CLOTTING DISORDERS AND DISSEMINATED INTRAVASCULAR COAGULATION.

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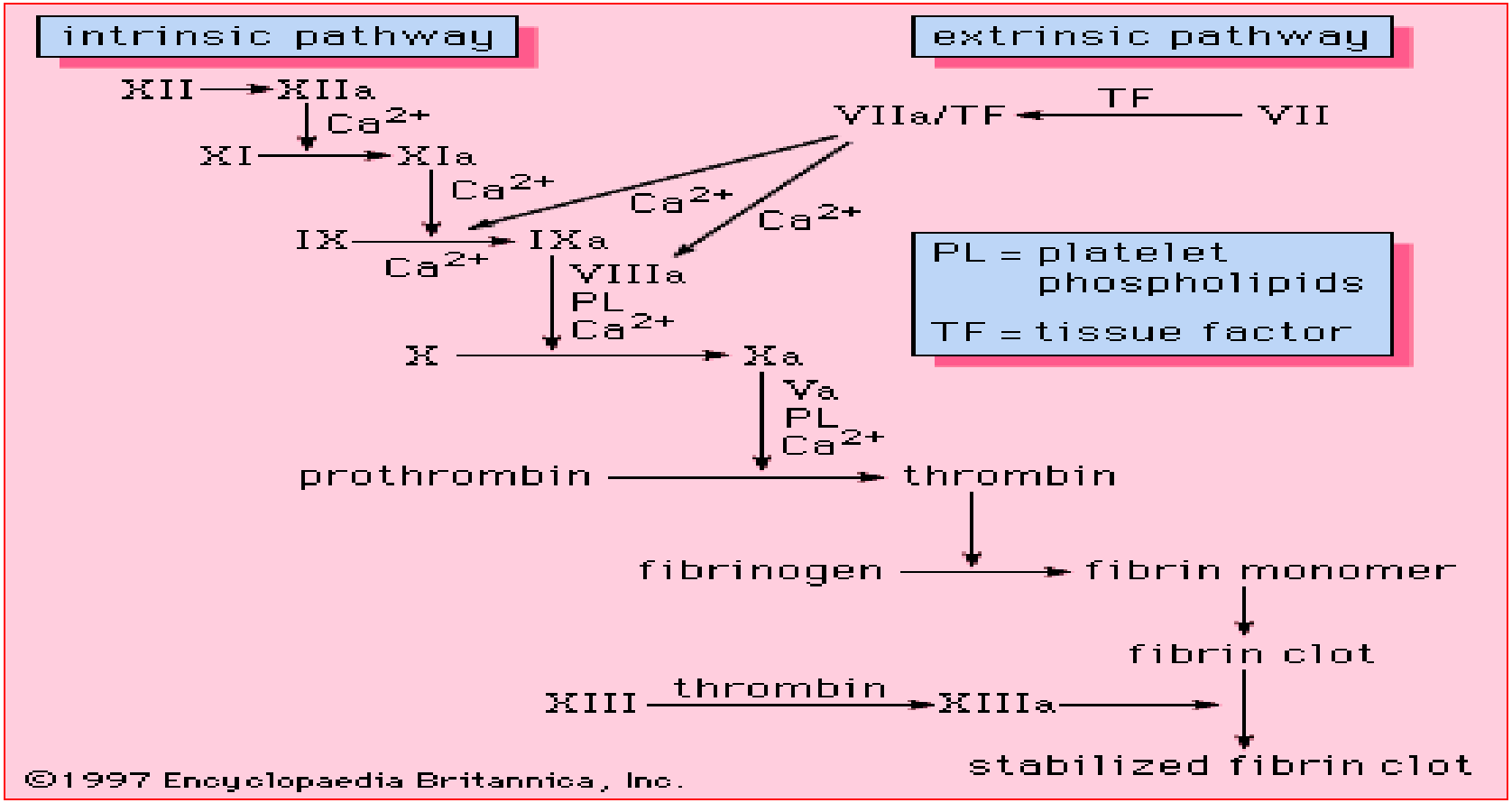
COAGULATION PATHWAYS

- INTRINSIC PATHWAY: activated by contact of coagulation proteins with negatively charged surfaces.
- EXTRINSIC PATHWAY: activated by contact of factor VII with tissue factor.
- COMMON PATHWAY: the intrinsic and extrinsic pathways converge in the common pathway.

