Bernard-Soulier Syndrome
An Inherited Platelet Disorder

Angie Pham, MD; Jun Wang, MD

• Bernard-Soulier syndrome is an inherited platelet disorder, which is transmitted in an autosomal recessive manner. This syndrome is characterized by variable thrombocytopenia and large defective platelets. Bernard-Soulier syndrome often presents early with bleeding symptoms, such as epistaxis, ecchymosis, menometrorrhagia, and gingival or gastrointestinal bleeding. Diagnosis can be confirmed by platelet aggregation studies and flow cytometry. The differential diagnosis includes the other inherited giant platelet disorders, as well as von Willebrand disease and immune thrombocytopenia purpura. Treatment is generally supportive with platelet transfusions when absolutely necessary and avoidance of antiplatelet medications. Recombinant activated factor VII and desmopressin have been used in attempts to shorten bleeding times; however, no definitive studies regarding their effectiveness have been reported. (Arch Pathol Lab Med. 2007;131:1834–1836)

Bernard-Soulier syndrome (BSS) was first recognized in 1948 by two French hematologists—Jean Bernard and Jean Pierre Soulier. They described a patient from a consanguineous family afflicted with severe bleeding episodes, thrombocytopenia, and very large platelets.1 Bernard-Soulier syndrome is a very rare quantitative and qualitative platelet disorder with an autosomal recessive mode of inheritance. Due to frequent misdiagnosis and underreporting, the true prevalence is unknown. However, based on reported cases from North America, Europe, and Japan, the estimated prevalence is less than 1 in 1 000 000.2 Heterozygous carriers are usually asymptomatic, although they may have mild bleeding tendencies.3 There have also been reports of a mild form of BSS with an autosomal dominant inheritance trait.4

PATHOPHYSIOLOGY
Platelets play a critical role in normal primary hemostasis and clot formation. The platelet membrane contains specific glycoprotein (GP) receptors, which function in platelet adhesion, activation, and aggregation.5 The GPIb-IX-V receptor complex, which is responsible for platelet adhesion through its interaction with von Willebrand factor on the exposed subendothelium,6 is composed of 4 transmembrane polypeptide subunits—disulfide-linked alpha and beta subunits of GPIb, and noncovalently bound subunits GPIX and GPV.7 The platelets of BSS lack or have a dysfunctional GPIb-IX-V receptor resulting in defective adhesion to the subendothelium.8 The dysfunctional platelets found in BSS can result from one of several different glycoprotein mutations such as missense, nonsense, or deletion mutations of the GPIb-a, GPIb-b, or GPIX genes. This variety of mutations is most likely responsible for the heterogeneity of BSS.9

CLINICAL MANIFESTATIONS
Bernard-Soulier syndrome presents early with bleeding symptoms, most commonly epistaxis, ecchymosis, and cutaneous and gingival bleeding, as well as menometrorrhagia and gastrointestinal bleeding. Rarely, patients will have severe hemorrhage at times of injury or surgery. The severity of these bleeding symptoms is variable among patients and may range from mild to life-threatening and may even become more or less severe during puberty and adulthood. Heterozygous patients may have mild to moderate bleeding tendencies.10

LABORATORY FINDINGS
Thrombocytopenia is variable in BSS, and the platelet count typically ranges from less than 30 to 200 × 10^3 /μL. Bleeding times may range from marginal to markedly prolonged.9 Evaluation of the peripheral blood smear will reveal large platelets; typically more than one third of the platelets are about half the size of a red blood cell (3.5 μm), and some platelets are as large or larger than a lymphocyte (Figure 1).10 Bone marrow biopsy specimens will show normal numbers of megakaryocytes without significant morphologic abnormalities.

Modern platelet function tests, such as the PFA-100, may be useful for identifying qualitative platelet disorders such as BSS, but with variable sensitivity, depending on the severity of the defect. Currently, their use is limited to screening for platelet dysfunction, and further testing, such as aggregometry or flow cytometry, is necessary for confirmation.11

In vitro platelet aggregation studies characteristically show a failure to aggregate with ristocetin and slow response with low doses of thrombin. This failure to aggregate cannot be corrected with the addition of normal plas-

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From the Department of Pathology, Loma Linda University Medical Center, Loma Linda, Calif.
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Reprints: Angie Pham, MD, Department of Pathology and Laboratory Medicine, Loma Linda University Medical Center, 11234 Anderson St, Room 2151, Loma Linda, CA 92354 (e-mail: akpham@ahs.llumc.edu).
Figure 1. Peripheral blood smear from a patient with Bernard-Soulier syndrome showing presence of large and giant platelets (modified Wright-Giemsa stain, original magnification ×1000).

The platelets show normal aggregation with epinephrine, adenosine diphosphate, collagen, and arachidonic acid.

Flow cytometry can be used to confirm defects in the GPIb-IX-V complex by antibodies directed against platelet surface antigen CD42b, revealing a severe reduction or deficiency of GPIbα (Figure 2, A through H). Other platelet antigens, CD41 (GPIIb) and CD61 (GPIIIa), are normal.

Differential Diagnosis

Included in the differential diagnosis for BSS are other inherited giant platelet disorders such as May-Hegglin anomaly and the other MYH9-related thrombocytopenia syndromes (Fetchtner syndrome, Sebastian syndrome, and Epstein syndrome), which are characterized by giant platelets, autosomal dominant inheritance trait, and mutations of the MYH9 gene on chromosome 22q12-13, which is the gene encoding for the heavy chain of nonmuscle myosin IIa (NMMHC-IIA). May-Hegglin anomaly is the most common inherited giant platelet disorder and has a clinical manifestation much like that of BSS with mild bleeding tendencies. These patients will often have other clinical findings including nephritis, familial spastic paraplegia, and pituitary growth hormone deficiency. In vitro platelet aggregation tests show normal response to adenosine diphosphate, collagen, epinephrine, and ristocetin; however, impaired response to epinephrine has been described. Peripheral smear evaluation shows large platelets and Dohle bodies, a blue spindle-shaped inclusion, within the cytoplasm of neutrophils.

