

Glanzmann's Thrombasthenia in a Young 11-Year-Old Girl Presenting with Menorrhagia: When to Suspect and How to Manage a Rare Disease

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Abstract: We report on an otherwise healthy 11-year-old girl without any past or family history of bleeding, presenting with abnormal menstrual blood losses since menarche which started 4 months back. The patient was evaluated by a gynecologist with evidence of a normal physical examination and pelvic ultrasounds except for the diagnosis of anovulatory cycles. Blood tests including complete blood cells count and first line coagulation assays were normal. She did not respond to oral tranexamic acid treatment suggested by a pediatrician. The patient was later admitted in a reference hospital for investigations and a hematology consult was requested. A second line coagulation assay was normal but platelets aggregation tests were suggestive of Glanzmann's thrombasthenia which was confirmed by flow cytometry. Treatment recommendations were made and with the additional estro-progestin treatment administration, a good control of excessive menstrual blood losses was achieved and haemoglobin levels remained stable.

Keywords: Bleeding, Platelet defects, Inherited platelets disease, Glanzmann thrombasthenia, Menorrhagia, Tranexamic acid, Recombinant activated Factor VII (rFVIIa), Platelet transfusion.

INTRODUCTION

Glanzmann's thrombasthenia (GT) is an inherited congenital hemorrhagic disease, occurring in an estimated 1 per 1 million individuals, characterized by a markedly reduced platelet aggregation. GT is an autosomal recessive disorder caused by quantitative or qualitative defects of $\alpha\text{IIb}\beta_3$, an integrin expressed on the platelet membrane, coded by the ITGA2B and ITGB3 genes [1, 2]. Integrin $\alpha\text{IIb}\beta_3$ is a heterodimeric receptor promoting platelets spreading and aggregation. This complex is formed via calcium-dependent association of GPIIb and GPIIIa subunits. Platelet activation favored by ADP, promotes this association and conformational changes enabling fibrinogen binding. As a result of $\alpha\text{IIb}\beta_3$ deficiency, hemostatic plug formation cannot occur and bleeding manifestations can be severe (Figure 1).

CASE REPORT

We here report the case of a 11-years-old girl, with normal mental and physical development, in the absence of personal history of surgery and/or comorbidities. The hematology consult was asked for excessive menstrual blood losses and metrorrhagia

since menarche (occurred four months before consult). Family history was negative for bleeding. The month after menarche a gynecological examination with transvaginal ultrasound diagnosed an anovulatory cycle. Blood tests performed the first month after menarche showed Hb= 12 g/dl, MCV =73,8 fL, ferritin= 6 ng/ml, PLT= 344000/mmc, INR=1, APTT= 25 sec, fibrinogen: 280 mg/dL. Due to the persistence of metrorrhagia, oral tranexamic acid therapy (1 gram daily for one week) was given at home by the pediatrician, without benefit. After two months the girl was then admitted at a reference pediatric hospital where mild microcytic anemia (Hb= 10 g/dl, MCV= 70 FL, ferritin 3 ng/mL) was observed. First line coagulation assays were in the normal range. A hematology consult was then requested, which indicated second level assays to rule out von Willebrand disease or functional platelet defects and prescribed oral iron supplementation for anemia. Platelet function analyser (PFA 100) showed abnormal platelet function for both collagen/epinephrine (206") and collagen/ADP (153"), while coagulation assays were normal: FVIII:c113% vWF: Rcof 51.2%, vWF: Ag 68% (Blood group 0 Pos). Light Transmission Aggregometry (LTA) was then performed and showed a marked inhibition of platelet aggregation for all agonists except for ristocetin. Due to the stability of hemoglobin levels, she was discharged home and then she was admitted to our clinic for hematology re-evaluation after LTA results became

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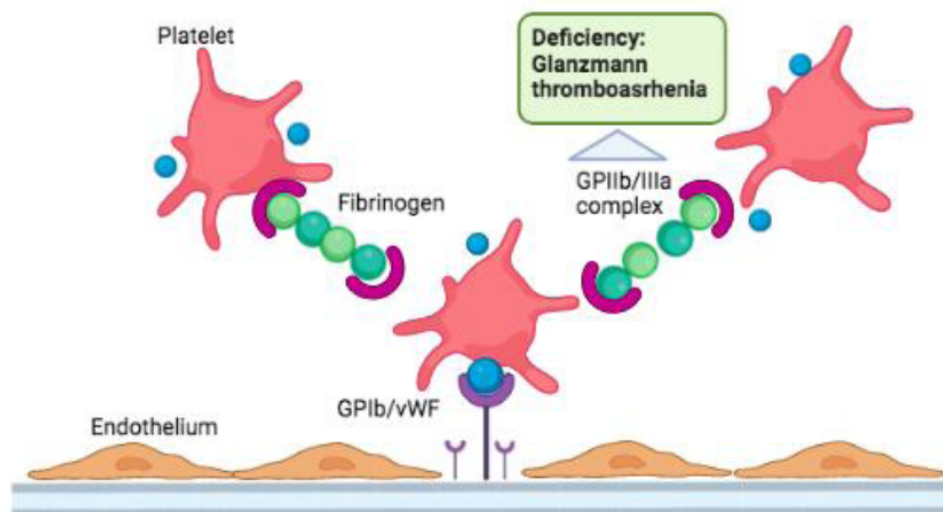


