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Current Knowledge on Inherited Platelet Function Disorders

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Inherited platelet function disorders (IPFDs) are rare and underdiagnosed in individuals with clinically significant bleeding diathesis. IPFDs are classified according to the causative molecular defects involved in the process of primary hemostasis of platelets, which include the following: 1) adhesion (e.g., Bernard–Soulier syndrome and pseudo-von Willebrand disease), 2) activation (e.g., adenosine diphosphatase receptor defect and thromboxane A2 receptor defect), 3) signal transduction and granule secretion (e.g., gray platelet syndrome, Paris–Trousseau/Jacobsen syndrome, Chediak–Higashi syndrome, and Hermansky–Pudlak syndrome), 4) aggregation (e.g., Glanzmann thrombasthenia), and 5) procoagulant activity (e.g., Scott syndrome). Patients with IPFDs typically present with unexpected mucocutaneous bleeding during early childhood. The diagnosis of these conditions requires several laboratory tests including complete blood cell count, peripheral blood smear, platelet function analysis, light-transmission aggregometry, flow cytometry, electron microscopy, and genetic analysis. Platelet transfusion has been the mainstay of treatment. However, antifibrinolytics, desmopressin, and recombinant activated factor VII are also effective when used as a monotherapy or adjunctive therapy. Importantly, the prevention of bleeding event is the most basic strategy in the management of IPFDs. This review aimed to assess the normal platelet physiology and summarize the current knowledge about the molecular defects, diagnostic evaluation, and treatment strategies of the respective IPFDs. If the cause of the bleeding tendency is difficult to identify, IPFDs should be considered.

Key Words: Blood platelet disorders, Bernard-Soulier syndrome, Platelet storage pool deficiency, Gray platelet syndrome, Thrombasthenia, Platelet function tests

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Introduction

The hemostatic process has two important components: platelet-associated primary hemostasis (response of platelets to endothelial damage and plug formation) and coagulation factor-associated secondary hemostasis (coagulation cascade and fibrin formation) [1]. In particular, platelets play an essential role in the appropriate initiation of hemostasis. Platelet dysfunction is characterized by mucocutaneous bleeding, including easy and extensive bruising, severe epistaxis, menorrhagia, postpartum bleeding, or unexpected bleeding after procedures despite a normal platelet count [2,3].

Platelets play an important role via the following mechanisms: adhesion, activation, granule secretion, aggregation, and procoagulant activity [4,5]. Thus, inherited platelet function disorders (IPFDs) can be classified according to the role of platelets [4,5]. The features of each disease classified under IPFDs include primary hemostatic defects with significant phenotypic heterogeneity and inherited transmission. However, due to the

extremely low incidence of IPFDs, medical personnel can overlook these conditions [6]. In this article, the normal physiological function of platelets, causes and clinical/laboratory characteristics of major representative IPFDs, and available therapeutic modalities were reviwed. The normal physiological platelet function and respective IPFDs are shown in Fig. 1, and the algorithm of access in patients with platelet dysfunction is depicted in Fig. 2. Meanwhile, Table 1 presents the outline and classification of the major IPFDs, and Table 2 shows the available therapeutic modalities for IPFDs.

Normal Platelet Function

The normal platelet function in primary hemostasis at the damaged vessel wall and the associated IPFDs are depicted in Fig. 1. Platelets are small, fragmented anucleate cells derived from megakaryocytes in bone marrow [7]. Moreover, they play fundamental roles in primary hemostasis after vascular damage and are involved in innate immune response, inflammatory reaction, wound healing, and hematogenic metastasis [7]. The process of pri-

