Haemorrhagic Disorders

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TUCOM

Aim of the lecture

- Approach to hemorrhagic disorders
- Causes of hemorrhagic disorders
- How to diagnose each disorders?
- How to manage each disorders?

Hemorrhagic Disorders

These include

- Disorders of platelets.
- Disorders of blood vessels.
- Disorders of coagulation & fibrinolysis.

Platelet Disorders

- Quantitative : Thrombocytopenia.
- Qualitative : Platelet defects.

Thrombocytopenia

- Thrombocytopenia exists when platelet count is less than 150 x 10^9 /L .
- Normal platelet count = 150 – 400 x 10^9 /L
- Bleeding is unusual when count is >50x10^9 /L
- Spontaneous bleeding occurs when count is < 20x10^9 /L

Causes of Thrombocytopenia

- 1.***decresed platelet production***

  Characterized by reduction of megakaryocytes in bone marrow & by small mean size of circulating platelets (Mean Platelet Volume –MPV) and association with anaemia and leucopenia :

  a. Aplastic anaemia.

  b. Megaloblastic anaemia (decrease Vit. B12 or /and decrease folic acid).

  c. Bone marrow infiltration by neoplasms.

  d. Cytotoxic drugs (Dose Dependant).

  e. Ionizing radiation (Dose Dependant).

  f. Drugs; cause thrombocytopenia in some recipients : Metheprim, Phenylbutazone, Gold compounds .

  g. Alcohol.

- 2. ***Increased destruction of platelets***

  Characterized by normal or increased numbers of megakaryocytes in bone marrow , circulating platelets appear larger than normal (raised MPV) and that platelets are usually only affected (no anaemia or leucopenia).

Causes of Increased Destruction of Platelets

- **hypersensitivity to drugs**

  Occurs suddenly following single dose drugs act as a hapten forming antigenic complex by binding to plasma protein and then antibody (usually IgG) is formed against this complex , this antigen-antibody complex then binds to platelets leading to destruction by phagocytosis usually in the spleen .

- Drugs : Chlorothiazides , Digoxin , Methyl-dopa ,PAS (para-aminosalicylic acid), Quinine, Quinidine, Sulphonamides .

Autoimmune Thrombocytopenia

Autoantibodies usually of IgG class either as

- isolated disorder :idiopathic (immune) thrombocytopenic purpura (ITP)
- in association with other autoimmune disorders : SLE ,myasthenia gravis ,Evan's syndrome(autoimmune hemolytic anemia + autoimmune thrombocytopenia), lymphoma , chronic lymphocytic leukaemia

ITP (Idiopathic((immune)) Thromocytopenic Purpura)

- Occurs chiefly in children and young adults

Character	Children	Adults
Behavior (onset)	Acute (sudden)	Chronic (insidious)
Peak age incidence	2-8 years	20-40 years
Sex	F=M	3F:1M
Duration	<6 months (usually weeks)	> 6 months (often years)
Associated disorders	Preceding viral infection	None

- Responsible antibody usually belongs to subclass 3 of IgG.
- Clinically
  - Varies from mild cutaneous bleeding to gross uterine or GIT hemorrhage .
  - In severe cases it lead to intracerebral hemorrhage .
- Treatment
  - Steroids
  - Immunosuppressive drugs
  - Splenectomy

Blood: Hb – Normal

WBC – Normal

Platelet count reduced

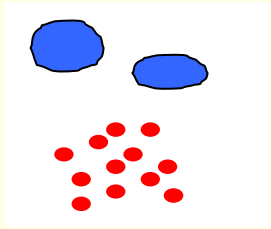
In severe cases 20 – 50 x 10^9/L.

In moderate cases (50 – 80) x 10^9/L.