COAGULATION PATHWAY



PARAMETER	CLOTTING DISORDERS	BLEEDING DISORDERS
1.SEX	1. More common in males	1. More common in females
2.FAMILY HISTORY	2. Often positive	2. Often negative
3.PETECHIE, BLEEDING GUMS, NOSE BLEEDS, MELENA	3. Rare	3. Common
4.SKIN HEMORRHAGES	4. Large and few	4. Small and many
5.Deep hematomas, hemarthrosis	5. Common	5. Not seen
6.Delayed bleeding	6. Characteristic	6. Not seen

CLOTTING DISORDERS

- HEREDITARY:
- Autosomal dominant inheritance: Von Willebrand disease.
- X-Linked recessive inheritance: Hemophilia A, Hemophilia B.
- Autosomal recessive inheritance.
- ACQUIRED:
- Liver diseases.
- Vitamin K deficiency.
- Disseminated intravascular coagulation.

HEREDITARY DISORDERS

FACTOR VIII

- Synthesized in endoplasmic reticulum and Golgi region of hepatocytes.
- The gene controlling the production of the factor VIII is located at the terminal end of the long arm of the X chromosome.
- Plasma contains some free factor VIII but most is stabilized by vWf in a 1:1 molar ratio. It is the smaller component of the factor VIII/vWf complex.

- Factor VIII is composed of two distinct, non-covalently bonded subunits:
- Factor VIII with pro-coagulant activity (VIII:C). It is also known as the anti-hemophiliac factor and serves as the cofactor in factor X activation by factor IX.
- The portion that carries the von willebrand factor activity (VIII:vWf).