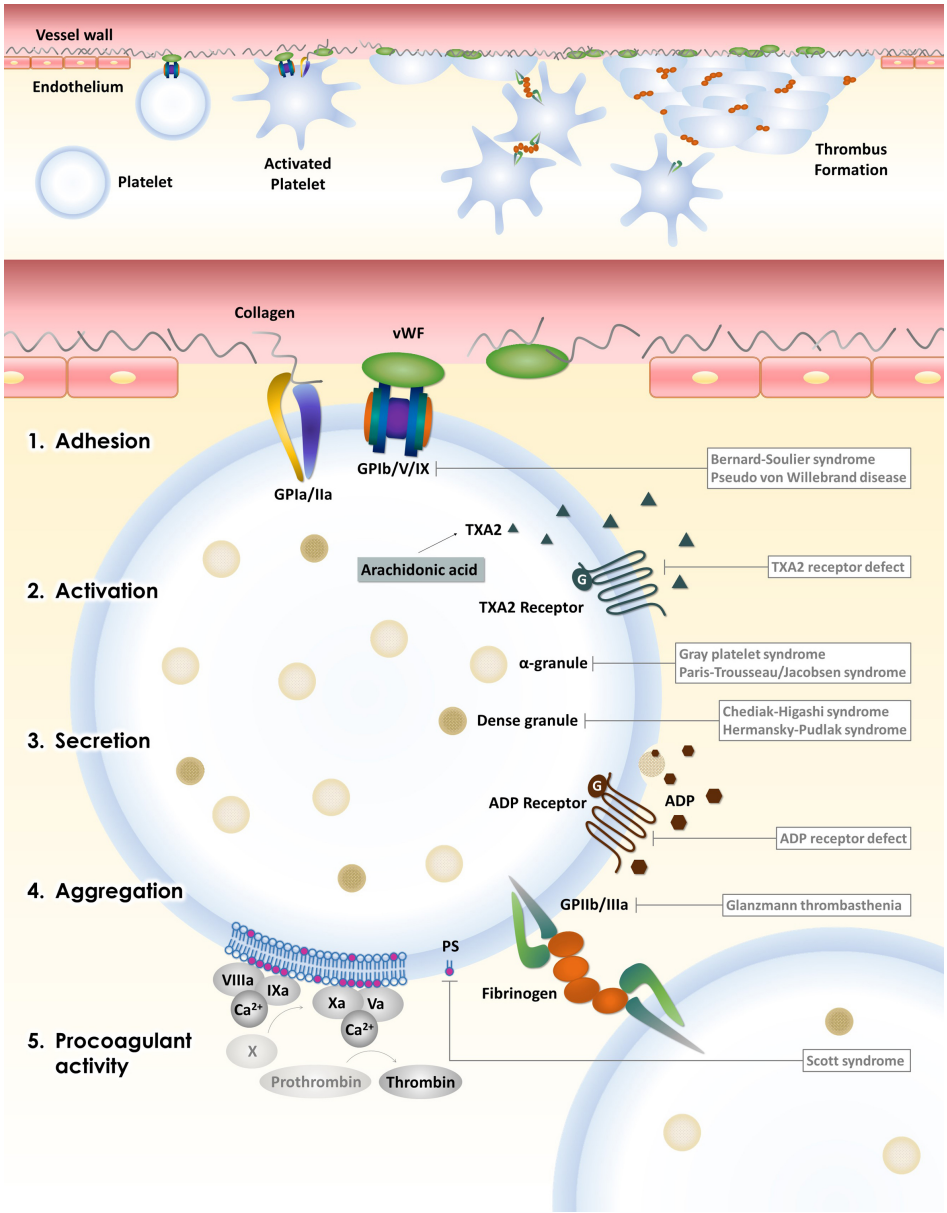

Fig. 1. Normal platelet function in primary hemostasis at the damaged vessel wall and the associated inherited platelet function disorders. vWF, von Willebrand factor; GP, glycopretein; TXA2, thromboxane A2; ADP, adenosine diphosphate; PS, phosphatidylserine.

