Inherited Giant Platelet Disorders

Classification and Literature Review

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Key Words: Inherited giant platelet disorders; IGPD; Classification; Review

Abstract

Inherited giant platelet disorders are extremely rare. The aim of this article is to review the clinical and laboratory features of this heterogeneous group and to arrive at a working classification. We conducted our literature search using the National Library of Medicine database. A total of 12 clinical entities were described. We classified them into 4 groups depending on the clinical and structural abnormalities. The pathophysiology of these disorders is largely unknown, and more research is needed, particularly in the light of recent advances in laboratory medicine. This review may provide a valuable reference for clinicians and may form a basis for future classification and research.

Inherited giant platelet disorders (IGPDs) are a group of rare disorders characterized by thrombocytopenia, large platelets, and variable bleeding symptoms. The purposes of this study were to summarize the incidence, frequency, clinical manifestations, laboratory findings, and pathogenesis in each of these disorders and to classify the IGPDs based on clinical and laboratory findings and pathogenesis.

Materials and Methods

Our search for references was conducted by using the National Library of Medicine database (MEDLINE). The classification of these disorders is difficult owing to their rarity and their heterogeneity, but by doing so, we may have better understanding of their pathogenesis and, therefore, may achieve better treatment for affected patients. The IGPDs can be classified in 4 groups. The first group is based on structural defects including glycoprotein (gp) abnormalities (Bernard-Soulier syndrome [BSS], velocardiofacial syndrome [VCFS], glycoprotein abnormalities with association with mitral valve insufficiency, and gpIV abnormality), a calpain defect (Montreal platelet syndrome [MPS]), and an alpha-granule defect (gray platelet syndrome [GPS]). The second group is based on a distinctive morphologic finding, such as neutrophil inclusions (May-Hegglin anomaly [MHA] and Sebastian syndrome). The third group is based on clinical association with systemic manifestations (hereditary macrothrombocytopenia with hearing loss, Epstein syndrome, and Fechtner syndrome, which also exhibits neutrophil inclusions). The fourth group is considered a

benign anomaly, such as Mediterranean macrothrombocytopenia **Table 1**.

Bernard-Soulier Syndrome

BSS is characterized by thrombocytopenia, large platelets, and bleeding symptoms.

Frequency and Inheritance

Bernard and Soulier first described this disorder in 1948.[1] The real prevalence of BSS is unknown owing to underreporting and misdiagnosis. However, based on cases reported from Europe, North America, and Japan, the incidence is estimated to be less than 1 in 1 million.[2] BSS has an autosomal-recessive mode of inheritance. Heterozygous persons have milder bleeding symptoms. Autosomal-dominant inheritance has been reported in some cases.[3]

Clinical Manifestations

BSS manifests early in life with bleeding symptoms, most frequently in the form of epistaxis and gingival and cutaneous bleeding. The severity of the symptoms varies between patients. It also may become progressively less severe throughout puberty and adult life. Frequently, a severe hemorrhagic episode occurs following surgery. Rare fatalities have been reported.[4] Pregnancy may be uneventful or have complications of variable severity.[5,6]

Laboratory Findings

The thrombocytopenia is variable, and the platelet count ranges from <30 to 200 × 10^3/μL (<30-200 × 10^9/L). The bleeding time is prolonged, and clot retraction is normal. The platelet survival is shorter than normal. The platelet aggregation in response to adenosine diphosphate (ADP), collagen, and arachidonic acid (AA) is normal. The platelet aggregation to ristocetin is defective and not corrected by the addition of normal plasma, as seen in von Willebrand disease.[7] The peripheral blood smear shows large platelets and absence of neutrophil inclusions **Image 1**. Ultrastructural studies of the megakaryocytes reveal a structural defect in the cell membrane system, such as an irregularly spaced demarcation membrane system (DMS) and disorganization of the microtubules.[8] Some of the platelets show an increased number and prominence of the surface-connected system, the dense tubular system, and the microtubular system, giving them a Swiss-cheese appearance.[9] The von Willebrand factor (vWF) is quantitatively and qualitatively normal. The adhesion of the giant platelets to the subendothelium is defective, and in vitro the platelets are not retained by the glass bead columns. The sodium dodecyl sulfate–polyacrylamide gel electrophoresis of washed platelets shows decreased or absent platelet gpIb-alpha, gpIX, and/ or gpV **Figure 1**.

Table 1
Classification of Inherited Giant Platelet Disorders

With structural defect
Glycoprotein abnormalities
Bernard-Soulier syndrome
Velocardiofacial syndrome
Association with mitral valve defect
Glycoprotein IV abnormalities
Calpain defect
Montreal platelet syndrome
Alpha granules
Gray platelet syndrome
With abnormal neutrophil inclusions
May-Hegglin anomaly
Sebastian syndrome
With systemic manifestations
Hereditary macrothrombocytopenia with hearing loss
Epstein syndrome
Fechtner syndrome
With no specific abnormalities
Mediterranean macrothrombocytopenia

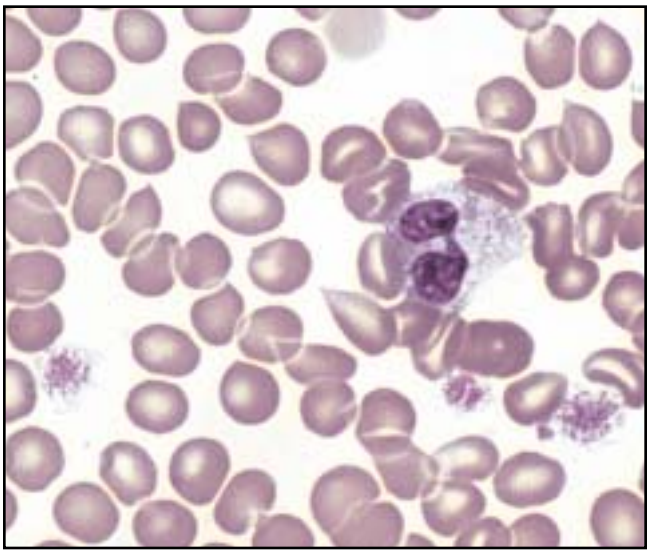

Image 1 Peripheral blood smear from a patient with Bernard-Soulier syndrome showing giant platelets. Note the absence of neutrophil inclusion bodies (Wright-Giemsa, ×1,000).

