CONGENITAL BLEEDING DISORDERS

MATERIALS FOR STUDENTS

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CONGENITAL BLEEDING DISORDERS

1. Von Willebrand Disease (VWD)
2. Hempohilia A
3. Hempohilia B
4. Rare deficiencies of fibrinogen and factors II, V, VII, X, XIII

VON WILLEBRAND DISEASE

VON WILLEBRAND DISEASE

- the most common inherited bleeding disorder in humans
- quantitative or qualitative abnormalities in von Willebrand factor (vWF)
- von Willebrand factor, a plasma protein serving as a carrier for factor VIII and as an adhesive link between platelets and the damage blood vessel walls
- The overall prevalence of von Willebrand Disease is 1% of the general population
- The prevalence of clinically significant disease is closer to 1: 1000
- Classification:

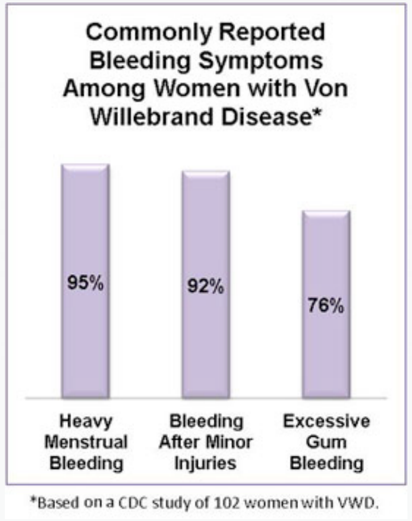
A. Types 1 and 3 are deficiencies of normal VWF, either partial (type 1) or complete (type 3)

B. Type 2 includes the qualitative abnormalities of VWF structure and/of function

- Clinical symptoms the most common symptom:

mucocutaneous bleeding

- **The goals of therapy are to correct the VWF deficiency and shorten or correct the bleeding time**



VWD- CLINICAL SYMPTOMS

- **the most common problems are:**

- ✓ epistaxis (60%)
- ✓ easy bruising and hematomas (40%)
- ✓ menorrhagia (35%)
- ✓ gingival bleeding (35%)
- ✓ gastrointestinal bleeding (10 %)
- ✓ bleeding after trauma is common
- ✓ spontaneous hemarthroses and muscle hematomas occur almost exclusively in patients with type 3 VWD

VWD -LABORATORY FEATURES

- **Screening tests:**
  - ✓ bleeding time- normal or prolonged
  - ✓ aPTT- prolonged or normal
  - ✓ PT- normal
- **The routine tests in a patient suspected of having VWD:**
  - ✓ assay of VWF activity
  - ✓ VWF antigen
  - ✓ Factor VIII activity
- **Additional tests:**
  - ✓ Ristocetin-induced platelet agglutination (RIPA)
  - ✓ Multimers analysis

VWD -THERAPY

- **Therapy -Desmopressin**

- ✓ increases the baseline levels of factor VIII activity, VWF antigen and ristocetin cofactor activity
- ✓ is regularly used in patients with type 1 VWD to treat mild to moderate bleeding, or as a prophylaxis prior to surgery
- ✓ a usual dose 0.3 mg per kg i.v or s.c. every 24 to 48 hours (tachyphylaxis)
- ✓ many type 2 patients and nearly all type 3 do not respond to DDAVP
- ✓ an intranasal form of DDAVP

- **Therapy - VWF Replacement**

- ✓ Patients unresponsive to DDAVP may be treated with VWF-containing factor VIII concentrates, such as Humate P
- ✓ Patients should be treated for 7 to 10 days after major surgical procedures and 3 to 5 days after minor

- **Nonreplacement therapy:**

- ✓ **Estrogen or oral contraceptives in treating menorrhagia and Fibrinolytic inhibitors, such as E-aminocaproic acid and tranexamic acid**

HEMOPHILIAS A AND B

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✔ X-linked hereditary blood clotting disorders due to:

- Deficiency of factor VIII (hemophilia A)
- Deficiency of factor IX (hemophilia B)

