Chapter

Bleeding Disorders Associated with Abnormal Platelets: Glanzmann Thrombasthenia and Bernard-Soulier Syndrome

Muhammet Mesut Nezir Engin

Abstract

Platelets, the smallest cells in the blood, are associated with hemostasis, bowel formation, tissue remodeling, and wound healing. Although the prevalence of inherited platelet disorders is not fully known, it is a rare disease group and is encountered in approximately between 10000 and 1000000. Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) are more frequently observed in inherited platelet disorders. In GT, the platelet aggregation stage due to deficiency or dysfunction of the platelet GPIIb/IIIa complex cannot take place. BSS is a platelet adhesion disorder due to the absence or abnormality of GPIb/IX complex on the platelet surface. If there is bleeding after easy bruising, mucous and oral cavities, menorrhagia, tooth extraction, tonsillectomy, or other surgical interventions, inherited platelet dysfunction should be considered if the platelet count is normal while the bleeding time is long. Firstly, other causes should be investigated by making differential diagnosis of GT and BSS. In this chapter, the definition, etiology, historical process, epidemiology, genetic basis, pathophysiology, clinical findings, diagnosis, differential diagnosis, and the follow-up and treatment approach of GT and BSS will be reviewed according to the current medical literature.

Keywords: Glanzmann thrombasthenia, Bernard-Soulier syndrome, thrombocyte function disorder, thrombocyte transfusion, rFVIIa

1. Introduction

Platelets, the smallest cells in the blood, are associated with hemostasis, bowel formation, tissue remodeling, and wound healing. Platelets perform their tasks in ensuring hemostasis in four stages: platelet adhesion, activation of platelet, platelet aggregation, and platelet procoagulant activity. When a damage occurs on the vascular endothelial surface, platelets bind to the collagen, fibronectin, von Willebrand factor, thrombospondin, and fibrinogen in the endothelial substrate with the glycoprotein receptors they carry on their surface. In this way, platelet adhesion takes place. Binding of platelet receptors to their respective ligands causes activation of the platelet. This activation occurs as a result of the change in the cytoskeleton system due to intracellular calcium. By importing the impulse from outside the cell, platelet α-granules secrete their contents. The released ADP causes structural

	Glanzmann thrombasthenia	Bernard-Soulier syndrome
Genetic mutation	17q21 chromosome. ITGA2B or ITGBS genes	GPIbα, GPIbβ, and GPIX genes
Pathophysiology	Deficiency or dysfunction of the platelet GPIIb/IIIa complex	Deficiency or dysfunction of the platelet GpIb/V/IX complex
Affected platelet function	Aggregation	Adhesion

Table 1.
Comparison of genetic mutation, pathophysiology, and affected platelet function status of Glanzmann thrombasthenia and Bernard-Soulier syndrome.

change in GPIIb/IIIa on the platelet surface. Fibrinogen binds two or more platelets via GPIIb/IIIa receptors that are structurally altered, resulting in platelet aggregation. After aggregation of platelets, platelet plugs are formed at the damage site. Activation of platelets leads to changes in phospholipids on their surface. These phospholipids enable the activation of some clotting factors and perform platelet procoagulant activity [1–6].

The problem in any of the functions of platelets creates a tendency for the primary hemostatic plug not to form and therefore to bleed. Platelet dysfunctions can be hereditary or acquired. Although the prevalence of inherited platelet disorders is not fully known, it is a rare disease group and is frequently encountered in approximately between 10000 and 1000000. Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) are more frequently observed in inherited platelet disorders.

In GT, the platelet aggregation stage due to deficiency or dysfunction of the platelet GPIIb/IIIa complex cannot take place. BSS is a platelet adhesion disorder due to the absence or abnormality of GPIb/IX complex on the platelet surface [1, 7, 8] (**Table 1**).

If there is bleeding after easy bruising, mucous and oral cavities, menorrhagia, tooth extraction, tonsillectomy, or other surgical interventions, inherited platelet dysfunction should be considered if the platelet count is normal while the bleeding time is long. Firstly, other causes should be investigated by making differential diagnosis of GT and BSS [1, 7]. In this chapter, the definition, etiology, historical process, epidemiology, genetic basis, pathophysiology, clinical findings, diagnosis, differential diagnosis, and treatment approach of GT and BSS will be reviewed according to the current medical literature.