Pathogenesis

The disorder is attributed to a dysfunction or an absence of the gpIb-IX-V complex,[10] which is responsible for the adhesion of platelets to the injured vessel wall via a receptor to the vWF residing on the gpIb-alpha subunits, and it also facilitates the activation of platelets by thrombin at low concentrations.[11] The gpIb-IX-V complex is composed of 4 transmembrane polypeptide subunits, disulfide-linked alpha and beta subunits of the gpIb, and the noncovalently associated subunits gpIX and gpV. Previous studies have shown that the complete set of subunits is required for the complex to be functional.[12] This complex is

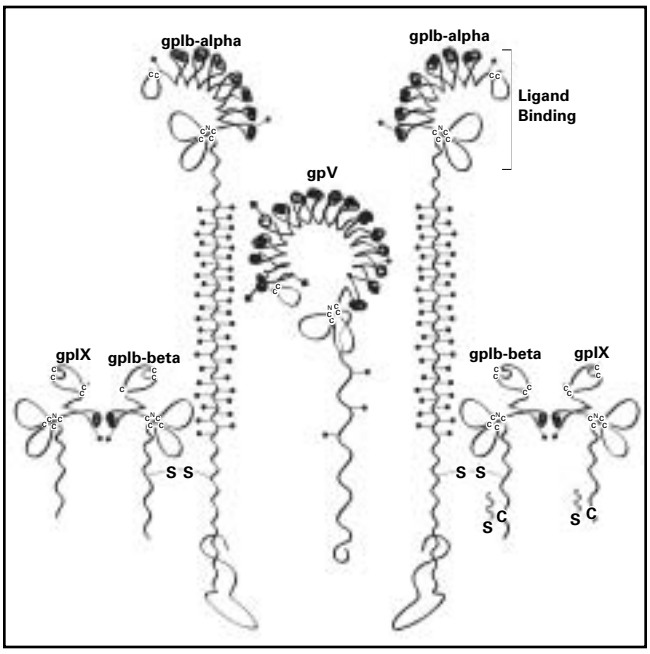

Figure 1 Schematic view of glycoprotein (gp) Ib-IX-V complex (courtesy of J. A. López, MD, Baylor College of Medicine, Houston, TX). C, carbon; N, nitrogen; S, sulfur.

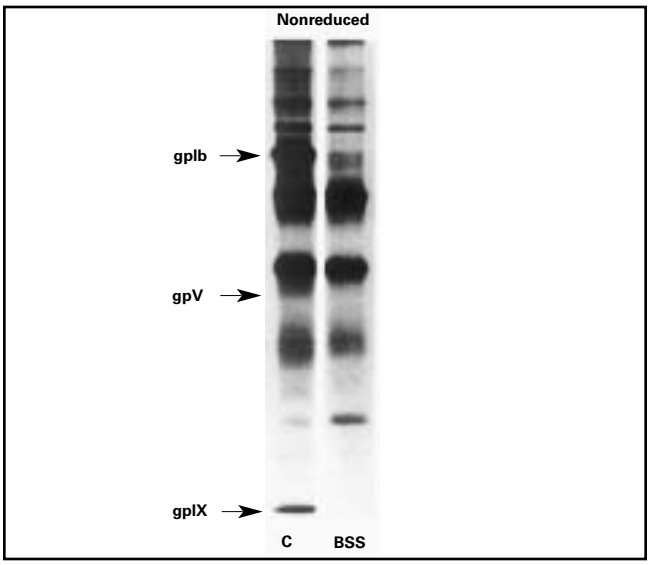

Image 2 Autoradiogram of surface [^{3}H]-labeled control (C) and Bernard-Soulier syndrome (BSS) platelets electrophoresed on sodium dodecyl sulfate polyacrylamide gels under nonreducing conditions. The positions of gplb, gpV, and gpIX, which are deficient in BSS platelets, are indicated by the arrows (courtesy of M. C. Berndt, MD, Baker Medical Research Institute, Melbourne, Australia).

linked to the membrane-associated cytoskeleton, and it has an important role in hemostasis **Image 2**.

The gene of each of the subunits has been cloned, and their chromosomal locations are identified as follows: gpIb-alpha gene (chromosome 17),[13] gpIb-beta gene (22q11.2),[14] gpIX gene (3q21),[15] and gpV gene (3q29).[16] Several different glycoprotein mutations have been reported in the form of missense, non-sense, or deletion mutations of the gpIb-alpha, gpIb-beta, and gpIX genes.[17-20] This variety of mutations could explain the heterogeneity of this syndrome. In general, the reported defects in gpIb-alpha can be grouped into 2 main categories. The first is a quantitative defect in which gpIb-alpha is present in small amounts, while the other components of the gpIb-beta-IX-V complex are affected to a varying degree. The second, a qualitative defect of gpIb-alpha, often is associated with a quantitative defect.[2] Other forms of glycoprotein defects include abnormalities in gpIX and gpV subunits.[21] As a consequence, gpIX and gpV are reduced severely, and the gpIb-alpha is defective qualitatively and subsequently reduced in amount. The bleeding tendency in BSS is caused by the inability of gpIb-alpha (due to a qualitative or a quantitative defect) to bind to vWF, resulting in a defect of platelet adhesion to the subendothelium.[22] The membrane glycoproteins are synthesized during megakaryocytopoiesis. Among the platelet surface glycoproteins, the gpIIb-IIa and gpIb-IX complexes are expressed specifically in the megakaryocytic lineage.[23] In addition, gpIb is expressed on the DMS. A deficiency of gpIIa-IIb, as in Glanzmann disease, is not associated with large platelets.[24] In contrast, a lack of gpIb-IX results in large platelets. This implies that the gpIb-IX complex has a role during megakaryocytopoiesis and in normal megakaryocytic maturation, DMS production, and platelet size.

Glycoprotein Ib normally is associated with sialic acid. The reduction of the amount of gpIb seen in BSS results in a reduction of sialic acid on platelets and causes the platelets to have a shorter life span,[25] which may explain the thrombocytopenia and the decreased platelet life span seen in BSS.

Giant Platelets With Velocardiofacial Syndrome

This disorder is considered a heterozygous variant of BSS. It is characterized by mild thrombocytopenia, giant platelets, absence of bleeding symptoms, and association with VCFS.

Frequency and Inheritance

Six cases have been reported in the literature.[26-28] The mode of inheritance is autosomal recessive.

Clinical Manifestations

The clinical picture of VCFS includes velopharyngeal insufficiency, conotruncal heart disease, and learning disabilities.[29] VCFS is a milder form of DiGeorge syndrome

(thymic hypoplasia, conotruncal cardiac defects, and cardiac abnormalities). No bleeding symptoms were reported in the reported cases.

Laboratory Findings

Mild thrombocytopenia usually is present, and the platelet count ranges from mildly low to normal (100-220 × 10^3/μL [100-220 × 10^9/L). The mean platelet volume (MPV) is 11.0 fL. The bleeding time is normal, the platelet life span decreased, and the platelet adhesion to collagen normal. The platelet aggregation in response to ADP, collagen, ristocetin, and AA is normal. Antiplatelet antibodies are not seen. The peripheral blood smear shows large platelets and an absence of neutrophil inclusions. Ultrastructurally, the platelets are increased in size with no other abnormalities. Florescence in situ hybridization using probe D0832 (courtesy of P. Scrambler, MD, Institute of Child Health, London, England) shows a submicroscopic deletion in 22q11 chromosome.[26]

Pathogenesis

This disorder is characterized by a defect of the platelet surface glycoprotein. Recent studies revealed that gpIb-beta is mapped on the chromosome 22q11.2,[14] which is located at the same region that is deleted in the vast majority of patients with VCFS. Thus, the patients with a 22q11 deletion are obligate heterozygous carriers for the gpIb-beta deletion and, therefore, are heterozygotes for BSS. The gpIb-IX/V complex, as discussed under BSS, may have a role in normal megakaryocytic maturation and in the DMS production. A defect of gpIb, as in VCFS, may result in large platelets and thrombocytopenia.[23] In addition, a decreased density of the gpIb-IX/V complex seems to correspond to the decreased platelet life span.[30]

Giant Platelets With Abnormal Surface Glycoprotein and Mitral Valve Insufficiency

This disorder is characterized by thrombocytopenia, giant platelets, and mild bleeding symptoms in association with mitral valve insufficiency.