✔ Both result from decreased production of deficient factor, production of factor with decreased functional activity , or a combination of these two abnormalities

✔ In patients with haemophilia, clot formation is delayed because thrombin generation is markedly decreased, leading to excessive bleeding

✔ The incidence rate:

- Hemophilia A is estimated to occur in 1 of 10 000 male births
- Hemophilia B is estimated to occur in 1 per 25 000 to 30 000 male births

✔ Found in all ethnic groups, in all parts of the world

HEMOPHILIAS- CLINICAL FEATURES

- **Excessive bleeding into various parts of the body**
  - ✓ hemarthroses and hematomas
  - ✓ hematuria
  - ✓ hemorrhage into the central nervous system
  - ✓ mucous membrane hemorrhage
  - ✓ pseudotumors (blood cysts)
  - ✓ dental and surgical bleeding
- **Hemarthroses** - bleeding into joints accounts for about 75% of bleeding episodes in severely affected patients
  - ✓ The joints most frequently involved: knees, elbows, ankles, shoulders , wrists and hips
  - ✓ Repeated hemarthroses destruction of articular cartilage, synovial hypertrophy and inflammation
  - ✓ The major complication of repeated bleeding is joint deformity complicated by muscle atrophy and soft tissue contractures - **hemopilic artropathy**

INHERITANCE PATTERNS FOR HEMOPHILIA A AND B

30%

DE NOVO MUTATIONS

50%

MEN- HEMOPHILIC MALE

		Hemophilic male Xh Y	
Normal female	X	XX^h Carrier female	XY Normal male
	X	XX^h Carier female	XY Normal male

WOMEN-CARRIER FEMALE

		Normal male XY	
Carrier female	X^h	XX^h Carrier female	X^hY Hemophilic male
	X	XX Normal female	XY Normal male

CLINICAL CLASSIFICATION OF HEMOPHILIA

Level	Percentage of normal factor activity in blood	Number of international units (IU) per millilitre (ml) of whole blood
normal range	50%-150%	0.50–1.5 IU
mild hemophilia	5%-40%	0.05–0.40 IU
moderate hemophilia	1%-5%	0.01–0.05 IU
severe hemophilia	less than 1%	less than 0.01 IU

1 UNIT OF FACTOR VIII/IX/ML = 100% OF NORMAL ACTIVITY

1 UNIT OF FACTOR VIII/IX: EQUAL TO THE AMOUNT IN 1ML OF POOLED FRESH NORMAL HUMAN PLASMA

HEMOPHILIAS- LABORATORY FEATURES

- ✓ Prolonged activated partial thromboplastin time (aPTT)
- ✓ the aPTT is corrected when hemophilic plasma is mixed with an equal volume of normal plasma
- ✓ Normal prothrombin time, thrombin-clotting time, bleeding time
- ✓ A definitive diagnosis of hemophilia A/B should be based on specific assay for factor VIII/IX coagulant activity

- **Carrier females**

- ✓ Carrier females - the average factor VIII level is 50%, but occasionally carriers have less than 30% and may have excessive bleeding
- ✓ Molecular genetic techniques are available to identify carriers
- ✓ Prenatal diagnosis can be made from fatal cells obtained by amniocentesis or by chorionic villus biopsy

THERAPY OF HEMOPHILIAS- GENERAL PRINCIPLES

- ✓ Avoidance of aspirin, non-steroid anti-inflammatory drugs and other agents interfering with platelet aggregation
- ✓ Addictive narcotic agents should be used with great caution
- ✓ Avoidance of intramuscular injections
- ✓ Treat bleeding episodes promptly
- ✓ Home treatment should be available to all patients
- ✓ Plan surgical procedures carefully
- ✓ DDAVP in the treatment of mild to moderate hemophilia A
- ✓ Fibrynolytic inhibitors (epsilon-aminocapric acid EACA, tranexamic acid) may be given as adjunctive therapy for bleeding from mucous membranes, particularly for dental procedure. Doses: tranexamic acid (Exacyl) 1g every 6 h, EACA 4 g every 6 h - adjunctive therapy for mucosal bleeding but contraindicated if the patient has hematuria