2. Glanzmann thrombasthenia

2.1 Definition

GT is an autosomal recessive congenital bleeding disorder characterized by a lack of platelet aggregation due to defect and/or deficiency of α IIbβ 3 integrin. Integrin is a platelet fibrinogen receptor, necessary for platelet aggregation and hemostasis. Patients with this disorder often experience lifelong bleeding episodes involving mucocutaneous membranes [9–13].

2.2 History

This disease was first described by Swiss pediatrician Eduard Glanzmann in 1918 as "hereditary hemorrhagic thrombasthenia." Braunsteiner and Pakesch, on the other hand, reviewed platelet dysfunctions in 1956, after which they identified thrombasthenia as a hereditary disease characterized by normal size platelets that did not spread

to the surface and did not support clot retraction. The diagnostic characteristics of GT including the absence of platelet aggregation as a primary feature, were reported in 1964 by Caen et al. has been clearly identified by the classical report on 15 French patients. Those patients without platelet aggregation and no clot retraction were later called type I disease patients and those with absent aggregation but residual clot retraction were called type II disease patients; variant disease was first identified in 1987 [8, 10, 14–16].

2.3 Etiology

GT is an autosomal recessive disease with mutations containing the 17q21 chromosome, especially the ITGA2B or ITGB3 genes. GT results when a patient is homozygous for the same mutation or is a compound heterozygote for different mutations. GT is usually caused by decreased or absent expression of αIIb or β3, abnormalities in protein folding, transport of the integrin subunit causing post-translational defective processing or decreased surface expression, or abnormalities affecting protein function. Other defects change the integrin function by altering the ligand binding pocket (interface between αIIb and β3) that changes the cytoplasmic domain and affects the binding of regulators or locks integrin in active form [8, 9, 12, 13, 17–20].

2.4 Epidemiology

GT has an increasing incidence in populations where marriage between close relatives is an accepted tradition. The prevalence is estimated to be approximately 1:1,000,000 in the general population. Research shows that women are slightly more frequently affected than men. For example, when 177 patients with GT in Paris were examined, 102 (58%) of the patients were shown to be women. In addition, 12 patients were in the USA, 55 were in Israel and Jordan, and 42 were in South India. Some patients may have mild symptoms and are never detected to have GT, so the true prevalence may be higher than reported. Type I is the most common subtype and accounts for about 78% of patients with GT type II and type III (functional variant in receptor) and accounts for about 14% and 8% of cases [8, 9, 12].

2.5 Genetic basis

The ITGA2B and ITGB3 genes are found on chromosomes 17q21.31 and 17q21.32, respectively, and are independently expressed. Due to autosomal recessive inheritance, compound heterozygosity is common, except for selected ethnic groups, where homozygosity is more likely due to kinship. A higher percentage of pathogenic variants occur in ITGA2B compared to ITGB3, which consists of 15 exons with 788 amino acids, probably because this gene is larger with 30 exons encoding 1039 amino acids. There is a constantly updated database on the Internet http://sinaicentral.mssm.edu/intranet/research/glanzmann: currently, it contains a list of 558 mutations that lead to GT. In addition, when the data in the database were examined, it was found that 269 patients had homozygous mutations. This shows us that consanguineous marriage is an important feature in the heredity of this disease. Some researchers described that pathogenic, nonsense missense, and splice site variants are commonly observed and large deletions and duplications are rarely observed. Pathogenic missense variants cause the disruption of subunit biosynthesis megakaryocytes or prevention of the exit of pro-αIIbβ3 complexes from endoplasmic reticulum to Golgi device or the cell surface mature complexes. Most of the genetic variants affect the β-propeller region of αIIb and domains of β3 of the epithelial growth factor [20–23].

2.6 Pathophysiology

The main mechanism in the pathophysiology of GT is the qualitative or quantitative disorder of the autosomal recessive platelet surface receptor of GPIIb/IIIa (ITG αIIbβ3). As a result, it results in erroneous platelet aggregation and reduced clot retraction. ITG αIIbβ3 is a large heterodimeric cell transmembrane receptor consisting of a larger αIIb and a smaller P3 subunit. These subunits were not covalently attached to permit bidirectional signal between the cell membrane and extracellular matrix when initiating intracellular signaling pathways. It contains cytoplasmic and transmembrane domains that act as the junction point for intracellular signal molecules and proteins. The activation of ITG αIIbβ3 is provided by the B3 subunit consisting of large disulfide epidermal growth factor (EGF) domains. Calcium binding sites for complex formation and platelet-platelet adhesion are found on the p-propeller region of the αIIb subunit. The receptor head function consisting of binding fibrinogen, VWF, vitronectin, and fibronectin is necessary for platelet communications by regulation of cell migration, platelet aggregation and adhesion, and the formation of a thrombus [24].

