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THROMBOCYTOPATHIES: ETIOLOGY, PATHOGENESIS, CLINICAL PRESENTATION, AND MODERN THERAPEUTIC APPROACHES

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Introduction

Thrombocytopathy is a disorder of the hemostatic system, based on qualitative defects and dysfunction of platelets. Platelets, or blood thrombocytes, are anuclear blood elements whose main function is to ensure proper hemostasis in the circulatory system. Platelet abnormalities also include quantitative deficiencies. A decrease in platelet count below the normal range (normal platelet count in circulating blood is 150,000–400,000/μL) is called thrombocytopenia [7]. Clinical signs of thrombocytopenia, expressed as increased bleeding tendency, are usually observed when platelet counts fall below 50,000/μL. Thrombocytopenias (as well as other platelet hemostasis disorders) are characterized by a microcirculatory type of hemorrhagic syndrome, including bruises, ecchymoses, petechiae, nose and gum bleeding, heavy and prolonged menorrhagia, and prolonged bleeding time in Ivy or Duke tests. Development of hemorrhagic syndrome at platelet counts above 50,000/μL is most often associated with functional platelet defects. The critical threshold for dangerous, spontaneous bleeding is considered 10,000–20,000/μL [4]. By mechanism, thrombocytopenias can be divided into: productive thrombocytopenias, associated with impaired platelet production in the bone marrow; thrombocytopenias caused by increased destruction or consumption of platelets in the circulation or organs of the macrophage system; dilutional thrombocytopenias, observed after major blood loss; and redistribution thrombocytopenias, caused by increased sequestration of platelets in the spleen in splenomegaly [7]. Among thrombocytopenias caused by increased destruction/consumption of platelets, two major groups are usually distinguished: immune forms, developing due to the production of auto- or alloantibodies against platelets, and non-immune forms, most often mediated by increased platelet consumption due to intravascular thrombosis. Hereditary thrombocytopenias can be distinguished as a separate group; they are much rarer than

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acquired forms and are often associated with qualitative defects of platelets, i.e., thrombocytopathies. It is assumed that most hereditary thrombocytopenias are caused by impaired platelet production; however, there are forms with increased consumption/destruction and mixed variants (see Table 1) [4,7,17,19].

1. Thrombocytopenias caused by reduced platelet production (productive)
2. Thrombocytopenias caused by increased destruction or consumption of platelets 2.1. Immune 2.2. Non-immune
3. Thrombocytopenias after massive hemorrhages (dilutional)
4. Thrombocytopenias in splenomegaly (sequestration)
5.Hereditary thrombocytopenias – mostly productive, but there are forms with increased destruction/consumption and mixed variants

Table 1. Classification of Thrombocytopenias

Thrombocytopenias Caused by Increased Destruction/Consumption of Platelets

Thrombocytopenias caused by increased destruction and/or consumption of platelets are divided into two major groups: immune and non-immune. Immune thrombocytopenias develop as a result of the production of auto- or alloantibodies against platelets, leading to accelerated destruction of antibody-sensitized platelets in the macrophage system of the spleen and/or liver.(8)

Disease	Characteristics of Antiplatelet Antibodies
1. Idiopathic (autoimmune) thrombocytopenic purpura	Autoantibodies against unmodified platelet antigens of the patient (usually GPIIb-IIIa and GPIb)
2. Transimmune neonatal thrombocytopenia	Maternal autoantibodies from autoimmune thrombocytopenia transferred to the fetus
3. Hapten (heteroimmune) thrombocytopenia 3.1. Drug-induced thrombocytopenias 3.2. Virus-associated thrombocytopenias	Hapten autoantibodies against altered or foreign antigens on platelet surfaces Antibodies against the drug-platelet antigen complex (heparin, quinine/quinidine, etc.) Antibodies against viral antigens fixed on platelets or against altered platelet antigens; immune complexes fixed on platelets
4. Alloimmune thrombocytopenias 4.1. Neonatal alloimmune thrombocytopenic purpura	Alloantibodies against alloantigens of fetal or transfused platelets Maternal alloantibodies transferred to the fetus, directed against fetal and paternal platelet alloantigens absent on maternal platelets (usually HPA-1a)

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4.2. Platelet transfusion refractoriness	Alloantibodies against donor platelet antigens (usually HLA antigens)
4.3. Post-transfusion thrombocytopenic purpura	Antibodies against HPA-1a alloantigen, cross-reacting with recipient platelets negative for HPA-1a

Non-immune forms are most often associated with increased platelet consumption in the vascular bed due to intravascular thrombosis and platelet aggregation. The main features of both immune and non-immune consumption thrombocytopenias, distinguishing them from productive thrombocytopenias, are normal or sometimes increased megakaryocyte content in the bone marrow.