Frequency and Inheritance

The disorder was described by Becker et al in 1998[31] in 2 siblings from Puerto Rico. It seems to be inherited as an autosomal-recessive disorder.

Clinical Manifestations

Persons with this disorder usually have a mild bleeding diathesis, most frequently in the form of ecchymosis and epistaxis. These symptoms occur early in childhood. The most important clinical finding distinguishing this disorder from the other giant platelet disorders is the association of mitral valve insufficiency.

Laboratory Findings

Moderate thrombocytopenia is present, and the platelet count is 50 to 60 × 10^3/μL (50-60 × 10^9/L). The mean platelet size is larger than 20 μm. The bleeding time is prolonged (>20 minutes). Platelet survival has not been reported. The platelet aggregation in response to collagen and ristocetin is normal. However, the platelet aggregation response to ADP, thrombin, and AA is slower than normal. No antiplatelet antibodies are detected. The peripheral blood smear shows large platelets and no neutrophil inclusions. Electron microscopic studies demonstrate large platelet size with no other abnormalities. Two-dimensional sodium dodecyl sulfate–polyacrylamide gel electrophoresis of the surface radioiodinated platelet glycoproteins demonstrates a striking absence of gpIb, gpIc, and gpIIa glycoproteins. The cytoskeleton protein examined by polyacrylamide gel electrophoresis fails to demonstrate remarkable abnormalities.

Pathogenesis

A glycoprotein defect is evident in this disorder. The platelet surface glycoproteins, such as gpIa, gpIc, and gpIIa, are absent.[31] However, other glycoproteins, gpIb, gpIIb, and gpIIIa, are normal. The surface glycoproteins involved in this disorder do not seem to have a clear role in platelet physiology. However, the abnormal bleeding time and the bleeding tendency clearly reflect a platelet dysfunction. The bleeding abnormalities could result from a defect in the glycoprotein composition itself, absence or defective function of an anchor protein necessary to attach the glycoproteins to the cytoskeleton, or both. The pathogenesis of the large platelets is unclear. The association with mitral valve insufficiency is not well understood. The potential mechanisms proposed to explain this association include a common defective expression or function of the same membrane proteins in platelets and the valvular tissue or, possibly, damage to the valve by the defective platelets.

Familial Macrothrombocytopenia With gpIV Abnormality

Familial macrothrombocytopenia with gpIV abnormality is characterized by thrombocytopenia, giant platelets, and variable degrees of bleeding tendencies.

Frequency and Inheritance

This disorder was described in 2 families, 1 family by

Yufu et al in 1990[32] and the second family by Kirchmaier et al in 1991.[33] The reported cases suggest an autosomal dominant inheritance.

Clinical Manifestations

The affected family described by Yufu et al[32] had no bleeding diathesis. However, in the report by Kirchmaier et al,[33] the patient had bleeding symptoms. No other associated clinical symptoms are seen.

Laboratory Findings

The thrombocytopenia varies, and the platelet count ranges from 45 × 10^3/μL (45 × 10^9/L) to normal. The median MPV is 15.5 fL. The bleeding time is prolonged and ranges from 15 to more than 30 minutes. Platelet survival studies have not been reported. Yufu et al[32] reported that the platelet aggregation in response to ADP, epinephrine, and collagen was enhanced, and the platelet response to ristocetin occurred at lower concentrations. In contrast, Kirchmaier et al[33] showed that the platelet aggregation to low concentrations of collagen (1-3 μg) is inhibited completely and at higher concentrations (5 μg) is inhibited slightly. However, the platelet aggregation to ADP and epinephrine is decreased slightly. The full range of vWF multimers is present in the plasma. Platelet adhesion to endothelial matrix and collagen-covered surfaces is inhibited, but platelet adhesion to siliconized glass is normal. The gpIb is normal. The gpIV, also known as gpIIIb, shows a normal amount of protein, but the abnormality seems to be a defect in the glycosylation of the gpIV. The peripheral blood smear shows large platelets and with no neutrophil inclusions. Ultrastructural findings were not reported.

Glycoprotein Defect and Pathogenesis

The role of gpIV in hemostasis has not been well evaluated. Some believe that gpIV has a role in thrombospondin-promoted platelet aggregation to thrombin and ADP and may have a collagen receptor.[34,35] These data are controversial. Asch et al[35] identified a role for gpIV in platelet collagen interaction. However, others have failed to identify a definitive role for gpIV in platelet aggregation; in adhesion to types I, III, or IV collagen; or in endogenous thrombospondin binding to platelets.[37] Beer et al[38] showed that gpIV deficiency by itself does not result in clinical bleeding. However, it could become symptomatic if combined with other defects, such as autoantibodies to gpIa/IIa, gpIV, and/or gpIIb/IIIa, all of which are involved in platelet-collagen interactions. Although no antibody studies were reported by Yufu et al[32] and Kirchmaier et al,[33] we believe that the data presented by Beer et al[38] may explain the difference of clinical presentations in the 2 families. The pathogenesis of the large platelets is unknown. More cases need to be studied and additional analysis is needed to resolve the pathogenesis of this disorder.

Montreal Platelet Syndrome

MPS is characterized by severe thrombocytopenia, giant platelets, and spontaneous platelet aggregation with bleeding symptoms.

Frequency and Inheritance

Lacombe and d'Angelo[39] first described this disorder in 1963. Inherited as an autosomal dominant trait, it has been reported in 3 generations of Canadian families.

Clinical Manifestations

Patients with MPS have a significant bruising tendency and episodes of hemorrhage.