Figure 1: Biological alterations associated with GT.

available. Glanzmann's disease was then suspected and confirmed by Flow Cytometry (FC), showing the absence of $\alpha\text{IIb}\beta_3$. The following treatment recommendations were then performed: tranexamic acid therapy for mild mucocutaneous bleeding, recombinant activated Factor VII (rFVIIa) and platelet transfusion for severe bleeding. Gynecological consult was also recommended to evaluate hormone therapy in order to control menorrhagia. Nomegestrol acetate/estradiol 2.5 mg/1.5 mg was then initiated. After estrogen-progestin treatment administration, a good control of excessive menstrual blood losses was achieved and CBC remained stable.

DISCUSSION

Although there is variability in the clinical phenotype, most patients affected by GT experience severe mucocutaneous bleeding at an early age, but rarely life-threatening hemorrhages. Epistaxis, menorrhagia and gum bleeding are the most common symptoms, occurring in 60-80%, 60-90% and 20-60% patients, respectively. Gastrointestinal bleeding and hematuria are less common but they can lead to severe complications. Mucocutaneous bleeding can be spontaneous or occur after minimal trauma [3]. Epistaxis is the most frequent symptom especially during childhood. In affected women menorrhagia is very common with the risk of major bleeding at the time of menarche due to the prolonged estrogen-mediated stimulation of the endometrium occurring during anovulatory cycles [4].

Bleeding assessment tools (BATs) are questionnaires assessing the presence or absence of

bleeding and the degree of their severity, calculated by a score. ISTH-BAT may support clinicians during the evaluation of hemorrhagic symptoms. Bleeding scores are usually significantly higher than normal in GT patients [5].

For the diagnosis of GT, like for any other inherited bleeding disorder, it is crucial to evaluate the patient's family and personal history. The occurrence of spontaneous cutaneous or mucosal bleeding, such as petechiae, purpura or easy bruising needs to be evaluated. Conventional tests including complete blood cells count (CBC) and first level coagulation assays are usually normal, even if platelets may have an increased volume. In some centers, (PFA-100) is performed to preliminarily evaluate platelets function. These tests have a low specificity but their utility is well recognized for screening purposes

Confirmatory diagnosis of GT is made by (LTA), the gold standard method due to its high sensitivity and specificity, in which platelet aggregation is absent for all agonists (ADP, collagen, thrombin, arachidonic acid), but the response to ristocetin is maintained. (FC), performed with monoclonal antibodies specific for platelets membrane receptors, rapidly confirms the deficiency of $\alpha\text{IIb}\beta_3$. Unconjugated and fluorescein isothiocyanate-conjugated monoclonal antibodies, CD41 and CD61 against human platelet GPIIb and GPIIIa receptors, respectively, are adopted. Other monoclonal antibodies may also be used like those dependent on conformational changes of the GPIIb/IIIa complex. PAC-1 is a monoclonal antibody directed against fibrinogen, which is exposed following the conformational change of GPIIb/IIIa due to platelet

activation. FC allows to distinguish three types of GT: type I, in which $\alpha IIb\beta 3$ is absent; type II in which reduced $\alpha IIb\beta 3$ is observed; and type III/variant in which $\alpha IIb\beta 3$ may be expressed but it is not functional.

Given the highly specific phenotype of GT, platelet aggregation studies and FC allow to reach the diagnosis, however genetic testing of ITGA2B and ITGB3 can be also performed for a specific characterization of the mutation [6]. The genetic diagnosis can help to improve disease management by directing genetic counseling, prenatal diagnosis, and carrier screening in asymptomatic family members, especially in regions with high consanguinity even if it is expensive (Figure 2).

Management of bleeding is based on a combination of hemostatic agents including local measure such us fibrin sealants and topical thrombin, or with antifibrinolytics or desmopressin, rFVIIa with or without platelet transfusions [3]. Refractory bleeding and platelet alloimmunization are common complications during the course of the disease. Refractoriness to platelets after transfusion is due to the development of antiplatelet alloantibodies (APAs), targeting human leukocyte antigens (HLAs) or the deficient glycoproteins (GPIIb/GPIIIa). A potential reduction in platelet refractoriness therefore could be reached by favoring transfusions of platelets from HLA-matched

donors. Unfortunately, the short half-life of platelets and platelets availability makes difficult to obtain HLA-matched donor platelets, especially in urgent cases.

