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Case Report

Glanzmann's Thrombasthenia: A rare platelet functional disorder

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Abstract:

Glanzmann's Thrombasthenia (GT) is a rare inherited autosomal recessive platelet functional disorder. Due to the deficiency of platelet function, it manifests as a bleeding disorder characterized by mucocutaneous hemorrhage of varying severity. It is difficult to diagnose as it closely mimics with others bleeding disorder, so it can be diagnosed after investigations & exclusion of others. Treatment is supportive care with platelet transfusion & proper counseling. With careful supportive care, GT has a very good prognosis. In this report, we describe a 13 years old female with Glanzmann Thrombasthenia.

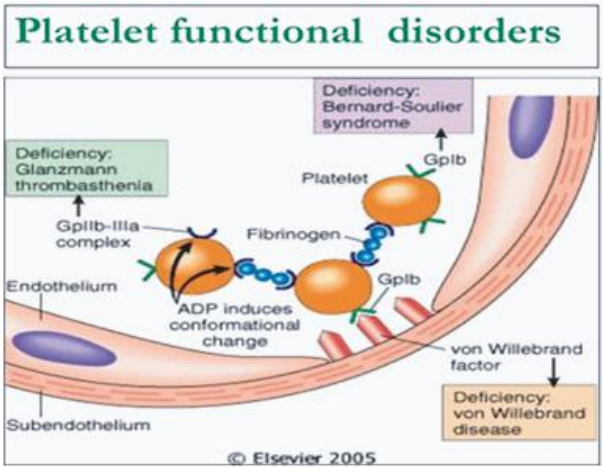
Key words: Glanzmann's Thrombasthenia (GT).

Introduction:

Glanzmann's Thrombasthenia (GT) is a rare inherited autosomal recessive platelet function disorder first described by a Swiss pediatrician Dr. Eduard Glanzmann in 1918[1]. GT presented with easy bruise, ecchymosis, mucosal bleeding, menorrhagia at menarche, epistaxis, gingival bleeding, gastrointestinal bleeding and postpartum bleeding. In which the platelet count is normal or subnormal, the bleeding time is prolonged, and platelet aggregation is deficient or absent[1,2]. In GT, platelet glycoprotein GP IIb/IIIa (CD41/CD61) complex is deficient or present but dysfunctional[3,4]. Defect in the GP IIb/IIIa complex leads to defective platelet aggregation and subsequent bleeding. Carrier detection in GT is important to control the disease in family members. It can be acquired as an autoimmune disorder.

The frequency of consanguinity in affected families is noticeable, and GT has an increased incidence in populations in whom marriage among close relatives is an accepted custom[1,2]. In certain ethnic groups, such as South Indian Hindus, Iraqi Jews, French gypsies, and Jordanian nomadic tribes, thrombasthenia may actually be a common hereditary hemorrhagic disorder, where as not so common in other parts of the world. For these reasons, it would be not easy to give an estimation of worldwide prevalence[1,2]. International frequency data are unknown. Though, over 500 cases have been reported in the international literature.

Platelet plug is formed by 1) Adhesion - Platelets stick to injured vessel wall. 2) Secretion - Platelets release granular contents and potentiates clotting. 3) Aggregation - Platelets stick to each other via fibrinogen bridges.



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Pathogenesis:

GT is an autosomal recessive condition caused by a deficiency or present but dysfunctional in platelet fibrinogen receptor glycoprotein (GP) IIb/IIIa (CD41/CD61) complex. Different genetic mutations of either GP IIb or IIIa genes result in a heterogeneity of thrombasthenia phenotype[3,4]. The genes of both of these proteins are on chromosome 17. Most of the encountered mutations are missense mutations or deletions in the GPIIb or GPIIIa gene[3]. Defect in the GP IIb/IIIa complex leads to defective platelet aggregation and subsequent bleeding. Aggregation of platelets occurs in response to ristocetin, but not to other agonists such as ADP, thrombin, collagen or epinephrine.