Laboratory Findings

Among all the inherited giant platelet syndromes, MPS is characterized by the most severe thrombocytopenia; the platelet count ranges from 5 to 40 × 10^3/μL (5-40 × 10^9/L). The platelet diameter is increased (median, 3 μm). The bleeding time is prolonged, but the clot retraction and the thromboplastin generation are normal. There is spontaneous platelet aggregation, which occurs in calcium and fibrinogen-free platelets and is enhanced by stirring. A hypervolumetric change in shape associated with platelet activation also is seen. Normally, the agonist stimulation to normal platelet results in a transient hypervolumetric change in shape. This change is followed by a partial decrease in platelet volume, and further decreases result in a more pronounced change in shape. In MPS, the initial increase in platelet volume usually is sustained. The platelet aggregation in response to ADP, collagen, AA, and ristocetin is normal. However, the platelet aggregation in response to thrombin is decreased slightly, and it seems to be even more pronounced at lower platelet counts. The peripheral blood smear shows large platelets with no neutrophil inclusions. Ultrastructurally, the platelets are large with no other abnormalities. Glycoprotein analysis shows normal gpIb, gpIa, gpV, gpIX, and gpIIb/IIIa. However, Milton et al[40] demonstrated that in 1 of 3 patients with MPS, there was a reduction in the surface glycoprotein gpIb and in the content of the sialic acid. Okita et al[41] showed a defect in calcium-activated neutral proteinase (calpain).

Pathogenesis

The findings in MPS suggest an intrinsic platelet membrane defect.[40-42] The spontaneous platelet aggregation

is a peculiar phenomenon. In the study by Milton et al,[40] there was a decrease of gpIb and sialic acid content, but the decreases did not correlate with the extent of the spontaneous platelet aggregation, suggesting that neither of these membrane components is related directly to the pathogenesis of the spontaneous platelet aggregation.

Okita et al[41] showed a reduction in calpain activity. They suggested that calpain, which is known to be involved in the cleavage of the cytoskeleton proteins, in particular actin-binding protein and talin, might have a role in spontaneous platelet aggregation. MPS platelets with low calpain proteolytic activity may result in a defect in the regulation of binding sites of platelets for the adhesive proteins. Therefore, the platelet binding sites may be abnormally exposed, leading to an abnormal binding of the adhesive proteins to the exposed platelet surfaces and spontaneous aggregation. In the same study, the hypervolumetric change also was attributed to calpain reduction. However, the role of calpain relative to the described abnormalities remains to be clarified. The pathogenesis of the giant platelets and the severe thrombocytopenia seen is unclear. The contribution of spontaneous platelet aggregation to the thrombocytopenia, by aggregate sequestration, is unknown.

Gray Platelet Syndrome

GPS is characterized by thrombocytopenia, bleeding tendency, and large agranular platelets.

Inheritance and Frequency

This disorder was first described by Raccuglia in 1971.[43] It is extremely rare, with 41 cases reported to date. It is possible that a number of cases may have been underreported or misdiagnosed. The cases described from Japan seem to indicate an autosomal-dominant mode of inheritance.[44] However, a considerable number of cases of GPS seem to be sporadic.

Clinical Symptoms

Patients with GPS have epistaxis, easy bruising, and prolonged menstrual bleeding. The bleeding symptoms begin early in childhood and seem to be mild to moderate in severity. Few cases of severe bleeding are encountered.[45] Splenomegaly can be present.[43,46] There is 1 case report of a Mexican family with GPS in association with Marfan syndrome.[47] There is a separate case report of an association of pulmonary fibrosis with GPS.[48]

Laboratory Findings

Thrombocytopenia is a common finding. The platelet count ranges from $20 \times 10^3/\mu L$ ($20 \times 10^9/L$) to normal values. The median MPV is 13 fL. The bleeding time usually is prolonged, 10 to more than 30 minutes, and it seems to be related to the degree of thrombocytopenia. The bleeding time also is prolonged in patients with normal platelet counts, indicating a qualitative defect of platelets. The platelet life span is shortened.[49]

Platelet aggregation in response to collagen and thrombin is reduced, whereas the platelet response to ADP and AA is normal. The platelet aggregation to ristocetin is normal to reduced but not absent.[46,49] The peripheral blood smear shows large agranular platelets that have a gray to gray-blue appearance on Wright-Giemsa stain. The bone marrow biopsy specimen shows normal number of megakaryocytes and the presence of reticulin fibrosis in most cases.[50]

In contrast with myeloproliferative syndromes, the fibrosis in GPS is stable and does not progress with time.[46] Histologically, the spleen shows passive congestion with sequestration of platelets and extramedullary hematopoiesis. Ultrastructurally, in comparison with normal platelets, the platelets in GPS have large vacuoles and an almost total absence of alpha granules but a normal number of dense bodies[51] **Image 3**. Biochemical studies show low concentrations of alpha-granule components (ie, vWF, platelet factor 4, beta-thromboglobulin, thrombospondin, fibrinogen, and fibronectin). The platelet concentrations of adenosine triphosphate and serotonin are normal. The platelet secretion of serotonin after thrombin and collagen stimulation is reduced or in the low normal range.[52] This finding indicates that the alpha granules may have a regulatory role in the dense granule release, potentially involving signal transduction.

Pathogenesis

The basic defect in GPS seems to be the inability of the megakaryocytes to pack endogenously synthesized secretory proteins into mature alpha granules, resulting in premature release of alpha granules from the cell. The defect is specific to the megakaryocytic line and selective to the alpha granules.[53] The bleeding tendency and the thrombocytopenia can be attributed to different factors, such as short platelet life span, sequestration of the platelets in the spleen, and a qualitative defect of the platelets. The qualitative defect of GPS platelets has a complicated pathogenesis. For platelets to function normally, it is essential to have an integrated signal transduction, normal protein packaging, and a normal cytoskeleton.[54] In GPS, each of these elements is defective.

Studies of GPS platelets show increased calcium uptake into the microsomes of the dense tubular system and increased calcium, magnesium, and adenosinetriphosphatase activity. These findings raise the question of whether alpha granules might be involved in intracellular homeostasis and phosphorylation C activity, and that therefore the functional abnormalities seen in GPS might result from the abnormality in calcium flux.[55]

Lages et al[55] demonstrated a 50% decrease of the content of alpha granule membrane-specific protein P-selectin in

