Original Article

A Study of Bernard-Soulier Syndrome in Tehran, Iran

Gholamreza Toogeh MD•[1], Manochehr Keyhani MD[1], Ramezanali Sharifian MD[1], Reza Safaee MD[1], Amirhossein Emami MD[1], Hossein Dalili MD[1]

Abstract

Background: Bernard Soulier Syndrome (BSS) is a hemorrhagic disorder with an autosomal recessive pattern of inheritance. We describe the demographic and clinical characteristics of Iranian patients with BSS followed in a major teaching and tertiary care hospital in Tehran, Iran.

Methods: We performed a retrospective medical record review of 97 patients with BSS who received care at the Imam Khomeini Hospital between 1969 and 2001. We collected data on the family history, clinical presentation, bleeding episodes, and lab profiles of these patients.

Results: Among all patients, 78 (81%) had a family history of consanguinity. The most common presenting symptom was epistaxis, seen in 62 (63.9%) patients. Peripheral blood smears demonstrated giant platelets on 67 (68.7%) of patients. Complete blood count demonstrated decreased platelets in 85 (87.4%) of patients ranging from 20,000/μL to 130,000/μL. Anemia was seen in 62 (64%) and 91 (93.8%) had prolonged bleeding time. The majority of patients (60%) had mild bleeding episodes, but 39 (40%) had at least one episode of severe bleeding in their past history.

Conclusion: Our data are consistent with other reports regarding clinical presentation of BSS, but consanguinity seems to be more common.

Key words: Bernard Soulier syndrome, clinical manifestation, consanguinity, giant platelet

Introduction

Bernard Soulier Syndrome (BSS) is a rare genetic disorder with an autosomal recessive transmission pattern first described by Bernard and Soulier in 1948.[1] Abnormalities are caused by genetic defects of the glycoprotein (GP) Ib/IX/V complex, which constitutes the Von Willebrand factor receptor on the platelet surface.[1,3,4,5] The complex is formed by association of four separate gene products: GPIbα is covalently linked to GPIbβ. This complex is non-covalently bound to GPIX and GVP.[1,3,4,5] The most frequent genetic causes of BSS are defects in the GPIbα gene which often leads to the protein truncation and loss of its trans-membrane domain.[1,3,4,5] Defects of the GPIbβ and GPIX genes are observed less frequently,[1,3,4,5] whereas defects of GPV have not been reported to date, although the gene is known to be polymorphic.

The prevalence of BSS is estimated to be less than 1 case in a million in Europe, North America and Japan but the incidence of this disorder is higher in counties with high rate of consanguinous marriages.[1,2]

BSS is clinically characterized by giant platelets, thrombocytopenia and a prolonged bleeding time.

Authors' affiliations: [1]Thrombosis and Homeostasis Research Center, Imam Khomeni Hospital Complex, Tehran University of Medical Sciences (TUMS), Tehran, Iran.
•Corresponding author and reprints: Gholamreza Toogeh MD, Thrombosis and Homeostasis Research Center, Imam Khomeni Hospital Complex, Tehran University of Medical Sciences (TUMS), Tehran, Iran. Telefax: +98-216-658-1667,
E-mail: gh_toogeh@yahoo.com
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Reported bleeding time range from marginally normal to over 20 minutes.[4,5] Clinical manifestations of BSS are diverse and may range from no clinically observable manifestation to severe bleeding.[6] Typical symptoms include easy bruising and bleeding episodes involving the gums and nose.[7,8] Severe and life threatening bleeding episodes are rare and may occur with surgery or after major trauma.

In this study, we describe the demographic and clinical characteristics of Iranian patients with BSS referred to one of the main teaching and tertiary care hospitals, the Imam Khomeini Hospital Hemophilia Center in Teheran. To our knowledge, this is the largest study of BSS patients reported in the literature.

Material and Methods

The Imam Khomeni Hospital is a 1200 bed hospital and is the largest teaching and referral center for patients with blood diseases including inherited disorders in Iran. As patients with BSS invariably require medical attention during child or early adulthood and are referred to Imam Khomeni Hospital, we are able to collect information on a large number of patients with this disease. We examined all 14,954 records of patients referred to Hemophilia clinic of Imam Khomeini Hospital from 1969 through 2001. Diagnosis of BSS was based on history of mucosal-dermal bleeding, prolonged bleeding time, thrombocytopenia and giant platelets, normal PT, PTT and clotting time and clot retraction test and no response of platelets to ristocitin in aggregometry study. We defined a severe bleeding episode as an episodes mandating blood transfusion and (or) hospitalization.