CONCLUSIONS

Inherited platelet function disorders (IPFDs) are heterogeneous in severity, mechanisms and frequency and probably the prevalence of these diseases is underestimated because of the difficulty in diagnosis [7]. IPFDs should be suspected especially in female patients with hemorrhagic symptoms, with an often-normal platelet count, in the absence of coagulation alterations. In particular Glanzmann's disease can be challenging for its diagnosis and treatment due to the difficult access to clinicians and laboratories with the required expertise and resources. There is no consensus or standardized approach to the diagnosis of IPFD and many laboratory techniques used for assessment are insufficiently standardized, technically challenging and poorly reproducible. Several surveys have shown a significant heterogeneity in diagnostic approaches, consequently only a minority of patients investigated for mucocutaneous bleeding are currently diagnosed with IPFD [8]. Also clinical research is critical because of the rarity of the disease. The absence of specific therapies, especially in young women with excessive menstrual blood losses is another unmet need. Diagnosis should be established

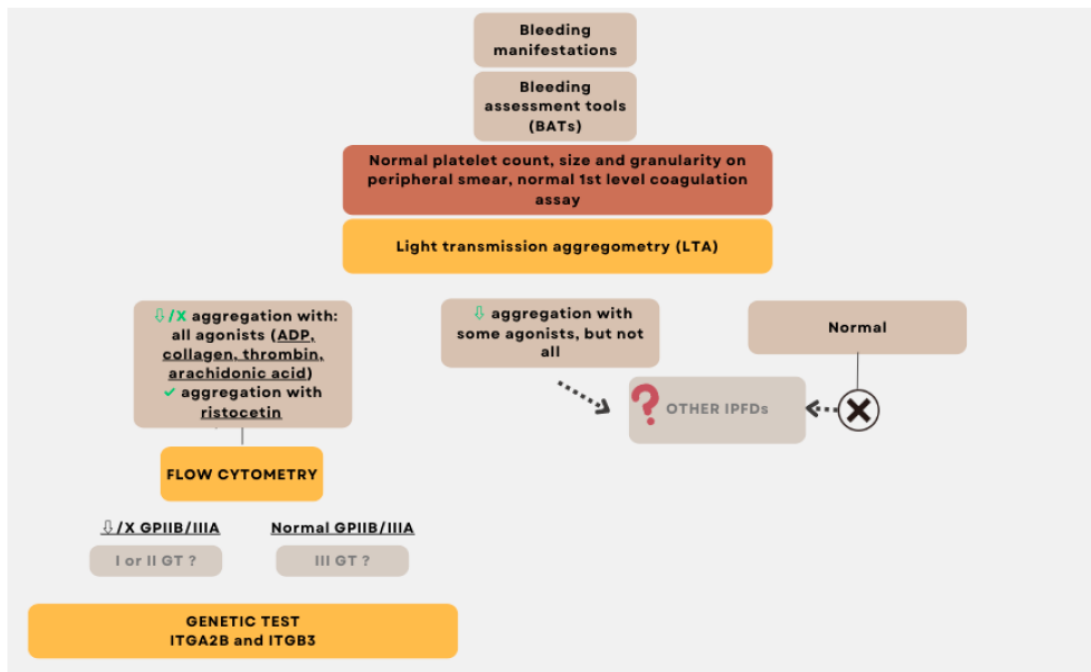


Figure 2: GT Flow chart: how to approach the diagnostic process starting from the clinical suspicion.

quickly to enact an effective bleeding control, it is thus mainly based on a combination of accurate clinical history and adequate laboratory assays.

CONFLICT OF INTEREST

MN acted as consultant for Bayer, Novonordisk, Amgen, CSL Behring and received speaker fees from: CSLBehring, Novonordisk, Bayer, Sobi, Amgen, Novartis, Sanofi Genzyme, Takeda. SS acted as consultant for Bayer, Novonordisk, Amgen, Biomarin, Novartis and received speaker fees from: Baxalta, CSLBehring, Novonordisk, Bayer, Sobi, Takeda, BioFVIIIx. All other authors have no relevant conflicts of interest to declare.

PATIENTS CONSENT

The patient signed Informed Consent for the management of personal and clinical data for health services and research purposes, as per policy of the Center, at the time of first visit at our outpatient clinic.

ABBREVIATIONS

GT (Glanzmann's thrombasthenia), LTA (light transmission aggregometry), FC (flow cytometry), CBC (complete blood count), BATs (Bleeding assessment tools), rFVIIa (recombinant activated Factor VII), APAs (antiplatelet alloantibodies), HLAs (human leukocyte antigens), IPFDs (platelet function disorders).

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