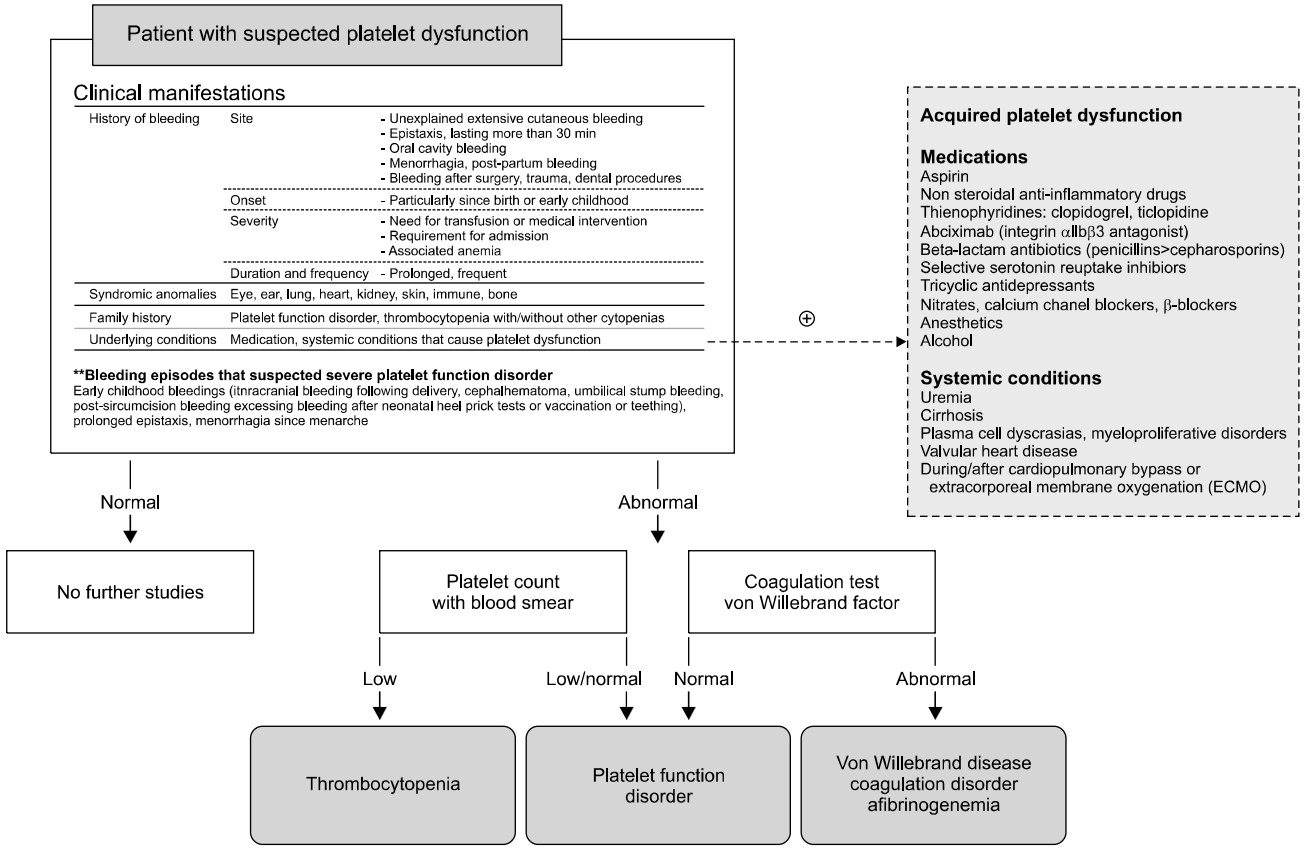

Fig. 2. Access algorithm for patients with suspected platelet dysfunction [2,11,12,15,19].

Table 1. Classification of inherited platelet function disorders according to the altered platelet functions

Function	Disease	Gene	Inheritance	Defect
Adhesion	Bernard-Soulier syndrome	*GPIBA, GPIBB, GP9*	AR (rarely AD)	GPIb/V/IX
	Pseudo-von Willebrand disease	*GPIBA*	AD	GPIbα
Activation	ADP receptor $P2Y_{12}$ defect	*P2RY12*	AR	ADP receptor
	TXA2 receptor defect	*TBXA2R*	AD	TXA2 receptor
Secretion	Gray platelet syndrome	*NBEAL2*	AR (rarely AD)	α-Granule
	Paris-Trousseau/Jacobsen syndrome	*FLI1*	AD	α-Granule
	Chediak-Higashi syndrome	*LYST*	AR	Dense granule
	Hermansky-Pudlak syndrome	*HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S6*	AR	Dense granule
Aggregation	Glanzmann thrombasthenia	*ITGA2B, ITGB3*	AR	GPIIb/IIIa
Procoagulant activity	Scott syndrome	*ANO6*	AR	PS expression

AR, autosomal recessive; AD, autosomal dominant; GP, glycoprotein; ADP, adenosine diphosphate; TXA2, thromboxane A2; PS, phosphatidylserine.

mary hemostasis occurs in multiple steps via several molecules. When a blood vessel is injured, circulating platelets adhere to the exposed subendothelium to stop the leak [8]. This process is mediated by the interaction between adhesive proteins and receptors on the platelet surface, including von Willebrand factor (vWF) which bind to glycoprotein (GP) Ibα in the GPIb/V/IX complex at high shear rates and collagen on the subendothelium binding to GPIa/IIa (integrin α2β1) at low shear rates [8]. After adhesion, agonist substances, adenosine diphos-

Table 2. Agents for the treatment of bleeding in patients with inherited platelet function disorders

Agent	Indication and dose	Caution
Tranexamic acid	PO: 15-25 mg/kg q 8 hours for menorrhagia and mild mucosal bleeding, including epistaxis [2,30] IV: 10-15 mg/kg q 8 hours for serious bleeding up to q 6 hours in selected cases [2,30] Mouth wash: 10 mL of a 5% solution 4-6 times a day for local mouth bleeding [2,84]	Obstructive uropathy in urinary tract bleeding, hematoma in pleural space bleeding
Aminocaproic acid	PO: 60-90 mg/kg q 6-8 hours [84] IV: 100 mg/kg over 15 min, followed by 10 mg/kg/h or 5 g bolus 4 h [30]	Shorter half-life, less potency, more toxicity than tranexamic acid [89]
Desmopressin	IV: 0.3 μg/kg in 20-50 mL of saline over 30 min, 1 h before procedure [2,4,30,53,87] 0.2 μg/kg with tranexamic acid 10 mg/kg [68] Not exceeding a total dose of 20 μg [84] SC: 0.3 μg/kg [2,4] Nasal spray: 300 μg for an adult, 150 μg for a child with a weight under ＜40-50 kg [2,4,30]	Fluid retention, hyponatremia-induced seizure, caution with the use in elderly with cardiovascular disease and children younger than 2 years
rFVIIa	IV: ≥90 μg (4.5 kIU)/kg/dose, q 2-3 h, ≥3 doses or until hemostasis for GT [88]	Thromboembolic complications (rare)