Demographic data including age at diagnosis, sex, family history of consanguinity and clinical data including primary presentation, number of previous bleeding episodes, and laboratory tests were extracted from files and were analyzed. We examined patient's demographic and clinical characteristics using simple descriptive statistics and statistical software (Stata 9.2, Houston, Texas).

Results

We identified 97 patients with the diagnosis of BSS. Approximately half of our patients were male. Mean age at diagnosis was 11.0±2.5 years. Nineteen (20%) patients were between ages 1 to 5, 40 (42.1%) between ages 6 to15 and 22 (23.1%) between 16 to 30 years at presentation.

Seventy-eight (81%) patients were born from consanguinous marriages. Thirty-nine (40%) had a past history of seven bleeding and 58 (60%) had episodes mild bleeding. In 67 (69%) patients giant platelets were present and in 32 (31%) platelet morphology was normal.

Hemoglobin levels were reduced in 62 (64%). The majority of patients 53(54.5%) had microcytosis; however, iron studies were unavailable in most cases.

Mild thrombocytopenia (50,000 – 130,000 μL) was seen in 66 (68.4%), 18 (19%) had moderate thrombocytopenia (20,000 – 50,000), and 12 (12.6%) had normal platelet counts.

Table 1 shows that the most common presentation of patients was epistaxis 62 (63.9%) followed by gingival bleeding in 15 (15.5%) of patients. Thirty-nine (40%) patients with mucosal bleeding required transfusions and also experienced hemodynamic instability. Major bleeding episodes such as central nervous system 1 (1%) and gastrointestinal bleeding were observed in 4 (4.1%).

Among women, almost a quarter 11 (22.4%) presented with menorrhagia. Four cases reported pregnancy, 2 of whom had a vaginal delivery complicated by bleeding which resulted in hysterectomy and 2 had a spontaneous abortion.

Among male patients who had undergone circumcision, 9 (53%) had a bleeding episodes while the remainder of patients 8 (47%) had no history of bleeding.

Discussion

We examined the clinical and demographic characteristics of 97 patients with BSS. Similar to previous studies in the literature, we found a relatively equal gender distribution[1] and bleeding symptoms are usually evident from early childhood.[1,2] In addition, similar to prior reports in the literature the most frequent presentation was mucosal-dermal bleeding.[1,2,3,7,8] A third of the patients with mucosal bleeding required transfusions and experienced hemodynamic instability. Unlike patients with classic hemophilia, we found no evidence of hematuria.[9] Life endangering bleeding such as central nervous system and gastrointestinal bleeding was very rare and we found no documented case of hemarthrosis.

Table 1. Number and percentage of Iranian Patients with BSS who had a given clinical manifestation at least once

Clinical manifestation	Number	Percentage
Epistaxis	62	63.9
Gingival bleeding	15	15.5
Menorrhagia	11	11.3
Ecchymosis	7	7.2
GI bleeding	4	4.1
Hematoma	3	3
Petechia and purpura	1	1
Cerebral bleeding	1	1

Similar to previous studies in the literature, in our study all of reported pregnancies were relatively unsuccessful or presented with complications.[1,10]

In our series population consanguinity was common. The common occurrence of marriage among cousins may lead to a higher occurrence of this disease in our country.[1,2] In Iran, only marriage among carriers of beta thalassemia is discouraged. Due to cultural barriers, consanguinous marriage in general is not discouraged. Our study suggests the need for a more pro-active approach to discouraging marriage among blood relatives with a history recurrent bleeding episodes even if mild.

This study is a medical record review with all the limitations therein. We relied on the documentation made during the course of regular clinical care. A strength of this study is the large number of patient, with Bernard Soulier syndrome we were able to collect data on. Up until 2000, the Imam Khomeini Hospital was the only center in Iran that specialized in genetic blood diseases. Therefore our sample is probably nationally representative.

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