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Clinical Phenotype of Bernard Soulier Syndrome Case Resulting from Compound Heterozygous Inheritance

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Clinical Phenotype of Bernard Soulier Syndrome Case Resulting from Compound Heterozygous Inheritance

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Background

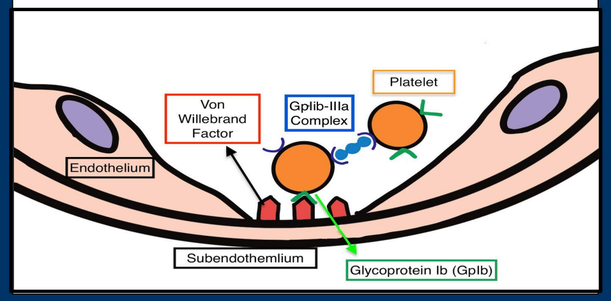
Bernard Souiler is a rare, inherited disorder of platelet function. Since its discovery in 1948, only 200 cases have been reported worldwide. Like many affected individuals with platelet disorders, those with Bernard Soulier syndrome typically present with easy bruising and excessive bleeding in early childhood. Bleeding is usually mucocutaneous in nature and they exhibit nosebleeds, exaggerated bleeding from minor injuries, and develop purpura or petechiae. These symptoms can present at birth with prolonged bleeding from umbilical cord cutting or, in males, excessive bleeding with circumcision. In women, the presentation can occur around puberty with abnormally heavy menstrual bleeding. However, some affected individuals remain asymptomatic after birth and will not present for diagnosis until adulthood.

Objective: We report a case with multiple episodes of exaggerated bleeding and easy bruising along with the workup associated with diagnostics.

Pathogenesis

The defect associated with BSS occurs at the level of platelet adhesion. This occurs when the GPIbIX-V, a four-subunit complex on the surface of platelets, interacts with von Willebrand factor, which is found on the endothelium of damaged blood vessels. When there is a defect in any one of the four subunits that composes the GPIb-IX-V complex it is unable to bind to vWF and platelet dysfunction occurs.

These subunits associate in the endoplasmic reticulum and then mature in the Golgi apparatus before translocating to the cell surface. There, the signal peptide is removed, and a matured GP has an extracellular N-terminal that contains leucine-rich repeats, a transmembrane helix, and a cytoplasmic tail. It is at the N-terminal that most binding of proteins occurs, including the exposed von Willebrand Factor after a vascular injury. More specifically, missense, nonsense, or deletion mutations have occurred on four identified genes and their chromosomal locations are identified as follows: GpIb-alpha gene (chromosome 17), GpIb-beta gene (22q11.2), GpIX gene (3q21), and GpV gene (3q29). This large variety in mutation type, chromosome location, and subunit involvement is largely responsible for Bernard Soulier's varying presentations.



Case Report

14-month-old Caucasian male born via SVD at 38w3d G3P1021 mother and non-consanguineous parentage. Delivery was uncomplicated. Blood type O positive and he was Coombs negative. Presented to pediatricians' office for newborn visit he was found to have hyperbilirubinemia and mild jaundice. Referred to the hematology/oncology clinic at 8 months for several episodes of prolonged bleeding and easy bruising. No hematochezia, hematemesis, hematuria, oral sores, or increased fussiness.

History of significant and prolonged bleeding with circumcision and disproportionate bleeding. Mild bruising with vaccines but had no hematomas at the injection site.

Mother and Father report no personal or family history of bleeding disorders. Mom had a history of menorrhagia but had no complications during the patient's birth. Father has a history of Hodgkin's Lymphoma which he completed therapy in 2018.

Patient Workup

Methods: We analyzed CBC, coagulation studies, platelet aggregation assays, platelet glycoprotein expression by flow cytometry, as well as screen both patient and parents for relevant genes responsible for BSS.

	Patient	BSS	Ref Range
CBC- Platelets	98k	20-100k	150-350k
Peripheral Smear	Large plts; increased MPV (12.3)	Macrothrom-bocytopenia	Normal cytology MPV
PT PTT	10.4 seconds 36.9 seconds	Normal	9.4-12.5 sec 25.1-36.6 sec
Von Willebrand Factor Antigen	223 IU/dL	Normal	50-230 IU/dL
Ristocetin Cofactor Activity	265%	Elevated	51-215%
Platelet Function Assay Phase 1 Phase 2	 72 sec (Low) ---	 Elevated Elevated	 89-153 sec <122 seconds
Coagulation Factor Assays Factor 8 Factor 9	 112% 55%	 Normal Normal	 69-143% 50-150%
Platelet Glycoprotein Flow Cytometry GpIb Monoclonal Antibody Binding GpIIb/IIIa Monoclonal Antibody Binding	 Abnormal Normal	 Abnormal Normal	 Normal Normal

CBC showed mild to moderate macrothrombocytopenia in the setting of an otherwise normal CBC. Peripheral smear showed large platelets without leukocyte inclusion bodies and increased MPV with normal RBC and WBC morphology.

