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Glanzmann's Thrombasthenia

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Objectives: To study the clinical presentation and laboratory findings of Glanzmann's thrombasthenia (GT).

Methods: This retrospective study was carried out from January 1st 1983 to 31st December, 2003. The records of the coagulation laboratory, Hematology clinic and medical records department were reviewed. Clinical data and family history were recorded. Laboratory investigations done included; complete blood count (CBC) peripheral blood smear (PBS), bleeding time (BT), activated partial thromboplastin time (APTT), prothrombin time (PT), clot retraction, platelet aggregation and in some patients flow cytometric analysis of platelet glycoproteins was carried out.

Results: Thirty-one patients were diagnosed with Glanzmann's thromboasthemia. Seventeen were males and 14 were females. All were Saudi patients (most from eastern province and the southern part of the Kingdom) except for one Sudanese male patient. The mean age of patients was 26 ± 12.34 years. The oldest was 71 years and the youngest 20 days. Many patients had bleeding from more than one site. The clinical presentations are as follows: epistaxis 16 (52%), menorrhagia 11 (35.5%), gum bleeding 10 (32.3%), bruises 7 (22.6%),

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bleeding at circumcision 4 (13%), hemoarthrosis 4 (13%), ecchymosis and petechial rash 5 (16.1%), gastrointestinal (GIT) bleeding 7 (23%), hematuria 2 (7%), delayed wound healing 1 (3%), bleeding with tooth eruption 1 (3%) and hemoptysis 1 (3%).

Thirty patients had a prolonged bleeding time, all 31 patients had normal APTT and PT. Thirteen patients (42%) had poor clot retraction, 12 (39%) no clot retraction and 6 (19%) had normal clot retraction. All patients had a marked reduction or absent aggregation to platelet agonists; adenosine diphosphate (ADP), collagen, epinephrine and arachidonic acid. Thirteen patients also had a reduction in aggregation with ristocetin. Flow cytometric analysis done on some patients showed a reduction in platelet membrane glycoproteins 41 and 62 (CD41, CD62).

Conclusion: In spite of the fact that GT is a rare disease worldwide, the situation might be different in our country. The spectrum of clinical presentation and complications in patients with GT appears to be wide, in addition to different platelet aggregation patterns i.e. reduction in aggregation with ristocetin. Still more studies are needed to clarify the pattern in Saudi patients and to raise awareness hoping to help in early recognition, presentation, and more appropriate management. Extensive collaborated studies are needed to predict the true incidence of hereditary bleeding disorders including GT among the Saudi population, as well as a national registry for these disorders.

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Glanzmann's thrombasthenia (GT) an inherited bleeding disorder of platelets first described in 1918 by Glanzmann, a Swiss Pediatrician, who described a group of patients with normal platelet count, prolonged bleeding time and impaired clot retraction[1]. GT is an autosomal recessive disorder characterized by a quantitative or qualitative abnormality of platelet glycoprotein (GP), GPIIb / IIIa receptors[1,2]. It is more common in communities where consanguineous marriages are

frequent but rare in a global context. It has a certain epidemiologic predilection being more common in Jordan, India, Saudi Arabia and Iraqi-Jews and Arabs living in occupied Palestine[1-3].

A previous report from our institution in 1988 also revealed a high incidence of this disorder in eastern province where 12 out of 34 patients with hereditary bleeding disorders had GT[4]. A study from Riyadh reported 18 cases of GT out of 168 patients with hereditary bleeding disorders where it was found to be the third common hereditary bleeding disorder[5]. It is characterized by intermittent severe mucocutaneous bleeding occurring at an early age and recurrent throughout patient's life. The commonest clinical manifestations reported are epistaxis, gum bleeding, and menorrhagia[2,3]. The laboratory diagnosis of GT and its differentiation from other bleeding disorders is usually not difficult. Essential diagnostic features include normal platelet count and morphology, normal PT and APTT, prolonged bleeding time, absence or reduction to all platelet aggregating agents, except ristocetin, abnormal clot retraction, and flow cytometry studies show reduction in GPIIb / IIIa using monoclonal antibodies[1-3]. GP IIb-IIIa is a calcium dependent heterodimeric complex, is a major surface adhesive protein receptor that plays a vital role in platelet function. GP IIa-IIIb, also known as α IIb β3 belongs to the integrin family. The genes for α IIb and β3 are distinct but physically linked within 260 kb on the long arm of chromosome 17 at q21-22[6-10].

