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Insights into Bernard-Soulier Syndrome - A Review

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ABSTRACT

Bernard-Soulier Syndrome (BSS) is a rare but clinically significant inherited platelet disorder characterized by macrothrombocytopenia and defective platelet adhesion, attributed to anomalies in the glycoprotein (GP) Ib-IX-V complex. As an autosomal recessive disease, it often presents in infancy or early childhood with mucocutaneous bleeding symptoms such as epistaxis, gingival bleeding, menorrhagia, and prolonged bleeding following trauma. The hallmark features include large platelets and defective platelet aggregation in response to ristocetin. The syndrome poses diagnostic challenges due to its phenotypic overlap with other platelet disorders like Glanzmann thrombasthenia and von Willebrand disease. Laboratory confirmation includes platelet function tests, flow cytometry, and genetic analysis of GP1BA, GP1BB, or GP9 mutations. Management remains supportive, with platelet transfusions and antifibrinolytics being the mainstays during bleeding episodes or surgical interventions. Emerging advances in molecular biology, including gene therapy and induced pluripotent stem cells (iPSCs), hold promise for more definitive treatments in the future.

Keywords: Bernard-Soulier Syndrome, autosomal recessive disease

INTRODUCTION

Bernard-Soulier Syndrome was first identified in 1948 by Jean Bernard and Jean-Pierre Soulier in a patient with a severe bleeding diathesis, thrombocytopenia, and abnormally large platelets. Since then, BSS has become an archetypal example of inherited platelet adhesion disorders.(1,2) At the core of this syndrome lies a defect in the GPIb-IX-V complex, the primary receptor responsible for platelet binding to von Willebrand factor under conditions of high shear stress. This interaction is essential for initial platelet tethering to sites of vascular injury, especially in arterioles and capillaries. The GPIb-IX-V complex is composed of four subunits: GPIbα, GPIbβ, GPIX, and GPV, with mutations in GP1BA, GP1BB, or GP9 leading to absence or dysfunction of the receptor complex. As a result, platelet adhesion is severely compromised, setting the stage for ineffective hemostasis. Understanding the molecular and clinical characteristics of BSS is essential for hematologists, especially in differentiating it from more common bleeding disorders and ensuring timely and appropriate management.(3,4))

Epidemiology

BSS is an exceptionally rare disorder, with a reported incidence of approximately 1 in 1,000,000 individuals. Its true prevalence, however, is likely underestimated due to frequent misdiagnosis or underdiagnosis, especially in resource-limited settings.(5,6) The condition is inherited in an autosomal recessive manner, leading to a higher frequency in populations where consanguineous marriages are common. Notably, familial clusters and consanguineous cases have been reported in the Middle East (Iran, Saudi Arabia), the Indian subcontinent, and parts of North Africa. In non-consanguineous populations, sporadic cases may still arise, but they are extremely rare.(7,8) The low diagnostic yield is also partially due to confusion with immune thrombocytopenic purpura (ITP), often leading to inappropriate treatments such as steroids or splenectomy before a definitive diagnosis of BSS is considered.(9)

Genetic and Molecular Basis

The primary molecular defect in BSS lies in one of three genes: GP1BA, GP1BB, or GP9, encoding GPIbα, GPIbβ, and GPIX respectively. These components, along with GPV, form a non-covalently linked receptor complex embedded in the platelet membrane. GPIbα contains the binding site for von Willebrand factor and is the most frequently mutated subunit in BSS.(10) Mutations in these genes can be missense, nonsense, frameshift, or splice-site changes, leading to abnormal protein synthesis, misfolding, or degradation. The net result is either a quantitative deficiency (complete or partial absence) or a qualitative defect

(dysfunctional complex).(11) Genetic testing can identify biallelic mutations in affected individuals, while heterozygous carriers are typically asymptomatic but may display mild macrothrombocytopenia. Advances in next-generation sequencing have facilitated the rapid identification of mutations and broadened our understanding of BSS heterogeneity.(12,13)

Pathophysiology

The GPIb-IX-V complex is the primary receptor that mediates platelet tethering to subendothelial vWF exposed at sites of vascular injury, particularly in high-shear arterial environments.(14) In BSS, defective or absent GPIb-IX-V impairs this critical step of primary hemostasis, leading to ineffective platelet plug formation. Beyond adhesion, the GPIbα subunit is also involved in thrombin binding, suggesting that BSS may impact secondary hemostasis as well. The megakaryocytic lineage in BSS patients also displays abnormalities, contributing to the presence of large, dysmorphic platelets seen on peripheral smears. The reduced platelet count (thrombocytopenia) is typically moderate but functionally significant due to concurrent qualitative defects. As such, BSS manifests as a dual defect in both platelet number and function, explaining the severity of bleeding symptoms compared to other isolated platelet disorders.(15,16)