Types:

Glanzmann's Thrombasthenia has three categories of severity, depending on the importance of the platelet deficiency in Glycoprotein IIb/IIIa. Type 1 (Severe): A level less than 5% of normal, Type II (Less severe): A level between 5% and 20% of normal & Type III (Least severe): A variant of Thrombasthenia with levels of more than 50% of normal, but with major abnormalities in the way platelets aggregate. Symptoms includes easy bruise, ecchymosis, mucosal bleeding, menorrhagia (98%) at menarche, epistaxis (73%), gingival bleeding (55%), gastrointestinal bleeding, postpartum bleeding, brain hemorrhages, and increased bleeding post-operatively.

Laboratory tests:

GT is characterized by normal platelet morphology and normal platelet count, low hemoglobin with microcytic hypochromia due to bleeding. Prolonged bleeding time (BT), normal clotting time (CT), prothrombin time (PT), activated partial thromboplastin time (APTT), absent or decreased clot retraction, and normal platelet aggregation in the presence of ristocetin[1,2]. Platelet aggregation is absent in the presence of epinephrine, collagen, arachidonic Acid, ADP, due to the dependence of these factors on fibrinogen attachment to the platelet for aggregation[1,3]. Platelet aggregation occurs normally in response to ristocetin due to its independence from fibrinogen. Flow cytometry can also be used to detect the presence of the GPIIb and GPIIIa complex, GPIIb (CD41), GPIIIa (CD61), and fibrinogen using monoclonal antibodies. This method can also be used to rapidly predict the carrier status of family members of patients with the disorder[3,5]. DNA analysis is the most accurate in carrier detection but only when the defect is known, limiting its clinical utility. GPIIb-IIIa quantification by monoclonal antibodies and platelet antigen detection may be used for prenatal diagnosis of Type I GT and heterozygous

Treatment:

Hemorrhage is naturally the main clinical concern and supportive care is critical. Platelet transfusion is necessary before any invasive procedure or heavy bleeding episode[1,6]. Platelet alloimmunization against HLA group and/or GPIIb/IIIa glycoproteins is a genuine concern, but the risk is no greater than for any transfused patient, and it is not a contraindication to this therapy[1]. In recent years the use of recombinant factor VIIa (rFVIIa) has increased significantly with excellent response rates in treating and preventing hemorrhage among GT patients. Other than transfusion, management is primarily preventive care. Antifibrinolytic drugs such as tranexamic acid or e-aminocaproic acid, Desmopressin (DDAVP) does not normalize the bleeding time in Glanzmann's thrombasthenia but anecdotally improves hemostasis, Hormonal contraceptives control excessive menstrual bleeding.

Drugs that affect platelet function, such as NSAIDS or aspirin, should be avoided. Immunizations for hepatitis B should be given due to the infectious risks of frequent transfusion. Oral contraceptives may be taken to treat menorrhagia[1]. Regular dental visits are encouraged to avoid gingivitis and gingival bleeding, and iron supplements are suggested during early childhood and adolescence to avoid iron deficiency anemia which is commonly caused by such bleeding[7].

Bone marrow transplants have been used successfully in rare cases though this remains a drastic treatment[1,8]. Gene therapy and stem cell transplantation offer a potential cure of this disease, but both are costly and remain experimental at this point.

Prognosis:

There is no known cure for GT. The overall morbidity and mortality have been difficult to estimate due to its rarity, but in most studies, the prognosis has proven to be very good[1,2]. About 5-10% death occurs due to bleeding (Mostly severe intracranial hemorrhage & gastrointestinal bleeding).

Case Summary:

A 13 years old female came from Jhenaidah admitted into Faridpur Medical College & Hospital with the complaints of irregular excessive per vaginal bleeding associated with no pain for 22 days. She gave history of multiple bruises & prolonged bleeding after minor cut injury & during tooth extraction since childhood. She also gave history of several episode of epistaxis but didn't give any history of fever, cough, chest pain,

abdominal pain, jaundice, fatigue, loss of appetite, weight loss, bone pain, joint pain, skin rash, cold intolerance, constipation, hematemesis, hemoptysis, hematuria, or melena. Her bowel & bladder habit were normal. She took medroxyprogesterone 10mg 8 hourly for 10 days & received 2 units blood within last month. On examination she was ill looking, severely anemic, not-icteric, not cyanosed. Clubbing, koilonychia, leukonychia, bony tenderness, lymphadenopathy were absent, there was no visible purpura, bruise and ecchymosis. BP-120/80 mm (Hg), pulse-94 beats/min, temperature-normal (98^0 F), thyroid gland and breast examinations were normal. Examination of alimentary system revealed tongue pale, smooth & no organomegaly was found. Other systemic examination revealed no abnormality.