Gray platelet syndrome is an extremely rare giant platelet disorder that appears to have an autosomal dominant

The cause of thrombocytopenia in BSS is unknown, and early studies suggested decreased platelet survival. However, a later study using indium-oxine labeled platelets shows little or no decrease in platelet survival time, suggesting ineffective or decreased thrombopoiesis.

Figure 2. Flow cytometric analysis of the expression of platelet surface antigens CD41a (GPIIb), CD42b (GPIIa), and CD61 (GPIIIa) is used to compare peripheral blood samples from a normal control (A through D) and a patient with Bernard-Soulier syndrome (E through H). The peripheral blood from the normal control shows presence of a distinct platelet population (gated) and a distinct erythrocyte population (not gated) (A). There is adequate expression of surface antigens CD41a (B), CD42b (C), and CD61 (D) on the platelets. Peripheral blood from a patient with Bernard-Soulier syndrome shows a merging zone between platelets (gated) and erythrocytes (not gated) (E) due to the presence of numerous large and giant platelets, as well as a complete loss of surface CD42b antigen expression on the patient’s platelets (G). However, CD41a (F) and CD61 (H) show adequate expression of GPIIb and GPIIIa on the patient’s platelets.
mode of inheritance as well as some seemingly sporadic cases. Patients tend to present early with epistaxis, ecchymosis, and other bleeding symptoms. Thrombocytopenia is common; however, bleeding time is prolonged even in patients with normal platelet counts, suggesting a qualitative platelet disorder. Platelet aggregometry shows reduced response to collagen and thrombin, but normal responses to adenosine diphosphate and arachidonic acid. Ristocetin may have normal or reduced, but not absent, response. The peripheral blood smear reveals large agranular platelets that appear gray-blue on Wright-Giemsa stain. The bone marrow biopsy specimen usually shows normal megakaryocytes and reticulin fibrosis.

Patients with von Willebrand disease, the most common inherited bleeding disorder, may present with symptoms similar to BSS such as mucocutaneous bleeding, epistaxis, and ecchymosis. However, von Willebrand disease is not typically associated with thrombocytopenia or significant peripheral smear findings. Platelet aggregation tests show failure to aggregate in the presence of ristocetin, much like BSS. Platelet aggregation tests show typically associated with thrombocytopenia or significant peripheral smear findings. Platelet aggregation tests show failure to aggregate in the presence of ristocetin, much like BSS. However, a ristocetin cofactor activity test, using the patient’s plasma and freshly washed platelets to measure the von Willebrand factor activity in the plasma, will be normal in patients with BSS and reduced in patients with von Willebrand disease.

Patients with BSS are often mistakenly diagnosed with immune thrombocytopenic purpura, an immune-mediated thrombocytopenia caused by antiplatelet antibodies, leading to the accelerated destruction of platelets. Peripheral smear evaluation will show decreased platelets, and bone marrow evaluation will show normal or increased numbers of megakaryocytes. The diagnosis of immune thrombocytopenic purpura requires the exclusion of other causes of thrombocytopenia. Possible causes of immune thrombocytopenia include infections, autoimmune diseases, lymphoproliferative diseases and drug therapy. Immune thrombocytopenic purpura can be separated into childhood and adult types. The childhood immune thrombocytopenic purpura is typically acute onset, often develops after viral infection or vaccination, and is frequently self-limited with resolution in weeks to months, while the adult type is usually a chronic disease with insidious onset, more often involves women, and rarely resolves spontaneously.

TREATMENT

Platelet and/or blood transfusions remain the best therapeutic measure for uncontrolled bleeding and prophylaxis to control bleeding during surgery. The benefits of receiving the transfusions must be weighed against the risks of exposure. Repeated exposure to blood products raises concern for alloimmunization and platelet refractoriness. The use of leukoreduced blood components has been shown to decrease alloimmune platelet refractoriness. Although some authors have suggested that patients should receive platelets from human leukocyte antigen–matched donors in order to avoid alloimmunization, currently this is not a widely accepted strategy. Activated factor VIIa (FVIIa) has been reported to reduce bleeding times in patients with BSS. However, FVIIa is an experimental drug in treatment of inherited thrombocytopenia, and adverse reactions have been reported. Desmopressin, a synthetic analog of antidiuretic hormone, may transiently increase factor VIII and von Willebrand factor by causing their release into blood. It is used for treatment of mild hemophilia A and von Willebrand disease. Desmopressin has been reported to shorten bleeding episodes for some patients, but a test dose is recommended to determine those patients who will benefit. Stem cell transplantation has been successfully used to treat 2 children with BSS who had severe, life-threatening bleeding episodes; however, based on the study results, the use of transplantation should only be considered in severe disorders and after patients have developed antiplatelet antibodies. Splenectomy, often performed when immune thrombocytopenia is mistakenly diagnosed, does not improve the platelet count or function in BSS. 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.

CONCLUSION

Bernard-Soulier syndrome is one of several inherited giant platelet disorders distinguished by a functional abnormality of the GPIb-IX-V platelet GPIb receptor complex. The disease is highly variable with bleeding tendencies that can range from mild to severe and life-threatening. Platelet aggregation studies and, more definitively, flow cytometry can provide an accurate diagnosis of this rare disease and allow for adequate therapeutic management.

References