly on the platelet membrane. Standard treatment includes platelet transfusion to stop bleeding when conservative measures fail, but repeated transfusions may result in the development of antibodies (alloimmunization) against GPIIb/IIIa and/or human leucocyte antigen (HLA), resulting in refractoriness to further platelet transfusion [4].

In Pakistan, consanguineous unions continue to be extremely common as in SouthWest Asia. The Pakistan Demographic and Health Survey (DHS) shows that two-thirds of marriages in Pakistan are consanguineous. As a result of consanguineous marriages, rare autosomal recessive disorders run in close families and tribes [5]. Therefore, the specific aim of this study was to assess the frequency of GT, to see the pattern of bleeding and their response to therapy in our patients by comparing them over worldwide presentation.

This is a retrospective study of GT patients who were diagnosed and followed at the National Institute of Blood Disease & Bone Transplantation (NIBD), Karachi, Pakistan from October 2008 to November 2011. The study was approved by the Institutional ethics committee, informed consent was obtained from all adult subjects, parents or legal guardians. The data were taken from hospital medical records which included outpatient files, emergency department notes, operative reports and inpatient charts. Information for each clinical encounter was recorded and tabulated. Patients were diagnosed on the basis of clinical suspicion of the disease, normal platelet count on complete blood counts (CBC), prolonged bleeding time (BT), normal prothrombin time (PT), activated partial thromboplastin time (APTT), normal to suboptimal platelet aggregation in the presence of ristocetin and defective aggregation with collagen, ADP and epinephrine. Patients with other coagulation and platelet function disorders were excluded from this study. Platelet aggregation studies were done on platelet-rich plasma (PRP) with a count adjusted to 200–250 $\times$ 10^9 L^{-1} by Helena Agg RAM using ristocetin, adenosine diphosphate (ADP), epinephrine and collagen. The following demographic and clinical data were obtained: age, gender and type of bleeding symptoms i.e. epistaxis, bruising, gum bleeding, bleeding at circumcision (in males), bleeding at dental extraction, muscle bleed, haematoma, subcutaneous bleed, haematuria, haematemesis, gastrointestinal(GI) bleeding, ear bleeding and menorrhagia (in females). Information was also obtained on the number of bleeding episodes, hospital visits, requiring or not requiring admission, duration of bleeds between two consecutive episodes were recorded and responses of the symptoms to different treatment modalities were observed. The initial treatment offered for minor bleeds was local haemostatic measures such as pressure bandage, ice therapy and antifibrinolytic agents such as tranexamic acid. Platelet transfusions were used if bleeding failed to stop and in the presence of severe bleeding, dental procedures and surgery. Response was assessed and when no response was observed another treatment modality such as DDAVP or rFVIIa was added to the treatment regimen and the response assessed. Female patients presented with episodes of menorrhagia were treated with oral contraceptives, tranexamic acid, iron supplements and if needed with platelet transfusions. If a patient required any other treatment modality, they were considered as non-responders for the previously offered treatments. The response to treatment was measured from the initiation of treatment until complete cessation of bleeding in less than 6 h, in more than 6 h, less than 24 h and more than 24 h and labelled as responders. Patients were considered as non-responders when they continued to bleed for more than 36 h from the start of the initial treatment.

The statistical package SPSS-13 was used to analyse the data. Frequency and percentage were computed for categorical variables and mean and standard deviation (SD) were estimated for quantitative variables.

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Table 1. Bleeding type per number of episodes recorded and the number of patients who had presented with that type of bleeding.

