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PATHOPHYSIOLOGY

CONCISE LECTURES, TESTS,
CLINICO-PATHOPHYSIOLOGICAL SITUATIONS
AND CLINICO-LABORATORY CASES

STUDENT MANUAL

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19. TYPICAL FORMS OF PATHOLOGY OF HEMOSTASIS

Hemostatic disorders are classified into the following clinical syndromes: thrombotic, hemorrhagic and thrombo-hemorrhagic syndromes.

THROMBOTIC SYNDROME

Immobilization after surgery, chronic congestive heart failure, atherosclerotic vascular disease, a malignancy and pregnancy predispose to thrombosis. Endothelial injury is a trigger of thrombosis. Other factors such as abnormal blood flow, increased platelet number, hypercoagulability, dysfibrinogenemias and fibrinolytic defect play a certain role in thrombosis. Slowing of blood flow, especially in veins, or thrombocytosis are considered as important factors of thrombosis. Mechanisms of thrombosis are described in fig. 22.

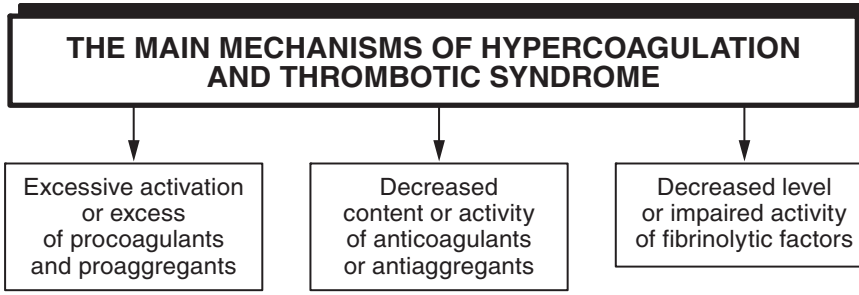

Fig. 22

Atherosclerotic lesion, hemodynamic stress associated with hypertension, bacterial endotoxins, virus and immune complexes are the most common causes of endothelial injury. Some drugs may damage blood vessels by causing allergic reactions.

Turbulence

Turbulence contributes to arterial and cardiac thrombosis by reducing the local release of prostacyclin (prostaglandin 12). In venous vessels, stasis or slowdown of blood stream prevent the dilution of the activated coagulation factors by fresh blood.

Hypercoagulability

Hypercoagulability is a risk factor that predisposes to thrombosis. A point mutation in the plasma clotting factor V makes the molecule of factor V resistant to degradation by activated protein C. This mutation may account for 25% of inherited prethrombotic states, and approximately 3% of the population worldwide is heterozygous for this mutation. In heterozygous state patients with protein C and protein S defects show disease if they have less than 50% of normal molecules. In contrast, slight reduction of plasma antithrombin III content increases the risk of thrombosis.

Dysfibrinogenemias and fibrinolytic defect

Dysfibrinogenemias and fibrinolytic defect lead to venous thrombosis. Abnormal plasminogen resists activation by streptokinase and urokinase. Impaired fibrinolysis may be due to increased plasma levels of plasminogen activator inhibitor-1 or decreased release of tissue plasminogen activator.

Paroxysmal nocturnal hemoglobinuria, essential thrombocytosis, and polycythemia vera predispose to venous and arterial thrombosis. Homocystinuria or administration of contraceptives lower antithrombin III levels that predisposes to thrombosis. Smoking and obesity promote hypercoagulability by unknown mechanisms. The heparin-induced thrombocytopenia syndrome occurs when administration of unfractionated heparin results in the generation of antibodies directed against platelet factor IV. Antiphospholipid antibody syndrome associated with the presence of antibodies directed against anionic phospholipids. These antibodies induce direct platelet activation, inhibition of prostacyclin production by endothelial cell or interference with protein C synthesis.

HEMORRHAGIC SYNDROME

Hemorrhagic syndrome may result from abnormalities in platelets, vessel wall and plasma proteins related to coagulation, anticoagulation and fibrinolytic systems.

Thrombocytopenia

Thrombocytopenia is caused by the following: decreased bone marrow production, increased splenic sequestration or accelerated destruction of platelets. Spontaneous bleeding does not became evident until the cell count falls below 20.000/mm^3. The most common causes of impaired platelet production are marrow aplasia, fibrosis, cytotoxic drugs, or infiltration of malignant cells.

Splenomegaly

The most common causes of splenomegaly are portal hypertension secondary to liver disease and splenic infiltration with tumor cells in leukemia.

Accelerated destruction

Accelerated destruction: thrombocytopenia is common in patients with vasculitis, the hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. Platelets coated with antibody, immune complexes, or complement are rapidly cleared by the mononuclear phagocyte system. The most common causes of immunologic thrombocytopenia are viral or bacterial infections, drugs and chronic autoimmune disorder referred to as idiopathic thrombocytopenic purpura. 10 to 15% of patients receiving heparin develop thrombocytopenia and, occasionally, may have severe bleeding or intravascular platelet aggregation and paradoxical thrombosis, sometimes called the «white clot syndrome». Most cases of heparin thrombocytopenia are due to drug–antibody binding to the platelet factor IV on the platelet surface.