Bleeding:

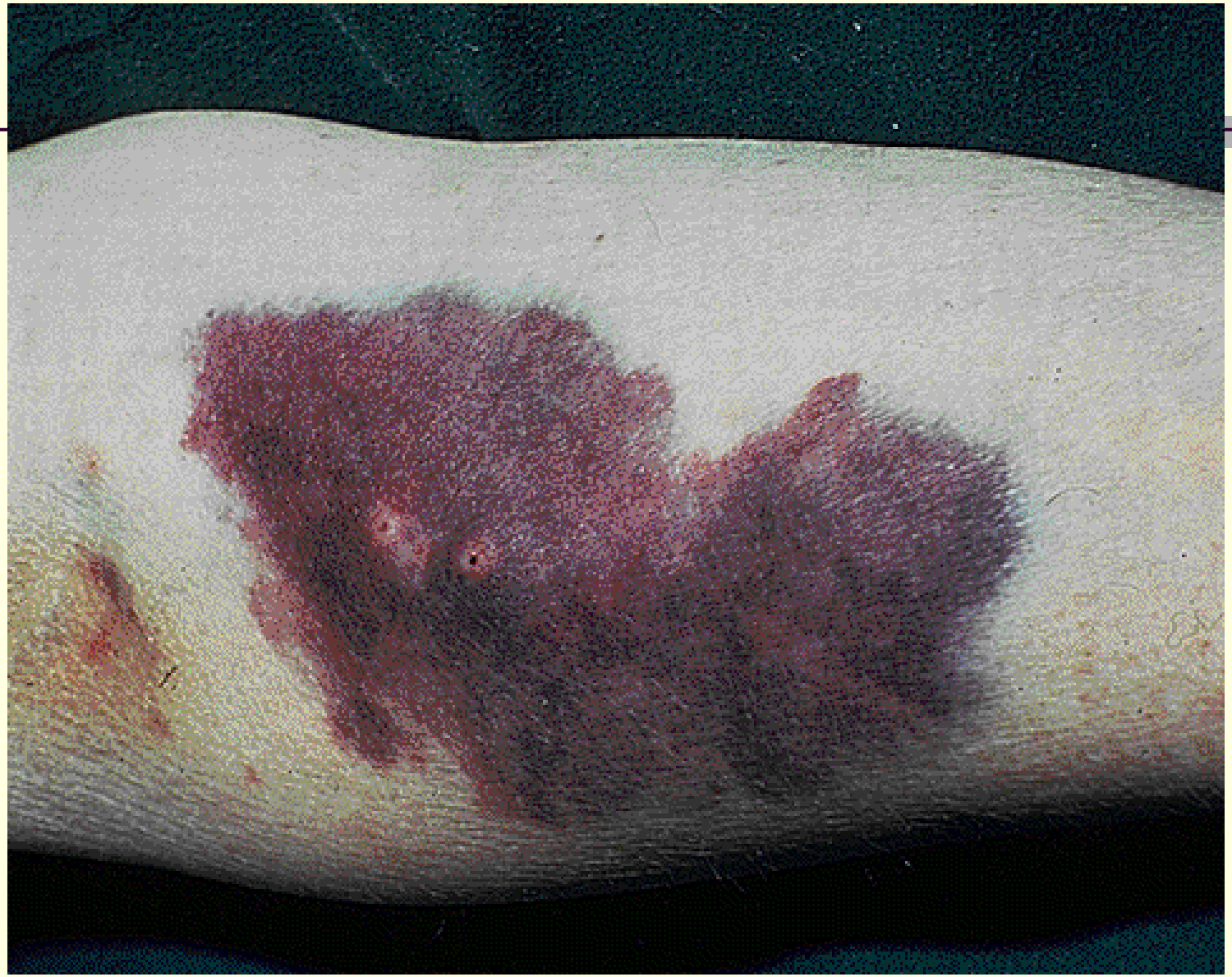
Skin: Ecchymosis (Bruises)

Petechie



- Epistaxis
- GIT, GUT bleedings.

CNS “ fatal” very rare.



platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present.

Initial approaches to the management of ITP include the following:

- No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier.
- This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun.
- This approach is far less costly, and side effects are minimal

- Per the American Society of Hematology Guidelines: "A single dose of IVIG [intravenous immunoglobulin] (0.8-1.0 g/kg) or a
- short course of corticosteroids should be used as first-line treatment.
- For Rh-positive patients, IV anti-D at a dose of 50-75 µg/kg causes a rise in platelet count to >20 ×109/L in 80-90% of patients within 48-72 hr.
- In the special case of intracranial hemorrhage, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids,and prompt consultation by neurosurgery and surgery.