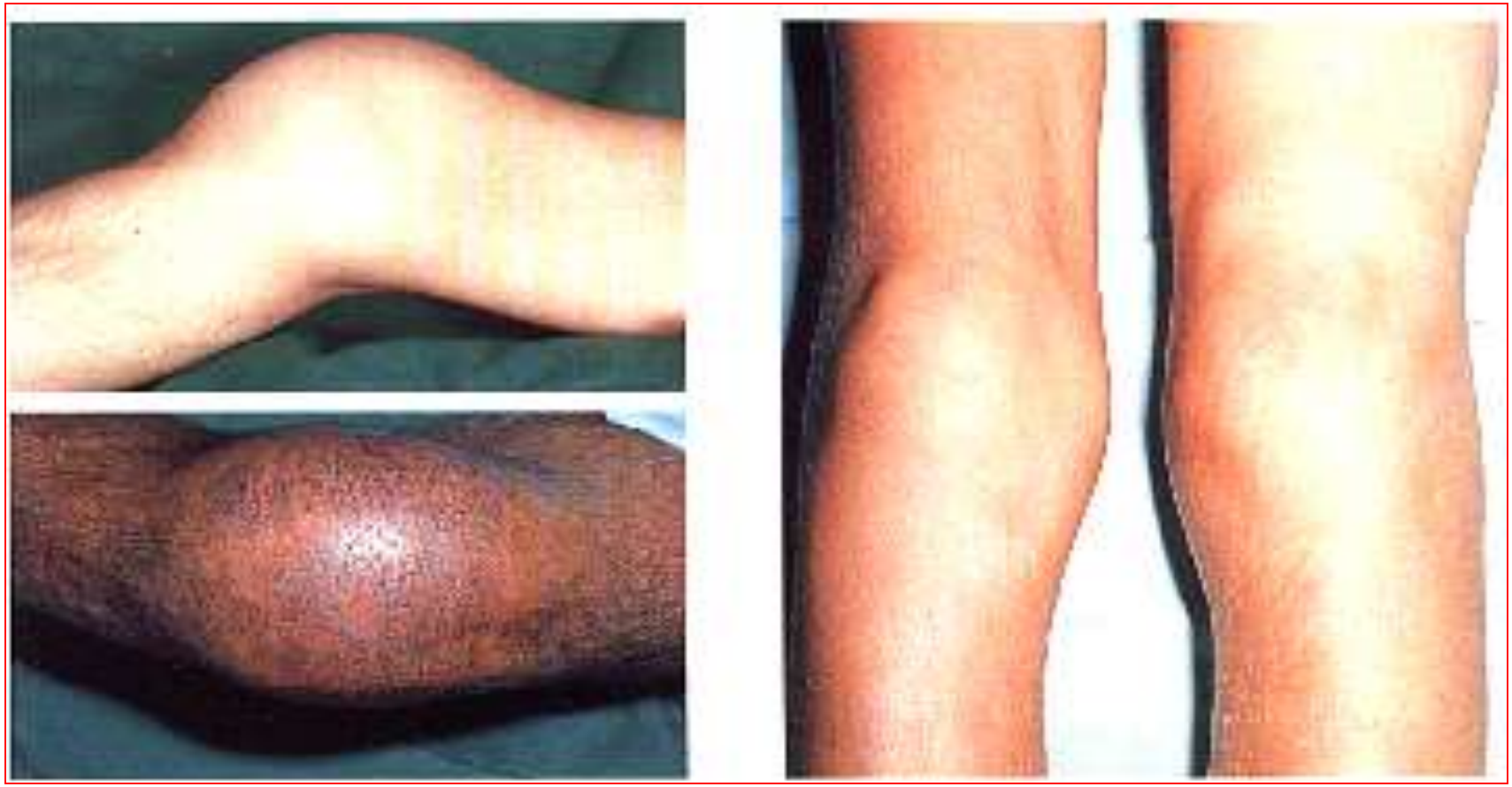
FACTOR VIII DEFICIENCY

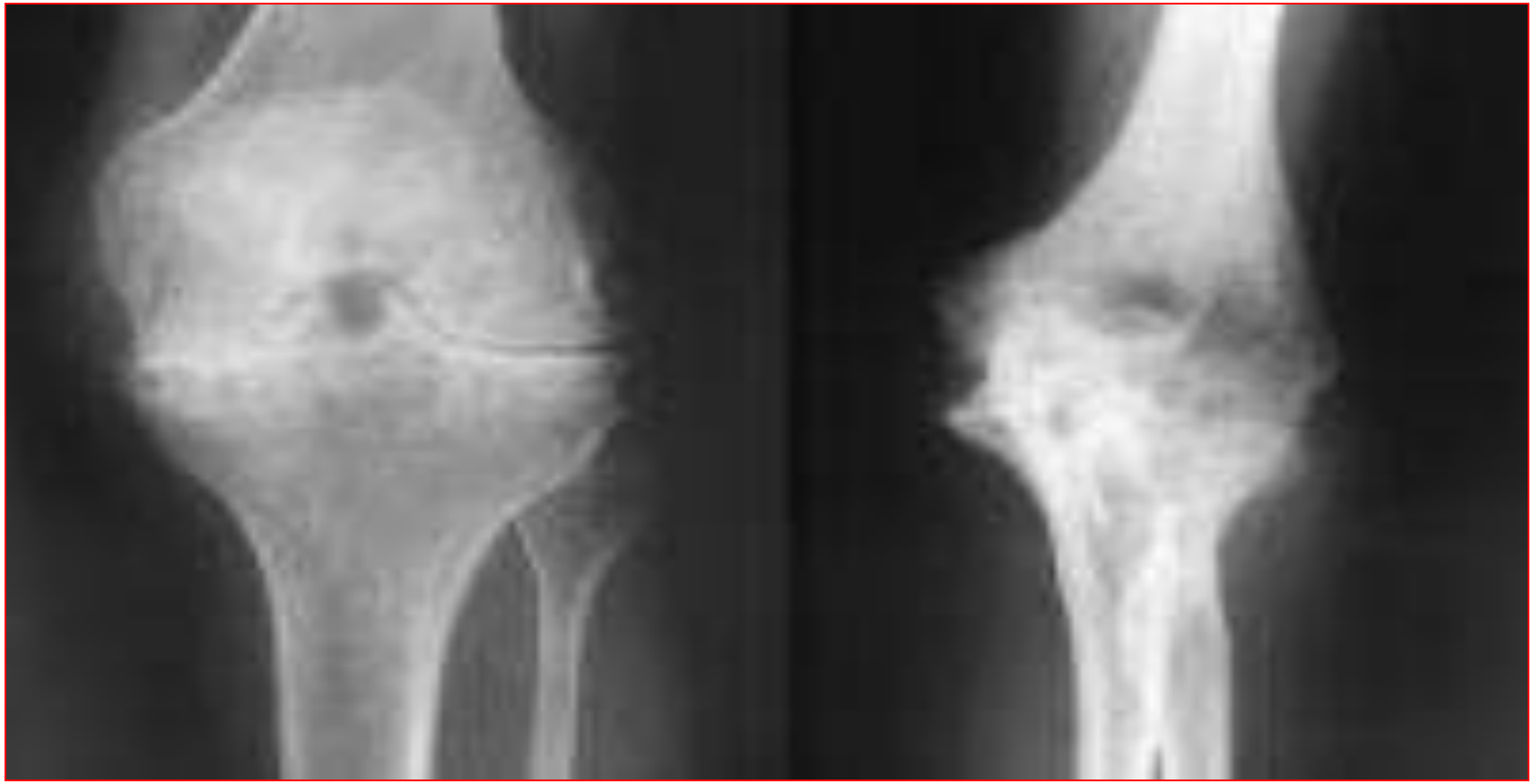
- Also known as Hemophilia A.
- It is the most common hereditary disease associated with life-threatening bleeding.
- It is caused by mutations in factor VIII gene, which is an essential co-factor for factor IX in the coagulation cascade.
- Hemophilia A is inherited as an X-Linked recessive trait and thus affects mainly males and homozygous females.

