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Case Report

# Case Report: Bernard Soulier in a 9 Years Old Child. A One in a Million Macrothrombocytopenia

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## Abstract

Bernard Soulier is an extremely rare autosomal recessive macrothrombocytopenia with incidence of one in a million children. Here we describe a 9 years old Syrian refugee to Egypt presented to us with an attack of epistaxis. The child has experienced multiple bleeding episodes throughout life ranging from mild epistaxis to one life threatening bleeding that required platelets transfusion. He had thrombocytopenia, prolonged bleeding time and delayed platelet aggregation to ristocetin. Flow cytometry showed deficient CD42a {GP1×] and CD61 [GP111a] expression consistent with Bernard Soulier syndrome.

***Keywords:*** *Bernard Soulier; Macrothrombocytopenia*

## Introduction

Bernard Soulier is a very rare bleeding disorder occurring in one in a million children [1]. It is an autosomal recessive disorder due to mutation of a glycoprotein on platelets surface that binds to von Willebrand factor and helps platelets adhesion. It is a surface receptor called platelet receptor GPIb-IX-V. The quantitative or qualitative deficiencies in the GPIb-IX-V complex give rise to BSS [2]. This protein is formed of 4 subunits but only 3 of them have known mutations. This syndrome is characterized by tendency for bleeding mostly epistaxis and subcutaneous bleeding, laboratory tests show thrombocytopenia, large platelets, prolonged bleeding time and delayed platelets aggregation [2].

Here we present a 9 years old Syrian refugee with Bernard Soulier syndrome.

## Case Report

A 9 years old Syrian refugee child of non-consanguineous marriage presented to us with a moderate attack of non-induced epistaxis proceeded with upper respiratory tract infection about one week earlier; it was controlled with anterior nasal pack. He had no other form of bleeding.

His blood count showed thrombocytopenia 16 * $10^9$, blood film showed large platelets, he had prolonged bleeding time, delayed platelets aggregation to ristocetin not corrected by plasma, deficient expression of CD42a {GPIX} and CD61 [(GPIIIa], unfortunately genetic testing for mutation was not done.

Both parents had normal platelets counts so did his other sibling. There was no history of bleeding tendency in the family.

One week later his platelets count rose to 145 * $10^9$ spontaneously without any specific treatment.

The child has had many bleeding episodes throughout life mostly epistaxis with one attack of life threatening hemorrhage which needed platelets transfusion. Multiple spontaneous and induced ecchymotic patches appeared throughout his life.

He had a trial of steroids therapy {before he was diagnosed as BSS mistaken for idiopathic thrombocytopenic purpura] in the past with no remarkable response. Vasopressin and active factor v11 were not tried before.

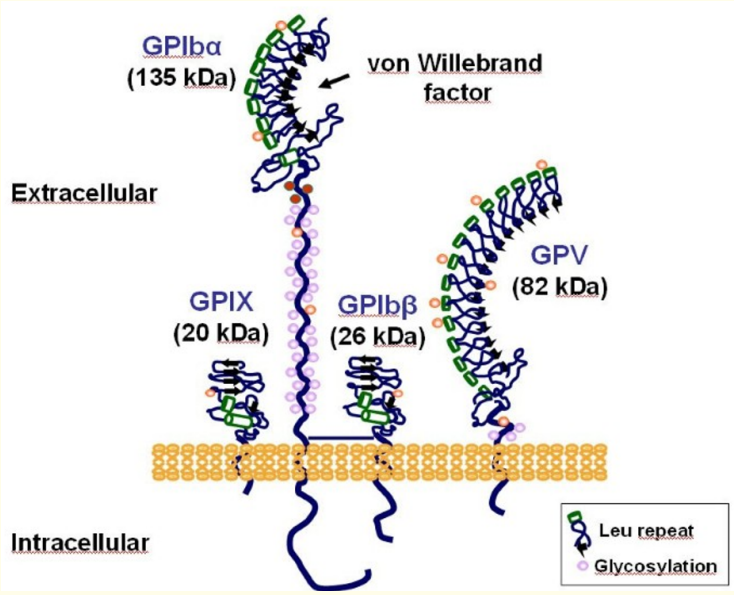


***Figure 1:*** *Patient 1, day two post-operative.*

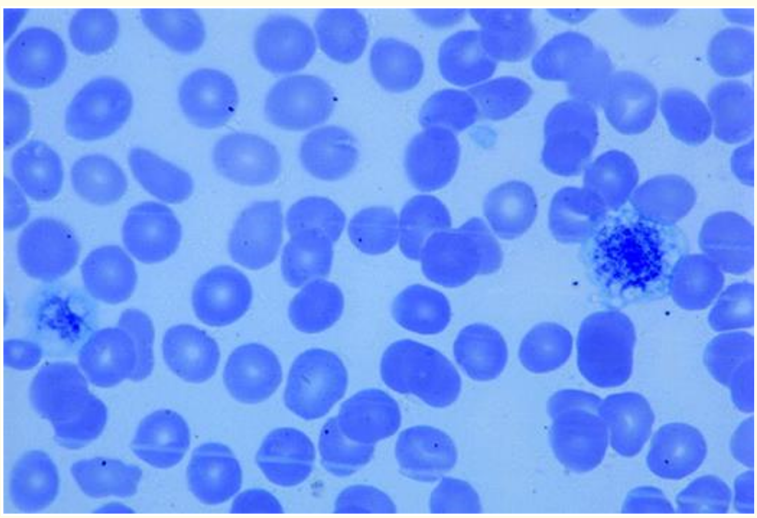

***Figure 2:*** *Peripheral blood smear from a patient with Bernard-Soulier syndrome showing presence of large and giant platelets (modified Wright-Giemsa stain, original magnification ×1000) [15].*

## Discussion

Bernard Soulier syndrome [BSS] was initially described by Bernard and Soulier in 1948 as an autosomal recessive disorder. They reported a 28 years old man who presented with repeated attacks of bleeding throughout his life and finally died from an intracranial hemorrhage after a bar fight [3]. It is a very rare disorder thought to have a prevalence of around one I a million children. Almost 100 cases only all around the world are present.