The ITGA2B gene, located on chromosome 17q21.31, encodes the platelet GPαIIb, while the gene encoding the glycoprotein subunit IIIa is found in chromosome ITGB3, 17q21.32. Both subunits are collected from the precursors of the endoplasmic reticulum by further processing in the Golgi apparatus. Nurden et al. examined more closely the p-propeller ectodomain mutations of the αIIb subunit. Nurden et al. concluded that a large series of mutations affecting the β-propeller field interrupts calcium binding and has numerous harmful effects on αIIbβ3 expression and function, and causes different types of GT [21, 25, 26].

Homozygous or heterozygous mutations in both gene locations determine the severity of abnormality seen in GT. Mutations can stop subunit production, prevent complex formation, and/or inhibit intracellular trade. When complex build-up is prevented, the subunits of αIIb or β3 are now broken. Now based on the expression and functionality of the subunits, GT is classified into three types: <5% of αIIbβ3 now specifies type I GT; now 5–20% of αIIbβ3 is type II GT; and rarely >20% of residual αIIbβ3 with dysfunctional features make up the variant type GT. Acquired GT is usually the result of autoantibody attack on platelet αIIbβ3 or isoanorbons that inhibit proper function. The production of autoantibodies has been associated with multiple hematological conditions, including immune thrombocytopenic purpura, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, hairy cell leukemia, and acute lymphoblastic leukemia, as well as platelet transfusions [21, 24, 26].

2.7 Clinical manifestations

The most common symptoms of bleeding are purpura, nosebleeds (60–80%), gingival bleeding (20–60%), and menorrhagia (60–90%). Gastrointestinal bleeding in the form of melena or hematochezia is found in 10–20% and intracranial hemorrhage is developed in 1–2%. Mucocutaneous bleeding may occur spontaneously or following minimal trauma. Epistaxis is the most common cause of severe bleeding especially in children. Menorrhagia is quite common in affected women, and there is a higher risk of serious bleeding during menarche due to the prolonged estrogenic effect on the proliferative endometrium that occurs during anovulatory cycles. Bleeding complications during pregnancy are rare; however, there is a high risk of obstetric bleeding during and after birth. Hematuria and spontaneous hemarthrosis have been described in some cases, but are generally not part of the bleeding phenotype. Currently, specific cuts could

not be identified to define a positive bleeding score. Although the types of bleeding are consistent among individuals, the degree of bleeding is quite variable. The severity of bleeding (except for menorrhagia and pregnancy-related bleeding) decreases with age [8, 20].

2.8 Diagnosis

The diagnosis of GT is often not noticed, because many platelet disorders share common clinical and laboratory features. GT should be remembered in the differential diagnosis of medical history (insidious or bleeding episodes or severe bleeding after minor trauma), family history (consanguinity). In order to diagnose GT, it is necessary to choose the appropriate laboratory tests. A normal platelet count on a on a routine blood smear does not exclude the diagnosis of GT. Because patients with GT usually do not show any abnormalities in the number of platelets, complete blood count may be normal or show iron deficiency. Prothrombin time and activated partial thromboplastin time may be normal if bleeding time is prolonged; further investigations should be done [24].

Let us examine the laboratory methods in detail.

2.8.1 Complete blood count

In the evaluation of peripheral blood smear with light microscopy, normal platelet count and normal granular size should be. If the bleeding is severe and/or chronic, patients may have a red cell distribution width that increases with low hemoglobin, microcytosis, and secondary iron deficiency. Other abnormalities of the complete blood count (CBC) suggest an alternative diagnosis [20].

2.8.2 Coagulation screening tests

Prothrombin time (PT), activated thromboplastin time (aPTT), and fibrinogen values are usually normal unless a patient is evaluated in a significant acute bleeding environment and there is no evidence of consumption coagulopathy [20].

2.8.3 Platelet function screening tests

Platelet function analyzer PFA-100 provides a measure of platelet function under reduced platelets. Very long closing times (>300 s) show GT but are heat-specific. Some other disorders such as severe von Willebrand disease, Bernard Soulier syndrome, and afibrinogenemia may produce the same result. A normal PFA-100 reveals a very high negative predictive value for GT and generally excludes this diagnosis [27].