Classifications

A. Hereditary forms of thrombocytopathies – Main pathogenetic groups:

1. Associated with membrane abnormalities (Bernard–Soulier syndrome, Scott syndrome, pseudo–von Willebrand disease, Glanzmann thrombasthenia, etc.)

2. Associated with intracellular abnormalities:

• Storage pool diseases – deficiency of dense and α-granules (Hermansky–Pudlak disease, TAR syndrome, gray platelet syndrome (GPS), Chediak–Higashi, Griscelli syndromes, dense granule deficiency, etc.)

• Defective granule release and component secretion (cyclooxygenase defect, thromboxane synthase defect, lipoxygenase defect, etc.)

3. Mixed platelet disorders (May–Hegglin syndrome, Wiskott–Aldrich syndrome (WAS), etc.)

4. Platelet dysfunction of plasma origin and in vascular dysplasias (von Willebrand disease, Ehlers–Danlos disease, etc.)

Functional-Morphological Forms

1. Platelet adhesion defects:

• Bernard–Soulier syndrome (deficiency or defect of GPIb-IX-V complex)

• von Willebrand disease (deficiency or defect of vWF)

2. Platelet aggregation defects:

• Glanzmann thrombasthenia (deficiency or defect of GPIIb–IIIa)

• Hereditary afibrinogenemia (deficiency or defect of αIIbβ3, fibrinogen)

3. Granule release defects and storage pool deficiencies:

• α-granules (GPS, APS syndrome, Quebec and Paris–Trousseau syndromes)

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• δ-granules (dense granule deficiency, Hermansky–Pudlak disease, Chediak–Higashi syndrome, TAR syndrome)

• α- and δ-granules (deficiency of dense and α-granules)

4. Defective signal pathway formation and deficiencies:

• Agonist receptor defects: thromboxane A, collagen, ADP, epinephrine

• G-protein activation defects: Gα deficiency, Gβ anomaly, Gγ1 deficiency

• Phosphatidylinositol metabolism defect – phospholipase C-2 deficiency

• Calcium mobilization defect

• Plectin phosphorylation defect – protein kinase C deficiency

• Arachidonic acid and thromboxane metabolism defects:

• Impaired arachidonic acid release

• Cyclooxygenase deficiency

• Thromboxane synthase deficiency

• Cytoskeleton element anomalies – WAS

• Platelet interaction defect – coagulation factor (membrane phospholipid defect) – Scott syndrome

• Combined congenital defects – May–Hegglin anomaly, Down syndrome, mesenchymal dysplasia syndrome, TAR syndrome

Thrombocytopathies Associated with Thrombocytopenia

1. Small platelets – WAS, X-linked thrombocytopenia

2. Normal-sized platelets – congenital amegakaryocytic thrombocytopenia, TAR syndrome, amegakaryocytic thrombocytopenia with congenital radio-ulnar synostosis, autosomal-dominant thrombocytopenia, familial thrombocytopathy with predisposition to acute myeloid leukemia

3. Large platelets – Bernard–Soulier syndromes, DiGeorge syndrome, platelet-type von Willebrand disease, GPS, APS syndrome, MYH9-related syndromes, X-linked thrombocytopenia with thalassemia, Paris–Trousseau syndrome, Mediterranean macrocytotic thrombocytopenia, dyserythropoietic anemia with thrombocytopenia

Acquired (Symptomatic) Thrombocytopathies

1. In hemoblastoses:

• Disaggregational hyporegenerative forms

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• Consumption forms (with development of disseminated intravascular coagulation syndrome)

• Mixed type

2. In myeloproliferative disorders and essential thrombocythemia

3. In vitamin B_{12} deficiency anemia

4. In uremia (adhesive-aggregation platelet dysfunction, less often – clot retraction disorder)

5. In multiple myeloma, Waldenström's disease, and gammopathies (platelet blockade by macro- or paraproteins)

6. In cirrhosis, liver tumors, and parasitic liver diseases (adhesive-aggregation platelet dysfunction due to metabolic disorders, platelet sequestration in the portal system, platelet consumption during disseminated intravascular coagulation)

7. In scurvy (impaired interaction with endothelium and ADP-induced aggregation)

8. In hormonal disorders – hypoestrogenism, hypothyroidism

9. Drug- and toxin-induced forms (aspirin and other NSAIDs, antibiotics – carbenicillin, penicillin; tranquilizers, nitrofurans, cytostatics, etc.)