- The older child (≥4 yr) with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy is a candidate for splenectomy
- As an alternative to splenectomy, rituximab has been used off-label in children to treat chronic ITP(more than 6 months)

- 3. ***Hypersplenism***

  Clinical syndrome :

- Enlargement of the spleen.
- Reduction in one or more of cell lines of blood (anaemia, leucopenia, thrombocytopenia).
- Normal bone marrow.
- Cure after splenectomy.

- 4.***DIC(disseminated intravascular coagulation)***

  This causes thrombocytopenia by excessive utilization & destruction of platelets .

- 5. ***Massive blood transfusion***

Qualitative Platelet Defects

- Platelet count is normal ,but there is defect in platelet aggregation .
- e.g. Glanzmann’s disease (thrombosthenia, autosomal recessive)

Disorders of Blood Vessels (Vascular Purpra)

- ***Congenital :***
  - Hereditary Hemorrhagic Telagiectasia
    - Autosomal dominant
    - Clinically: usually epistaxis , multiple telangiectatic spots in the skin & mucus membranes leading to hemorrhage & iron deficiency anemia ,haemoptysis.

- ***Acquired :***
- Purpura simplex in women .
- Senile purpura :on the dorsum of hands & arms due to poor capillary support from collagen as also in :
- Steroid therapy or Cushing syndrome
- Scurvy ,vit. C needed for polymerization of mucopolysaccharides necessary for collagen synthesis .

- Henoch Schonlein Purpura : necrotizing vasculitis give rise to small hemorrhages especially in the skin & gut ,there may be associated glomerulonephritis ,usually follow streptococcal infection.
- Damage to capillaries as in :
  - severe acute bacterial infection: septicaemia.
  - subacute bacterial endocarditis .

Inherited Disorders of Coagulation

- Of these coagulation factors deficiencies factor VIII deficiency is important .it can lead to Haemophilia A and von Willebrand's disease .

Structure of factor VIII

- Plasma factor VIII is now considered to be a complex of two components ;the larger of the two ,factor VIII /von Willebrand factor (VIII R: WF) is coded by autosomal genes and is deficient in von Willebrand ‘s disease , it promotes primary haemostasis by interacting with platelets and also appears to function as a carrier of smaller component factor VIII coagulant (VIII C) which is coded by an X chromosome which participates directly into cascade clotting reaction & is deficient in classical haemophilia ,when assayed immunologicaly these two components are expressed as antigen (Ag)

  i.e. VIII R: Ag and VIII C : Ag .

Haemophilia A

- Hereditary abnormality of coagulation.
- Sex linked : affect ♂ ,while ♀ are carriers .

- All sons of diseased ♂ are normal .
- All daughters of diseased ♂ are carriers .

X♌ Y XX

YX YX X♌ X X♌ X

Normal ♂ Carrier ♀

- 50% of daughters of carrier female are carriers .
- 50% of sons of carrier female are diseased .

XY

X♀ X

XX♀

XX

YX♀

YX

Clinically

- Male child will suffer from bleeding following circumcision , haemarthrosis usually after crawling .
- Severity of haemophilia is graded according to the level of VIII C into:

i. Severe (VIII C < 1% of normal).
ii. Moderate (2-3% of normal).
iii. Mild (5-20% of normal).

Diagnosis

- APTT ↑
- Clotting time either normal or ↑
- Bleeding time normal
- VIII C activity ↓
- VIII C : Ag ↓
- VIII R: Ag normal

Von Willebrand's Disease

- Inherited hemorrhagic disease in which bleeding time is prolonged due to deficiency of von Willebrand's factor (vllll R) as this factor is important for platelet adhesion to vascular subendothelium.

