

# Glanzmann's Thrombasthenia: A Review of Literature

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## ABSTRACT

**Introduction:** Glanzmann's thrombasthenia is an inherited autosomal recessive bleeding disorder in which there is a deficiency of platelet glycoprotein GpIIb/IIIa. These receptors allow platelets to aggregate by sticking to each other, releasing granular contents to potentiate the process of clotting. Platelets are not able to clump together when stimulated, resulting in failure to form platelet aggregates. In such instances, bleeding time is prolonged and the clot retraction is defective, resulting in increased bleeding tendency. GT is diagnosed by tests that determine whether there is a deficiency of the  $\alpha 11b\beta 3$  (GpIIb/IIIa) receptor. The diagnosis is confirmed mainly by flow cytometry and monoclonal antibodies. In the platelet function analyzer 100 (PFA-100), platelets fail to plug on the filter, as platelet aggregation response is defective. The condition may present in early childhood causing repeated nasal bleeds, or in adulthood as menorrhagia, antenatal, and postpartum hemorrhage. Patients may require many leukocyte-depleted blood products during bleeding episodes.

**Objectives:** Objectives of this review article is to understand the implications of Glanzmann's thrombasthenia, its pathogenesis, diagnostic modalities and treatment options as it is a rare platelet disorder. Surgeons have to be on the alert if the case is a Glanzmann's thrombasthenia, as uncontrolled hemorrhage not responding to usual treatment can have fatal consequences.

**Materials and methods:** An extensive search and review of current literature was undertaken via PubMed and EMBASE to know the historical background with its latest management options available.

**Results and evidence:** Studies have suggested that GT is a hereditary disorder occurring predominantly in consanguineous populations with female preponderance.

**Remarks and conclusions:** As consanguinity is very high in this part of the world awareness among clinicians of this medical disorder is necessary to avoid unanticipated hemorrhage and its untoward complications.

**Keywords:** Epistaxis, Glanzmann's thrombasthenia, Menorrhagia, Mucocutaneous bleeding, Platelet transfusion, rFV11a.

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## HISTORY

In 1918 in a tiny Swiss village—Le Valais, Dr Eduard Glanzmann (a pediatrician) first reported the incidence of Glanzmann's thrombasthenia in children. He observed prolonged bleeding time and an isolated appearance of platelets on a peripheral blood smear.<sup>1</sup> In 1956, Braunsteiner and Pakesch observed platelets of normal size that did not help in clot retraction.<sup>2</sup> Later, Caen et al. noted that abnormal platelet aggregation was the primary feature in GT.<sup>3</sup> Absence of both platelet aggregation and clot retraction was termed as type-I and absence of aggregation but residual clot retraction as type-II disease in 1981.<sup>4</sup> Incidence of GT is around 1/10,00,000 and is seen mostly in consanguineous marriages.<sup>5,6</sup>

## Pathophysiology

Each platelet has 50–100 glycoprotein receptors, which help in the formation of clot by an interaction between the cellular components of blood and coagulation proteins.<sup>7,8</sup> Activation of these receptors is dependent on stimulation by ADP (adenosine diphosphate), epinephrine, collagen, or thrombin.

Platelets have no cell nucleus but they are fragments of cytoplasm derived from the megakaryocytes of the bone marrow. The inactivated platelets are biconvex discoids (lens-shaped) with a greatest diameter of 2–3  $\mu\text{m}$ . The platelet membrane contains receptors for collagen, vessel wall von Willibrand factor (vWF), and fibrinogen. Their cytoplasm contains actin, myosin, glycogen, lysosomes, and two types of granules. Dense granules (delta granules) contain serotonin, ADP, and adenine nucleotides; alpha granules contain clotting mediators such as factor V, factor V11, fibrinogen, fibronectin, platelet-derived growth factor, and chemotactic agents.<sup>9</sup>

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Injuries to the vessel wall cause platelets to bind to vWF. Platelets are activated by thrombin, and upon activation, they anchor to the collagen of the vessel wall. Their shape changes with the formation of pseudopodia, and after discharging their granules, they stick to other platelets by binding of  $\alpha 11b\beta 3$  with vWF or fibrinogen. Platelet-activating factor (PAF) also helps in aggregation process. In GT, platelets cannot bind to fibrinogen and aggregation does not occur.<sup>10</sup> As a result, no fibrinogen bridging of one platelet to another occurs, delaying clot retraction and resulting in potentially major mucocutaneous bleeding.<sup>11</sup>

GT is associated with the abnormal integrin  $\alpha 11b\beta 3$ . These are heterodimer transmembrane proteins that mediate cell adhesion and cell migration by attaching to the cell cytoskeleton to the extracellular matrix. The integrin family of proteins consists of alpha and beta subtypes. Mutations causing GT affect either ITGA2B or ITGB3 genes. There are three grades of the disorder. Type 1 has severe deficiency with less than 5% GpIIb/IIIa receptors. Type II show a mild-to-moderate deficiency (5–20%) of IIb/IIIa receptors

and type III has an almost normal amount of IIb/IIIa receptors but defective function.<sup>12</sup>

The mutational defects in genes may happen due to splicing abnormalities, insertions or deletions, non-sense mutation, and single amino-acid substitution.<sup>13-15</sup> A Turkish study by Tokgoz et al.<sup>16</sup> noted various further mutations in 7 of 20 Turkish GT patients (four novel and two previously described mutations) in ITGA2B and one novel mutation in ITGB3 besides the already documented mutations in literature.

