EDUCATIONAL COMMENTARY – PLATELET DISORDERS

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to:

- describe how platelets function.
- use laboratory testing methods to identify platelet abnormalities.
- explain immune, congenital, and acquired platelet disorders.

Introduction

Platelets were recognized as a class of blood cells in 1882. These cells are produced in the bone marrow by megakaryocytes and remain in the spleen for 36 hours before being released into circulation. The blood of an average adult carries more than a trillion platelets; the reference range for all ages is 150-350 × 10^3/µL (150-350 × 10^9/L).[1] The life span of a platelet is 7 to 10 days.

Platelet disorders are defects of primary hemostasis. Patients who bleed because of platelet disorders exhibit petechiae and purpura; those who bleed because of secondary hemostasis exhibit deep bleeding in muscles and joints.[2] Abnormalities of platelets can be congenital or acquired through disorders of production or function. Abnormalities can be acquired by decreased production of platelets secondary to bone marrow failure. Thrombocytopenia, or a decreased number of platelets, may be caused by viral infections or drug toxicity. Increased platelet consumption may be caused by immune or nonimmune mechanisms.

Laboratory Tests for Evaluating Platelet Function

A thorough clinical examination and family bleeding history is important in the assessment of platelet disorders. The history should include the type, severity, and pattern of the bleeding problem. The mean platelet volume (reference range, 7-11 µm^3 [7 -11 fL]) indicates platelet size and can indicate platelet turnover as well, because younger platelets tend to be larger. Unlike platelet disorders with rapid turnover, congenital macrothrombocytopenias usually have uniformly large platelets.[3]

Examining the blood smear and a bone marrow smear may help in evaluating thrombocytopenia or thrombocytosis. It is important to rule out platelet clumping in a patient's blood smear as the cause of thrombocytopenia. Examining the bone marrow is useful in determining the presence or absence of

megakaryocytes; absence indicates dysfunctional marrow, and increased numbers suggest peripheral destruction.[3]

Coagulation testing should include the prothrombin time and the activated partial thromboplastin time to rule out any other bleeding disorders. Most platelet disorders do not cause abnormal results in these screening tests.

Platelet aggregation studies measure the ability of agonists to cause in vitro platelet activation and binding. Platelet aggregation is measured by the increase in light transmission after adding an aggregation agonist such as adenosine diphosphate (ADP), collagen, arachidonic acid, or epinephrine. Patterns of response to the agonists aid in the diagnosis of platelet disorders.

Immune Platelet Disorders

Immune thrombocytopenic purpura (ITP) is an autoimmune bleeding disorder in which the immune system produces antibodies that destroy platelets. This can occur because of underlying disease or it can be idiopathic.[4] The autoantibody produced is usually immunoglobulin G (IgG), directed against antigens on the platelet membrane. Antibody-coated platelets are removed by the reticuloendothelial system, reducing the life span of the platelet to a few hours. The platelet count may vary from less than 5 × 10^3/μL (5 × 10^9/L) to near normal.[5]

ITP can be either chronic or acute, and occurs in persons of all ages. In adults, it is more often a chronic disease and can occur after a viral infection, use of certain drugs, pregnancy, or as a result of an immune disorder.[6] There is no single test to diagnose ITP; it is established by the exclusion of other causes of thrombocytopenia. Drugs that may cause thrombocytopenia should be discontinued. The peripheral blood film should be examined to rule out thrombocytopenia resulting from clumping. Giant platelets may be present on the smear, reflecting the thrombopoietin-induced stimulation of bone marrow. Bone marrow examination, which is not always necessary, shows increased megakaryocytes.[4]

Neonatal alloimmune thrombocytopenia is the result of antigenic stimulus from platelet-specific antigens. In 80% of cases, the antigen is human platelet antigen 1a; a mother negative for this antigen forms antibodies when sensitized by a fetus positive for the antigen. Firstborn infants are frequently affected, and successive pregnancies are equally or more likely to be affected. Neonatal alloimmune thrombocytopenia is the most common cause of severe neonatal thrombocytopenia. It is suspected when severe bleeding or intracranial hemorrhage occurs after an uncomplicated pregnancy.[6]

Heparin-induced thrombocytopenia occurs during heparin treatment in up to 5% of patients. It occurs 5 days after exposure to heparin and has an earlier onset on re-exposure to the drug.[2] In this disorder, IgG

antibodies form against platelet factor 4 complex, leading to thrombosis and thrombocytopenia caused by the activation and in vivo aggregation of platelets. The diagnosis is clinical, despite the availability of several laboratory tests. These tests include the serotonin release assay, the heparin-induced platelet aggregation test, and the platelet-factor 4 enzyme-linked immunosorbent assay. Patients are treated with direct thrombin inhibitors. Low-molecular-weight heparin has a high cross-reactivity rate.