GT is classified into three types, Type I where platelets have no ability to retract a fibrin clot and lack internal stores of fibrinogen, and GPIIb / IIIa receptors are less than 5%, Type II – platelets have a reduced ability to retract a fibrin clot and have low levels of platelet fibrinogen, and GPIIb / IIIa is in the range of 10-25% and variant types which have a differential ability to retract a fibrin clot and contain appreciable levels of platelet fibrinogen with 100% of normal receptor levels[1].To date more than one hundred distinct genetic defects have been described ranging from point mutations, small deletions and inversions occurring with even distribution on both αIIb and β3genes. These defects have shown to lead to disruption of GPIIb / IIIa synthesis receptor assembly and / or function[6-10]. Molecular biology techniques have enabled us to diagnose heterozygote carriers who are asymptomatic and an inborn fetus in the second trimester[1]. The prognosis of GT is reported to be a severe disease but with generally good survival[2].

The aim of this paper to study the clinical presentation and laboratory findings of Glanzmann's thrombasthenia (GT).

METHODS

A retrospective review of all Glanzmann's thrombasthenia patients managed in KFHU. Data was extracted from the records of the coagulation laboratory, Hematology clinic and medical records department. This review covered 20 year period from January 1st 1983 to December 31, 2003. Clinical data as well as family history were recorded.

Laboratory investigations included: complete blood count (CBC) (Coulter STKS and Coulter GENS), peripheral blood smear examination for platelet morphology (Wrights stain). Bleeding time by IVY method, activated partial thromboplastin time (APTT) and prothrombin time (PT) by using a Fibrometer (Becton, Dickinson and Co., Cockeysville Md.) and recently by using BCT fully automated coagulation instrument (Dade-Behring-Marboug Germany). Clot retraction was done by observing whole blood clot for retraction and assessed qualitatively according to Dacie and Lewis [11]. Platelet aggregation studies by platelet aggregation profiler (Pap-3) (Bio-data Corp, Hatboro, Pa) using platelet aggregating agents; adenosine diphosphate (ADP), epinephrine (Epi), collagen (Co), ristocetin (Risto) and arachidonic acid (AA). In four patients flow cytometric analysis of platelet membrane glycoproteins was done, using monocloncal antibodies (McAb) anti-CD41, anti-CD62 (Becton Dickinson FACScan).

RESULT

Thirty-one patients were diagnosed with GT during the study period, 17 males and 14 females. All patients were Saudis (from the Eastern and Southern parts of the Kingdom) except for one Sudanese male. A positive history of first-degree consanguinity was observed in 26 of the families (84%), the remaining five families, the parents were also relatives in some degree. In all families, there was a positive family history in siblings and / or other family members. The mean age of the patients was 26 ± 12.34 years. The oldest was 71 years and youngest 20 days.

The commonest clinical presentations are as follows: epistaxis 16 (52%), menorrhagia 11 (35.5%), gum bleeding 10 (32.3%), bruises 7 (22.6%), bleeding at circumcision 4 (13%), hemoarthrosis 4 (13%), ecchymosis and petechial rash 5 (16.1%), GIT bleeding 7 (24%), hematuria 2 (7%), 1 (3.2%), delayed wound healing 1 (3.2%), bleeding with tooth eruption 1 (3.2%), and hemoptysis 1 (3.2%). (Table 1 summarizes patients' data and clinical presentation).

Table 1.

Laboratory findings:

All patients had normal PT and APTT. All patients had a prolonged bleeding time except one patient. Aggregation was subnormal to platelet agonists, ADP, collagen, epinephrine and arachidonic acid. While most patients (18) had normal responses to aggregation with ristocetin, 13 had reduced aggregation.