There is a relatively high incidence of GT in various closed populations, such as the French gypsies, South Indians, Jordanian tribes, Arabs, and Iraqi Jews.<sup>12</sup> Siddiq et al.<sup>11</sup> observed a higher female preponderance for Glanzmann's thrombasthenia.

## SIGNS AND SYMPTOMS

Bleeding tendency may be bruising in some individuals or severe fatal hemorrhage in others. Repeated episodes of epistaxis is a common occurrence in children noted to affect up to 9% of children.<sup>17</sup>

The main signs and symptoms are increased mucosal and gingival bleeding, menorrhagia, easy bruising, epistaxis, increased postpartum hemorrhage, and lifelong risk during surgical procedures. Bleeding may occur with minimal trauma or by harmless events such as sneezing, crying, coughing, eruption of a tooth, or even common cold. The condition is usually diagnosed in childhood. Menorrhagia in women and a rare bleeding complication after circumcision in men can also occur. Menorrhagia affects 25-30% of women, and post-circumcision bleeding may require platelet transfusion if uncontrolled.<sup>18,19</sup> Hematuria was reported in some but hemarthrosis and hematomas rarely occur.<sup>20</sup> In some patients with angiodysplasia, gastrointestinal hemorrhages are also observed. Even unusual presentation of intracranial hemorrhage has been reported in some cases.<sup>21,22</sup> Pregnancy along with GT is associated with a high risk of fetal and postpartum bleeding. Newborn thrombocytopenia (which is always transitory but serious) may occur sometimes.<sup>23</sup> Women with GT are screened for platelet alloantibodies throughout pregnancy and postpartum.<sup>24</sup>

Increased prevalence in consanguineous populations in KSA was found by testing patients for GT by platelet immunophenotyping and comparing results with a PFA. In their study,<sup>25</sup> platelet aggregometry revealed type I GT being the most common variety with female preponderance and they recommended using flow cytometry as a screening test.

Kazemzadeh et al.<sup>26</sup> reported that Glanzmann's Thrombasthenia may modulate the symptoms of MTHFR gene mutation, but further investigations are recommended to identify the effects of thrombogenic polymorphisms on coagulation factors or on platelet glycoprotein in regions where hemorrhagic disorders are prevalent so as to analyze the interactions of these factors on bleeding tendencies.

## DIAGNOSIS

Platelet function is measured by flow cytometry, which is helpful for diagnosing inherited deficiency of platelet surface glycoprotein receptors.<sup>27</sup> Other laboratory tests related to GT includes complete blood count, prothrombin time, activated partial thromboplastin time, platelet function analyzer 100 (PFA-100), monoclonal antibody assays, and platelet aggregation studies. The platelet count and coagulation test results should be normal. The red blood cell count

may be decreased due to bleeding or concomitant iron deficiency. The bleeding time should be prolonged. On PFA-100 testing, the platelets fail to plug the collagen-based filter.

Ali et al.<sup>20</sup> reported that GT can be diagnosed on the basis of platelet aggregometry when decreased platelet aggregation response to adenosine diphosphate (ADP), epinephrine and collagen and normal response to ristocetin (an antibiotic) is noted when compared to the Bernard-Soulier syndrome where a defective response to ristocetin and a normal von Willebrand assay response is elicited. Both these conditions cause a bleeding disorder due to platelet defects. In GT by failed aggregation and clot retraction and in the Bernard-Soulier, the defect lies in decreased platelet adhesion and not in aggregation. The Bernard-Soulier syndrome (BSS) is the second most common inherited platelet defect, where, at the molecular level, there is an absence of the platelet membrane glycoprotein complex, which is the receptor for vWF. This results in deficient binding of vWF to the platelet membrane at the sites of vascular injury, leading to defective platelet adhesion. The end result in both these disorders is the lack of formation of the primary platelet plug, together with an increased bleeding tendency.<sup>28</sup> Few more sophisticated tests for diagnosis of GT such as western blotting, immunoprecipitation analysis, and gene sequencing are used in highly specialized centers in reference laboratories.<sup>29,30</sup>

Thromboelastography (TEG) is a method of testing the accuracy of blood coagulation by estimating the platelet function, clot strength, and fibrinolysis. It is used mainly in surgery and anesthesiology as a great tool for perioperative assessment of coagulation disorders.<sup>31</sup>

Narani<sup>32</sup> demonstrated that perioperative TEG can prove to be an invaluable tool for bedside monitoring of coagulation status in patients with preexisting hemostatic disorders or in a profusely bleeding patient with a deranged hemostatic profile. TEG can monitor hemostasis and guide replacement of blood components and pharmacological agents. Thromboelastography measures the visco-elastic and mechanical properties of a developing clot. It detects all phases of the hemostatic activity from a single sample of blood. Clot formation, stabilization, retraction, and dissolution are displayed in graphical and numerical forms.<sup>33</sup>

Loroch et al.,<sup>34</sup> as well as researchers who studied recent advances in proteomics have documented several technologies for visualization, quantitation, and identification to elucidate the platelet processes, which are relevant to bleeding and clotting disorders, transfusion medicine, and regulation of angiogenesis. Platelets from GT patients showed less than 5% relative levels of the integrin subunit  $\alpha 11b\beta_3$ .