PO, per oral; IV, intravenous; SC, subcutaneous; rFVIIa, recombinant activated factor VII; GT, Glanzmann thrombasthenia.

phate (ADP) or thromboxane A2 (TXA2), activate platelets via the signal transduction of tyrosine kinase, G-protein coupled receptors, or GPIIb/IIIa (integrin αIIbβ3) [8]. Activated platelets change shape with the formation of pseudopodia and the centralization of granules [7]. The α-granules contain adhesive glycoproteins, such as vWF and fibrinogen, mitogenic/angiogenic factors, and coagulation factors [9]. Dense granules (also known as δ-granules) contain calcium, adenosine triphosphate, ADP, serotonin, and epinephrine [9]. The contents of these granules secreted via exocytosis promote the activation of platelets and the recruitment of circulating platelets into the initial plug [10]. Via cross-linking between the ligands (fibrinogen and vWF) and the receptor GPIIb/IIIa, aggregated platelets become firmly connected [8]. Moreover, coagulation factors bind to phosphatidylserine (PS) on the platelet phospholipid bilayer membrane of aggregated platelets to generate thrombin in secondary hemostasis. Owing to thrombin formation on the platelet surface, a more stable hemostatic plug can be formed [7].

Clinical Manifestations and History of Patients with IPFDs

Although there are no standardized guidelines for the evaluation of IPFDs, clinical history can provide the most important information for the diagnosis of IPFDs [2,11,12]. Patients with secondary hemostatic disorder present with delayed, deep muscular bleeding. By contrast, those with platelet dysfunction commonly experience immediate, mucocutaneous bleeding after an injury or procedure [2]. The common symptoms include easy bruising, epistaxis, gingival bleeding, menorrhagia, and postpartum bleeding, and the severity of symptoms can be heterogeneous even among patients with the same defect [4]. Various tools for the assessment of the severity of bleeding tendency are available [13]. Not only platelet function disorders but also acquired platelet dysfunction must be considered in patients with a bleeding tendency [14,15]. The algorithm of access for patients with platelet dysfunction is shown in Fig. 2.

Diagnostic Tools for IPFDs

To obtain an accurate diagnosis of IPFDs, several laboratory tests should be performed. According to the recent worldwide survey, laboratories frequently use platelet count, peripheral blood (PB) smear, platelet function analysis, and light-transmission aggregometry as the first-step tests of IPFDs, and flow cytometry, electron microscopy, and genetic tests as the second-step tests [16].

1) Complete blood count and peripheral blood smear

Complete blood count (CBC) and PB smears are suitable for the initial workup of IPFDs since they provide important information about the number, size, and morphology of blood cells [2,17]. Some IPFDs are characterized by abnormal findings based on CBC and/or PB smears, which include large platelets in Bernard-Soulier syndrome (BSS) [12,18,19]. In addition, the presence of thrombocytopenia itself cannot rule out IPFDs; thus, further evaluations must be conducted on patients suspected with these conditions [19].

2) Analysis using the platelet function analyzer-100

Platelet function analyzer (PFA)-100 is a simple and rapid screening tool used to assess platelet function by obtaining in vitro bleeding time using a membrane coated with collagen/epinephrine or collagen/ADP [20,21]. The results should be cautiously interpreted because they are affected by several variables, including platelet function, vWF level, platelet count, and hematocrit level [20].

3) Platelet aggregation test using a light transmission aggregometer

The platelet aggregation test with a light transmission aggregometer is the most widely used platelet function test, and it can identify the patterns of aggregation of platelet-rich plasma to agonist panels, such as ADP, epinephrine, ristocetin, and collagen [21]. Several IPFDs, including Glanzmann thrombasthenia (GT), BSS, pseudo-vWD, ADP receptor defect, and gray platelet syndrome, can be diagnosed using the characteristic patterns of aggregation [12,19,22]. However, the test requires at least 15 mL of blood even in young children and thrombocytopenic patients [12].

4) Flow cytometry

Flow cytometry is a method used for measuring the expression of molecules, including glycoprotein, phospholipid, and granules of platelets [23]. This technique is effective in the diagnosis of surface glycoprotein defects, such as GT and BSS [19]. In addition, it is advantageous as only a small amount of blood is required [23].

5) Electron microscopy

Electron microscopy can be used in the diagnosis of platelet structure and granule defects [2].

6) Genetic test

Although genetic tests are available in few laboratories, the genetic tests are essential in the diagnosis of IPFDs and genetic alterations in family members should be identified [2,19]. In particular, next-generation sequencing, including targeted gene panels, is effective in the diagnosis and differential diagnosis of IPFDs [6].