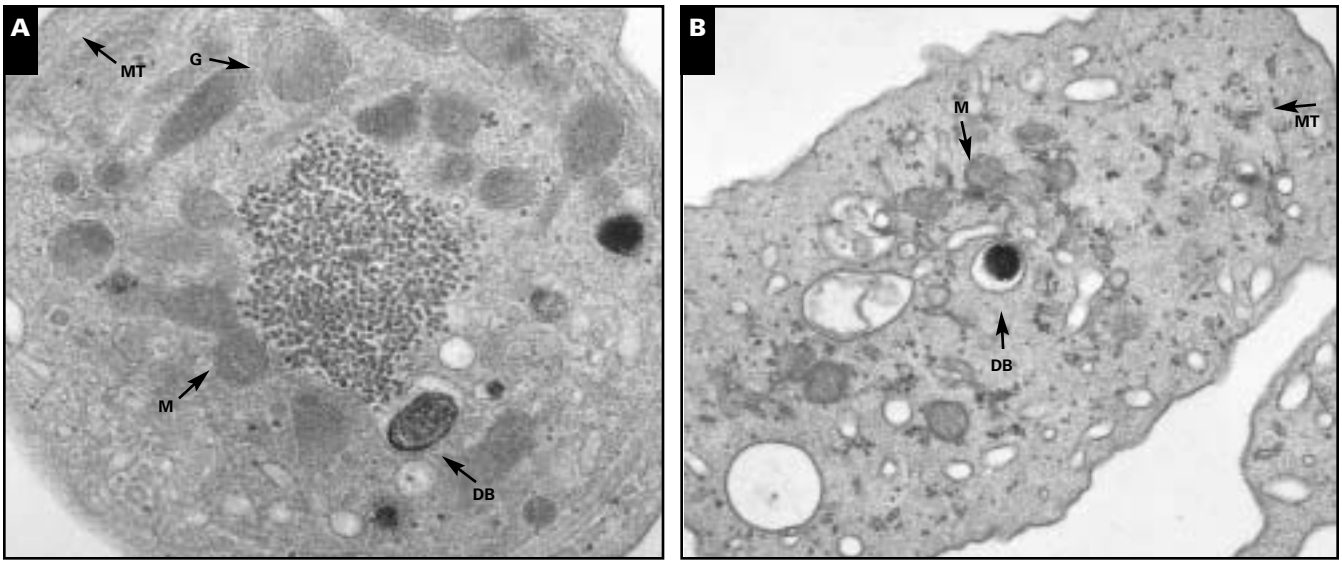

Image 3 A, Thin section of normal platelet. A circumferential coil of microtubules (MT) lying just under the surface membrane supports a discoid shape. The cytoplasm contains numerous alpha granules (G), a few mitochondria (M), and occasional dense bodies (DB), the storage sites for adenine nucleotides and serotonin (×45,000) (courtesy of J. G. White, MD). B, Platelet from a patient with gray platelet syndrome. The cell cytoplasm contains the microtubule coil (MT), mitochondria (M), and a dense body (DB) but is devoid of alpha granules (×27,000) (courtesy of J. G. White, MD, University of Minnesota Medical School, Minneapolis).

GPS. However, Rosa et al[56] showed normal content of P-selectin, and this variation led the authors to postulate the possible existence of variable phenotypic expression of GPS.

The existence of an osteonectin, immunologically different from the osteonectin found in the bone, has been reported in alpha granules.[57] It normally is expressed as a complex with thrombospondin on degranulation and seems to be involved in the stabilization of platelet aggregates. Gray platelets show about 20% of the normal quantity of osteonectin, and this abnormality may contribute to a platelet function defect.[58]

The platelet alpha granules contain platelet-derived growth factors, and the inability of the gray platelets to pack this constituent results in the liberation of this product in the bone marrow stroma and in fibrosis.

It has been reported that the normal alpha granule membrane expresses glycoproteins similar to the surface membrane. In GPS, there is normal expression of gpIb, gpIX, gpV, and gpIIa/IIIb in the alpha granule membrane.[59]

May-Hegglin Anomaly

MHA is characterized by the presence of giant platelets, thrombocytopenia, neutrophil inclusions, and mild bleeding symptoms.

Frequency and Inheritance

MHA was first described by May in 1909[60] and later by Hegglin in 1945.[61] This is the most common type of IGPD, and more than 180 cases have been reported. All reported cases indicate an autosomal-dominant trait inheritance.

Clinical Manifestations

The majority of the patients with MHA have mild bleeding tendencies, and a few are asymptomatic. Cases with severe bleeding also are seen. Easy bruising, menorrhagia, and postoperative hemorrhage are the most frequent manifestations. The bleeding tendency seems to depend on the severity of the thrombocytopenia. Some patients with MHA have myocardial infarction due to coronary artery thrombosis.[62] Although patients with MHA have primarily hematologic manifestations, other clinical findings have been reported, including nephritis,[63] familial spastic paraplegia,[64] and pituitary growth hormone deficiency.[65] Although familial spastic paraplegia and pituitary growth hormone deficiency are inherited as autosomal-dominant traits, the relation of these findings to MHA is unclear. Pregnant women with MHA can be asymptomatic or have mild bleeding manifestations. These patients usually are treated with prophylactic platelet transfusion and cesarean section to avoid maternal and neonatal bleeding. However, cases of successful vaginal deliveries without complications have been reported.[66,67]

Laboratory Findings

Mild to moderate thrombocytopenia is present, and the platelet count is 60 to 100 × 10^3/μL (60-100 × 10^9/L). The median MPV is 12.5 fL. The bleeding time is prolonged.

The platelet life span is normal,[68] as are the fibrin clot retraction and the collagen gel retraction. The platelets show defective pseudopodial formation and lack of platelet spreading. The platelets show normal aggregation in response to ADP, collagen, epinephrine, and ristocetin. Impairment of platelet aggregation to epinephrine stimulation has also been described.[69] The peripheral blood smear shows large platelets and 2- to 4-µm bright-blue spindle-shaped neutrophil inclusions (Döhle bodies), located in the periphery of the cytoplasm **Image 4**.

Ultrastructural studies reveal that many of the normal-sized platelets have prominent circumferential bundles of microtubules, as normally expected. In contrast, the giant platelets show dispersed organization of the microtubule bundles. The neutrophil inclusions are oval or round and localized in the periphery of the cytoplasm. They are free of specific granules, devoid of limiting membrane, and contain clusters of ribosomes and segments of endoplasmic reticulum and microfilaments **Image 5**. A case report of a Chinese girl with MHA and neutrophil inclusion bodies did not show the usual morphologic features seen in MHA.[70] At the ultrastructural level, the neutrophil inclusions consisted of small electron-dense fibrils arranged in a haphazard or whorled pattern. As suggested by the authors, this case may represent a variant of MHA in the Chinese population.

The neutrophils show normal random motility and have an impairment of chemotaxis and chemokinetic responses.[71] However, patients with MHA do not have an increased susceptibility to infection.

Pathogenesis

There is no evidence of surface platelet glycoprotein abnormalities.[72,73] However, Ricci et al[74] detected a change in the antigenic structure of gpV in 1 family. The underlying cause of large platelets is unknown, but it may result from an altered organization of the DMS during platelet formation. The circumferential bands of the platelet microtubules have an important role in maintaining the normal discoid shape of the platelets and help in the changes in shape and in pseudopod formation. There is clear evidence of an anomalous distribution of the platelet microtubule system in MHA, and this may be responsible for the defective function of the platelets.[75] This defective platelet function could lead to bleeding symptoms. The cause of the thrombocytopenia is unknown.

Patients with MHA can present with myocardial infarction. Although low platelet count is a strong negative risk factor for arterial thrombosis, recent studies show that the large platelets seen in MHA may compensate functionally for the low platelet count.[76] The large platelets have a major role in binding to soluble vWF and in platelet-platelet aggregation, and they become resistant to the shearing effect of the blood flow. This phenomenon is aggravated by the presence of injury to the blood vessels. Patients with MHA tend to have restenosis of their coronary arteries after their first angioplasty.

Fechtner Syndrome

Fechtner syndrome is characterized by deafness, cataract, nephritis, thrombocytopenia, and giant platelets.