10. In radiation sickness

11. After massive hemotransfusions and Reopoliglyukin infusions

12. In large thromboses and giant angiomas (consumption thrombocytopathy)

Clinical manifestations depend on the qualitative and quantitative defects of platelets – the severity of the hemorrhagic syndrome can vary greatly and does not directly correlate with the degree of defect. Mild bleeding may present as easy bruising from minor trauma or pressure (e.g., rubber band), occasional mild epistaxis, prolonged family menstrual bleeding in women, etc. In massive hemorrhagic syndromes, life-threatening blood loss may occur.

Gray Platelet Syndrome (GPS) First described by Raccuglia in 1971 (OMIM #139090), GPS is characterized by thrombocytopenia, mild bleeding, and the presence of agranular platelets in peripheral blood. Biochemical and electron microscopy studies show all organelles, except α-granules, are normal. GPS is thought to result from megakaryocytes' inability to form specific vesicles and fill them with α-granular components. Megakaryocyte count in the bone marrow is usually normal. Microscopically, large, pale-staining platelets are observed. Platelet dysfunction manifests as reduced aggregation with collagen and/or thrombin. Patients often have varying degrees of macrothrombocytopenia, mucosal bleeding, and may develop myelofibrosis and splenomegaly over time. Bleeding is usually not life-threatening, but massive hemorrhage can occur during surgery or severe trauma. Platelet aggregation tests are highly variable, and inheritance patterns are diverse. X-linked GATA-1 mutations and autosomal-dominant GFI1B

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nonsense mutations have been identified. NBEAL2 gene mutations are most frequently associated with GPS.

Bernard–Soulier Syndrome (BSS) A hereditary thrombocytopathy caused by a genetic defect or decreased functional activity of the platelet GPIb-IX-V complex, the receptor for von Willebrand factor (vWF) and thrombin binding. Functionally, platelet adhesion to the subendothelial matrix is impaired. Key diagnostic criteria include macrothrombocytopenia and absent vWF-dependent aggregation with ristocetin, with normal vWF quantity and activity. Thrombin-induced aggregation may also be reduced. GPIb-IX-V complex deficiency can be confirmed by flow cytometry and genetic analysis of GPIBA, GPIBB, and GP9. BSS manifests with severe microvascular and mixed-type bleeding from birth. Inheritance is autosomal recessive.

Wiskott–Aldrich Syndrome (WAS) Microthrombocytopenia and impaired platelet aggregation indicate a qualitative or quantitative defect of the WASP protein. Classic WAS includes bleeding, recurrent bacterial, viral, or fungal infections, and eczema. A milder form is X-linked thrombocytopenia without significant immunodeficiency or eczema. Bone marrow puncture and myelogram analysis are required for diagnosis. Megakaryocyte count is normal. Immunological defects result from lymphocyte homeostasis disruption, with reduced T- and B-cell proportions. Platelet functional studies show increased phosphatidylserine exposure and microparticle formation. Thrombocytopenia likely arises from enhanced clearance of phosphatidylserine-expressing platelets by splenic macrophages. Diagnosis is confirmed via WASP protein expression and gene mutation analysis.

MYH9 Syndrome Group. The presence of large basophilic inclusions (Döhle bodies) in granulocytes and monocytes in a blood smear stained by Romanowsky–Giemsa is a marker of the MYH9 syndrome group. This group includes May–Hegglin anomaly, Fechtner, Epstein, and Sebastian syndromes. May–Hegglin anomaly was first described by German physician R. May (1863–1937) and later by Swiss physician R.M. Hegglin (1907–1969). The pathology is based on a mutation in the MYH9 gene, encoding the heavy chain of non-muscle myosin IIA (NMMHC–IIA). It is asymptomatic in most cases, but some patients exhibit increased bleeding. Inheritance is autosomal dominant. It is accompanied by thrombocytopenia, kidney involvement (nephritis), sensorineural hearing loss, and cataracts, but the presence of these pathologies is not obligatory, especially in children. Patients with May–Hegglin anomaly often show impaired platelet aggregation with collagen while aggregation with other agonists, especially ristocetin, remains normal. Detection of NMMHC–IIA aggregates in neutrophils by immunofluorescence confirms the diagnosis. Genetic analysis is recommended to determine the specific mutation [54].