Idiopathic thrombocytopenic purpura (ITP). In this disorder accelerated platelet destruction in the spleen occurs after sensitization of the platelets by autoantibodies which also may impair platelet production and function. ITP is associated with drugs (quinine, gold compounds, heparin), systemic lupus erythematosus, Hodgkin's disease, chronic lymphocytic leukemia and a variety of infections, including AIDS.

Platelet membrane defects

Platelet membrane defects: there are two rare platelets defects characterized by a loss of or a defect in the platelet glycoprotein receptors. Patients with the Bernard–Soulier syndrome have reduced platelet adhesion induced

by abnormal Ib–IX receptor. Glanzmann's disease or thrombasthenia is characterized by a defect in the glycoprotein IIb–IIIa complex.

Von Willebrand's disease

Von Willebrand's disease (VWD): VWD is also characterized by abnormal platelets adhesion, but in this case, due to abnormality of the von Willebrand's factor (VWF), a plasma protein is involved in the attaching of platelets to bare collagen at the site of injury. VWF also serves as a carrier for factor VIII that prolongs the half-life of factor VIII in the circulation. VWD is characterized by spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia, and a prolonged bleeding time in the presence of a normal platelet count.

Platelet release defect

Platelet release defect: the most common mild bleeding disorders arise from the ingestion of aspirin.

Platelet storage pool defect

Platelet storage pool defect or insufficient release of mediators from platelet granules may be inherited as an isolated disorder or be the part of systemic granule defects the (Chediak–Higashi syndrome).

Hemorrhagic diatheses related to abnormalities in clotting factors: the bleeding manifests as the development of large ecchymoses or hematomas following an injury or as a prolonged bleeding after any form of surgical procedure. Bleeding in the gastrointestinal and urinary tracts and particularly into weight-bearing joints is a common manifestation.

Clotting abnormalities may occur as acquired defects or may be hereditary in origin. The most common acquired hemorrhagic disorders are the hemorrhagic diathesis of liver disease and vitamin K deficiency and complications of anticoagulant therapy.

The most common among hereditary coagulation disorders are hemophilias.

Hemophilia A is inherited as an X-linked recessive trait. However excessive bleeding has been described in heterozygous females. Although normal hemostasis requires at least 25% of factor VIII activity, symptomatic patients usually have factor levels below 5%. Severe factor IX deficiency (hemophilia B) is a disorder clinically indistinguishable from hemophilia A.

Fibrinolytic defect

Fibrinolytic defect: patients with α-2 plasmin inhibitor deficiency or plasminogen activator inhibitor are characterized by rapid fibrinolysis following fibrin deposition after trauma and may experience recurrent hemorrhage.

THROMBO-HEMORRHAGIC SYNDROME

There are a lot of disorders accompanied by the thrombo-hemorrhagic syndrome. Some infections, such as meningococcemia, measles and rickettsioses, can lead to thrombosis and bleeding as well. Thrombotic microangiopathies is another group of thrombo-hemorrhagic syndromes that includes thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome.

Thrombotic thrombocytopenic purpura (TTP or the Moschcowitz' syndrome) is rare, fulminant, often lethal disorder causing extensive microscopic thromboses to form in small blood vessels throughout the body (thrombotic microangiopathy). Most cases of TTP arise from the inhibition of zinc-containing metalloprotease enzyme that cleaves VWF. If large VWF multimers persist, there is a tendency for increased coagulation. The idiopathic form of TTP is linked to the inhibition of enzyme by antibodies, rendering TTP to an autoimmune disease. Secondary TTP is associated with cancer, bone marrow transplantation, pregnancy, medication use (quinine, platelet aggregation inhibitors and some immunosuppressants) and HIV-1 infection. TTP is caused by spontaneous aggregation of platelets and activation of coagulation in the small blood vessels. Platelets are consumed in the coagulation process, and bind fibrin, the end product of the coagulation pathway. These platelet–fibrin complexes form microthrombi which circulate in the vasculature and cause shearing of red blood cells, resulting in hemolysis.

The hemolytic-uremic syndrome differs from the DIC syndrome by the absence of neurological symptoms. It is also accompanied by a widespread formation of hyaline thrombi in the microcirculation, which are composed primarily of dense aggregates of platelets that are surrounded by fibrin. The development of myriad platelet aggregates induces thrombocytopenia and the intravascular thrombi without any inflammatory signs in the vessels. Verotoxins produced by certain strains of E. coli are the triggers of endothelial injury in the hemolytic-uremic syndrome. This syndrome is common in child.