When do you suspect inherited platelet disorders and what to do for diagnosis?

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Inherited platelet disorders (IPDs) are a heterogeneous group of mucocutaneous bleeding disorders of variable severity caused by genetic defects. Relevant genes encode an array of molecules of diverse function, reflecting megakaryopoiesis, platelet formation, and platelet function. Many IPD genes are widely transcribed across blood cell types and other tissues. Hence, patients with an IPD frequently present with pathologies reaching well outside of the blood system.\textsuperscript{1)}

Accurate diagnosis of IPDs is important for the appropriate clinical management of individual patients but also enables reliable estimate of the real prevalence of these disorders. Glanzmann thrombasthenia (GT) and Bernard–Soulier syndrome (BSS), which often present with severe bleeding symptoms early in life and are easily recognized by the pattern of platelet aggregation defect.\textsuperscript{2,3)} And also, some IPDs present with syndromic features such as hearing loss, renal impairment or cataracts (MYH9-related disorders), heart, face or bone dysmorphisms (thrombocytopenia absent radii, amegakaryocytic thrombocytopenia with radio-ulnar synostosis), ocular involvement, mental retardation, eczema, infection, and small platelets (Wiskott–Aldrich syndrome), reduced or delayed skin pigmentation (Hermansky–Pudlak syndrome) can help in recognition and diagnosis\textsuperscript{4)}, but the diagnosis remains quite challenging for the majority of IPDs.

Current guidelines favor a tiered approach to IPD diagnosis.\textsuperscript{3, 5)} Initial evaluation must include careful history taking with family and consanguinity. IPDs should be suspected when patients have the following characteristics: 1) bleeding not proportional to platelet count; 2) family history of thrombocytopenia, myelodysplasia, or leukemia; 3) family history of undefined mucocutaneous bleeding disorder regardless of the platelet count; and 4) whenever von Willebrand disease (vWD) is being considered as the cause of bleeding.\textsuperscript{4)} If clear abnormalities emerge from the clinical assessment and/or the bleeding score,\textsuperscript{6)} the proband should then undergo preliminary laboratory investigations, including full blood count,
prothrombin time, activated partial thromboplastin time and von Willebrand factor (VWF) screening tests VWF antigen, ristocetin cofactor activity and factor VIII coagulant activity). If these are normal, a diagnostic work-up for IPD should be pursued. Given that several IPD are associated with thrombocytopenia, a mildly reduced platelet count should not exclude further testing for IPD.

Diagnostic algorithm flowchart suggested by Scientific and Standardization Committee (SSC) International Society on Thrombosis and Haemastasis (ISTH) is shown in figure. GT is the most frequently encountered IPD with lifelong sustained mucocutaneous bleeding. The hemorrhagic diathesis is notable for its variability and the lack of correlation between the biochemical platelet abnormalities and clinical severity. Platelets fail to aggregate in response to stimuli because they reduced or absent functional αIIb3 integrin (formerly known as GPIIb-IIIa). BSS is a rare autosomal recessive bleeding disorder characterized by defects of the GPIb- IX- V complex, a platelet receptor for VWF and moderate thrombocytopenia and giant platelet in peripheral blood smear. Shim described that genetic abnormalities of IPDs identified in recent studies by genome wide association study and next-generation sequencing and genetically confirmed Korean IPD patients. Korean Pediatric Hematology-oncology Group (K-PHOG) study which was recently done using targeted exom sequencing in Korean multicenter was also presented. Considering elaborated diagnostic steps in IPDs and the differences in available diagnostic techniques by institutions the application of high-throughput sequencing will simplify the diagnostic process and reduce the delay of diagnosis.

Establishing a conclusive molecular diagnosis is the bedrock of good hematologic practice because it informs optimal treatment and can provide clarity about disease progression. For IPDs, this is particularly important for the severe cases and those associated with early-onset clinical pathologies such as myelofibrosis, lung fibrosis, renal insufficiency, and
malignancy. Thrombocytopenias caused by variants in RUNX1, ETV6, and ANKRD26 are associated with increased risk of myeloid malignancy, whereas for Wiskott-Aldrich syndrome and amegakaryocytic thrombocytopenia caused by MPL variants, treatment by allogeneic hematopoietic stem cell transplant or gene therapy may require consideration.\(^9\)\(^{10}\) Moreover, genetic counseling can be provided if the diagnosis is confirmed at the DNA level. We just begun nationwide survey of IPDs with next generation sequencing as a K-PHOG study. Due to clinical diversity as well as genetic heterogeneity pediatrician must pay more attention to their diagnosis. In the genomic era it is hoped that genetic panel for IPDs will be set up soon and implemented with medical insurance.
Reference

7. Shim Genetic classification and confirmation of inherited platelet disorders and current status in Korea J pediatrics. 2019
Figure legend

Fig 1. Diagnostic Algorithm Flowchart of Inherited Platelet Disorders: adapted from Gresele P, Subcommittee on Platelet Physiology of the International Society on Thrombosis and Hemostasis. ³) ARC, arthrogryposis renal dysfunction and cholestasis syndrome; BSS, Bernard-Soulier syndrome; GATA1, macrothrombocytopenia with dyserythropoiesis/anemia/beta-thalassemia; GPS, grey platelet syndrome; GT, Glanzmann thrombasthenia; MYH9-RD, MYH9-related disorders; PTS, Paris Trousseau syndrome; PT-VWD, platelet type von Willebrand disease; VCF, giant platelets and velo-cardio-facial syndrome; WAS, Wiskott-Aldrich syndrome; XLT, X-linked thrombocytopenia.
Figure

Diagnostic Algorithm

Clinical evaluation:
- Personal and family history and bleeding score
- Bleeding manifestations typical of HPS
- Physical examination: bleeding manifestations typical of HPS
- Syndromic forms: hearing loss, immunodeficiency, renal function, cardiac function, mental retardation, facial dysmorphism, eyes, bone, skin

Clinical decision:
- Normal
- Abnormal

First-step laboratory tests:
- Light transmission aggregometry (LTA)
- Granule release (lumihemostasis: ELISA)
- Flow cytometry

Second-step laboratory tests:
- LTA (extended)
- Flow cytometry (extended)
- Granule content
- Serum thrombinase activity
- Transmission electron microscopy
- Coagulation

Third-step laboratory tests:
- Biochemical studies:
  - Surface glycoprotein
  - Protein phosphorylation
  - Second messengers
- Receptor binding studies
- Next generation sequencing

Diagnosis:
- Thrombocytopathy
- Bleeding clotting defect
- Abnormal

Flowchart:
- No further studies
- Normal
- Abnormal

Small: WAS, XLT
Large: ARC, BSS, GATA1, D5, GT-variant, MYH6-RD, PFT, PT-vWD, VCF, Filmopathy
Medich platelet syndrome
White platelet syndrome