DISORDERS of HEMOSTASIS

CLINICAL FEATURES of HEMORRHAGIC DIATHESIS

- petechiae, purpura, bruising – cutaneous/mucosal
- recurrent, severe nosebleeds (no obvious local cause)
- excessive bleeding after dental extraction, surgery, trauma
- recurrent hemarthrosis
- menorrhagia

CLASSIFICATION of HEMOSTASIS DISORDERS

- disorders of blood vessels
- disorders of platelets
- disorders of soluble hemostatic factors

THE MOST COMMON MANIFESTATIONS of:

**VASCULAR/PLATELET DISORDERS**
- mucosal / cutaneous petechiae,
- easy bruising
- nosebleeds
- bleeding during and immediately after surgery or dental extraction,

**SOLUBLE HEMOSTATIC FACTORS DISORDERS**
- bleeding into muscles,
- bleeding into joints
- delayed bleeding after surgery

INITIAL SCREENING TESTS:

Assessment of primary hemostatic mechanism:
1. platelet count (150-400 G/l)
2. temolate bleeding time (up to 8 min)

Assessment of fibrous thrombus formation:
1. prothrombin time (PT: 12-16s);
2. activated partial thromboplastin time (APTT: 22-55s)
3. thrombin time (TT: 15 s)
• prolonged PT with normal APTT indicate factor VII deficiency
• prolonged APTT with normal PT indicate deficiency of one of the factors: VIII, IX, XI, XII prekallikrein, HMW
• prolonged both APTT and PT indicate factor V or X deficiency or acquired depletion of a group of clotting factors (liver diseases, DIC, hemorrhagic disease of the newborn)

newborns and neonates up to 6ms of age present prolonged APTT and INR because of the reduced level of most of the coagulation factors: II, VII, IX, X, XI, XII, PK i HMV (vit K deficiency, hepatic immaturity)

HENOC-SCHÖNLEIN PURPURA
• follows infection or vaccination
• a palpable purpuric rash with the typical lower limbs, buttocks, scrotum and elbows predominance,
• pain and swelling of joints, predominantly ankles
• gastrointestinal pain, bleeding
• hematuria, proteinuria, hypertension in 50% of cases
• normal values of coagulation tests.
• treatment: symptomatic steroids
• possible recurrent attacks

IMMUNE (IDIOPATHIC) THROMBOCYTOPENIC PURPURA
(ITP) the most common platelet disorder in children
peak of incidence between ages 2 and 6 years,
abrupt onset,
petechiae, purpura, ecchymoses, easy bruising –skin/mucosal nose bleeds, menorrhagia, hematemesis, melena, hematuria
laboratory findings: only decreased platelet count, bone marrow normal, often with increased number of megakaryocytes
clinical course: usually acute and self-limited (a few weeks) chronic form> 6 months
management: rest, in severe cases: methylprednisolon 30mg/kg for 3 days, then 20mg/kg for 4 days Prednison 1-2mg/kg for 3-6 weeks
or IVIG 0.4g/kg for 5 days or 1.0 g/kg for 2 days
contradictions: antihemostatic drugs (aspirin), intramuscular injections, vaccination, allergy immunotherapy
Splenectomy-only in chronic form

OTHER NONTHROMBOCYTOPENIC PURPURAS
Acquired:
• drug induced (e.g.,sulfonamide)
• allergic disorders
• secondary to infections
• malnutrition, vit.C deficiency
Congenital:
• Osler-Weber-Rendu disease.
• Ehlers-Danslos Syndrome.

OTHER THROMBOCYTOPENias
Secondary
• infections (CMV, HIV), autoimmune disorders (SLE)
• drug induced
• microangiopathic (DIC, HUS), cyanotic heart disease, hypersplenism
• generalized bone marrow disorders ( aplastic anemia, leukemia)
• allo and autoimmune neonatal purpura
Congenital
• Fanconi anemia
• TAR syndrome
• Wiskott-Aldrich syndrome
• Gaucher disease

DISORDERS of SOLUBLE HEMOSTATIC FACTORS=DISORDERS of COAGULATION
Congenital:
• von Willebrand disease (VWF),
• hemophilia A and B,
• inherited isolated deficiencies of other coagulation factors: XI, X, V, VII, fibrinogen
Acquired:
• vit K deficiency
• liver diseases
• DIC
• acquired inhibitory antibodies to coagulation factors
von WILLEBRANDA DISEASE – the most common inherited bleeding disorder

deficiency or dysfunction of von Willebrand factor autosomally inherited

Clinical manifestations due to variable combinations of:

platelets disorders  factor VIII deficiency

excessive, prolonged bleeding after dental extraction, injury, surgery
recurrent nose bleeds, menorrhagia, bruising, rarely joints and soft tissue bleeds

Lab evaluation: bleeding time, APTT

vWF:RCo (vWF activity), vWF:Ag

multimeric structure of vWF

TYPES of von WILLEBRAND DISEASE

Type 1
80% patients, mild disorder, bleeding after surgery, menorrhagia, parallel vWF:Ag and vWF:RCo