2.8.4 Platelet light transmission aggregometry

Light transmission aggregometry (LTA) is widely accepted as the gold standard diagnostic tool for evaluating platelet function. Although this test provides specific data, LTA is very time-consuming and dependent on staff and requires the use of experienced laboratories [24].

2.8.5 Whole blood impedance aggregometry

Although it can be performed using whole blood samples and lower volumes, there is insufficient evidence to support equivalent sensitivity and reproducibility compared to LTA [28].

The best way to fully diagnose GT is by mutation analysis. The genomic DNA sequence of 45 exons containing the αIIb and 3 unit should be investigated together with the junctions of the ITGB3 and ITGA2B gene and established mutations should be confirmed by a second DNA sample analysis. Genetic analysis is clinically useful for confirming the diagnosis, identifying carriers at risk, reproductive risk counseling for a particular couple/family, and definitive prenatal or preimplantation genetic diagnosis. Consequently, the diagnosis of GT involves the presence of normal platelet count (typically at the lower end of normal), long bleeding time, and long PFA time [24].

2.9 Differential diagnosis

Leukocyte adhesion deficiency type III, RASGRP2-related platelet dysfunction, BSS, Hermansky-Pudlak syndrome, von Willebrand disease, Medich platelet syndrome, Scott syndrome, and Acquired Glanzmann thrombasthenia are among the differential diagnoses [20].

2.10 Treatment

A gradual treatment standard is applied in GT treatment. The first treatment for mild bleeding is local measures including local compression, cauterization, stitching, or ice therapy. The treatment applied in case of unresponsiveness to these treatments or in heavier bleeding is antifibrinolytic therapy first, followed by platelet transfusion, and recombinant active factor VII (rFVIIa) if bleeding persists. Platelet concentrates may be single-donor and HLA-matched due to the risk of developing alloantibodies against the platelet glycoproteins, αIIbβ3, or αIIbβ3, and/or the HLA antigens. Platelet concentrates may be repeatedly transfused. If HLA-matched platelets are not found, patients should be given leukocyte-reduced platelets. This has been shown to reduce the rate of HLA immunization. Patients with severe bleeding cases should continue to receive platelet transfusion for 48 h until bleeding ceases and wound healing occurs in operated cases. These patients should be trained to avoid over-the-counter drugs that increase the risk of bleeding, such as nonsteroidal anti-inflammatories and aspirin products. Prescription drugs that may affect hemostasis should be carefully monitored [9, 24, 25, 29, 30].

Let us examine the treatment of GT according to the frequently observed conditions.

2.10.1 Treatment of minor to moderate bleeding

Local measures and/or antifibrinolytic drugs can stop mild to moderate bleeding. Local measures include compression, gelatin sponges, fibrin sealants, and topical thrombin. Antifibrinolytic agents include epsilon aminocaproic acid and tranexamic acid. Since both agents can be given orally or intravenously, they have been used successfully in the treatment of nosebleeds, bleeding gums, and menorrhagia, as well as prophylaxis before tooth extraction and other minor surgical procedures. Antifibrinolytic agents, such as tranexamic acid, can be used as a mouthwash for gingival bleeding. Antifibrinolytic use in cases of hematuria should be avoided due to the risk of a clot in the urinary tract and should be used with caution in patients undergoing procedures at high risk of thrombosis [26].

2.10.2 Treatment in epistaxis

One of the most common bleeding symptoms in GT patients is epistaxis. Local compression to epistaxis, application of tampons to the nose, topical thrombin,

antifibrinolytics, and a combination of these may respond. If bleeding persists, further treatments with platelets transfusion and/or rFVIIa should be given. Antifibrinolytic agents, nasal cautery, rFVIIa, and nasal packing with synthetic materials may be used to control bleeding. If these treatments fail nasal packing with salt pork strips may be successfully used for life-threatening nasal hemorrhage in a child with GT [6, 31].

2.10.3 Treatment of menorrhagia

Antifibrinolytic agents should be first-line therapy to control menorrhagia. If it fails, hormone supplementation either progesterone alone or progesterone with estrogen may be given. A continuous estrogen-progestin oral contraceptive agent or intramuscular depot medroxyprogesterone acetate regimen given every 3 months in women with GT has been used successfully. It can be tried on hormonal intrauterine devices to reduce bleeding. Severe menorrhagia, which may be seen in many women with GT, can be treated with high-dose conjugated estrogen intravenously for 24–48 h and later by following with a combination of high doses of oral estrogen-progestin. Intensive menstrual bleeding does not always respond to typical treatment. rFVIIa has been utilized with anecdotal success in GT when anti-fibrinolytics and platelet transfusions did not control excessive menorrhagia. In addition, surgical treatments such as hysterectomy or endometrial ablation in treatment-resistant severe menorrhagia are therapeutic options [24].