CLINICAL PRESENTATIONS

- Clinical severity correlates well with the level of factor VIII activity:
- Less than 1% of normal levels : severe
- 2% to 5% of normal levels : moderate
- 6% to 50% of normal levels : mild
- The varying degrees of factor VIII deficiency are largely explained by heterogeneity in the causative mutation.

- Easy bruising and massive hemorrhage after trauma or surgery.
- Spontaneous hemorrhages frequently occur in the regions of the body normally subject to trauma, particularly the joints. Recurrent bleeding into the joints leads to progressive deformities that can be crippling.
- Petechiae are characteristically absent.





LABORATORY FINDINGS

- PLATELET TESTS: normal
- COAGULATION FACTOR TESTS:
  - PT normal
  - APTT increased
  - Thrombin time normal
  - Factor VIII assay decreased
  - vWf:Ag assay normal
  - Factor IX assay normal
- FIBRINOLYSIS normal

TREATMENT

- Factor VIII concentrates.
- Recombinant factor VIII.

FACTOR IX

- Factor IX is a vitamin-K dependent serine protease that functions in the intrinsic pathway of fibrin formation.
- Glycoprotein.
- It is synthesized in hepatocytes.
- The gene is located on the terminal end of the long arm of the X-chromosome near the gene for factor VIII.

FACTOR IX DEFICIENCY

- Clinical presentation resembles that of factor VIII deficiency.
- PT will be normal, APTT prolonged . Definitive diagnosis is possible only by assay of factor levels.
- This disease is treated with infusions of recombinant factor IX and factor IX concentrates.

VON WILLEBRAND DISEASE

- Von willebrand disease is caused by deficiency of von willebrand factor.
- Von willebrand factor acts the bridge that, along with the glycoprotein Ib receptor, helps platelets adhere to collagen fibers after an injury.

VON WILLEBRAND FACTOR

- Glycoprotein and the larger of the two components of the factor VIII/von Willebrand complex.
- Gene controlling the production of vWf is located on chromosome 12.
- Synthesized in endoplasmic reticulum and golgi region of megakaryocytes and endothelial cells.
- Stored in Weibel-Palade bodies of the endothelial cells and α-granules of platelets.
- It circulates in the plasma bound to Factor VIII by non-covalent bond in 1:1 ratio.

FUNCTIONS

- Platelet adhesion.
- Prevents degradation of factor VIII in the plasma.
- Fibrin formation.

CLINICAL PRESENTATION

- HETEROZYGOUS:
- Mild.
- Symptoms may not begin until second decade of life.
- Resemble clinical features of platelet disorder.
- HOMOZYGOUS:
- Severe.
- Symptoms begin early.
- Resemble clinical features of coagulation factor deficiency.

CLINICAL PRESENTATION

- Symptoms seen most frequently are mucosal and cutaneous hemorrhages like epistaxis, gingival bleeding, easy bruising, and hypermenorrhea.
- Excessive bleeding at child-birth is comparatively rare, because in pregnancy the activity of entire complex increases.