Type 3
severe form, manifestations since infancy, joints bleeds, vWF:AG i vWF:RCo virtually undetectable

FVIII 1-3%

Type 2A
clinically more severe than type 1

vWF:RCo domineering

Type 2B
platelet count

Type 2N
differentiate from mild hemophilia, FVIII: vWF:RCo < 1

Type 2M
vWF does not bind to platelets- qualitative defect of vWF

THERAPY of von WILLEBRAND DISEASE

• Type 1: Desmopressin (DDAVP) of choice: 0.3µg/kg i.v.
• Type 2, Type 3: concentrate containing both FVIII and vWF 20-40-50j/kg
• Type 2B: DESMOPRESSIN CONTRAINDICATED

HEMOPHILIA – X-linked recessive coagulation disorder

HEMOPHILIA A – FVIII (VIII:C) DEFICIENCY
(< 50% of normal level)
incidence of 1:10 000 births
point mutations, inversions, deletions

HEMOPHILIA B – FIX (IX:C) DEFICIENCY
(<50% of normal level)
about 5x less common than hemophilia A
point mutations

SEVERE TYPE of hemophilia: missing factor<1% of normal level

• first bleeding episode < 1 yr of age
• spontaneous hemorrhage
• recurrent joint bleeds
• arthropathy
• life threatening postsurgical bleeds

MODERATE TYPE: missing factor 1-5% of normal level

• serious bleeding after surgery and trauma
• joint bleeds rarely
• arthropathy rarely

MILD TYPE: missing factor 5-50% of normal level

• rare bleedings after surgery, trauma, dental extraction

• mutant gene is carried by females to affect males
• all daughters of an affected male are carriers and all his sons are normal
• certain female carrier:
  a. a daughter of an affected male
  b. mother of at least two affected sons
  c. mother of an affected son and at least one affected relative
JOINT BLEEDS  onset of occurrence 2-3 yr of age
large joints of limbs (knee, ankle, elbow)
painful swelling with warmth
motion limited
ASPIRATION of INTRAARTICULAR BLOOD BEFORE
REPLACEMENT of MISSING FACTOR IS FORBIDDEN
recurrent joint bleeds lead to hemophylic arthropathy

MUSCLE BLEEDS
muscles of thigh, calf, forearm,
may lead to anemia, contractions, neurovascular complications and pseudotumors,
bleeding into iliopsoas may be life threatening.
ASPIRATION of INTRAMUSCULAR HEMATOMA IS FORBIDDEN

LIFE THREATENING BLEEDINGS
• bleeding to the floor of the mouth, throat and the tongue
• retroperitoneal hematoma, injury of spleen
• intracranial bleeding

Headache is an alert symptom in hemophilia and requires the replacement therapy

MANAGEMENT of HEMOPHILIA
Factor replacement therapy:
A. on demand  B. prophylactic
• plasma-derived missing factor concentrate
• recombinant (genetically engineered) missing factor concentrate
  1iu/kg FVIII raises the factor level by 2%
  1iu/kg FIX raises the factor level by 1%
therapeutic level desired in routine bleeds is 30-40%,
in intracranial hemorrhage, before major surgery – 80-100%
antifibrinolytic therapy (epsilon-aminocaproic acid) should be avoided in urinary tract bleeding
aspirin should be excluded,
intramuscular injections are forbidden
rehabilitation
In mild type of hemophilia A : desmopressin i.v.

DEFICIENCY of VIT K-DEPENDENT COAGULATION FACTORS
• classic type: between days 2 and 7 of life in breast-fed babies.
• gastrointestinal, umbilical, intracranial bleedings
prophylaxis:
routine administration of vit K to all newborns.
treatment:
vit. K 2-3 mg sc. or iv.
fresh frozen plasma, concentrates containing factors; II, VII, IX, X.

DIC
I. generalized intravascular activation of the coagulation system,
II. widespread fibrin formation-disseminated thrombosis and fibrinolysis,
III. consumption of clotting factors and platelets-hemorrhagic diathesis
etiology:
infection, injury, burn, hypoxemia, shock, malignancy,
manifestations:
oozing from venipuncture sites, diffuse bruising and petechiae,
bleedings, symptoms of organs' dysfunction,
lab work-up:
in advanced stage:  platelet count, AT, fibrinogen
↑ APTT, PT, D-dimers,
therapy: treat the underlying cause,
  blood products replacement therapy: fresh frozen plasma, platelets concentrates

THROMBOPHILIA
Congenital:
• factor V Leiden – activated protein C resistance,
• mutation in the prothrombin gene,
• Antithrombin (AT) deficiency, protein C deficiency, protein S deficiency, plazminogen deficiency,
• Hyperhomocysteinemia.
Acquired:
• neonatal and early-infancy age,
• intravenous catheters, shock, dysproteinemias.
Antithrombotic and thrombolytic therapy:
• heparin 75 iu/kg bolus, then 20 iu/kg/h, monitoring APTT,
• LMWH 1mg/kg every 12 h sc.
• Streptokinase, IPA