Table 2.

Clot retraction was reduced or nil in 25 patients and normal in six patients. (Table 2 summarizes the laboratory findings). Because flow cytometric analysis of platelet glycoproteins was recently introduced into our laboratory it was done on 4 patients and a sibling of patient number 2. Platelet glycoproteins CD41a and CD61 were reduced in all these patients (Table 3).

Table 3.

DISCUSSION

The spectrum of clinical presentation and complications in patients with GT appears to be wide, the commonest three clinical presentations in our study; epistaxis, gum bleeding and menorrhagia are similar to worldwide reports[1,2,3]. We cannot say that it is a rare condition in Saudi Arabia, as different national studies[4,5] and our study have demonstrated many patients with varying clinical presentations and severity. In this study and a previous study, from our institution[12], patients have even presented with haemarthorsis commonly of the knee, 13% and 16% respectively, which resembled the clinical picture of hemophilia[2]. GT in general is characterized by intermittent mucocutaneous bleeding of variable severity recurrent throughout patient's life. Two of our patients who were siblings died as a result of GT. Their parents were asymptomatic first-degree cousins. These two patients (Table1) had severe recurrent GIT bleeding, in addition to menorrhagia in the female patient. They both developed Hepatitis C, and depression as a result of their disease, and apparently became refractory to platelet transfusions, they also have another affected brother. Another female patient had to undergo hysterectomy at the age of 25 because of intractable menorrhagia (her brother also has GT and cerebral palsy), while another male patient lost his vision in the right eye as a result of blunt trauma. Most patients are diagnosed in infancy and early childhood, and in this study some male patients were first diagnosed when bleeding occurred after circumcision. Hematuria, hemoptysis and poor wound healing, which are reported as rare clinical features are seen in some of our patients[2].

It is important to diagnose GT and to differentiate it from other inherited bleeding disorders and similar platelet function abnormalities. In this study the classical laboratory features for its diagnosis were demonstrated in all our patients and unusual findings were also found; unlike the typical aggregation pattern in GT, ristocetin induced platelet aggregation was also reduced in some patients, which is not a classical feature of GT, but observing this may suggest an additional unidentified variant form, or a rare form of GT. It may on the other hand be revealing a feature resulting from different or new genetic mutation(s), as there have been reports also of some variants of GT showing aggregation to ADP[1]. Analysis of platelet glycoproteins is an additional very important investigation used,it was first introduced in the mid eighties for the study of Bernard Solier and GT[13]. It should be part of the laboratory investigations for diagnosis of this disorder.

The management of GT patients in our hospital follows standard protocols seen in most hospitals, which includes platelet transfusions, hormonal therapy (for menorrhagia), antifibrinolytic agents, iron and folate supplementation and preventive in case of measures in case of dental hygiene etc. In view of the repeated platelet transfusions it is recommended that platelets should be HLA matched to avoid refractoriness, which occurred in our patients. Other measures which have been reported to control and manage GT are recombinant activated factor VII (rVIIa), erythropoietin, D-Diamino vasopressin (DDAVP), locally applied autologous fibrin glue, gene therapy and bone marrow transplantation[1,14,15,16]. Because GT is a rare disease worldwide, the situation might be different in the Kingdom, it might not be that rare and studies on GT in the Kingdom are scarce. It is not a simple disease and has a wide spectrum of clinical presentation and severity. It has resulted in discovery of many variants and a model for elucidating the complex interactions between genes, and platelet receptors.

CONCLUSION

We recommend extensive collaborated studies, which are needed to predict the true incidence of hereditary bleeding disorders including GT among the Saudi population with a greatly needed national registry. Patient and family education especially in relation to nature of the disease, marriage counseling, laboratory investigations, (as many of our patients are reluctant to frequent blood drawing and laboratory tests), vaccination and early management, including the importance of HLA-matched platelets, will hopefully reduce the incidence and the severity of the disease. Research on the underlying molecular defect in the Kingdom may help unravel the unusual features of the disease. (Which is an ongoing study in our laboratory, hopefully to provide some answers).

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