Peripheral blood film showed RBC: Anisocytosis anisochromia, Microcytic hypochromic with elongated cells.WBC: Mature with normal count

Investigations findings were as follows:

Date	Hb%	ESR	TWC	MCV	MCH	MCHC	RDW CV	Total platelet count
06.07.17	5.9	28	6200	77.4	24.3	31.4	23.6%	156000
17.07.17	6.5	45	5000	88.4	25.1	28.4	23.1%	221000

& distribution. Platelet: Normal in number & morphology. Comment: Microcytic Hypochromic Anemia (Suggestive of Iron deficiency Anemia). S. Ferritin = 10 ng/ml (Ref: 12-150 ng/ml) USG of whole abdomen: Normal study. TSH= 4.36 µIU/ml. Bleeding Time (BT) = 15 Min (Ref: 2-7 min). Clotting Time (CT) = 11 min (Ref: 8-15 min). Prothrombin time (PT) = 14 Sec (Control: 12 sec). INR= 1.10 (Ref: 0.8-1.2). Activated partial thromboplastin time (APTT) = 28 Sec (Control: 28 sec). Clot retraction test: 20% (ref: > 35%). Platelet aggregation test: Impaired aggregation of platelet in response to agonist (ADP, Collagen, epinephrine & Arachidonic acid) except Ristocetin. So clinical diagnosis is platelet functional disorder (Glanzmann's Thrombasthenia) as flow cytometry was unavailable as well as financial constraints.

She received Tab. Norethisterone 5 mg 3 times daily, Inj. Tranexamic acid 500 mg IV 8 hourly until control of bleeding. Inj. Ferric carboxymaltose 500mg IV once weekly for 4 doses then Tab. Ferrous sulphate 1 tab twice daily. Her bleeding was stopped & physical condition improved, then she was discharged with adequate counseling.

Discussion:

GT is a rare inherited autosomal recessive bleeding disorder. GT has an increased incidence in populations in whom marriage among close relatives is an accepted custom[1,2].

Our patient was 13 years old female presented with irregular excessive per vaginal bleeding during menstruation since menarche. She had history of prolonged bleeding during tooth extraction & after minor cut injury since childhood. She had history of several episode of epistaxis but didn't give any history of fever, weight loss, bone pain, joint pain. She took medroxyprogesterone 10mg 8 hourly for 10 days & received 2 units blood within last month. She was pallor, not-icteric, clubbing, koilonychias, leukonychia, bony tenderness, lymphadenopathy or organomegaly was absent. Peripheral blood film showed microcytic hypochromic anemia with normal platelet in number & morphology. Low S. Ferritin, normal ultrasonography of whole abdomen. Thyroid function test normal. Prolonged Bleeding Time (BT) but normal Clotting Time (CT), Prothrombin time (PT), Activated partial thromboplastin time (APTT). Clot retraction test: impaired. Platelet aggregation test: Impaired aggregation of platelet in response to agonists (ADP, Collagen, epinephrine & Arachidonic acid) except Ristocetin. So, clinical diagnosis platelet functional disorder (Glanzmann's Thrombasthenia) as flow cytometry was unavailable as well as financial constraints.

Our patient responded well with supportive treatment. Then she was discharged with proper counseling regarding avoidance of traumatic work, IM injection, Aspirin, NSAIDs and vaccination against HBV to prevent transfusion associated hepatitis. She was given advice about the maintenance of dental hygiene to prevent episodes of gingivitis which tend to precipitate gum bleeding. Marriage & antenatal advice were also given.

Conclusion:

GT is a rare disease. Careful history, thorough physical examination & relevant investigations will establish the diagnosis. GT should always be considered as differential diagnosis while evaluating any case of bleeding disorder. With careful supportive care, GT has a very good prognosis.

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