Defects in Platelet Adhesion

1) Bernard-Soulier syndrome

BSS is also known as hemorrhagiparous thrombocytic dystrophy [24]. In 1948, Jean Bernard and Jean-Pierre Soulier first described a male patient with bleeding tendency characterized by prolonged bleeding time, low platelet count, and large platelets (macrothrombocytopenia) [24]. BSS is an extremely rare type of IPFD, with a prevalence of 1/1,000,000 individuals. However, the actual rate may be higher due to the misdiagnosis or underreporting of such condition [25]. This disease can be misdiagnosed as immune thrombocytopenia (idiopathic thrombocytopenic purpura, ITP) based on clinical manifestations alone, and the standard therapy for ITP may not be effective [26]. In Korea, no BSS cases have been reported yet. In patients with BSS, the platelets have defects in the surface expression of GPIb/V/IX complex (receptor of vWF) for platelet adhesion at the vascular injury site [27,28]. The associated genes coding for the subunits of the GPIb/V/IX complex are *GPIBA*, *GPIBB*, *GP5*, and *GP9* [29]. BSS is generally caused by two variants with autosomal recessive inheritance, and this is referred to as bi-allelic BSS. However, this condition rarely has an autosomal dominant inheritance with only one variant, and this is referred to as the milder type of mono-allelic BSS [28]. In BSS, defects in the *GPIBA*, *GPIBB*, and *GP9* genes, but not in the *GP5* gene, were observed. The clas-

sic form of BSS presents as unexplained bruising, gingival bleeding, excess hemorrhage after invasive procedures, or severe menorrhagia [2,25,28]. Some patients with this condition experience gastrointestinal hemorrhage or hematuria. However, hemarthrosis or spontaneous intracerebral hemorrhage is not common [30]. The milder form of mono-allelic BSS may be easily missed or misdiagnosed because platelet mass is significantly conserved in patients with mono-allelic BSS as they only present with mild thrombocytopenia [31]. In laboratory tests, the platelet counts in patients with BSS can vary from extremely low ($<30\times10^9$/L) to near normal ($100-200\times10^9$/L) and can fluctuate [28]. The PFA-100 closure time was remarkably prolonged on both cartridges [2]. In platelet aggregation tests, there is an isolated defect in the ristocetin-induced response; aggregation to ADP, epinephrine, and collagen is normal [2,25]. Defects in ristocetin-induced agglutination are not corrected by the addition of normal plasma, unlike in vWD [2,25]. Flow cytometric analysis using a specific monoclonal antibody, GPIb (CD42), can confirm BSS [32].

2) Pseudo-vWD

The clinical manifestations and laboratory test findings between vWD type 2B and pseudo-vWD, also known as platelet-type vWD, are extremely similar. The vWD type 2B is an autosomal dominant disorder caused by functionally defective vWF due to a mutation in the *VWF* gene located on chromosome 12, and this condition was first described in 1980 [33]. Pseudo-vWD, which was first described in 1982, is caused by mutations in the *GP1BA* gene located on chromosome 17, resulting in excessive binding of abnormal platelet GPIbα receptor to normal vWF [34,35]. Pseudo-vWD is also an autosomal dominant inheritance [34,35]. Both conditions are extremely rare, and the exact incidence rates are not known. This gain of function variant of *GP1BA* makes the altered GPIbα receptor qualitative, thereby increasing affinity to vWF, and high-molecular-weight vWF multimers and large platelet aggregates are removed from the blood circulation [36]. Thus, patients with pseudo-vWD have thrombocytopenia, decreased ristocetin cofactor activity, and altered vWF multimers, similar to vWD type 2B [34,36]. The differentiation between pseudo-vWD and vWD type 2B is important for therapeutic implications. Most patients with vWD type 2B require treatment with a vWF/factor VIII concentrate [37]. By contrast, patients with peudo-vWD need platelet transfusion to treat hemorrhages due to platelet abnormality and thrombocytopenia [37]. The use of VWF/factor VIII concentrates, desmopressin, or cryoprecipitate in pseudo-vWD remains controversial because the incidence of thrombocytopenia has been increasing [37]. Thus, genetic analysis is required for accurate diagnosis and differential diagnosis.

Defects in Platelet Activation

1) ADP receptor $P2Y_{12}$ defect

$P2Y_1$ and $P2Y_{12}$ are the two G protein-coupled ADP receptors expressed in human platelets. The concomitant activation of both P2Y receptors is required for normal responses to ADP and platelet activation [38]. The $P2Y_{12}$ receptor defect, which was first described in 1991, is an extremely rare type of IPFD [39]. To date, only anecdotal cases with $P2Y_{12}$ receptor defects have been described worldwide, and the actual incidence is not known [2]. No cases have been reported in Korea. The $P2Y_{12}$ receptor defect is caused by mutations in the *P2RY12* gene on chromosome 3, resulting in premature truncation or dysfunction of the $P2Y_{12}$ receptor [40]. Clopidogrel, which is a commonly used anti-platelet drug, causes a phenomenon similar to ADP receptor defect by blocking $P2Y_{12}$ activity [41]. The $P2Y_{12}$ receptor defect is an autosomal recessive IPFD characterized by mucocutaneous hemorrhagic symptoms (easy bruising, epistaxis, gastric mucosal bleeding, gum bleeding, menorrhagia, or bleeding after trauma or invasive procedures) [39,40,42]. The patients present with impaired platelet aggregation with ADP and a varying decrease in aggregation to other agonists [39,42]. This disorder is generally inherited in an autosomal recessive manner; however, heterozygous individuals may have a reduced secondary aggregation response to ADP [39,40]. Currently, platelet transfusion is the available treatment [41].

