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Glanzmann thrombasthenia: Cerrahpaşa Medical Faculty experience

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Summary

Aim: Glazmann thrombasthenia is a rare autosomal recessive disease characterized by a defect in platelet aggregation. Herein, we report the management of children with Glazmann thrombasthenia followed up at Cerrahpasa Medical Faculty Pediatric Hematology Department.

Material and Method: The files of nineteen patients (42% girls, 58% boys; median age: 10 months) were retrospectively reviewed.

Results: The median age of onset of bleeding symptoms was 9 months (2 weeks-24 months). All patients presented with easy bruising and mucosal bleeding. Fourteen patients' parents were consanguineous. In 15 patients, flow cytometry was performed. According to this, 7 patients had type I, 6 patients had type II and 2 patients had type III disease. Nine patients were treated with thrombocyte transfusion, tranexamic acid, recombinant active factor VII and fibrin glue as a single or combined therapy; none of them had a major bleeding complication.

Conclusions: Bleeding control during invasive procedures may be challenging in children with Glazmann thrombasthenia; local treatments, DDAVP, steroid and antifibrinolytics may be used with success. *(Turk Arch Ped 2012; 47: 106-8)*

Key words: Glanzmann thrombasthenia, thrombocyte function disorder

Introduction

Glanzmann thrombasthenia (GT) was described by Dr. Eduard Glanzmann in 1918 for the first time as abnormal clot retraction and defects in platelets (1). Glanzmann thrombasthenia is a rare autosomal recessive disease characterized by an abscence in platelet aggregation (2,3). It is more prevalent in populations with a high incidence of consanguineous marriages. The main defect in Glanzmann thrombasthenia is absence of binding of platelet membrane receptor (IIb/IIIa) to fibrinogen (4,5). Its molecular base is related to qualitative and quantitative abnormalities of alpha IIb beta 3 integrin. The disease is divided into three subtypes according to glycoprotein IIb-IIIa levels. Patients with a glycoprotein level less than 5% of the normal value are classified as type I and patients with a glycoprotein level between 5% and 20% are classified as type II. In type III, GP levels are normal or near normal, but they have defective function (6,7). In recent years, patients with leucocyte adhesion disorder (LAD) type 3 who have frequent infections and show bleeding diathesis similar to GT patients have been considered as a subgroup of GT (8). In platelet agregometer test, GT platelets do not aggregate following interaction with any substance except for ristocetin. In addition to aggregometer, low than normal levels of glycoprotein (GP) IIb-IIIa can be determined with flow cytometer using CD41 and CD61 monoclonal antibodies (Figure 1). Platelet count is normal, bleeding time is increased and peripheral smear reveals single platelets without aggregates. Very rarely, platelet count may be low or slightly low (3). Glanzmann thrombasthenia may have different clinical manifestations. While only purpurae are observed in some patients, life-threatening bleedings may occur in others. In Glanzmann thrombasthenia, purpura, epistaxis, gingival bleeding and menorrhagia occur frequently, while gastrointestinal bleeding and hematuria are observed less frequently (3).

In this study, we wanted to present our diagnostic and therapeutic approaches in patients with GT whom we followed up in Cerrahpaşa Medical Faculty, Division of Hematology.

Material and Method

19 patients who were diagnosed as GT and followed up in Cerrahpaşa Medical Faculty, Division of Hematology-Oncology

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(between 1995 and 2011) were examined retrospectively. The patients were evaluated in terms of age, gender, baseline findings, familial history of consanguineous marriage and similar disease, bleeding frequency, transfusion frequency, laboratory findings and treatments administered in case of bleeding.

Results

19 patients (8 (42%) female and 11 (58%) male) were evaluated. The median age was 10 months (1 month-9 years). The median age of onset of bleeding complaints was 9 months (2 weeks-24 months). In all patients, the complaint at presentation was unusual cutaneous and mucosal bleeding (Table 1). Complete blood count revealed normal platelet count and peripheral blood smear revealed absence of aggregation of platelets. Coagulation variable of the patients were found to be normal. Iron deficiency anemia was present in all patients.

In our study, parental consanguineous marriage was present in 14 patients. Siblings of 5 patients had the same complaints. In one family, the disease was found in three siblings. Flow cytometry could be performed in 15 patients. According to this, 7 patients were classified as type I, 6 patients were classified as type II and 2 patients were classified as type III. Bleeding

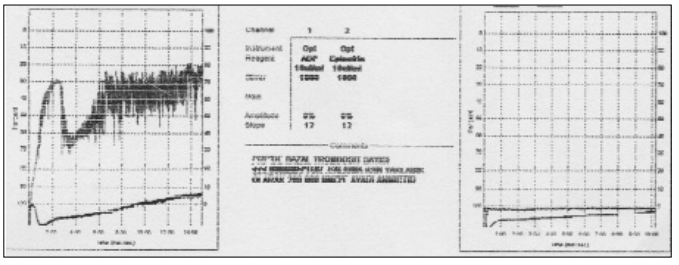

Figure1. Platelet aggregation curve in one of our patients

Table 1. Complaints at presentation	
Complaint	**(n)**
Epistaxis	7
Bleeding in oral mucosa	1
Oral bleeding and epistaxis	2
Persistent bruises on the body	6
Bleeding in the gastrointestinal system	1
Gingival bleeding	2