Storage Pool Deficiency Syndromes. These include Hermansky–Pudlak and Chediak–Higashi syndromes, inherited in an autosomal recessive manner. These syndromes are characterized by albinism, frequent infections, pulmonary fibrosis, granulomatous colitis, prolonged bleeding time, and mild coagulation defects. The disease is caused by a deficiency of dense granule contents and/or the granules themselves. Platelet function studies reveal impaired aggregation in response to ADP, adrenaline, ristocetin, and collagen. In Chediak–Higashi syndrome, dense granules

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observed by electron microscopy are larger than normal and resemble melanosome, leukocyte, and fibroblast granules [55].

Scott Syndrome. A platelet disorder inherited in an autosomal recessive manner, caused by a defect in phosphatidylserine exposure upon platelet activation, resulting in impaired interaction with plasma coagulation factors. In this case, incomplete Va–Xa and VIII–IXa complexes form on the membrane. Defects in these complexes lead to incomplete activation of factor X and prothrombin, as well as impaired platelet factor 3 activity [56].

Diagnostic Algorithm

Differential diagnosis of platelet disorders is extremely challenging. Platelet disorders often present as nosebleeds, menorrhagia, and other mucosal bleeding. The first diagnostic step is a detailed medical history, including a family tree documenting minimal bleeding tendencies in relatives. Important questions include: the first bleeding episode, bleeding during tooth eruption, exfoliation, or extraction; history of tonsillectomy and any prolonged bleeding complications; gum bleeding during brushing; presence, timing, frequency, and duration of nosebleeds; menstrual volume in pubertal girls; prior surgeries and hemorrhagic complications. If clinical signs of platelet disorders are present, the second diagnostic step is a complete blood count. In many platelet disorders, counts may remain within normal limits. Changes in platelet size may not be detected by automatic analyzers, so manual counting in Romanowsky–Giemsa stained smears is important. Morphological analysis provides additional information on platelet number and size, presence of aggregates, and other features: absence of α-granules in large gray platelets indicates gray platelet syndrome; inclusions in leukocytes suggest MYH9 gene mutation-related diseases; abnormal erythrocyte morphology may indicate GATA-1 mutation-related disorders. Detection of platelet aggregates in smears requires differential diagnosis with blood collection defects. Pseudothrombocytopenia may result from platelet clumping in EDTA tubes, which can be confirmed by repeating blood collection in a citrate tube. Although relatively few comparative studies of platelet aggregation in adults and children have been conducted, existing data allow us to conclude that differences in aggregation. Screening tests indicating a platelet hemostasis disorder include prolonged capillary bleeding time (Duke or Ivy tests) and automated platelet function analysis using the PFA-100. However, these tests lack sufficient sensitivity and specificity for diagnosis.

Platelet aggregation disorders in certain plateletopathies

Diagnosis	Aggregation Defect	Additional Features / Tests
Bernard–Soulier Syndrome	No response to ristocetin	Macrothrombocytopenia; rule out von Willebrand disease; GPIb quantification by flow cytometry
Glanzmann Thrombasthenia	No response to all agonists except ristocetin	Flow cytometry for integrin IIb/IIIa quantity and function
Secretion defect, β-granule	Reduced response to multiple	Electron microscopy for

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deficiency (Hermansky–Pudlak and Chediak–Higashi syndromes)	agonists: ADP, collagen, epinephrine	dense granules, flow cytometry
ADP receptor defect	Reduced or absent response to ADP	History of ADP inhibitor use; flow cytometry for P2Y12/P2Y1 receptors
Gray Platelet Syndrome (GPS)	Reduced response to thrombin and/or collagen	Presence of pale-staining platelets on smear; electron microscopy; flow cytometry

Conclusion:

This disorder occurs equally in males and females. Platelet disorders can be hereditary or acquired. Since hereditary forms are lifelong and incurable, patients must follow certain precautions, such as avoiding specific foods or medications, high-risk sports, and certain medical procedures.

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