2) TXA2 receptor defect

The TXA2 receptor is also included in the G protein-coupled receptor family and plays an important role in interacting with TXA2, resulting in platelet aggregation [43]. The TXA2 receptor defect was first reported in 1994, and is caused by a mutation of *TBXA2R* gene on chromosome 19 in an autosomal dominant manner [43, 44]. Only a few patients with TXA2 receptor had mild hemorrhagic symptoms, and the actual prevalence is not known [2]. There has been no case of TXA2 defect in Korea. The patients presented with defective platelet aggregation with a TXA2 receptor agonist and arachidonic acid [44].

Defects in the Secretion of Platelets

1) Gray platelet syndrome

Gray platelet syndrome (GPS) is an α-storage pool disease among IPFDs. Recently, the condition had found to be caused by *NBEAL2* gene mutation on chromosome 3, which involves α-granule biogenesis in megakaryocytes [45]. The α-granules are abundant vesicles in platelets and contain platelet factor 4, β-thromboglobulin, fibrinogen, vWF, fibronectin, platelet-derived growth factor, TGF-β, thrombospondin, P-selectin, and albumin/immunoglobulin that has transferred into cells; thus, α-granules play a major role in thrombus formation and wound healing [46]. GPS is usually a mild to moderate IPFD that can be infrequently severe; mild to moderate macrothrombocytopenia, defective wound healing, early onset myelofibrosis, and splenomegaly [47]. Although the exact cause of myelofibrosis is unclear, the megakaryocytes release platelet-derived growth factor and pro-fibrotic substances into the bone marrow, which may be associated with myelofibrosis [48]. GPS is a rare IPFD, and the exact incidence of GPS is unclear [2]. In Korea, two cases of GPS were reported [49,50]. The diagnosis of GPS is based on typical clinical manifestations, such as large gray platelets on Wright-Giemsa-stained peripheral blood smears, and absence of the α-granules of platelets on electron microscopy [47,48]. Bone marrow studies are required to evaluate myelofibrosis and rule out other diseases [47,48].

2) Jacobsen syndrome and Paris-Trousseau syndrome

Jacobsen syndrome (JS) and Paris-Trousseau syndrome (PTS) are rare autosomal dominant IPFDs with giant α-granule abnormalities caused by microdeletion of chromosome 11q [51,52]. Chromosome 11q23.3 includes the *FLI1* gene, which encodes an important transcription factor for megakarypoiesis [53]. Due to the hemizygous deletion of *FLI1*, the hematopoietic progenitor cells cannot undergo the normal differentiation process, resulting in several small immature megakaryocytes lysis [53]. JS was first observed in 1973 [54], and the prevalence of this condition is about 1 in 100,000 births [55]. Only few cases have been reported in Korea [56-58]. JS is a heterogeneous disorder with variable phenotypes, which is confirmed via the deletion of chromosome 11q extending to the telomere [59]. Most deletions are found at 11q23 and some cases are reported as occurring at q21, q22, q24, or q25 [54,57,60]. JS patients have similar phenotypes, including dysmorphic features, skeletal anomalies, cardiac or visceral anomalies, neurocognitive impairment, several hormonal problems, and macrothrombocytopenia with giant α-granules due to small organelle fusion [51, 61]. When the defective area is wider, the symptoms are more severe [52,59]. PTS is a milder form with deletion of 11q23.3, thereby indicating chronic macrothrombocytopenia with giant α-granules and abnormal megakaryocytes [52,62].

3) Chediak-Higashi syndrome and Hermansky-Pudlak syndrome

Chediak-Higashi syndrome (CHS) was first reported about 60 years ago, and it is a syndromic dense storage pool deficiency caused by mutations in the *LYST* gene on chromosome 1q42.3 [63,64]. Platelet dense granules are lysosome-related organelles that include melanosomes, cytotoxic T-lymphocytes, and natural killer cells [2]. Thus, dense granule-defective IPFDs are generally more complex congenital disorders associated with defects in several other lysosome-related organelles [2]. CHS is a rare