2.10.4 Treatment of postpartum hemorrhage

Pregnant women with GT have high complications and are best managed in a specialized center with a multidisciplinary team. Although most complications are associated with bleeding and occur during delivery, treatment of pregnant GT patients should start in the prenatal period. According to the recommendations in the guidelines, platelet transfusions, or rFVIIa in combination with an antifibrinolytic can be used as a prophylaxis for vaginal delivery. A systematic review of 35 pregnant women with GT showed that hemorrhage during or after delivery is common and severe, and occurred up to 20 days postpartum. If patients were not given any platelet transfusions as prophylaxis, they were more likely to experience postpartum hemorrhage (63% versus 38%). The use of rFVIIa as prophylaxis was documented in three pregnancies, and it did not prevent hemorrhage in those cases. A study showed that maternal platelet alloantibodies were documented in 16 pregnancies, and plasma exchange successfully reduced the alloantibody titer in one case. Four of the 16 cases resulted in neonatal deaths, 3 of which resulted from intracranial hemorrhage between 24- and 31-weeks' gestation. One study reported successful use of rFVIIa for permanent postpartum hemorrhage. In one study, the patient was followed up with the diagnosis of GT and 18 units of random platelet concentrates, 6 units of apheresis platelet concentrates, and 2 units of erythrocyte suspension were given in the peripartum period. Although various forms of treatment have been reported about the treatment of obstetric bleeding occurring during and after birth of women pregnant with GT, there is no consensus on the most appropriate treatment. Further studies on this subject are needed [21, 26, 32].

2.10.5 Role of transfusions in the therapy of GT

Platelet transfusion allows partial correction of functional defect in patients with GT. Platelet transfusion is the standard prophylaxis when local precautions and/or antifibrinolytics cannot control bleeding and the patient is undergoing

major surgery. It is not uncommon for patients with severe bleeding after trauma or delivery to require multiple platelet transfusions. Multiple platelet transfusions can be performed if necessary. An important risk associated with platelet transfusion is the possibility of developing isoantibodies. Up to 30% of patients develop anti-GPIIb/IIIa or anti-HLA antibodies after platelet transfusion. Platelet alloimmunization can lead to relative or absolute platelet refractory, causing rapid destruction of platelets and therapeutic failure of platelet transfusions. For this reason, platelet transfusions should be reserved for only major surgeries, life-threatening bleeding, and significant bleeding that does not respond to the above measure. When possible, platelet concentrates should be single-donor derived and HLA-matched. If HLA-matched platelets are not available, patients should be given leukocyte-reduced platelets because this has been shown to reduce the rate of HLA immunization. Transfusions in women of reproductive age should ideally be avoided as the antibodies can cross the placenta and affect the fetus [13, 21, 22, 33–35].

2.10.6 Use of rFVIIa in GT

Treatment of rFVIIa in a GT patient was successfully used for severe and uncontrolled bleeding in a 2-year-old child in 1996 for the first time. The worldwide use of rFVIIa continued afterward, and it was observed that most patients with GT were effective in successfully controlling bleeding. But it was also observed that it was not effective in all GT patients. The mechanism of rFVIIa is not fully delineated. It is thought are poorly attached to the surface of platelets and increase the activation of factor IX and X, thereby increasing thrombin production. Increased amount of thrombin increases platelet adhesion and supports platelet aggregation, including those not containing GPIIb/IIIa [6, 25, 33].

High success rates and relatively low risks associated with the use of rFVIIa as a treatment or prevention of bleeding in GT patients have yielded good results, especially in those who are refractory to platelet transfusion or have antiplatelet antibodies. HLA-compatible platelets have been used in the past and have been recommended as prophylaxis for major surgical procedures, including cesarean section. rFVIIa can be used to completely prevent platelet transfusion, which will reduce the risk of platelet alloimmunization in case of life-threatening bleeding when local measures and antifibrinolytics fail. The optimal dosage for use in GT patients has not been established. However, the recommended dose is bolus injections of 90 mcg/kg intravenously 3 times a day or every 2 h until bleeding stops, followed by one or more maintenance doses [6, 8, 21, 24, 33, 36, 37].

