Hemorrhagic Diatheses

Hemorrhagic diatheses (HD) = bleeding disorders

- Bleeding states of different etiology and pathogeny
- Common sign is increase of bleeding - spontaneous or excessive bleeding inadequate relative to stimulus or injury intensity
- Hemorrhagic diatheses can result from each disturbance of hemostatic processes.

According to pathogenetic mechanisms HD can be divided into:

- vasculopathies (disorders of the vascular wall) – increased fragility of vessels
- thrombocytopenias and thrombocytopathies (platelets disorders – functional or their number)
- coagulopathies (disorders of the clotting factors)

These three basic categories can be divided into inborn (congenital, hereditary) and acquired disorders.

1. VASCULOPATHIES

Disorders of the vascular wall causing the decrease of its mechanical resistance against powers acting on the vessel. Rupture of the vascular wall is easier during gentle pressure to the tissue or by the blood pressure. The positivity of Rumpel-Leede test is based on this phenomenon (see Practical exercise textbook).

A. Congenital disorders of vascular wall

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)

- rare, autosomal dominant (AD) disorder, manifesting mostly in adults
- dysplasia of connective tissue leads to teleangiectasies (dilatation of distal parts of small vessels) in the mucosa of the nose, oral cavity, on the facial skin
- symptoms from the their rupture - profuse spontaneous bleeding from the nose (epistaxis) and GIT

Ehlers-Danlos syndrome

- impairment of perivascular tissue (collagen) – leads to the different bleeding (mostly massive)
- 6 main types depending on location

Syndrome Hippel-Lindau

- vessel wall disturbance in retina

Marfan syndrome

- AD genetic disorder of the connective tissue, gene mutation in the chromosome 15, encodes a connective protein fibrillin 1 (required for synthesis of elastic fibers)
- typically, tall people, long limbs, long thin fingers (arachnodactyly); ectopia lentis – dislocation of ophthalmic lens, severe complication - aortal and heart valves defects (mitral prolapse, aortic aneurysm, aortic dilatation with regurgitation). Common cause of death – rupture of aortal aneurysm

B. *Acquired disorders of vascular wall*

Avitaminosis C – scurvy

- vitamin C – important co-factor for synthesis of collagen (insufficient nutrition)
- mucosa impairment, mostly very small vessels – gingival, subperiostal bleeding, perifollicular location on the extremities, sometimes greater area (sugilatio)
- in newborns or very young children the bleeding may destroy the growth split in bones, movements of extremities are damaged – this variety of vitamin C deficiency is called Möller-Barlow´s disease

Anaphylactoid purpura (Henoch-Schönlein)

- systemic autoimmune vasculitis, bleeding is only one of many different symptoms
- production of immune complexes as antigen response to the infection (typically streptococcus) leads to the increase of vascular wall permeability
- occurs mainly in young children and teens; the relapses are more frequent

Vasculitis in viral and bacterial infections

- viral (enteroviruses, rubeola, varicella) or bacterial (streptococci) etiology
- sometimes with severe course, possible influence of consumption coagulopathy (DIC)

Senile purpura

- decrease of vascular wall quality in old people

- skin atrophy development together with degenerative changes of vascular wall, mostly in patients with nutrient deficiency (alcoholics)

Steroid purpura

- as consequence of protein catabolism, loss of connective tissue in hypercorticalism
- most frequently iatrogenic – long-term glucocorticoid therapy, Cushing syndrome

2. THROMBOCYTOPENIA AND THROMBOCYTOPATHIA

Group of disorders caused by decrease of platelet number (= thrombocytopenia) or their functional disturbance (= thrombocytopathy); sometimes both of them can be combined. Symptoms are identical or similar – petechial bleeding into the skin, purpuras, hematomas. Hemorrhagic signs on the mucous membrane – epistaxis, gingival bleeding, menorrhagia, enterorrhagia, hematuria etc.; CNS hemorrhage is prognosticly the most dangerous

A. thrombocytopenia

Normal platelets concentration in blood is 150 - 300 000 x 10^9/l. Increase of bleeding occurs under range 100 x 10^9/l. Severe manifestation can be in platelets count under 50 – 20 x 10^9/l.

Thrombocytopenias originate as a disbalance between platelets production and destruction. They are mostly acquired; inborn disorders are rare.

Aa/ Decrease of platelets production: aplasia (or hypoplasia) of megakaryocytes – isolated or more often during suppression of myeloid precursors

- etiology – ionizing radiation, viral infection, tumorous infiltration of the bone marrow (leukemias, metastasis), toxic substances, myelofibrosis)
- thrombocytopenia with normal (or increased) platelets number in bone marrow – usually morphologically changed; megaloblastic anemias - vitamin B_{12} or folic acid deficiencies, myelodysplastic syndrome

Ab**/ Increase of platelets destruction** (survival shortening): pathogenetic mechanism is mostly immunological

Immune thrombocytopenia (M. maculosus Werlhofi)

- more often idiopathic form (primary)
- in 20% secondary – viral and bacterial infections, tumors, systemic diseases (SLE)
- acute form (in childhood, bleeding is manifested during hours)
- chronic form (in adult age)

Drugs-induced thrombocytopenias

- immunocomplex formation – sulfonamides, chinidine, food ingredients

Thrombocytopenia after transfusion

- as a consequence of incompatibility of platelets surface antigens

Neonatal alloimmune thrombocytopenia

- as a consequence of antigen incompatibility between mother and fetus; antibodies produced by mother and passed through placenta lead to the destruction of fetal platelets

Consumption thrombocytopenia

- as a consequence of platelets consumption during microthrombi production in peripheral circulation (most often in DIC – see later)

Thrombotic thrombocytopenic purpura (Moschcowitz)