autosomal recessive IPFD characterized by platelet dysfunction, oculocutaneous albinism, various neurological problems, and recurrent infection due to immunodeficiency (defect of natural killer cell function) [63]. These syndromic characteristics of CHS develop due to the disruption of lysosomes and related structures in cells [63]. Few Korean patients with CHS have been diagnosed clinically to date [65]. Hermansky-Pudlak syndrome (HPS) is also a rare autosomal recessive IPFD group that is associated with heterogeneous genetic defects in the *HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*, and *BLOC1S6* genes [66,67]. HPS is common in Puerto Rico (affecting 1 in 800 individuals) [68]. However, no cases of HPS have been reported in Korea. Proteins encoded by the aforementioned genes are involved in the transport of intracellular vesicles, protein sorting, and docking/fusion of vesicles [2,69]. CHS and HPS have common clinical manifestations including oculocutaneous hypopigmentation and platelet dysfunction due to dense granule defects; however, patients with CHS present with more profound symptoms at a young age [63]. Individuals with HPS can present with additional clinical manifestations, including neutropenia, immunodeficiency, pulmonary fibrosis, and granulomatous colitis, according to the associated genes [2,66,70]. Due to dense granule defects, CHS and HPS platelets result in defects in aggregation with the absence of second wave aggregation in response to adrenaline [2]. Absence of dense granules is confirmed by electron microscopy. The treatment is hematopoietic stem cell transplantation, which is effective for managing hematologic and immunologic defects [63].

Defects in Platelet Aggregation

1) Glanzmann thrombasthenia

In 1918, Eduard Glanzmann first described GT as a bleeding disorder characterized by hereditary hemorrhagic thrombasthenia without reduction in platelet numbers [71]. There are quantitative or qualitative defects in the platelet GPIIb/IIIa complex in GT patients, which is the binding receptor for fibrinogen and vWF [72,73]. GT generally develops due to the loss-of-function variants of *ITGB2A* or *ITGB3* genes encoding GPIIb or GPIIIa, respectively, [74]. Moreover, cases involving the gain-of-function variants in the *ITGB3*, which result in enhanced fibrinogen binding and hemorrhagic symptoms, are rarely reported [75]. GT is a rare autosomal recessive IFPD with a prevalence of about 1 in 1,000,000 individuals [76]. However, a higher prevalence of up to 1 in 200,000 individuals has been observed in some populations with consanguineous marriages [71]. Several patients with GT in Korea have been reported to date, and some cases have been confirmed via the genetic analysis of *ITGB2A* or *ITGB3* [77]. In a large-scale analysis of the clinical spectrum of patients with GT, most patients presented with typical hemorrhagic symptoms during the first year of life [78]. The median age at the diagnosis of GT was 7 years [78]. Easy bruising and severe persistent epistaxis were the most common symptoms in GT patients [72,78], and menorrhagia was evident during menstruation in female patients with GT [72]. Although hemorrhage of the central nervous system was rare, approximately 1% of the GT patients had intracranial hemorrhage [72,78]. In total, over 80% of GT patients require red cell transfusion [72]. Because of the platelet GPIIb/IIIa defect, the GT platelets exhibit normal count and morphology; however, the closure time in PFA-100 is significantly prolonged on both ADP/collagen and adrenaline/collagen cartridges in GT patients [2]. In the platelet aggregation test using a light transmission aggregometer, only platelet agglutination in ristocetin (binding of GPIb/IX and vWF) is intact, and platelet aggregation is severely diminished in response to ADP, epinephrine, and collagen [2,78]. Flow cytometry using antibodies against GPIIb (CD41) or GPIIIa (CD61) is also effective for the diagnosis of GT [2]. The genetic test for the *ITGB2A* or *ITGB3* genes are diagnostic. The mainstay of treatment is platelet transfusion. However, in 2004, to use recombinant activated factor VII (rFVIIa) in cases of bleeding episodes or prophylaxis prior to invasive procedures in GT patients was approved [71]. The European Medicines Agency recommends rFVIIa for GT patients who cannot be managed with platelet transfusions due to development of platelet antibodies or

refractory bleeding to platelet transfusion [71].

Defects in the Procoagulant Activity of Platelets

1) Scott syndrome

Scott syndrome is an extremely rare autosomal recessive IPFD, and it was first reported as an isolated deficiency of platelet procoagulant activity in 1979 [79,80]. Recently, the condition was found to be caused by a homozygous mutation in the *ANO6* (*TMEM16F*) gene on chromosome 12q12 [81]. The anoctamin-6 (transmembrane protein 16F) encoded by *ANO6* is an important component for the Ca^{2+}-dependent exposure of PS at platelet surface, that is necessary for triggering secondary hemostasis with clotting factors [81]. Only cases of anecdotal patients with Scott syndrome have been reported worldwide [82], and this condition has not been observed in individuals in Korea. In normal conditions, when platelets are activated, the PS of the inner leaflet of the platelet bilayer moves and is expressed on the outer leaflet. PS is a binding site for factors VIIIa/IXa complex (tenase activity) and factors Va/Xa complex (prothrombinase activity), which are essential for the convertsion of prothrombin to thrombin [83]. However, platelets in Scott syndrome do not express PS; thus, platelets have an impaired ability to promote both tenase and prothrombinase activity, thereby resulting in defective thrombin and fibrin formation [83]. The platelet count or structure is normal, and no other abnormalities, including platelet adhesion, secretion, metabolism, or aggregation, have been described in Scott syndrome [80]. At present, the only treatment for bleeding in Scott syndrome is platelet transfusion [82].