The adverse or thromboembolic events have not been reported in patients given the rFVIIa bolus. The incidence of thrombotic events is not known in GT patients treated with rFVIIa. Controlled clinical trials are needed to further assess risk [26, 36].

A UK study showed that rFVIIa was successful in 71% of patients treated within 12 h of onset, but only after 12 h, only 18% of patients responded to rFVIIa. Therefore, rFVIIa should be administered as early as possible in bleeding episodes. Minor surgeries in GT patients have been successfully treated by rFVIIa prophylaxis without the need for platelet transfusion. rFVIIa prophylaxis used is recommended by the United Kingdom Hemophilia Centre Doctors' Organization for minor surgical prophylaxis including dental extractions [6, 26, 33].

2.10.7 Other treatments

Desmopressin (DDAVP) causes VWF, FVIII, and tissue plasminogen activator to be released into the plasma. Although DDAVP is successful in treating other platelet disorders, there is little data to support its use in GT patients [26].

Rituximab (anti-CD20) is a human-mouse chimeric monoclonal antibody that targets the B cell CD20 antigen. Successful treatment has been reported for acquired GT patients. Multiple case reports have demonstrated the efficacy of rituximab in patients with treatment-resistant GT and bleeding symptoms or ecchymosis [38].

Bevacizumab (Avastin) is an anti-VEGF antibody used in combination with chemotherapy in various cancers. A single case report in the literature documented success using bevacizumab in a patient with type I GT who had severe, recurrent GI bleeding due to angiodysplasia. The patient was resistant to platelet transfusion, tranexamic acid, and embolization, but responded to bevacizumab [25].

Hematopoietic stem cell transplantation (HSCT) provides a treatment for patients with severe, recurrent bleeding episodes and resistant cases to platelet transfusion due to platelet alloantibodies. There is currently no clearly defined algorithm for transplantation in GT, and HSCT is rarely used for GT. The first successful bone marrow transplantion in GT was performed in a 4-year-old child with anti-GPIIb/IIIa antibodies in 1985. It has been reported in the literature that successful stem cell transplantation has been performed in 19 severe GT patients [26, 33, 39].

2.10.8 Future therapy

Gene therapy is very promising for GT patients to provide a treatment with significant progress using different techniques, vectors, and model organisms [40–42].

3. Bernard-Soulier syndrome

3.1 Definition

BSS is a rare autosomal recessive platelet dysfunction that is characterized by a low levels, absence, or dysfunction of the GpIb/V/IX complex on the platelet surface. BSS thrombocytopenia <20,000/mm^3 is characterized by decreased platelet adhesion, abnormal prothrombin consumption, and low-surviving large platelets. Mucocutaneous hemorrhages such as purpura, epistaxis, oral mucosa bleeding, GIS bleeding, and menorrhagia are generally seen in BSS as in other platelet function disorders [43, 44].

3.2 History

BSS with autosomal recessive transition was first described by Bernard and Soulier in 1948 as congenital bleeding disorder characterized by thrombocytopenia and large platelets [45].

3.3 Etiology

Mutations in GP1BA [GPIbα], GP1BB (GPIbß), and GP9 (GPIX) cause BSS. There of the four genes encode for the subunita of the GP Ib-IX-V complex. This key platelet receptor constituted of four subunits, GPIbα, GPIbß, GPIX, and GP5 (GPV), which included in the ratio 2:4:2:1 in endoplasmic reticulum. They because mature in Golgi apparatus before localizing at the cell surface. The GPIb-IX-V complex can attach to von Willebrand factor, fitting together like a lock and its key. Von Willebrand factor is located on the inside surface of blood vessels when there is an injury. These platelets form clots, plugging holes in the blood vessels to help stop bleeding. Due to the specified conditions occurring in BSS, clot formation is impaired and excessive bleeding occurs [46–50].

3.4 Epidemiology

The incidence of BSS is estimated to be 1 in 1 million live births, but is likely to be higher since it is often misdiagnosed [50]. In a study with 97 BSS patients in Iran, consanguineous marriage was reported in 81% of the cases' families [51].