Clinical Presentation

Symptoms of BSS typically begin in infancy or early childhood and include mucocutaneous bleeding such as petechiae, purpura, recurrent epistaxis, gingival bleeding, easy bruising, and menorrhagia in post-pubertal females. More severe hemorrhagic episodes may be provoked by dental procedures, circumcision, or minor trauma. Life-threatening bleeding, although less common, can occur in surgical or obstetric contexts.(17) Unlike immune thrombocytopenia, BSS lacks systemic manifestations and splenomegaly, although misdiagnosis is common. The presence of large platelets and persistent bleeding despite normal platelet counts often prompts further investigation. Clinical variability exists even among patients with the same mutation, suggesting a role for modifier genes or environmental influences in phenotype expression.(18)

Diagnosis

The diagnostic approach to BSS is multi-modal. The first clue is often a complete blood count revealing mild-to-moderate thrombocytopenia accompanied by giant platelets on a peripheral smear. Bleeding time or PFA-100 closure times are typically prolonged. Platelet aggregation studies show absent agglutination in response to ristocetin, which cannot be corrected by the addition of normal plasma—a distinguishing feature from von Willebrand disease.(19) Flow cytometry is an essential tool for detecting absent or reduced expression of GPIbα, GPIbβ, or GPIX on the platelet surface. Electron microscopy can be used to confirm platelet size and granule content. Genetic confirmation by Sanger sequencing or next-generation sequencing offers definitive diagnosis and is useful for family counseling and prenatal diagnosis. Misdiagnosis remains a concern, particularly in cases misidentified as ITP or other thrombocytopenic conditions.(20)

Differential Diagnosis

BSS must be differentiated from a variety of inherited and acquired platelet disorders. Von Willebrand disease (especially type 2B) can present with abnormal ristocetin aggregation but is distinguished by vWF levels and multimeric analysis. Glanzmann thrombasthenia is characterized by a defect in GPIIb/IIIa, resulting in impaired aggregation with all agonists except ristocetin. ITP may be suspected in patients with thrombocytopenia and bleeding, but the large platelets and abnormal ristocetin response in BSS are distinguishing features. May-Hegglin anomaly and other MYH9-related disorders also cause macrothrombocytopenia but are associated with leukocyte inclusions and other systemic findings.(21)

Management

Management of BSS is primarily supportive and requires a personalized approach. Bleeding episodes are treated with platelet transfusions, which are typically effective but carry the risk of alloimmunization.(22,23) Leukocyte-depleted or HLA-matched platelets are preferred. Antifibrinolytics such as tranexamic acid or aminocaproic acid are useful in controlling mucosal bleeding and during minor surgical procedures.(24) For severe bleeding or surgical prophylaxis, recombinant activated factor VII (rFVIIa) has shown efficacy, especially in patients refractory to platelet transfusions.(25) Hormonal therapy can be used for menstrual bleeding in adolescent females.(26) Desmopressin is ineffective due to the nature of the defect. Hematopoietic stem cell transplantation (HSCT) has been attempted in a few severe cases but is not routine due to its high risk. Genetic counseling is essential for affected families. (27)

Table 1.1 Management of Bernard-Soulier Syndrome (BSS)

Management Strategy	Indication/Use	Notes
Platelet Transfusion	For severe bleeding episodes or during surgery	Use HLA-matched platelets when possible to reduce alloimmunization risk.
Recombinant Activated Factor VII (rFVIIa)	For patients refractory to platelet transfusions or with alloimmunization	Used off-label; may be effective in controlling bleeding.
Antifibrinolytics (e.g., Tranexamic Acid, Epsilon-aminocaproic acid)	For mucosal bleeding or prophylaxis during minor procedures	Useful for dental work, menorrhagia, and nosebleeds.
Hormonal Therapy (e.g., oral contraceptives)	For menorrhagia in female patients	Regulates menstrual bleeding and reduces the need for transfusions.
Avoidance of Antiplatelet Drugs	All patients	Drugs such as aspirin and NSAIDs should be avoided to reduce bleeding risk.
Gene Therapy (Experimental)	Future potential	Currently under investigation; not yet clinically available.

Recent Advances

Molecular research has brought new hope for BSS through the development of gene therapy techniques and iPSC-derived megakaryocytes. Experimental correction of the GPIbα defect using lentiviral vectors has been successful in murine models, laying the groundwork for potential clinical trials. CRISPR-Cas9 gene editing is also being explored as a curative approach.(28) In vitro models using patient-derived iPSCs allow detailed study of megakaryopoiesis and GPIb-IX-V complex assembly, potentially enabling drug discovery and functional correction. These advances suggest that future therapies may shift from supportive to curative, although substantial research is still required to ensure safety, efficacy, and long-term outcomes.(29, 30)

Conclusion

Bernard-Soulier Syndrome is a rare yet significant inherited platelet disorder marked by defects in platelet adhesion and macrothrombocytopenia. Diagnosis requires a high index of suspicion, particularly in patients with mucocutaneous bleeding and giant platelets. Laboratory evaluation, flow cytometry, and genetic testing are essential to confirm the diagnosis and guide family screening. While current treatment is mainly supportive, advances in molecular genetics and regenerative medicine hold promise for disease-modifying therapies. Increased awareness and research are crucial to improve the diagnosis, management, and quality of life of individuals affected by BSS.

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