Management for IPFDs

Patients with platelet function disorders should be managed in centers that can provide accurate diagnosis and specialized management to treat and prevent bleeding and related complications. The accessible therapeutic modalities for IPFDs are summarized in Table 2.

1) Prevention of bleeding

The prevention of hemorrhagic events is the most important management for IPFDs. Patients should be educated to prevent performing hard core exercises and intake of medications that can affect hemostasis; nonsteroidal anti-inflammatory drugs or salicylate [2]. Regular dental examination and good oral hygiene every 6 months can help prevent dental and periodontal diseases that cause chronic gum bleeding and require invasive procedures [84]. Prior to invasive dental procedures, preventive medication can be used for reducing the bleeding risk [85]. Vaccination against transfusion-transmitted infections, such as hepatitis A and B, should be provided on schedule. In terms of route of administration, subcutaneous injection is the preferred over intramuscular injection [86]. Oral or intravenous iron replacement is required for patients with anemia to maintain a hemoglobin level >10 g/dL [84]. Genetic counseling is required for the family members of patients with inherited disorders who are planning to get pregnant. Moreover, obstetricians should cautiously manage pregnancy in collaboration with neonatologists or pediatric hematologists [2].

2) Treatment modality

(1) Antifibrinolytics

Antifibrinolytics, for example, tranexamic acid and aminocaproic acid, are effective in managing mucosal bleeding and preventing bleeding in minor surgical procedures [30]. Furthermore, they are used in adjunctive therapy for treating major bleeding [30]. Either oral or intravenous preparation of the drug is available.

(2) Desmopressin

Desmopressin, a synthetic analogue of antidiuretic hormone vasopressin, is effective for managing mild/moderate bleeding in patients with IPFDs although its efficacy is limited in GT [87]. This mechanism is believed to be correlated to the enhancement of platelet subendothelial interaction and procoagulant abilities of platelets [4]. After the administration of desmopressin, fluid intake should be restricted for the next 24 hours due to

the risk of fluid retention.

(3) Recombinant activated factor VII (rFVIIa, Novoseven®)

The rFVIIa, alone or in combination with platelets and/or antifibrinolytics, is an effective and safe treatment for all patients with GT [88]. In South Korea, the use of rFVIIa at 90 (80-120) μg/kg/dose at intervals of 2 (1.5-2.5) hours has been approved for the treatment of bleeding and use prior to invasive procedures in patients with GT with platelet antibodies or platelet refractoriness. In addition, there are several cases that report the efficacy of rFVIIa in other platelet function disorders, including BSS, platelet storage pool defect, Wiskott-Aldrich syndrome, and pseuso-vWD [4].

(4) Platelet transfusion

In patients with IPFDs, platelet transfusion is the standard management for severe or uncontrolled bleeding and is helpful in perioperative care. Adverse reactions, including allergic reactions, transfusion-transmitted infections, and development of antibodies to HLA antigens or platelet surface proteins, should be considered. HLA-matched single donor leukocyte-depleted platelets are the most effective products that can reduce the risk of developing alloimmunization [4].

(5) Hematopoietic stem cell transplantation

Some patients with GT and BSS underwent successful transplantations [4,30]. In patients with platelet disorders associated with severe bleeding problems or progressive marrow aplasia or high potential for malignant transformation, hematopoietic stem cell transplantation can be considered as a curative treatment [2]. In case of CHS or HPS, treatment is hematopoietic stem cell transplantation that is effective for hematologic and immunologic recovery [63].

Conclusions

Platelets have important functions in wound healing and normal immune barrier formation. Various genetic diseases are associated with platelet function. Respective IPFDs are extremely rare and bleeding symptoms are similar. Further, the modalities for diagnosis and differential diagnosis of IPFDs are difficult for access. Thus obtaining an accurate diagnosis is challenging. In Korea, the exact prevalence of genetically confirmed IPFDs has not been reported yet, which might be attributed to the extremely low prevalence of IPFDs in Koreans. However, as observed in this review, IPFDs can be overlooked and underestimated. For example, the mild form of mono-allelic BSS may be diagnosed as ITP, and pseudo-vWD as type 2B vWD. Thus, we should be aware that IPFD may be diagnosed incorrectly. The low prevalence of respective IPFDs and the high proportion of patients with unclassified bleeding disorders indicate the need to create networks among us for the accurate diagnosis and comprehensive management of IPFD patients.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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