Von Willebrand's Disease

- autosomal dominant except Type III
- patients range from asymptomatic to spontaneous bleeding similar to a severe hemophiliac
- characterized by mucocutaneous bleeding

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Von Willebrand's Disease test

- aPTT
- Factor VIII activity
- von Willebrand's Factor
- Ristocetin Cofactor
- von Willebrand's Factor multimers

Von Willebrand's Disease Rx

- DDAVP (Stimate)
  - 0.3 micrograms/kg IV in 50cc NS over 30 minutes
  - intranasally 2 puffs for adults, 1 puff for children
- Factor VIII product containing Vwf

- Cryoprecipitate ONLY IF VWF/VIII PRODUCT NOT AVAILABLE!
  - 1 bag/10 kg q 12 to 24 hours depending upon the bleeding
- epsilon amino caproic acid (Amicar)

Comparison Between Haemophilia & von Willebrand's Disease

Character	Haemophilia A	Von willebrand's disease
Inheritance	Sex linked (♂ affected)	Autosomal (♂ & ♀)
Bleeding time	Normal	Prolonged
VIII C	↓	↓
VIII C: Ag	↓	↓
VIII R	Normal	↓

Factor IX deficiency (Haemophilia B or Christmas Disease)

- Inherited disorder shows the same pattern of inheritance as haemophilia A (sex linked).
- Same clinical picture but incidence of disease = 1/5th of the haemophilia A .
- Treated by factor IX concentrate .

Acquired Disorders Of Coagulation

- **Vitamin K deficiency**

Vitamin K is necessary for γ carboxylation of precursors of factor II (prothrombin) & some other coagulation factors(VII ,IX & X). It is fat soluble ,present in leaf vegetables & also synthesized by the normal intestinal flora.

Dietary deficiency of sufficient severity to produce bleeding is well recognized in:

- Neonates (Haemorrhagic Diseases of the newborn) in whom normal bacterial flora is not yet established.
- In children & adults(malnourishment).
- ↓ absorption in billiary obstruction, coeliac disease.

Liver disease

- Liver is the site of synthesis of most coagulation factors.
- Severe impairment of liver lead to combined factor deficiency particularly II , VII ,IX ,X, &
- I (fibrinogen).

- **Renal Impairment**

- Lead to thrombocytopenia ,platelet dysfunction ,(II ,VII ,IX ,X ,XIII) ,DIC.

- **Warfarin therapy**
- Oral anticoagulant act as competitive inhibitor of vit. K ,suppressing the synthesis of four vit. K dependant clotting in the liver prothrombin (factor ll ,VII ,IX & X .

Control of Warfarin Therapy by

- Doing prothrombin time
- Control = seconds.
- Test = seconds.
- Test/control ratio (R) =
- INR (international normalized ratio) =
- Accepted INR = 2 - 3.5
- INR = (R)^s
- S= sensitivity index ,fixed figure provided by manufacturer of the kit (e.g S = 2)

Heparin therapy control

- Coagulation (Clotting) time
- Thrombin time
- Activated Partial Thromboplastin Time (APTT)

Disseminated Intravascular Coagulation (DIC)

- wide spread deposition of fibrin in the small vessels of many organs causing tissue necrosis & multiple organ dysfunction and subsequent bleeding state due to consumption of platelets & clotting factors and secondary enhancement of fibrinolytic activity . Microangiopathic haemlytic anaemia is a common accompaniment.

Causes of DIC

- Extensive burn
- Septicaemia
- Shock
- Liver disease
- Renal disease
- Complications of labour : retroplacental haemorrhage & aminotic fluid embolism.

DIC: Disseminated Intravascular Coagulation:

1) Bleeding: " Consumption coagulopathy"

- ↓ Platelets (severe)
- ↓ Coagulation factors (I, II, VIII, IX, X)
- ↑ Fibrinolysis

2) Haemolytic Anemia " Microangiopathic"

↓ Hb * RBC Fragmentation

↓ PCV * ↑ Retic

* ↑ Indirect S. Bilirubin.

* Hb uria

3) Thrombotic manifestations:

1) Acute Renal failure
2) Skin Necrosis.
3) CNS ischemia
4) Respiratory Distress.

THANK YOU