Thrombotic thrombocytopenic purpura (TTP) is a rare but serious disorder that was initially described as a combination of thrombocytopenia, purpura, fever, neurologic symptoms, schistocytes, and renal failure. It has been indicated that this disorder results from unusually large multimers of von Willebrand protein. In a subject without TTP, the ultra large precursors are processed by ADAMTS13, a plasma enzyme synthesized in the liver. The sporadic forms of TTP are caused by an antibody or toxin inhibiting the activity of ADAMTS13; the chronic, recurrent form of TTP may be caused by a congenital deficiency of the enzyme.[7]

Congenital Platelet Disorders

When a blood vessel is injured, platelets are activated and adhere to the exposed subendothelium. Platelets contain granules, and activated platelets secrete α granules (e.g., platelet factor 4, β-thromboglobulin, thrombospondin, platelet-derived growth factor, fibrinogen, von Willebrand factor) and dense granules (e.g., ADP, serotonin). Platelets have surface receptors that respond to several subendothelial components and enable the platelets to rapidly adhere to the damaged area of the blood vessel. When these receptors are decreased, bleeding may occur.[8]

Von Willebrand disease (vWD) is an autosomal dominant hereditary bleeding disorder that affects up to 1% of the population. It is a qualitative platelet disorder that affects platelet aggregation and adhesion, resulting in mild to severe bleeding. Patients with vWD have an altered receptor form of von Willebrand factor, resulting in an amino acid substitution.[9] Because there are 3 types (I, II, and III) and many subtypes of vWD, diagnosing the disorder may be difficult and require several levels of testing. It is important to know the type and subtype of the disease to determine patient treatment. This is done by multimer analysis. Bleeding in vWD manifests as easy spontaneous bruising, menorrhagia, and mucosal membrane bleeding.[10]

Bernard-Soulier syndrome is an autosomal recessive disorder with decreased or absent expression of the glycoprotein (GP) Ib/IX/V receptors. This results in impaired platelet adhesion. Patients have giant platelets, thrombocytopenia, and increased bleeding tendencies.[11] Decreased or absent GPIIb/IIIa receptor results in an autosomal recessive disorder known as Glanzmann thrombasthenia, characterized by absence or severe impairment of platelet aggregation when tested in the laboratory for all platelet

agonists. Severe forms result in a lack of fibrinogen in the platelet granules. Patients experience various mucosal membrane bleeding symptoms.[11]

Acquired Platelet Disorders

Acquired platelet disorders are commonly caused by underlying hematologic disease, surgical procedures, medical conditions, and medications.

There are more than 100 drugs, foods, and supplements that have been reported to inhibit platelet function. The most common disorders of platelets are acquired secretory disorders, usually secondary to drug effects (especially aspirin or nonsteroidal anti-inflammatory drugs, which block cyclooxygenase [COX-1 inhibitors] and prevent thromboxane formation).[12] Clopidogrel and prasugrel are drugs that inhibit ADP-induced platelet aggregation. Their inhibitory effect lasts about 7 days. The platelet GPIIb/IIIa inhibitors abciximab, tirofiban, and eptifibatide are used in percutaneous cardiac interventions. Other drugs that may affect platelet function are some antibiotics, cardiac medication, anticoagulants, antidepressants, and antihistamines.[12] Platelet function returns to normal when these medications are stopped.

Certain medical conditions can cause abnormal platelet function. These include:

- renal failure;
- cardiac valvular disease and use of cardiopulmonary bypass; and
- hematologic disorders including myeloproliferative disorders, myelodysplasia, and paraproteinemias.[12]

Conclusion

Several disorders can affect platelet function. They can be immunologic, congenital, or acquired. It is important to understand how to identify the underlying cause of platelet dysfunction and to treat the patient accordingly.

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