LABORATORY FINDINGS

- PLATELET TESTS
- Platelet count normal
- Platelet aggregation normal with ADP, collagen, epinephrine
- COAGULATION FACTOR TESTS
- PT normal
- APTT normal or increased
- Thrombin time normal
- Factor VIII assay decreased
- VWF:Ag assay decreased
- Factor IX assay normal
- FIBRINOLYSIS normal

TREATMENT

- CRYOPRECIPITATE – which contains all molecular forms of Von Willebrand factor.
- A modified antidiuretic hormone deamino-D-argenine vasopressin(DDAVP) is found to induce release of stored von willebrand factor in endothelium.
- Therapy is given symptomatically and is monitored by the bleeding time.

FACTOR I DEFICIENCY

Inherited as autosomal recessive trait.

Three forms are seen

- AFIBRINOGENEMIA:
  - Homozygous
  - No antigenically detectable fibrinogen is found
- HYPOFIBRINOGENEMIA:
  - Heterozygous
  - plasma levels of fibrinogen are between 20 and 100 mg/dl
- DYSFIBRINOGENEMIA:
  - Structural alteration of molecule

CLINICAL FEATURES

- AFIBRINOGENEMIA
  - Severe disease.
  - At birth, umbilical cord bleeding.
  - Post-traumatic and post-surgery bleeds.
  - Rarely, joint bleeds.
- HYPOFIBRINOGENEMIA
  - Few bleeding symptoms.
- DYSFIBRINOGENEMIA
  - Most patients are asymptomatic.
  - Rarely mild, post-traumatic bleeding can be seen.

LABORATORY FINDINGS

- AFIBRINOGENEMIA:
- PT, APTT, Thrombin time, bleeding time –prolonged.
- Diagnosis is confirmed with antigenic and functional assay for fibrinogen, which reveal almost no fibrinogen.

- HYPOFIBRINOGENEMIA:
- PT, APTT, Thrombin time – prolonged.
- The fibrinogen functional assay is roughly equal to an antigenic assay, indicating decreased protein as opposed to abnormal protein.
- Platelet function tests are not affected.

TREATMENT

- Fibrinogen in the form of cryoprecipitate and fresh frozen plasma is used as therapy.

FACTOR II DEFICIENCY

Autosomal recessive disorders.

TYPES

- HYPOPROTHROMBINEMIA
  - decreased protein synthesis.
- DYSPROTHROMBINEMIA
  - normal amounts of non-functional protein.

CLINICAL PRESENTATION

- Clinical symptoms in both dysprothrombinemia and hypoprothrombinemia are proportional to the level of functional protein and are present in both heterozygous and homozygous individuals.
- Homozygotes have severe bleeding after trauma or surgery, epistaxis, menorrhagia, hematuria and easy bruising.
- Heterozygous patients have a milder disease, with epistaxis and bleeding after tooth extraction.

- Both the PT and APTT are prolonged since prothrombin is a factor in the common pathway
- Treatment:

fresh frozen plasma or stored plasma

prothrombin complex concentrates

FACTOR V DEFICIENCY

- Also known as parahemophilia.
- Homozygous and heterozygous states are identified.
- Only the homozygous individuals are symptomatic.
- Both PT and APTT are prolonged.
- Definitive diagnosis is factor V assay.
- Treatment is with fresh or fresh frozen plasma.

FACTOR VII DEFICIENCY

- CLINICAL PRESENTATION:
- homozygous patients may bleed from the umbilical cord, the nose, and the GIT.
- Fatal intracranial bleeds occur frequently.
- Hemarthrosis occur in men and severe menstrual bleeding is seen in women

MANAGEMENT

- It is the only plasma coagulation disorder in which the prothrombin time alone is prolonged.
- Treatment is with fresh frozen plasma or prothrombin concentrates.

FACTOR X DEFICIENCY

- Also known as Stuart-Prower deficiency.
- Heterozygous patients are clinically asymptomatic and homozygous patients present with bleeding.
- PT, APTT, Russell's viper venom tests are prolonged. Factor X assay is definitive.
- Treatment is with plasma or prothrombin complex concentrates.

FACTOR XI DEFICIENCY

- Also known as Hemophilia C.
- Only homozygous patients present with symptoms of bleeding, heterozygous patients are asymptomatic.
- The bleeding symptoms tend to be mild, occurring largely after traumatic injury, surgery or childbirth.
- Laboratory tests reveal a prolonged APTT. Specific assay for factor XI is the definitive test.
- Treatment of factor XI deficiency is fresh frozen plasma .