## TREATMENT

Leuko-reduced or human-leukocyte-antigen-matched platelets should be used, as patients need repeated platelet transfusion to avoid becoming refractory to this treatment. Platelet transfusion should be given immediately prior to the procedure. Recombinant factor VIIa as an adjuvant can be used 48 hours postoperatively in refractory states with antibodies.<sup>35</sup>

Antifibrinolytics such as tranexamic acid and aminocaproic acid are used as adjuvants in emergency situations in GT and other bleeding dyscrasias. These drugs are utilized for enhancing hemostasis, whereas fibrinolysis results in hemorrhage due to the enhancement of clot breakdown. Both these drugs act by reversibly blocking the lysine-binding sites of plasminogen, thus preventing its activation to plasmin and thereby stopping the lysis of the

polymerized fibrin.<sup>36</sup> Antifibrinolytics such as tranexamic acid and aminocaproic acid are successfully used by maxillofacial surgeons in cases of various hematological disorders such as the Bernard Soulier syndrome, hemophilia, alcoholic cirrhosis of liver, hereditary angioedema, and the Trousseau syndrome.<sup>37,38</sup> Wardrop et al.<sup>39</sup> reported that the use of antifibrinolytics in hematology patients may be useful adjuncts to platelet transfusions so that platelet use and the complications associated with their use can be reduced. The negative side-effect of both these drugs is the increased thromboembolic effects. A condition of acquired thrombasthenia due to glycoprotein IIb-IIIa platelet antibodies may also result after platelet transfusion.<sup>40</sup> Females with menorrhagia may be benefitted by using hormonal contraception.

Recombinant factor VIIa with antifibrinolytic agents has been used both as a prophylactic and as a therapeutic measure in patients undergoing pelvic surgery, cesarean section, and vaginal delivery. Recombinant factor V11a acts on platelets in the absence of tissue factor to activate factor IX and X, thus enhancing thrombin generation. Recombinant factor V11a binds to the platelet surface and activate factor IX and X to increase thrombin formation. The increase in thrombin formation stimulates platelet adhesion and platelet aggregation, which also include the GpIIb/IIIa lacking platelets. The increased generation of thrombin may provide a strong signal for the recruitment of other platelets.<sup>41</sup> Treatment with rFV11a is well tolerated but hugely expensive and increases the risk of thromboembolism.<sup>42</sup>

Recent treatment options include the use of Retiuximab, Bevacizumab, bone marrow transplantation, and stem cell therapy.<sup>43</sup> Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A).<sup>44,45</sup>

Desmopressin raises the plasma levels of factor V111, vWF, and tissue plasminogen activator. It has no effect on platelet count or aggregation but enhances platelet adherence to the vessel wall. Desmopressin is successfully considered as a treatment option for various platelet disorders. No enough data are available to support the usage.<sup>46</sup> Thalidomide is another interesting medical management lately experimented by several groups in management of angiodysplasia for severe and recurrent GI bleeds. The antiangiogenic effects suppress the expression of VEGF and promote vessel maturation.<sup>47</sup>

Permanent treatment is done by hematopoietic stem cell transplantation and donor cord blood transplantation.<sup>48</sup> Gene therapy remains still the ultimate prospect of cure in these cases. The abnormalities of the cytoplasmic proteins that regulate the activation state of  $\alpha 11b\beta 3$  for adhesion is yet to be explored.<sup>49</sup> Kunicki et al.<sup>50</sup> reported that some platelet receptor haplotypes along with use of proteomics and gene microarray can markedly reduce bleeding in cases of Von Willebrand disease and GT.

The management also includes avoidance of using antiplatelet agents such as aspirin and NSAIDs. The general measures are to use iron and folate supplements, hepatitis vaccine, and hormonal contraception. Minor bleeding can be controlled by local pressure, nasal packing, fibrin glues, or oral antifibrinolytics.

## CONCLUSION

Glanzmann thrombasthenia is a disease of clotting with lifelong risk of bleeding, especially during surgical procedures. Preoperative preparation of such cases by infusion of platelets, rFV11a and blood products can avoid life-threatening hemorrhage. In these cases,

platelet count is normal, but clot retraction is abnormal. Stem cell transplantation and gene therapy will be the future therapies for treating this disease.

## AUTHOR CONTRIBUTION

Dr Hansa Dhar has contributed to data collection, manuscript preparation, research of the literature, and editing of the manuscript. Dr Asha has contributed to manuscript preparation and editing of the same. Both the authors approved the final version.

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