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Unexplained Bleeding: Case Report of Glanzmann Thrombasthenia

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Abstract

Background: Glanzmann Thrombasthenia (GT) is a rare inherited genetic platelet disorder characterized by a qualitative, or quantitative mutation in GPIIb/IIIa receptor; which results in defective platelet aggregation and diminished clot retraction.

The Case: A 19-year-old Arab descent female presented to emergency department with severe menorrhagia. On examination an ill looking pale patient in addition to generalized fatigue of one-week duration.

Conclusion: Acquired platelet disorders are more frequently encountered in practice than inherited ones, usually due to medical therapy or an underlying medical condition. GT, was previously known as hereditary hemorrhagic thrombasthenia, is an autosomal recessive disorder that is often disregarded as it has many clinical and laboratory findings similar to some acquired platelet disorders.

Key Words: Glanzmann Thrombasthenia, inherited platelet disorder, the disorder of hemostasis

(Source: MeSH-NLM).

Introduction:

Platelets have many roles in physiological processes in the human body, including hemostasis. In which adhesive proteins such as collagen and thromboplastin are released by damaged endothelium, which binds and aggregate platelets leading to thrombus formation with subsequent activation of coagulation pathways. Any disruption of this pathway acquired or inherited, will result in bleeding.

Glanzmann Thrombasthenia (GT), which was known as Hereditary Hemorrhagic Thrombasthenia, is a rare autosomal recessive disorder of GPIIb/IIIa surface receptor that was first described in 1918. The exact number of affected cases is unknown, but it is estimated that one in a million have GT, with women being affected more than men, 60% to 40% respectively. GT, was noticed to be more common in certain ethnic groups such as Arabs and French gypsies[i] [ii].

GPIIb/IIIa is heterodimeric transmembrane cell receptor that consists of two subunits: a αIIb and a smaller β3 that are linked non-covalently[iii]. This receptor binds fibrinogen, vitronectin, and fibronectin, which are necessary for platelet aggregation; also, it regulates cell migration. Deletions, insertions and frameshift mutations in this receptor have been reported to cause GT[iv]. Based on the expression and functionality of the receptor, GT, is divided into three types, depending on the level of GPIIb-IIIa present. However, it is important to note that the clinical severity of GT, does not correlate with subtype as it was noted by Fiore et al that phenotypic bleeding is more influenced by a mutation in ITGB3 gene[v]. The following subtypes include:

- Type 1: < 5% of normal GPIIb/IIIa levels (severe).
- Type 2: 10-20% of normal GPIIb/IIIa levels (Moderate).
- Type 3: Normal GPIIb/IIIa levels, but functionally inactive (Variant).

The Case:

A 19 years old Arab descent female presented to the emergency department with severe menorrhagia with generalized fatigue for ten days. The patient denied any bleeding in between cycles but complained from frequent epistaxis, an initial diagnosis of von Willebrand disease was made but ruled out soon after due to normal coagulation parameters. On examination a pale, ill-looking female with signs of anemia including conjunctival pallor and tachycardia.

Patient was admitted to female medical ward and initial lab results showed RBCs: 1.70X1012/L, Hb 4.20 g/dL, Hct 14.40%, MCV 84.50fL, MCH 24.70 pg, MCHC 29.30g/dL, RDW 21.60%. Platelets 156.00 x103/mcL, and normal coagulation profile, with prolonged bleeding time. A thorough history was taken from the patient that revealed that the patient went for gynaecology clinic three years ago with complaint of late menarche, similar issue was noted in the family, and had an extensive hormonal and biomedical examination, all of which came out negative for a cause of late menarche also history revealed a multiple previous episodes of epistaxis that was controlled by simple measures such as nasal compression, a positive family history of GT was noted, Flow-cytometry was done which showed decreased levels of CD41 and CD61. Thus, diagnosis of GT was made. The patient was treated with a blood transfusion and then discharged.

Discussion:

Glanzmann Thrombasthenia diagnosis of is often challenging and overlooked. GT, shares many clinical and laboratory finding with other more common acquired bleeding disorders. GT, should be considered as a differential diagnosis in patients with a history of severe bleeding flowing minor trauma or unprovoked bleeding. The family history of consanguinity or for other affected members, such as in this case, plays a fundamental role in GT, diagnosis.

The majority of GT, affected patients will be diagnosed in the first five years of their lives due to recurring gingival bleeding or epistaxis as the most common presentations [i]. In males, excessive bleeding after circumcision has been reported as the first sign of the disease. However, females could be diagnosed later in life when menses ensue. Although fatal bleeding can happen to both genders at any stage in life, it usually tends to decrease in incidence as patients age [vi].

Menorrhagia is a critical hemorrhagic problem. Bleeding at menarche represents a particular risk, and is sometimes severe enough to require transfusion. This is consistent with the prolonged proliferative estrogen stimulation of the initial anovulatory cycles, that can cause greater and more prolonged bleeding with the first menstrual periods in normal adolescent. Control of menstrual bleeding is a major problem. Severe menorrhagia, usually associated with an excessively proliferative endometrium caused by estrogen dominance, can be effectively treated by a high dose of a 19-norprogesterone. Maintenance treatment with birth control pills, such as a combination of norethindrone acetate and ethinyl estradiol, should be started[vi].

Light Transmission Aggregometry is the gold standard for the diagnosis of GT, but it is a time-consuming procedure that is done in highly specialized centers. Other diagnostic procedures include Flow-cytometry, witch denotes the presence or absence of CD61, CD41 and GPIIb/IIIa, and Platelet Function Analyser [iv]. Finally, family history plays a significant role in diagnosing GT [vii].

Up to this point, medical therapy is the only option most GT, patients have. However, most patients do not require treatment on a regular basis. The current treatment guideline for GT, bleeding episodes is to use local measures, such as nose compression in case of epistaxis, alone or in addition to anti-fibrinolytic remedy [iii]. If bleeding continues, platelet transfusion and rFVIIa administration are advised.

Patient education and awareness play an important aspect in GT management, as almost all patients will receive a blood transfusion at least once in their lifetime [iv]. Accordingly, all GT, patients are advised to

have hepatitis B vaccination and avoid contact sports. Also, patients should avoid the use of Aspirin or non-steroidal anti-inflammatory drugs.

The early workup with GT patients lead to the discovery of some of the currently known potent antithrombotics, when a patient with GT who developed a unique powerful antibody against GPIIb/IIIa following multiple transfusions appeared to be a potential source of a therapeutic agent. This antibody was used as ait was used to make a murine humanized monoclonal antibody, (abciximab) was introduced into clinical practice showing significant reduction in the combined endpoint of acute myocardial infarction, need for emergency coronary artery bypass grafting and mortality in patients undergoing percutaneous coronary intervention[vii].

TAKE HOME POINTS:

1. Suspicion of Glanzmann Thrombasthenia should be raised in cases of family bleeding after a minor trauma in males and females.

2. Patient education is a cornerstone in the management of Glanzmann Thrombasthenia as bleeding episodes can occur at any time.

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