Frequency and Inheritance

Since this disorder was described by Peterson et al[77] in 1985, 34 affected members in 3 families have been described. The transmission of Fechtner syndrome, as demonstrated by the pedigrees of the families described, is consistent with autosomal-dominant inheritance.[78] The ratio of affected males to females is 1:1.

Clinical Manifestations

Patients with Fechtner syndrome have classic hereditary nephritis progressing to end-stage renal failure by the age of 20 to 40 years, necessitating hemodialysis and renal transplant. There is high-frequency hearing loss, usually detected by the third decade. The eye abnormalities include juvenile glaucoma and cataracts, occurring at early age. The bleeding symptoms are variable and begin early in childhood. Some family members have menorrhagia, easy bruising, and hemorrhage after excision or surgery.

Laboratory Findings

Thrombocytopenia is moderate to severe; platelet counts range from 30 to 90 × 10^3/µL (30-90 × 10^9/L). The bleeding time can be normal or prolonged. The median MPV is 20 fL. The platelet aggregation in response to epinephrine, AA, thrombin, ADP, collagen, and ristocetin is normal. The peripheral blood smear shows large platelets. The neutrophils contain 1 or more 1- to 2-µm irregularly shaped cytoplasmic inclusions that appear pale-blue with Wright-Giemsa stain and are faintly positive with methyl-green pyronin. They occasionally are seen in eosinophils. In contrast with MHA, neutrophilic inclusions in Fechtner syndrome are smaller and less well stained.

The bone marrow smear shows multinucleated megakaryocytes with a high density of azurophilic granules. No platelet clumps are seen around the granular mature megakaryocytes.

Light microscopic examination of the renal biopsy specimen shows increased mesangial cells and focal glomerular hyalinization. Electron microscopic studies show thickening of the glomerular basement membrane with focal areas of attenuation. The chemiluminescence assay shows normal neutrophil function.[77]

Ultrastructurally, most of the giant platelets are

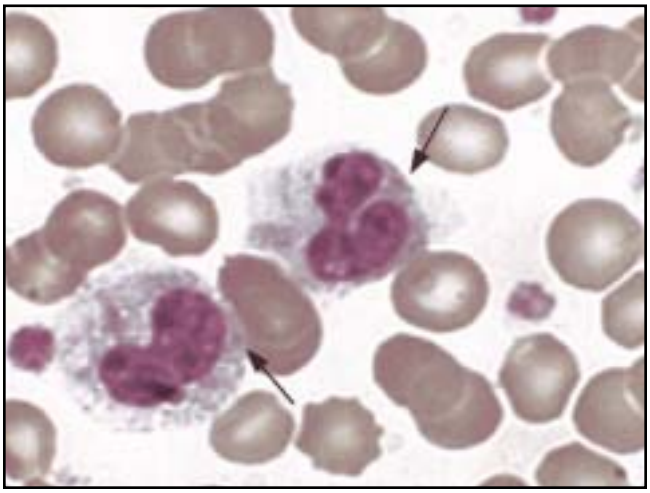

Image 4 Peripheral blood smear from a patient with May-Hegglin anomaly showing giant platelets and inclusion bodies in the cytoplasm of the neutrophils (arrows) (Wright-Giemsa, ×1,000).

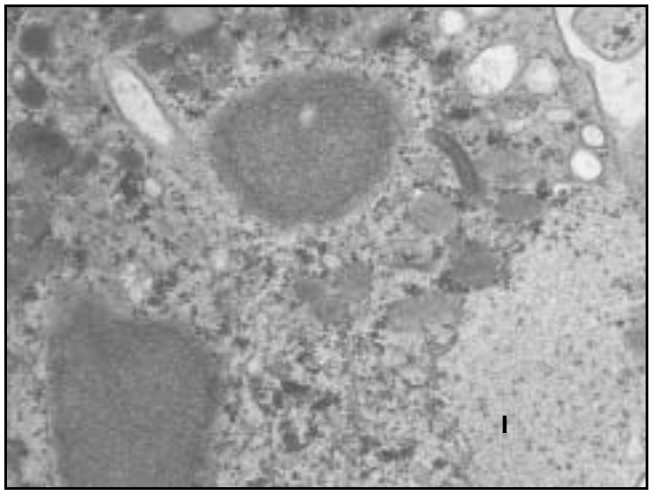

Image 6 Inclusion (I) in neutrophil from a patient with Fechtner syndrome. Neutrophils from patients with Sebastian syndrome contain identical inclusions. The inclusions are relatively spherical or irregular in appearance but may be elongated or rectangular. Intermediate filaments and clusters of ribosomes are irregularly dispersed in the organelle matrix. Membranes do not enclose these inclusions (×18,000) (courtesy of J. G. White, MD).

spherical, and the microtubule bundles are rarely organized in a single plane. In addition, the megakaryocytes have an unusual concentration of the DMS in a large area. Granules, dense bodies, and mitochondria are dispersed randomly in the cytoplasm.[79] Many neutrophil inclusions are spherical, while some are rectangular. They contain clusters of single ribosomes and small segments of rough endoplasmic reticulum **Image 6**. In addition, they lack the parallel bundles of filaments characteristic of

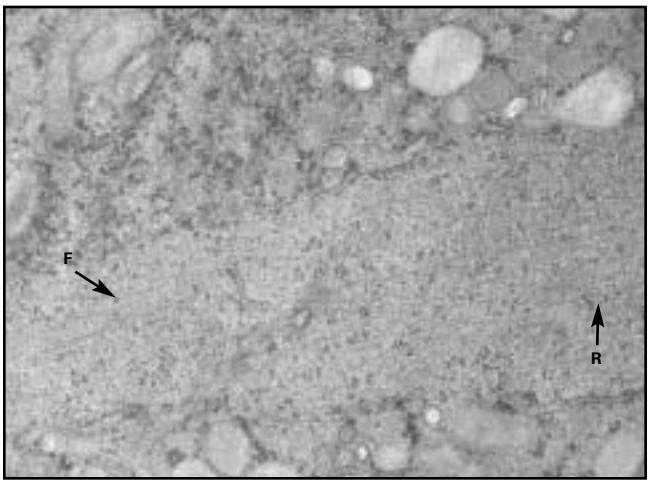

Image 5 Neutrophil inclusion from a patient with May-Hegglin anomaly. The spindle shape is supported by parallel intermediate filaments (F). Clusters of ribosomes (R) are on and between the filaments, suggesting a longitudinal orientation. The structure is not enclosed by a membrane (×31,000) (courtesy of J. G. White, MD).

neutrophil inclusions in MHA.

Pathogenesis

Platelet surface glycoprotein studies have not been reported. DMS may have a role in platelet size, and the abnormal accumulation of DMS in large areas of the megakaryocytes may result in fewer and larger platelets. The thrombocytopenia may be explained by ineffective megakaryocytopoiesis, as reflected by large numbers of megakaryocytes and low platelet count. A study by Heynen et al[79] showed complete fragmentation of the granular zone of the platelet-producing megakaryocytes into platelet territories, but for unknown reasons, the next step in platelet formation was not seen, which led to thrombocytopenia.

