Bleeding disorders

Blood vessels

- Occurs in : Connective tissue diseases, chronic steroid intake, systemic amyloidosis, vasculitic infections, vitamin C deficiency (scurvy)
- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes

Platelets

- Thrombocytopenia (ITP,AIDS), and occasionally thrombocytosis (dysfunctioning)
- Platelets function tests: bleeding time (obsolete), platelets aggregation test, Von willibrand factor tests.

1) Glanzmann Thrombasthenia

- Rare autosomal recessive
- Acquired (autoimmune disease)
- Deficiency or blockage of platelets glycoproteins IIb-IIIa (CD41/CD61 complex)
- Fibrinogen cannot bind platelets -> prolonged hemorrhage
- it's detected by flow cytometry test

2) Bernard Soulier syndrome

- Very Rare, autosomal recessive
- Deficiency in platelets membrane glycoprotein Ib (CD42b), which binds VWF
- Platelets are large, can show thrombocytopenia and it's detected by flow cytometry test

3) Immune Thrombocytopenic Purpura (ITP)

- Patients have isolated thrombocytopenia (sometimes anemia's of blood loss)
- Most bleeding occurs in skin, mucosal surfaces (Petechiae and ecchymoses), also in GIT, urinary tract and CNS
- Acute ITP: affects children, commonly follows viral infection, self-limited
- Chronic ITP : affects middle age adults (F>M)
- IgG auto-antibodies against platelets membrane glycoproteins IIb/IIIa(chronic ITP)
- Coated platelets are engulfed by macrophages in spleen
- Splenomegaly is not always present, but patients benefit from splenectomy
- Peripheral blood shows large platelets, bone marrow shows increased no. Of megakaryocytes, spleen shows large aggregates of B and plasma cells

4) Heparin-induced thrombocytopenia

- 5% of patients receiving unfractionated heparin
- IgG antibody develops, against platelet factor-4 on platelets aggregation and thus thrombosis
- Can also develop in low-molecular weight heparin

5) Thrombotic Microangiopathies

- Includes thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)
- TTP: fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits and renal failure
- HUS: similar symptoms, dominance of renal failure, no neurologic symptoms, common in children
- In both diseases, the small circulation in the body is filled with platelets-rich microthrombi, without activation of clotting factors (PT and PTT are normal)

6) Thrombotic Microangiopathies

- TTP: deficiency in ADAMTS13, a plasma protein required for VWF. The precursor of VWF is a large multimeter that is capable to bind many platelets causing aggregation
- HUS: enterohemorrhagi E.coli in the gut produces shiga-toxin that reaches kidney and causes endothelial damage and thrombosis
- Blood film: schistocytes, thrombocytopenia

Clotting factors

Coagulation disorders

- Related to clotting factors
- Inherited, or more commonly acquired
- Vitamin K deficiency: decreased synthesis of factor II (prothrombin), VII, IX, X.
- Liver disease
- Disseminated intravascular coagulation (DIC)
- Warfarin
- Autoantibodies (single or multiple factors)

- Prothrombin time(PT): assess extrinsic (factors V, VII) and common pathways (factors X, prothrombin or fibrinogen)
- Partial thromboplastin time (PTT): assess intrinsic (factors XII, XI, IX,VIII, V) and common pathways
- In addition to deficiency, an autoantibody (inhibitor) can interfere with the function of clotting factors
- Mixing study: adding a normal serum to patient's serum then repeating PT and PTT tests. If they're are corrected, then the patient has true deficiency. If not corrected, then the patient has an inhibitor antibody.

1) Von Willibrand disease

- Most common inherited bleeding disorder (1% of population)
- Autosomal dominant
- Spontaneous bleeding frontal mucus membrane, wounds and menorrhagia
- VWF is synthesized in endothelium (Weibel-Palade bodies), also present beneath endothelium,inside platelets
- It circulates the plasma, carry factor VIII
- After endothelial damage, subendothelial VWF binds platelets through glycoprotein Ib, forming platelets plug
- Ristocetin aggulatination test: it activates VWF to bind GPIb causing platelets clump.
- VWD causes a compound defect: non-functional platelets and deficiency in factor VIII
- Symptoms are mainly related to platelets defects except in homozygous state (resembles hemophilia A, prolonged PTT)
- Type I VWD: most common, decreased level of serum VWF
- Type IIA : absent high-molecular weight multimers of VWF
- Type IIB : the high molecular weight multimers have very short half life and ar hyper functioning, consuming platelets, patients have mild chronic thrombocytopenia

2) Hemophilia A

- X-linked inheritance, AKA classic hemophilia
- Reduced factor VIII
- Can affect females (random inactivation of X)
- 30% of cases appear as a new mutation
- Mild deficiency results in excessive bleeding after trauma
- Sever, life-threatening bleeding occurs if level drops <1% of normal level
- 10% have normal level but non-functioning factor
- Bleeding tends to occur in deep tissues with mechanical stress (joints, body cavities). Patients develop deformity in joints
- Skin petechiae is absent
- Prolonged PTT, corrected by mixing study
- Specific assay test is available

3) Hemophilia B

- X-linked
- AKA Christmas disease
- Deficiency in factor IX
- Much less common than hemophilia A
- Clinically similar to hemophilia A
- Prolonged PPT, corrected by mixing study
- Factor assay test is available

Endothelium

- Widespread endothelial damage causing release of tissue factor, a prothrombotic agent, causing disseminated intravascular coagulation (DIC)
- Rapid consumption of clotting factors (prolonged PT, PTT) and platelets, exceeding replacement process
- Patients then develop life-threatening bleeding
- Peripheral blood shows schistocytes, anemia and thrombocytopenia
- Causes of DIC — Endothelial damage: septicemia and viremia, snake venom , complicated labor, advanced cancer, severe trauma, severe inflammation (acute pancreatitis)

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