FACTOR XII DEFICIENCY

- Also known as Hageman trait.
- No bleeding symptoms are associated with this disease, even with severe trauma or during surgery. Paradoxically increased incidence of thromboembolism is seen.
- Prolonged APTT.
- Because there is no bleeding, no treatment is needed, but treatment for thrombotic episodes is required.

FACTOR XIII DEFICIENCY

- Clinically, homozygous factor XIII deficiency can be life threatening. About 90% of patients present with umbilical cord bleeding. Intracranial bleeding is common and severe bleeding can develop after trauma or surgery.
- In vitro clot formation is abnormal.
- Treated with plasma.

ACQUIRED DISORDERS

LIVER DISEASES

- Liver disease affects all hemostatic functions
- Most hemostatic proteins, those which are involved in fibrin formation, fibrinolysis, and inhibitors are synthesized in the liver.
- The liver macrophages play a major role in removal of activated factors and products of activation, such as the fibrinopeptides, fibrin split products, and plasminogen activators.

COMPONENTS OF HEMOSTASIS SYNTHESIZED IN THE LIVER

- Factor I, factor II, factor V, factor VII:C, factor IX, factor XI, factor XII, factor XIII
- Prekallikrein
- HMW kininogen
- Antithrombin III
- Protein C
- Protein S
- α2-macroglobulin
- α2-antiplasmin
- plasminogen

CLINICAL MANIFESTATIONS

- Minimal except in severe liver disease.
- Ecchymoses and epistaxis may occur.
- Bleeding from local lesions in the gastro-intestinal tract are common.

LABORATORY MANIFESTATIONS

- PT, APTT, thrombin time – prolonged.
- Platelet count – decreased.
- Fibrin split products – increased.

TREATMENT

- Therapy involves the use of replacement products as needed.

VITAMIN K

- Source: green leafy vegetables in the diet and through synthesis by bacteria in the gastro-intestinal tract
- Vitamin K is needed by hepatic cells to complete the post-translational alterations of factors II, VII, IX, X, protein C and protein S.
- If the level of functional factors fall below 0.3μm/ml, bleeding symptoms may result.

HEMORRHAGIC DISEASE OF THE NEWBORN

- Symptomatic vitamin K deficiency is most often seen in newborns in the first days of life because:
- Liver is still immature.
- Human milk contains little vitamin K.
- Bacterial colonization of gastro-intestinal tract is incomplete.
- Those factors that are present at birth are metabolized so that they may become even lower during the first few days of life.

MANIFESTATIONS

- Bleeding from the umbilicus or circumcision, generalized ecchymoses, large intramuscular hemorrhages and intracranial bleeds.
- PT , APTT – prolonged.
- Specific factor assays for factors II, VII, IX, X markedly decreased.

- Other causes of vitamin K deficiency that may be seen in adults are:
- Mal-absorptive syndromes such as sprue.
- Obstruction of biliary tract because bile salts are necessary for adsorption.
- Prolonged broad spectrum antibiotic therapy that abolishes normal flora of the intestine.

DISSEMINATED INTRAVASCULAR COAGULATION

- Disseminated intravascular coagulation is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.
- Also known as defibrination syndrome, consumption coagulopathy.

ETIOLOGY

- INFECTIONS: bacteria, virus, fungus, rickettsia, protozoa
- COMPLICATIONS OF PREGNANCY: toxemia, retained placenta, amniotic fluid embolism, abruption placenta.
- NEOPLASMS: luekemias, carcinoma.
- MASSIVE TISSUE INJURY: burns, traumatic injury, extensive surgery, extracorporeal circulation.
- VASCULAR INJURY: shock, hypotension, hypoxia, acidosis.
- MISCELLANEOUS: snake bite, heat stroke, any disease.

CLINICAL PRESENTATION

- TYPES:
- ACUTE:
- More commonly recognized.
- Begins with sudden onset of severe bleeding.
- Hemorrhagic symptoms.

- CHRONIC:
- Exists for a long period of time.
- May have either mild or no symptoms.
- Thrombotic symptoms.

- Generally bleeding begins abruptly and occurs from at least three sites at the same time. Sites of bleeding tend to correspond to the tissue involved in the event. Hematuria, gastrointestinal bleeding, epistaxis, oozing from needle puncture sites, ecchymoses and petechiae are some common manifestations.
- Obstruction of the microvasculature by thrombi causes tissue anoxia and micro-infarcts of the heart, kidney, brain, liver and pancreas, all leading to shock. Shock is also induced because products of complement and kinin system cause increased vascular permeability and hypotension.