Type of bleeding	Bleeding per total number of episodes	% episodes	Number of pts with bleeding	% of patients
Epistaxis	129/173	74.5%	29/43	67.4%
Gum bleeding	121/173	70%	19/43	44.1%
Easy bruising	107/173	61.8%	25/43	58.1%
Gastrointestinal bleeding	41/173	23.6%	9/43	21%
Circumcision	12/173	7%	*12/20	60%
Bleeding on dental procedures	41/173	23.6%	24/43	55.8%
Haematuria	15/173	8.6%	6/43	14%
Ear bleeding	11/173	5.7%	4/43	9.3%
Muscle bleeding	9/173	5.2%	5/43	11.6%
Haematoma	08/173	4.6%	4/43	9.3%
Menorrhagia	18/173	11.5%	†5/23	21.7%
Bleeding after Trauma	12/173	7%	3/43	7%

*Total male patients were 20 in the study.
†Of 23 female patients five had attained the age of Menarche.

A total of 43 GT patients were diagnosed at NIBD hospital of the 123 congenital platelet function disorders (35%). These patients were followed in OPD, inpatient and emergency department. There were 20 males with a mean age of 12.1 years (range, 6 months–30 years) and 23 females with a mean age of 10.5 years (range, 1–17 years). Parents of 34 (79%) patients were first or second cousins. Positive family history of bleeding was noted in 26 (60%) patients, no history of bleeding in 7 (16.2%) patients and unknown in 10 (23%) patients. A total of 245 bleeding episodes were identified during different time periods requiring visit to hospital, but only 173 bleeding episodes could be evaluated because of the availability of complete details. The average number of medical visits per patient was 12 (range, 2–66). Hospitalization was required in 147/173 (85%) of these visits for a mean of 31 days spent as an inpatient (range, 1–54) in day care and ward. The most common indication of hospitalization was epistaxis; with a mean of 4 days duration (range, 1–11 days) followed by gum, dental and GI bleedings. ICU admission was required in one patient due to severe uncontrolled epistaxis. This patient responded to treatment with rFVIIa (NovoSeven) and bleeding stopped within 24 h after nasal cautery. No death was observed in this population. The remaining 26/173 (15%) episodes visited hospital outpatient clinics only for bruises, gum bleeding and haematoma. Mean duration between the two bleeding episodes was 64.5 days (range, <1–400 days). Table 1 shows the results of 173 bleeding episodes. Of note, the most common types of bleeding were as follows: epistaxis (74.5%), gum bleeding (70%), easy bruising (61.8%), bleeding on dental extraction (23.6%), GI bleeding (23.6%), menorrhagia (11.5%) and circumcision (7%) respectively. Response to different treatment modalities is shown in Table 2. Of 43 patients, there were only four patients who were non-responders to different treatment modalities having similar demographic and clinical features (age, gender, haemoglobin and platelet count). Patients received platelet transfusions only when local measures and other medical management failed. rFVIIa was considered if bleeding was considered to be life threatening (n = 4). Thus, despite variations in the severity and frequency of bleeding episodes, most GT patients received platelet transfusions with tranexamic acid and responded. Other methods used to control bleeding were nasal packing with or without antifibrinolytic agents followed by posterior nasal packing if needed (n = 12). Only two children required cautery for recurrent nose bleeds.

The results of this study show that the majority of patients had parents with consanguineous marriages among first and second cousins. Among 43 patients, eight belonged to the same family and children presented with phenotypic expression of the disease. Work on the genetic basis of GT should be done to identify mutations prevalent in our population that would help to identify carriers and for prenatal diagnosis.

Of 43 patients, the most common clinical manifestations were epistaxis (74.5%), gum bleeding (70%), easy bruising (61.8%) and bleeding on dental extraction (23.6%) as reported in the literature [6]. Menorrhagia is the main clinical problem among five female patients who have attained menarche. These patients were treated with iron supplements, oral contraceptives and antifibrinolytic agents. Platelet transfusions were given to control acute uncontrollable bleeding. The data from multiple studies of coagulation and platelet disorders strongly suggest that menorrhagia is more prevalent in women compared with the rest of the female population [7]. The study published by M Karimi showed a high frequency of menorrhagia (46%) among women with bleeding disorders and rightly pointed out that these patients suffer from chronic stress and from different psychological problems. In addition, sociocultural factors and prevailing moral values prevent them from talking about their heavy menstrual bleeding. Even in a clinical setting, women with bleeding disorders are unwilling to discuss such intimate matters [8]. Therefore, a Comprehensive Haemophilia Care Centre is needed with a multidisciplinary approach to improve their quality of life and their reproductive health.