Sebastian Syndrome

Sebastian syndrome is a hereditary thrombocytopenia with giant platelets, neutrophil inclusions, mild bleeding diathesis, and no other clinical manifestations.

Frequency and Inheritance

Sebastian syndrome is an extremely rare disorder. Since it was first described by Greinacher et al[80] in 1990, only 4 cases have been reported.[80-82] It is inherited as an autosomal-dominant trait.

Clinical Manifestations

The clinical signs and symptoms are variable. The patients are asymptomatic or have mild bleeding diathesis, such as epistaxis occurring early in childhood. Severe postoperative hemorrhage also can occur. Patients with Sebastian syndrome do not have other clinical symptoms, such as deafness, congenital cataract, and interstitial nephritis.

Laboratory Findings

Patients with Sebastian syndrome have mild to moderate thrombocytopenia (40-120 × 10^3/μL [40-120 × 10^9/L). The median MPV is 18 fL. The bleeding time is prolonged mildly (10-12 minutes). Platelet aggregation is normal in response to ADP, collagen, AA, and ristocetin. The peripheral blood smear shows large platelets and faintly blue cytoplasmic inclusions in the neutrophils, similar in appearance to Döhle bodies.

At the ultrastructural level, the platelets are enlarged. They are less discoid than normal platelets, but they have normal distribution of microtubules, alpha granules, mitochondria, glycogen particles, and elements of the dense tubular system. The neutrophils show 1- to 3-μm cytoplasmic areas of randomly dispersed ribosome clusters. Also found are occasional filaments that are not organized in parallel arrays. The platelet surface glycoproteins IIb/IIIa, Ib, IX, and IIIa are normal.[82]

Pathogenesis

The pathogenesis of the thrombocytopenia and the neutrophil inclusions is unresolved. It is believed that the absence or the mild bleeding symptoms could be attributable to the large platelet size, which may compensate functionally for the low platelet count.

Hereditary Macrothrombocytopenia

Hereditary macrothrombocytopenia is characterized by mild thrombocytopenia, giant platelets, bleeding tendency, and high-frequency hearing loss.

Frequency and Inheritance

This disorder was described by Gilman et al[83] in 1995 in 8 members of 1 family, and it seems to be an autosomal-dominant trait.

Clinical Manifestations

The patients with hereditary macrothrombocytopenia have a mild bleeding tendency, most often gingival bleeding after brushing teeth, epistaxis, easy bruising, and menorrhagia. Surgery and childbirth usually are well tolerated, without complications, except when thrombocytopenia is severe. The bleeding symptoms appear early in childhood. The onset of hearing loss appears later in life. The patients do not have ocular or renal symptoms.

Laboratory Findings

Mild thrombocytopenia is present, and the platelet count ranges from 50 to 123 × 10^3/μL (50-123 × 10^9/L). The bleeding time may be normal or prolonged. Platelet survival studies have not been reported. Platelet aggregation is normal in response to ADP, collagen, and ristocetin but diminished in response to epinephrine and AA. The peripheral blood smear shows large platelets and absence of neutrophil inclusions. The bone marrow biopsy specimen reveals mild megakaryocytic hyperplasia. Ultrastructurally, the platelets are large with no additional abnormalities. Flow cytometric studies show 2 distinct populations of giant platelets based on the intensity of the staining with CD42b and CD41a monoclonal antibodies. In addition, 40% to 60% of the giant platelets that stained less intensely with the CD41a monoclonal antibody also stain with anti–glycophorin A. No normal control platelets stain with anti–glycophorin A.[83]

Pathogenesis

The platelet surface glycoproteins, gpIbV/IX and gpIIb/IIIa, are normal. The most intriguing finding is the unusual expression of glycophorin A at the surface of the giant platelets, as reported by Gilman et al.[83] Glycophorin A, generally considered an erythroid-specific protein, is not expressed on normal platelets, and its expression on the early megakaryocyte precursors in the bone marrow is not proven. The pathogenesis of the thrombocytopenia and giant platelets is unclear. Gilman et al[83] proposed that the unusual expression of the glycophorin A on the giant platelets could be an indication of disordered megakaryocytopoiesis. This could lead to abnormal fragmentation with the release of very immature giant platelets. The association with hearing loss may have several explanations, such as linkage disequilibrium of the genes affecting the megakaryocytopoiesis and the auditory and renal cortical cells, or it may be a coincidence.

Epstein Syndrome

Epstein syndrome is characterized by thrombocytopenia, large platelets, and mild bleeding diathesis, in association with nephritis and sensorineural hearing loss.

Frequency and Inheritance

Since the original publication by Epstein et al[84] in 1972, 17 members from 10 families have been described. Inheritance is autosomal dominant.

Clinical Manifestations

Patients with Epstein syndrome have persistent

proteinuria, microscopic hematuria, moderate hypertension, and bilateral high-frequency (>2,000 Hz) sensorineural hearing loss. These patients also have a mild bleeding tendency, most frequently in the form of epistaxis, as well as gastrointestinal and female genital tract bleeding. Intracranial hemorrhage with fatal outcome has been reported. The bleeding symptoms occur early in life and may disappear later in life. The hypertension may exaggerate the bleeding symptoms.

Laboratory Findings

Often, the thrombocytopenia is severe and the platelet count is 30 to 60 × 10^3/μL (30-60 × 10^9/L). The bleeding time may be normal or prolonged. The platelet size varies between 4 and 12 μm. The platelet life span is normal. Few reports describe reduced adhesion and weak clot retraction.[85] The platelet aggregation in response to collagen, epinephrine, and ADP is reduced, but these findings are not always present. The peripheral blood smear shows increased platelet size in approximately 50% of the platelets, and no neutrophil inclusions are seen. Ultrastructurally, the giant platelets are spherical and have a prominent surface-connected open canalicular system leading to a sponge-like peripheral zone.[86] Microscopically, the kidney shows glomerular mesangial expansion and cellular proliferation.

Pathogenesis

In our review of this rare disorder, we found no studies evaluating the platelet surface glycoproteins. The pathogenesis of the thrombocytopenia and the large platelets are not elucidated.

Mediterranean Macrothrombocytopenia

Mediterranean macrothrombocytopenia is characterized by thrombocytopenia and large platelets with no bleeding symptoms.

Frequency and Inheritance

This disorder has a high prevalence among persons originating from Greece, Italy, and the Balkan peninsula. The incidence is unknown.

Clinical Manifestations

Persons with Mediterranean macrothrombocytopenia are asymptomatic. Episodes of hemolytic anemia have been reported.[87] Physical examination may reveal mild splenomegaly.[88]

Laboratory Findings

Thrombocytopenia is mild; platelet counts range from 89 to 290 × 10^3/μL (89-290 × 10^9/L). The platelet biomass (platelet size × platelet count) is normal.[89] The peripheral blood smear shows large platelets, erythrocyte stomatocytes, and absence of neutrophil inclusions. The platelet aggregation was not reported. Electron microscopic examination shows large platelets with no other abnormalities.