Table 2. Frequency of cutaneous and mucossal bleedings	
Frequency of bleeding	**(n)**
Bleeding only for once	1
Bleeding 1-2 times a month	6
Bleeding 2-11 times a year	8
Bleeding <2 times a year	4

frequency and severity of the patients showed variance (Table 2). We had patients who had severe bleeding, although they were in the type II group (3 patients: receptor levels 8%, 12% and 19%). Erythrocyte transfusion was administered in 6 patients because of anemia caused by frequent bleedings. Positivity was found in one of three patients in whom antithrombocyte antibody was tested. In 9 interventional procedures (dental extraction: 2, ophthalmic operation: 2, circumscision: 5), hemostasis was provided by single or combined use of thrombocyte transfusion, tranexamic acid, recombinant activated factor VII (rVIIa) and fibrin glue. No severe bleeding complication was experienced in any interventional procedure. The median follow-up time was 5 years (18 months-16 years). No death related to bleeding occured in the follow-up.

Genetic testing was not done in any of our patients. Therefore, we considered LAD III related GT in 2 patients who had high leucocyte count and frequent infections and who presented to the emergency department with recurring bleedings, but have not been able to proove this, yet.

Discussion

Glanzmann thrombasthenia is the diagnosis which should be considered primarily in patients with normal platelet count and unusual cutaneous and mucosal bleedings starting from birth and early childhood. Rarely, the diagnosis may be shifted to advanced ages. When the literature is examined, it is observed that the diagnosis is frequently made before the age of 5. In our study, the median age at the time of diagnosis is 10 months with a range of 1 year and 10 years of age (6,7). A patient who was diagnosed at the age of ten had been followed up in another center with a diagnosis of vWF type 2 deficiency.

Since Glanzmann thrombasthenia is a disease caused by platelet dysfunction, there is defect in primary clot formation and mucosal bleedings are observed frequently. Since fibrinolytic activity is present in the mucosa, the clot formed rapidly dissolves and bleeding lasts long as it will not be formed again. Especially epistaxis and gingival bleedings are predominat. Complaints including hematuria, menorrhagia and gastrointestinal system bleeding may also be the primary causes for referral. In 12 (63%) of our patients, complaints at presentation included gingival bleeding and epistaxis. One patient presented with gastrointestinal system bleeding. During the follow-up, one of the patients lost one eye because of intraocular bleeding which developed following trauma.

In patients with Glanzmann thrombasthenia, it may be difficult to provide bleeding control during interventional procedures (9,10). During these interventions, local applications, DDAVP, steroid and antifibrinolytic agents may be beneficial for treatment. We mostly used antifibrinolytic drugs in our patients. As antifibrinolytic drug, we administered tranexamic acid (TransaminR) which is available in Turkey orally, intravenously and as oral rinse (for intraoral bleedings). In case of massive bleedings, hemostasis could be provided

by using thrombocyte suspension, rFVII and fibrin glues as a single or combined therapy.

None of our patients were lost. Erythrocyte suspension had to be administered in 6 (31%) of our patients who presented because of frequent bleedings. In case of uncontrolled bleedings, we tried to keep hemoglobin value above 10 g/dL. Therefore, we administered more than one transfusions in some of our patients (three patients). Oral iron supplementation was given in all patients because of iron deficiency secondary to chronic blood loss.

Thrombocyte suspension was administered to 6 (31%) patients in different times because of bleedings which could not be controlled. In our division, thrombocyte suspension is preferred only in bleeding episodes in which local control and antifibrinolytic drugs are not sufficient, since we know that the risk of alloimmunization is high in these patients because of frequent transfusions (6).

In case of surgical procedure, we generally started the antifibrinolytic drug one night before and continued for 5 days at a dose of 25 mg/kg/dose. We belive that the need for thrombocyte transfusion is decreased to a great extent with this approach. Hence, we had to administer the previosuly prepared thrombocyte suspension in only one of 5 patients who were circumcised. The other four patients were successfully operated using antifibrinolytic agent and fibrin glue which was used during the circumscision and thrombocyte suspension was not used. In one patient who lost one eye because of trauma and in whom we could not administer thrombocyte suspension, since antithrombocyte antibody was positive, laser intervention for the other eye was done using rFVIIa. No advers effect was observed during the procedure or afterwards.

Administration of rFactorVIIa for treatment of bleeding episodes in Glanzmann thrombasthenia has been shown to be effective (10,11). It has been used even in serious operations including brain tumor operations in patients with GT successfully, but thrombosis was observed as a side effect (12). Development of thrombosis with use of Factor VII in patients with Glanzmann thrombasthenia is present in the literature (12,13). Factor VII acts by increasing subendothelial fibrin production (14). Although Factor VII is an efficient treatment in GT, care should be taken in terms of possible side effect (thrombosis etc.) (10). Since use of FVIIa is an expensive treatment, studies showing that hemostatis can be provided in these patients by use of their own platelet-rich clot in combination with antifibrinolytic have been performed in recent years (15).

Conflict of interest: None declared.

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