3.5 Genetic basis

BSS occurs as a result of homozygous or compound heterozygous mutations that affect the expression of genes encoding GPIbα, GPIbß, and GPIX proteins. Two types of mutations have been reported in the GP Ib-IX-V complex. The first one is biallelic mutations, often homozygous mutations. It is characterized by a severe decrease or absence of the GP Ib-IX-V complex. To date, more than 50 biallelic mutations have been identified in the GPIbα, GPIbß, and GP9 gene. In a few cases, there is a compound heterozygous mutation. Most of the mutations identified are missense and nonsense mutations. Most BSS mutations occur in the GPIbα gene, and most of these mutations lead to a decrease in GPIbα expression on the platelet surface, and some to a loss of function. GPIbα is connected to GPIbß by disulfide bond. These are connected by noncovalent bonds with GPIX and GPV. GPV is the proteolytic subunit in this complex, and its extracellular part is destroyed by GPIbα-bound thrombin activates platelets. As a result, mutations in GP1BA, GPIbß, and GP9 in humans generally lead to a decrease in the total expression of the GP Ib-IX-V complex on the platelet surface and the disease occurs [6, 43, 44, 50, 52].

3.6 Pathophysiology

Platelets play a critical role in normal primary hemostasis and clot formation. There are specific GP receptors on the platelet membrane, which function in platelet adhesion, activation, and aggregation. The GPIb-IX-V receptor complex is responsible for platelet adhesion through its interaction with von Willebrand factor on the exposed subendothelium. The GPIb-IX-V receptor complex is composed of four transmembrane polypeptide subunits-disulfide-linked alpha and beta subunits of GPIb, and noncovalently bound subunits GPIX and GPV. The platelets of BSS cases lack or have a dysfunctional GPIb-IX-V receptor. This results in defective adhesion to the subendothelium. The dysfunctional platelets found in BSS can result from one of several different glycoprotein mutations such as missense, nonsense, or deletion mutations of the GPIbα, GPIbβ, or GPIX genes [53].

3.7 Clinical manifestations

As with other inherited platelet disorders, BSS can manifest with a tendency to bleed in early childhood. Mucocutaneous bleeding is seen predominantly. Easy bruising, purpura, epistaxis, bleeding gums, menorrhagia, and excessive bleeding after surgery or trauma are common symptoms. Menorrhagia is an important problem for female BSS patients. Prolonged menstruation may be the first symptom to help diagnose BSS in some patients. Although the severity of bleeding is associated with a genetic defect that affects receptor function and platelet count, it is highly variable in patients with the same mutations. Although bleeding sites are well defined for BSS, it is difficult to predict the severity of bleeding in patients with BSS. In some cases, no serious bleeding is observed and diagnosis may not be established until adulthood. Other genetic differences and acquired conditions affecting hemostasis are thought to affect the severity of bleeding in these patients,

studies related to this need to be done. Heterozygotes may not have signs of bleeding, but giant platelets may appear in peripheral blood smear [6, 43, 46, 50, 54, 55].

3.8 Diagnosis

Although thrombocytopenia is generally observed in BSS, the number of platelets is variable. The platelet count typically ranges from 30 to 200 × 10^3/μL. Giant platelets are seen in peripheral blood smear (**Figure 1**). In order to the differential diagnosis of other giant platelet syndromes, leukocyte counts and morphology should be carefully examined. Skin bleeding time and PFA-100 closure time are found to be prolonged. Routine coagulation tests should be found normal. Prothrombin consumption and thrombin generation tests are found markedly decreased because of the defective binding of FXI and thrombin. Results of platelet aggregation studies are pathognomonic for BSS. In vitro platelet aggregation studies characteristically indicate that aggregation with ristocetin failed and responded slowly with low doses of thrombin. Flow cytometric analysis of platelet also show characteristic for BSS normal binding with CD41 (GPIIb) and CD61 (GPIIIa) antibodies, but defective binding with CD42a (GPIX), CD42b (GP Ib), CD42c (GP Ib), and CD42d (GPV) antibodies suggest BSS. Immunoblotting after separating components of the GP Ib-IX-V complex with sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) may describe the defective fragments but needs specialized interpretation. Also, in recent years, most families are offered molecular genetic testing to identify which gene carries the mutations [6, 53, 56–59].

3.9 Differential diagnosis

GT, idiopathic thrombocytopenic purpura (ITP), von Willebrand disease, May-Hegglin anomaly, and other inherited giant platelet disorders, for example, gray platelet syndrome are among the differential diagnoses [52, 53].