BSS occurs due to abnormalities in GPIb-IX-V complex. It acts as a surface receptor needed to bind von Willebrand factor when there is a vascular injury [12]. GPIb-V-IX complex is formed of four subunits namely GP Ibα, GP Ibβ, or GP IX and GP-V. Genes for the four subunits are present on chromosomes 17p12, 22q11.2, 3q29, and 3q21 respectively.

Mutations types include missense, nonsense and frame shift insertions or deletions resulting in defect in expression of the GP Ib-IX-V complex. BSS due to isolated GPV gene mutation are not yet reported [4].

BSS usually presents with tendency for bleeding from early childhood. Easy bruising as purpura or ecchymosis, gum bleeding, epistaxis, and heavy menses are very common. Heavy bleeding following surgery or trauma may be difficult to control.

Hemoarthrosis, intracranial hemorrhage, and deep visceral hematomas are relatively rare complications of BSS. However, bleeding is reported to be fatal in around 16% of cases [5].

Bernard Soulier syndrome investigations are characterized by thrombocytopenia, very large platelets size ranges from 2.5 to 8 um; prolonged bleeding time and defective adhesion of the platelets. BSS platelets have isolated defect in ristocetin-induced agglutination. In contrast to von Willebrand disease, this abnormality is not corrected by normal plasma. Platelet aggregation in response to other agents like collagen and adenosine diphosphate (ADP), as well as clot retraction, is usually normal [6].

BSS diagnosis is usually confirmed by Flow cytometry which shows defective binding with CD42a (GPIX), CD42b (GP Ibα), CD42c (GP Ibβ), and CD42d (GPV) antibodies [7].

### Management

BSS is usually managed with supportive care. Patients are usually warned about the risks of bleeding. They are advised to wear 'alert bracelets' clearly identifying their diagnosis. They are especially advised about dental hygiene, avoiding contact sports and how to manage attacks of epistaxis.

BSS patients do not consume aspirin or similar drugs because they can affect platelet aggregation. Paracetamol is an accepted alternative.

Tranexamic acid, as an antifibrinolytic agent is a primary treatment in cases of mild bleeding.

Desmopressin (DDAVP), the synthetic analog of vasopressin induces endogenous release of tissue plasminogen activator and increases platelet aggregation. It can shorten bleeding time in some, but not all, patients with BSS. it still carries the risk of fluid retention, hyponatremia, hypotension, and mild headaches. It can be used if there is mild bleeding [8] its use in BSS is still controversial.

The use of recombinant FVIIa has been described in cases of BSS. However, it is a very procoagulant agent; therefore, proper care must be taken in the parturient already predisposed to develop a thrombotic event [14].

Platelet transfusion is still an option for BSS patients usually offered in cases of life threatening hemorrhage or before operations. Some patients turn (refractory) to platelet transfusions because they develop antibodies against the GPIb protein. HLA-matched single donors' platelets should be used. Otherwise, if not available leucocyte-depleted platelets are used [14].

Hemobiotic stem cell transplantation remains the last resort for all inhered platelets disorders when adequate donor is available. This is usually reserved for patients with too many antibodies and with a severe bleeding disorder [10].

## Differential diagnosis

BSS is considered in the differential of any bleeding child especially if bleeding has started early in life.it should be differentiated from the following conditions.

Idiopathic thrombocytopenic purpura [ITP]: BSS patients are often misdiagnosed and mistreated as idiopathic thrombocytopenic purpura [ITP] because of the similarity in presenting features. Treatment with steroids is falsely offered without much success. Features which may help in differentiating BSS from ITP include:

- History of BSS in the family.
- Failure of intravenous immunoglobulin and steroids.
- Unique laboratory features of blood film and flow cytometry.

Despite this, many patients are mistakenly diagnosed with ITP [5].

## Von Willebrand disease

Type IIB VWD is the closest type to BSS. This type has an increased affinity of large multimers to platelets leading to rapid clearance of platelets and subsequently thrombocytopenia. Also, platelets are large in size in type IIB VWD. Yet they can differentiated from BSS by their increased aggregation in response to ristocetin. Another type of von Willebrand is similar to BSS which is the platelet type. Still it can be differentiated by increases the affinity of platelets to VWF [11].

May-Hegglin anomaly is the most common inherited giant platelet disorder and is much like BSS with mild bleeding episodes. These patients often have features like 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. Blood films also show large platelets and Dohle bodies, a blue spindle-shaped inclusion, within the cytoplasm of neutrophils [13].

Hemophilia is a coagulation disorder that may present early in life. As hemophilia A is x linked disorder it had to be excluded in our patient which can be easily done by investigations. Hemophilia patient would have normal platelet count and function with prolonged partial thromboplastin time and decreased factor v111 level.

### Prognosis

BSS patients usually live their lives quite normally. They just need to follow preventive measures and precautions [3].

### Complications

Bleeding is the most important complication. Others include:

1. Blood borne infection like HIV and hepatitis.
2. Alloimmunization and development of autoantibodies.

## Conclusion

Bernard Soulier is a very rare macrothrombocytopenia with autosomal recessive inheritance. It mainly presents with variable degrees of severity and multiple forms of bleeding commonly as epistaxis. Bleeding episodes are usually mild; nevertheless life threatening hemorrhage can occur sometimes. Treatment is usually supportive with multiple future treatment modalities under study.

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