Epistaxis was a common manifestation among our patients, particularly in children (n = 16) and is usually moderate or severe in intensity with a reduction in frequency and severity with adolescence. These observations were similar to studies published by Rosas *et al.* [9] and in Poon's series (84%) of children with epistaxis [10]. Patients in our study were mainly treated with antifibrinolytic agent (tranexamic acid, dose 15–25 mg kg^{-1} orally or intravenously) either alone or in conjunction with another therapy, such as platelet transfusion with reasonable results (89.4%). Platelets were

Table 2. Response to different treatment modalities used to manage bleeding episodes (n = 173).

Treatment Modality	Treatment offered	Responders	% Response	Response <6 h	Response >6 <24 h	Response >24 h	Non-responders
Platelets Tx + Tranexamic acid	123	110	89.4%	10	34	26	13
Tranexamic acid + Platelets transfusion + DDAVP	11	10	90.9%	02	04	04	01
Tranexamic acid + Platelets Tx+ DDAVP + rFVIIa	01	01	100%	0	01	0	0
Tranexamic acid + Platelets Tx + rFVIIa	03	03	100%	0	2	0	0
*Tranexamic acid + Oral Contraceptives	23	19	82.6%	0	01	10	4
*Tranexamic acid + Platelets Tx + Oral Contraceptives	12	12	100%	0	04	0	0

*Offered to females presenting with Menorrhagia.

1. **Anchor Name: NovoSeven Print Detail Aid** *[Agency Havas - Orla Waters]*

used in treatment because they were readily available from our hospital blood bank and are cost-effective when compared with desmopressin and rVIIa. However, multiple platelet transfusions in some patients lead to allergic reactions requiring antihistamines to control it. Our four patients became refractory to platelet transfusions giving to the development of alloantibodies to HLA antigens, but no patients have been positive for transfusion-transmitted infections so far.

Recombinant factor VIIa is becoming one of the primary medical treatments for control of serious bleeding in patients with GT [10]. It is now licensed for use in GT with GPIIb/IIIa and/or HLA antibodies with past or present refractoriness to platelet transfusions, but the cost implication is an important consideration especially for a developing country. We used 90 μg kg^{-1} of rVIIa intravenously in our patients (n = 4) who were not responding to platelet transfusions and it was found to be effective in treating severe bleeding episodes (epistaxis, GI bleeding). We have also used desmopressin in some patients (n = 12) in addition to platelet transfusions and tranexamic acid to control bleeding with satisfactory outcomes. In the literature, the role of desmopressin in severe platelet disorders is limited [6].

In conclusion, we have reported the first large study from Pakistan showing that GT is associated with a significant bleeding diathesis, but with clinical variability. Epistaxis, gum bleeding and easy bruising are the most frequent bleeding presentation in both genders. Menorrhagia becomes the most frustrating bleeding manifestation after menarche. Earlier diagnosis of these patients would be helpful for their clinical management particularly in the offspring of consanguineous marriages. Platelet transfusion is a standard therapy for securing haemostasis in individuals with GT, when the local measures and antifibrinolytic agents are inadequate. rFVIIa is licensed for GT patients who have become refractory to platelet transfusion. There is a need to develop a national registry for congenital platelet disorders. Attempts should be made to develop the techniques to diagnose refractoriness to platelet transfusion, zygosity and GP IIb/IIIa on flowcytometer.

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Author contribution

MB takes the primary responsibility of themanuscript. MB, TS contributed for patient's management. The lab diagnosis was done by AN and HP. HF helped in computer data entry and analysis. MB recruited the patients and wrote the manuscript. TS reviewed and advised corrections.

Disclosures

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