3.10 Treatment

BSS treatment is generally supportive. Platelet transfusion is used to treat when surgery is needed or when there is a risk of life-threatening bleeding. The patient may develop antiplatelet antibodies due to the presence of glycoproteins Ib/IX/V,

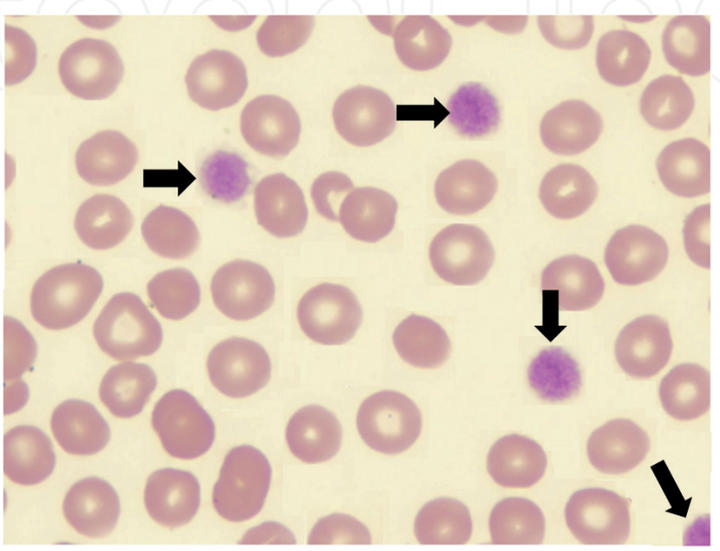

Figure 1.
Giant platelet appearance in peripheral blood smear in Bernard-Soulier syndrome.

which are present on the transfused platelets but absent from the patient's own platelets. Although some publications have suggested that patients should receive platelets from human leukocyte antigen-matched donors in order to avoid allo-immunization, this is not currently a widely accepted strategy. Antifibrinolytic agents such as p-aminocaproic acid or tranexamic acid may be useful for mucosal bleeding. rFVIIa has been reported to reduce bleeding times in patients with BSS. Desmopressin has been found to shorten bleeding episodes for some patients. A test dose should be used to determine those patients who will benefit. Stem cell transplantation has been successfully used to treat two children with BSS who had severe, life-threatening bleeding episodes. Transplantation should be considered in severe disorders when the patients have developed antiplatelet antibodies. Patients with BSS should be counseled about the importance of preventing even minor trauma as well as avoiding aspirin-containing medications and other platelet antagonists [52, 53, 60].

4. General recommendations for GT, BSS, and other inherited diseases

1. Should pay attention to dental health by brushing your teeth regularly.

2. Avoid sports activities with potential trauma (wrestling, boxing etc.).

3. Should not use salicylate and nonsteroid drugs that affect platelet function.

4. Oral contraceptives should be considered in patients with hypermenorrhoea.

5. It should be vaccinated against hepatitis A and B since blood products may be required.

6. The patient should carry a small information card describing the condition, blood group, and what to do in an emergency.

5. Conclusion

Genetic defects of the blood platelet membrane glycoproteins, GPIIb-IIIa (CD41/CD61) and GPIb-IX-V (CD42) are the origin of several rare bleeding disorders, the best known of which are GT and BSS. GT results in defective or absence of GPIIbIIIa. As a result of this, patients with GT are unable to undergo platelet aggregation, a critical step in stemming blood flow. Either gene can be affected and mutations leading to lack of expression or to expression of poorly functional forms have been identified. BSS occurs due to defective or absence of GPIb-IX-V. As a result of this, platelets from patients with BSS are unable to adhere to the damaged vessel wall at high-shear stress and also have a reduced platelet response to thrombin.

Since GT and BSS are rare diseases, diagnosis of patients can be delayed. When diagnosed early, patients will be able to prevent bleeding that may occur due to protective measures. If there is bleeding after easy bruising, mucous and oral cavities, menorrhagia, tooth extraction, tonsillectomy, or other surgical interventions, GT or BSS should be considered among the differential diagnoses. Although GT cannot be diagnosed with routine laboratory tests, BSS is suspected in the presence of thrombocytopenia and giant platelet. Detailed examination is required for a definitive diagnosis. Treatment includes local measures, platelet infusion, rFVIIa,

and other treatments. Although there is no permanent treatment for now, research is still ongoing. For this, it is more important for patients to avoid situations that may increase their tendency to bleed.

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Author details

Muhammet Mesut Nezir Engin
Department of Child Health and Diseases, Faculty of Medicine, Düzce University, Düzce, Turkey

*Address all correspondence to: doktormesut@hotmail.com

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