Pathogenesis

There are no data evaluating platelet glycoproteins. The thrombocytopenia may be due partially to splenic sequestration[90]; however, the pathogenesis of this disorder remains to be determined. Researchers believe that Mediterranean macrothrombocytopenia is a benign anomaly and an incidental finding in patients from the Italian, Greek, and Balkan peninsula.[88]

Diagnosis

The diagnosis of IGPDs is not always easy. Acquired disorders, which are relatively common, should be excluded first by carefully obtaining the history. Once it is established that the disorder is hereditary, the mode of inheritance is helpful in the differential diagnosis. An autosomal-dominant mode of inheritance indicates GPS, MHA, Fechtner syndrome, Sebastian syndrome, hereditary macrothrombocytopenia, or Epstein syndrome, while a recessive mode of inheritance suggests BSS, VCFS, or giant platelets with mitral valve insufficiency. Surface glycoprotein analysis is most helpful for diagnosis of the giant platelet disorders with an autosomal-recessive mode of inheritance. Electron microscopy of the platelets and neutrophils can help in the diagnosis of GPS, MHA, and Fechtner syndrome. Systemic manifestations, such as hearing loss and nephritis, are seen in Fechtner syndrome, Epstein syndrome, and hereditary macrothrombocytopenia; finally, no abnormality is described in Mediterranean macrothrombocytopenia.

Treatment

There is no general recommendation about treatment for patients with IGPDs. Platelet transfusion is the treatment of choice for patients with bleeding symptoms. The role of DDAVP (1-deamino-8-arginine vasopressin) and splenectomy is controversial.[43,46,49,90,91]

Conclusion

IGPDs are extremely rare. The classification of these disorders is an attempt to promote understanding of the disorders and to provide a comprehensive review about this

Table 2
Summary of the Clinical and Laboratory Findings and Pathogenesis of Inherited Giant Platelet Disorders

Disorder	Inheritance	Bleeding Diathesis	Clinical Association	Platelet Count, × 10^3/μL (× 10^9/L)	Aggregation Abnormality	Neutrophil Inclusions	Structural Defect
Bernard-Soulier syndrome	AR	Variable	None	<30 (<30); N	Ristocetin: absent	No	gpIb-IX-V complex defect
Velocardiofacial syndrome	AR	No	Velopharyngeal insufficiency; conotruncal heart disease; learning disabilities	100 (100); N	Normal	No	gpIb-beta defect
Mitral valve insufficiency	AR	Mild	Mitral valve insufficiency	60 (60)	ADP, AA, thrombin: slow	No	Absence of gpIa, gpIc, gpIIa
Glycoprotein IV abnormality	AD	Yes	None	45 (45); N	Variable	No	Defect in glycosylation of gpIV
Montreal platelet syndrome	AD	Yes	None	5-40 (5-40)	Thrombin: decreased	No	Calpain defect
Gray platelet syndrome	AD	Mild to moderate	Splenomegaly; Marfan syndrome; pulmonary fibrosis	20 (20); N	Thrombin, collagen, ristocetin: decreased	No	Alpha-granule defect; calcium flux abnormality; P-selectin reduction; osteonectin reduction
May-Hegglin anomaly	AD	Mild	Nephritis, FSP, growth hormone deficiency; myocardial infarction	60-100 (60-100)	Normal	Yes	DMS abnormality?
Fechtner syndrome	AD	Variable	Hereditary nephritis; high-frequency hearing loss; juvenile glaucoma and cataract	30-90 (30-90)	Normal	Yes	DMS abnormality?
Sebastian syndrome	AD	Variable	None	40-120 (40-120)	Normal	Yes	Unknown
Hereditary macrothrombocytopenia	AD	Mild	High-frequency hearing loss	50-123 (50-123)	Epinephrine and AA: decreased	No	Normal gp; expression of glycophorin A
Epstein syndrome	AD	Mild	Nephritis; high-frequency hearing loss	30-60 (30-60)	Collagen, ADP, thrombin: decreased	No	Unknown
Mediterranean macrothrombocytopenia	Unknown	No	Hemolytic anemia; splenomegaly	90 (90); N	NA	No	Unknown

AA, arachidonic acid; AD, autosomal dominant; ADP, adenosine diphosphate; AR, autosomal recessive; DMS, demarcation membrane system; FSP, familial spastic paraplegia; gp, glycoprotein; N, normal; NA, not available.

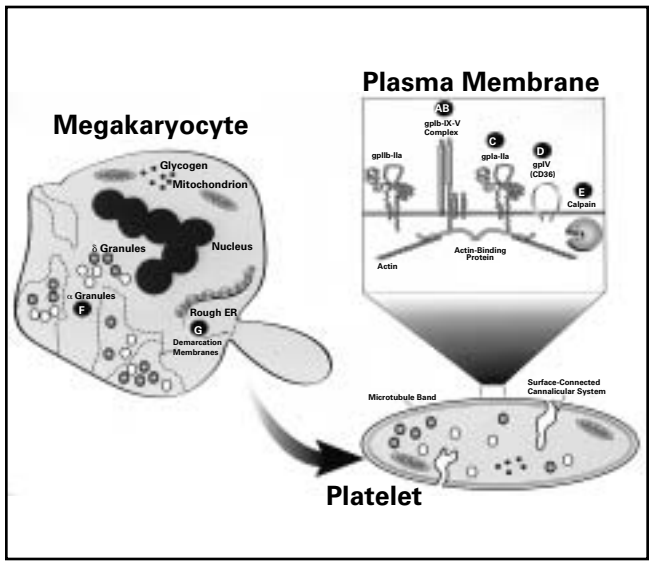

Figure 2 Site of molecular defects in megakaryocytes and platelets in the inherited giant platelet disorders. A, Bernard-Soulier syndrome: gpIb-IX-V complex defect. B, Velocardiofacial syndrome. C, Glycoprotein abnormality with mitral valve insufficiency: gpIa, gpIIa defect. D, gpIV abnormality. E, Montreal platelet syndrome: calpain defect. F, Gray platelet syndrome. G, May-Hegglin anomaly (courtesy of J. López). ER, endoplasmic reticulum.

topic. A summary of the findings in the IGPDs is given in **Table 2**. In addition, the known pathogenesis involved in IGPDs is summarized in **Figure 2**. As for therapy, in cases of minor bleeding episodes, no treatment is necessary. However, for severe bleeding problems, platelet transfusion is the treatment of choice. The classification of IGPDs is not easy because of the heterogeneous nature of the disorders and the overlapping clinical features. For example, Fechtner syndrome may be classified under IGPDs with systemic manifestations and those with neutrophil inclusions. MPS showed glycoprotein abnormalities in only 1 of the 3 reported cases, so it is difficult to classify under glycoprotein defects. We believe that more investigative work is needed, particularly in the area of surface glycoprotein analysis. We hope that future research will provide clues to the many unanswered questions.

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