LABORATORY FINDINGS

- PLATELET COUNT : decreased
- PROTHROMBIN TIME : increased
- APTT : increased
- THROMBIN TIME : increased
- FIBRINOGEN : decreased
- PROTAMINE SULFATE TEST : positive
- FIBRIN SPLIT PRODUCTS : positive
- CIRCULATING FIBRINOPEPTIDE A : increased
- PLASMINOGEN : decreased
- ANTITHROMBIN III : decreased
- BLOOD SMEAR : schistocytes

TREATMENT

- Treatment for DIC is to first eliminate the primary condition, if possible.
- ACUTE FORM: disease is often self limited and will disappear when the fibrin is completely lysed. Replacement therapy using platelets, red cells or plasma are used when indicated.
- CHRONIC FORM: Heparin therapy sometimes may be useful if thrombosis is life threatening.

ANTICOAGULANT THERAPY

- Patients with thrombotic diseases are treated with drugs that either inhibit the formation of blood clots or remove the clots that have formed. The use of them is called anticoagulant therapy or thrombolytic therapy.
- The drugs interfere with normal hemostasis and can potentially cause serious hemorrhage if given in excess. If the dose isn’t high enough, however, the drug will be ineffective. Because of individual response to these drugs, there is no standard dosage that is both safe and effective in all patients. The most clinically effective dose is established by trial or error, using in vitro laboratory test results as a guide.

Approaches to anticoagulant therapy

- Prevention of extension of venous thrombosis: heparin, oral anticoagulants.
- Antiplatelet drugs: aspirin, dipyridamale, sulfinpyrazole, ditran, clofibrate, prostaglandins, phenolthiazine, antihistamine.
- Thrombolytic agents: streptokianase, urokianase.

HEPARIN

- Treatment of thromboembolic disorders.
- DVT.
- Pulmonary embolism.
- Prophylaxis of the thromboembolic disorders.
- Treatment of arterial thrombosis or embolism.
- Treatment of DIC in some patients.
- Prevention of clots in extracorporeal circulation and renal dialysis.
- As an anticoagulant for blood sampling for selected laboratory tests.

Heparin therapy monitoring

- The APTT, which uses plasma, has become most popular because it is already available in most laboratories as a screening test for coagulation abnormalities, and because it provides adequate information.
- With continuous therapy and with intermittent injections, the APTT is performed daily and the next dose is adjusted accordingly until the desired effect is achieved. With intermittent therapy, the test is usually timed 1 hour before administration of the next dose.
- It is standard practice to adjust the dose of heparin so that the APTT is about 1.5 to 2 times the patient baseline value before treatment. This corresponds to a heparin concentration of 0.3 to 0.5 units/Ml.

Disadvantage

- Disadvantages of using the APTT for monitoring heparin therapy lie in the wide variety of instruments and reagent systems in use in clinical laboratory. Each laboratory uses its own combination of instruments and reagents, making standardization between laboratories difficult.

Oral anticoagulant

- Oral anticoagulants inhibit carboxylation of vitamin K dependent factors and make these factors inactive.
- PT is the standard test for monitoring treatment with oral anticoagulants

INR

- Various types of thromboplastin reagents obtained from different sources are available for PT test. These differ in their responsiveness to deficiency of vitamin K dependent factors. Technique of PT is also different in different laboratories. For standardization and to obtain comparable results, it is recommended to report PT in the form of an International Normalized Ratio i.e, ratio of PT of patient to PT of control.
- International Sensitivity Index of a particular tissue thromboplastin is derived by comparing it with a reference thromboplastin of known ISI.

- INR should be maintained in the therapeutic range for the particular indication.
- INR 2.0-3.0 for prophylaxis and treatment of DVT
- INR 2.5-3.5 for mechanical heart valves
- Therapeutic range provides adequate anticoagulation for prevention of thrombosis and also checks excess dosage, which will cause bleeding.

REFERENCES

- ROBBINS AND COTRAN, PATHOLOGIC BASIS OF DISEASE, 8TH EDITION.
- MACKENZIE TEXT BOOK OF HEMATOLOGY, 2ND EDITION.

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THANK YOU

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