Subsequent visits showed normal coagulation studies (PT, PTT, and factor 8 and 9) were all within normal limits. Due to these normal findings the workup was narrowed down to disorders of platelets dysfunction.

Next PFA-100 demonstrated a slowed closure time of 72 seconds (normal 89-153). While this is abnormal for BSS, PFA-100 does not rule out mild or moderate platelet dysfunction.

To distinguish from von Willebrand Disease, Ristocetin Cofactor Activity was performed and revealed persistent deficit of aggregation despite the addition of normal plasma.

A final confirmatory test was done by flow cytometry to assess for platelet glycoprotein antibody expression. PGE showed significantly reduced binding of monoclonal antibody to platelet GPIb and normal binding to GPIIb/IIIa, which is consistent with the diagnosis of BSS.

Genetic Testing

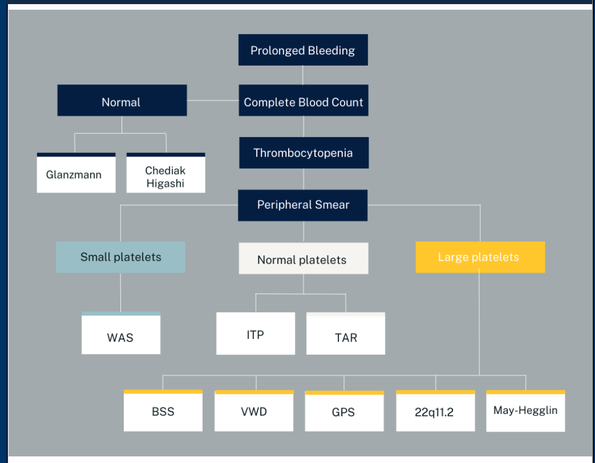
In the absence of a significant family history, a genetic workup was done with both parents and the patient being assessed. Mother of the patient's genetic profile showed a heterozygous pathogenic variant on the GP9 gene with a cysteine to tyrosine missense mutation at codon 135. Father of the patient had a missense mutation of asparagine to serine on the same gene at codon 61, which, significantly, is located within the leucine-rich repeat domain. Functional studies of the father's variant in mammalian cells demonstrated significantly decreased ability to associate with GBIb. This specific mutation has a minor allele frequency of 0.0005077. This is in contrast to the mother's mutation which has a minor allele frequency of 0.000005198.

Prognosis and Treatment

Those with mild to moderate disease should focus on preventing large bleeds. For example, avoiding anti-platelet drugs such as aspirin or NSAIDs and maintaining good dental hygiene to avoid unnecessary dental procedures. Female patients should consider hormonal control to prevent heavy menstrual periods. Patients should also be educated about what actions to take if a bleed does occur.

If a patient requires surgery or there is a life-threatening hemorrhage, platelet transfusion will be used. However, some may develop antibodies against the GPIb protein, as it is technically a foreign body. Current recommendation is to use HLA-matched or leukocyte depleted platelets. In addition, antifibrinolytic agents can be used after surgeries to reduce the amount of bleeding.

Differentials



Platelet Aggregation	ADP	AA	Epi	RIstocetin
BSS	N	N	N	D
VWD	N	N	N	D*
GT	D	D	D	D
Aspirin	D	D	D	D

N- normal; D- decreased; *corrected with normal plasma

Conclusion

Like many platelet adhesion disorders, the pathophysiology of BSS can mimic the symptoms of a myriad of other syndromes. Lab tests become extremely important to the diagnosis but, in addition, a thorough history and genetic workup should not be excluded. For this reason, we believe that BSS is underdiagnosed and, therefore, under researched. For our patient, having a genetic workup revealed two rare variants occurring on the gene for GPIX and increased the number of known genetic defects associated with the manifestation of BSS.

Furthermore, genetic testing of children with prolonged bleeding will lead to a greater understand of the inheritance pattern associated with BSS.

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