- multiple creation of microthrombi, predilectionally in CNS and kidney
- etiopatogeneticaly – inborn (AD) or acquired (autoantibodies) deficit of vWF-depolymerase (von Willebrand factor); without activation of clotting cascade! (dif. dg DIC)
- hemorrhage, hemolytic anemia, fever, neurological symptoms

Hemolytic - uremic syndrome

- epidemic form in childhood; the reaction against E. coli toxin (capillarotoxic), predilectionally in kidney, originates usually as a hemorrhagic gastroenteritis, later the renal failure appears
- sporadic in adults, chronic renal failure

Ac/ Thrombocytopenias from platelets loss and sequestration

- massive bleeding, polytraumatic injuries, great surgical operation using an extracorporal circuit (due to platelets adherence on the surface of artificial materials)
- increased amount of platelets retained outside the circulation (splenomegaly and hypersplenism of different origin, e.g. in portal hypertension)

B. thrombocytopathia
= functional platelets disturbance either with their normal amount or with decrease number (thrombocytopenia); inborn or acquired

Ba/ inborn

- **defect of superficial membrane of platelets;** leads to the impairment of adhesion (Bernard-Soulier syndrome) or aggregation (Glanzmann´s thrombasthenia)
- **lesion of irreversible aggregation** (different etiology – e.g. inhibition of cyclooxygenase, so-called aspirin type)

Bb/ acquired (more often, many pathological states lead to the secondary disorders of platelet functions

- **myeloproliferative diseases, myelodysplastic syndrome**
- **chronic kidney disorders with uremia**
- **hepatopathies**
- **drugs -** nonsteroidal anti-inflammatory and anti-rheumatic (acetylsalicylic acid, ibuprofen) - inhibition of cyclooxygenase, and decrease of thromboxane synthesis = antiaggregation effect

3. COAGULOPATHIES

Disorder of hemostasis is caused by the clotting factors deficit or their functional abnormality

A. Inborn

Hemophilia

- gonosomal recessive disease with the lack of factor VIII (hemophilia A) or factor IX (hemophilia B)
- localization in X chromosome – manifestation in men, women are carriers
- positive family history in 70% of patients, in 30% the spontaneous mutations appear
- the most common symptom is bleeding into joints (predilectionally knee and elbow) and muscles, less frequently in GIT, urogenital tract and CNS (severe form)
- for diagnosis is important the assessment of factor levels, gene analysis
- the principle of treatment is substitution of corresponding factors, formerly (or as a first aid) transfusion of fresh or frozen plasma (due to short half-life of factors)
- rare hemophilia C (factor XI deficit), autosomal recessive heredity; moderate clinical symptoms, bleeding after large injuries and during surgical operations, more intense menstruation in women

Von Willebrand disease

- one of most common hereditary coagulopathies
- quantitative or qualitative deficit of vWF (plasmatic glycoprotein which stimulates of the platelets adhesion to endothelium and stabilizes of factor VIII)
- mostly AD mutation of gene encoding a quantity and structure of vWF, severe forms are AR
- bleeding into mucosa, GIT, spontaneous epistaxis, menorrhagia
- sometimes more intense bleeding after tooth extraction is the first sign
- the principle of treatment is substitution of vWF and factor VIII (concentrates)

Other clotting factors deficiency

- factor I (fibrinogen), II (prothrombin), V, VII, X, XI (hemophilia C), XII, XIII – isolated or rarely in combination
- mostly AR heredity, bleeding - different location and intensity
- it can be also secondary – hepatopathies, dicumarols intoxication, vit. K malabsorption

B. Acquired

Vitamin K deficiency

- etiology – hepatopathies, obstructive jaundice, disturbance of vit. K absorption in the intestine, iatrogenic: caused by long-term ATB therapy (GIT sterilization)
- pathogeny – disturbance of vit. K – dependent clotting factors synthesis (II, VII, IX, X, C and S protein); consequence is the lack of binding capacity for Ca^{2+} leading to their functional deficit
- principle of therapy – substitution of vitamin K and relevant clotting factors; after sufficient vit. K substitution, synthesis of clotting factors initiates *de novo*, so the hemostasis is normalized gradually. For this reason, in the acute situation is necessary to apply vit. K - dependent factors directly (or fresh plasma containing factors)

Circulating anticoagulant antibodies

- specific inhibitors (Ig G) suppressing activity of clotting factor
- more common against factor VIII, less IX
- in patients with hemophilia A as the reaction to substitutional therapy, in women after birth, in autoimmune (collagenosis) diseases and tumors

Disseminated intravascular coagulation syndrome (DIC)

- complex disturbance of homeostasis and physiological blood fluidity; main consequence is **massive thrombi formation** (blocking the microcirculation of different organs) on the one side, and **massive bleeding** caused by consumption of clotting factors (often also platelets) and activation of fibrinolysis on the second one.
- **basic etiological factors:** heavy infections (bacterial sepsis with endotoxins production, less viral), obstetric complications (stillbirth, septic abortion, amniotic fluid embolism), polytrauma (crush sy, extensive burns), malignant tumors, immunodeficiency
- **pathogenetic mechanisms:** activation of hemostasis (extrinsic or intrinsic pathway), often complex; uncontrolled release of tissue factor (III) or endothelium activation which becomes thrombogenic causes disruption of whole system

- multiple microthrombotisation practically in all organs leads to their ischemia, simultaneous platelets and clotting factors consumption leads to hemorrhagic manifestations (petechias, sugilatio, bleeding into GIT, urogenital, around cannulas – everywhere)
- clinical signs (latent or manifest) depends on the ability of organism to compensate these changes and on the development of organ complications (acute renal and liver failure, shock lung, adrenal insufficiency etc.)
- principle of therapy: identification and treatment of invoking pathological states, then substitutional and anticoagulant strategy