Abstract
Hemorrhagiparous Thrombocytic Dystrophy also known as Bernard-Soulier Syndrome is a hereditary bleeding disorder transmitted as an autosomal recessive trait. Clinical manifestations usually include epistaxis, menorrhagia, gingival and gastrointestinal bleeding. Severe bleeding episodes are associated with trauma and surgical procedures such as tonsillectomy, appendectomy, splenectomy, or occur during dental extractions and menses. The underlying defect is a deficiency or dysfunction of the glycoprotein GPIb-V-IX complex, a platelet receptor for von Willebrand factor, which is required for platelet adhesion to the subendothelium and aggregation at high shear forces. Genes coding for the four subunits of the receptor, GPIbα, GPIbβ, GPV and GPIX, map to chromosomes 17p12, 22q11.2, 3q21, and 3q29, respectively. Genetic defects have been identified in GPIbα, GPIbβ, and GPIX but not in GPV. This syndrome is extremely rare, only ~100 cases have been reported. Diagnosis is based on a prolonged skin bleeding time, the presence of a small number of very large platelets (macrothrombocytopenia) and defective ristocetin-induced platelet agglutination. Prothrombin consumption is reduced as reported in the first description. Treatment of bleeding or prophylaxis during surgical procedures usually requires platelet transfusion.

Keywords
Bernard-Soulier Syndrome, hemostasis, hemorrhagia, giant platelets, thrombocytopenia

Disease name and synonyms
- Hemorrhagiparous thrombocytic dystrophy
- Bernard-Soulier Syndrome (BSS)
- Dystrophie thrombocytaire hémorragipare congénitale

Definition
Hemorrhagiparous thrombocytic dystrophy (BSS) is an autosomal recessive disease associated with bleeding tendency, giant blood platelets and low platelet counts. The defect is restricted to the megakaryocytic lineage.
Differential diagnosis
Congenital platelet disorders are often difficult to distinguish on the basis of clinical manifestations and require specialized laboratory tests. For example, BSS has often been misdiagnosed as idiopathic thrombocytopenic purpura (ITP), an immunological disorder, and treated unsuccessfully with steroids or splenectomy. Functional analysis of platelet suspensions by aggregometry is needed to differentiate BSS from other rare inherited disorders accompanied by macrothrombocytopenia, such as the May-Hegglin, Sebastian, Fechtner and Epstein’s syndromes (Nurden, 1999).

Etiology
Defects in three genes give rise to the typical clinical features and platelet anomalies associated with BSS. This is due to the multisubunit nature of the affected GPIb-V-IX complex receptor, whose structure is shown in Figure 1.

Figure 1: The Platelet GPIb-V-IX complex

The main function of the GPIb-V-IX complex in hemostasis is to initiate platelets adhesion at vascular injury sites (Clemetson, 2003), through GPIb\(\alpha\) binding to von Willebrand factor, which is located in the vessel wall subendothelium. Four distinct transmembrane proteins, GPIb\(\alpha\) (MW 135kDa), GPIb\(\beta\) (MW 26 kDa), GPIX (MW 20 kDa) and GPV (MW 82 kDa) assemble to form the functional receptor at the surface of bone marrow megakaryocytes, the precursors of mature circulating platelets (Andrews et al, 1999). GPIb\(\alpha\), GPIb\(\beta\), and GPIX are closely associated and are all required for efficient biosynthesis of the receptor (Ulsemer et al, 2001). A lack of a single subunit dramatically decreases surface expression of the whole complex. GPV is more loosely associated and its absence does neither prevent expression, nor von Willebrand binding function. The four subunits are separately encoded by genes mapping to chromosomes 17p12 (GPIb\(\alpha\)), 22q11.2 (GPIb\(\beta\)), 3q21(GPV) and 3q29 (GPIX) (Lopez et al, 1987; Wenger et al, 1989; Lopez et al, 1988; Yagi et al, 1994; Lanza et al, 1996; Hickey et al, 1990; Yagi et al, 1995). The four genes belong to the leucine rich family of proteins and are exclusively expressed in platelets under physiological conditions. They have a simple structure with the coding sequence contained within a single exon, except for GPIb\(\beta\) which contains an intron of 10 bases after the start codon.

To date, 44 different genetic defects associated to the BSS have been reported (Table 1). Most defects are due to mutations in GPIb\(\alpha\), which is the largest subunit and bears the von Willebrand binding site. The other defects are equally distributed between GPIb\(\beta\) and GPIX. The defects can be separated into three major classes: 1) missense mutations or short in-frame deletions which give rise to
bleeding episodes are associated with trauma and surgical procedures such as tonsillectomy, appendectomy, splenectomy or occur during dental extractions and menses. However, the severity and frequency of bleeding vary between individuals. Bleeding mainly affects mucocutaneous tissues, and major hematomas are very rarely observed.

Diagnosis criteria
Skin bleeding times are moderately (5-10 min) to severely (>20 intracellular min) prolonged in BSS. A constant feature is the presence of a small number of very large platelets with a rounded shape (main volume 11-16µm³; diameter 4-10 μm). The initial laboratory test should therefore include blood cell counts and examination of blood smears. Platelet counts typically range from 20,000 to 100,000/µl. Manual counting is required for an accurate determination as the very large platelets in BSS are often mistaken for lymphocytes in automatic counters. The distinctive abnormality of BSS platelets is an isolated defect in ristocetin-induced agglutination. Unlike the defect in von Willebrand disease, this anomaly is not corrected by the addition of normal plasma. Levels of FVIII-von Willebrand complex are assessed. Aggregation responses to agonists such as ADP or collagen are normal, however decreased responses to thrombin can be observed. A marked defect in prothrombin consumption is constantly observed and may be useful for the diagnosis: it is attributed to a defective binding of FXI due to a lack of GPIb (Baglia et al, 2002), and to a decrease in GPIb-fibrin-dependent thrombin generation (Beguin et al, 1999, Al Dieri et al, 2003). Flow cytometry analysis using a panel of specific monoclonal antibodies will confirm this diagnosis in some specialized laboratories. Furthermore additional tests performed in specialized research units may include glycoprotein analysis by SDS-polyacrylamide gel separation and immunoblotting, and finally study of genetic abnormalities.

Frequency
This syndrome is extremely rare. It has been mainly diagnosed in European, Japanese, North African and North American populations, where its prevalence has been estimated to less than 1 in 1 million. This low frequency can probably be explained by the fact that the affected genes are very compact being interrupted by only 1-2 introns.

Genetic counseling
Genetic counseling should follow the standards established for all autosomal recessive diseases.
Antenatal diagnosis
Prenatal diagnosis is theoretically feasible when the genetic defect has been identified in a particular kindred. This is probably not justified as the syndrome rarely gives rise to life threatening bleeding. With a good prophylaxis, a fairly normal quality of life can be maintained. In addition, cord blood or chorion villus sampling bear a high risk of bleeding and premature abortion.

Management
Therapeutic approaches include both general and specific treatment of bleeding. Patients shall be warned to avoid traumas, antiplatelet medication such as aspirin, to maintain adequate dental hygiene and to use contraceptive in female at puberty. Treatment of bleeding or prophylaxis during surgical procedures usually requires blood or platelet transfusion with the associated risk of developing antiplatelet alloantibodies. Desmopressin has been shown to shorten the bleeding time in some patients. In rare cases of patients with life-threatening disorders, bone-marrow or umbilical-cord hematopoietic stem cell transplantation may be considered (Locatelli et al, 2003). As a fairly simple genetic defect, BSS appears to be an ideal candidate for future gene therapy.

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