- Factor prophylactic therapy should be considered in all severely affected patients (plasma-derived factor concentrates or produced by recombinant DNA technics)

- ✓ Hemophila A: the administration of 25-40 U factor VIII/kg three times weekly **markedly decreases the frequency of hemophilic arthropathy** and other long-term effects of hemorrhages episodes
- ✓ Hemophilia B: the administration of 25-40 U factor VIII/kg three times weekly **markedly decreases the frequency of hemophilic arthropathy** and other long-term effects of hemorrhages episodes

PRINCIPLES OF FACTOR REPLACEMENT THERAPY

- **Factor VIII replacement therapy**

- ✓ The site and severity of hemorrhage determine the frequency and dose of factor VIII to be infused
- ✓ The dose of factor VIII calculation for practical purpose:
- ✓ 1 unit of factor VIII/kg will raise the circulating factor VIII level about 2% (0.02 U/ml)
- ✓ after the initial dose of factor VIII further doses are based on a half- life of 8 to 12 h

- **Factor IX replacement therapy**

- ✓ The dose of factor IX calculation for practical purpose:
- ✓ 1 unit of factor IX/kg will raise the circulating factor IX level about 1% (0.01 U/ml)
- ✓ intravascular recovery of factor IX is about 50% (probably f. IX binds to collagen type IV of the vessel wall)
- ✓ the initial dose of factor IX should be followed by one-half this amount every 12 to 18 h

DOSES OF FACTOR VIII

Site	Desired f. VIII level %	F.VIII Dose Unit/kg	Frequency q hours	Duration, days
Hemarthroses	30-50%	25	12-24	1-2
Superficial intramuscular hematoma	30-50%	25	12-24	1-2
Gastrointestinal tract	50%	25	12	Until resolved
Epistaxis	30-50%	25	12	Until resolved
Hematuria	30-100%	25-50	12	Until resolved
Central nervous system	50-100%	50	12	At least 7-10 days
Retropharyngeal, retroperitoneal	50-100%	50	12	At least 7-10 days

THERAPY OF HEMOPHILIAS - FDA-APPROVED TREATMENTS- LONG HALF-LIFE PRODUCTS

- ✔ **Antihemophilic factor (recombinant), Fc fusion protein (Brand name: Eloctate)** for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, FACTOR VIII with the potential for extended dosing intervals—up to every 5 days

- ✔ **Emicizumab-kxwh (Brand name: Hemlibra)** received expanded approval for the routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors, has a half-life of 4 weeks

Half-life prolongation techniques include the following:

- (1) site directed or non–site-specific pegylation,
- (2) fusion with prolonged half-life proteins, such as IgG-Fc or albumin,
- (3) protein modifications

FACTOR INHIBITORS

- ✔ Develop as alloantibodies in patients with congenital hemophilia
- ✔ Replacement therapy becomes ineffective or markedly impaired
- Treatment with bypassing products (rFVIIa or FEIBA), is generally the first choice in a patient with hemophilia A or B who has a high-titer inhibitor and requires treatment
- ✔ **rFVIIa** (NovoSeven) – Dosing of rFVIIa is typically 90 to 120 mcg/kg every two to three hours until hemostasis is achieved and at three- to six-hour intervals after hemostasis has been restored
- ✔ **FEIBA** (activated prothrombin complex concentrates (aPCCs) such as FEIBA - factor eight inhibitor bypassing agent) – Dosing of FEIBA is typically 50 to 100 units/kg every 6 to 12 hours, not to exceed 100 units/kg/dose or 200 units/kg/day
- ✔ Recombinant porcine factor VIII (hemophilia A) — Another option for a patient with hemophilia A and a high-titer inhibitor is recombinant porcine (pig) factor VIII (Obizur)

OTHER UNCOMMON INHERITED DEFICIENCIES

THE OTHER UNCOMMON INHERITED DEFICIENCIES OF COAGULATION FACTORS

1. Bleeding tendencies caused by inherited deficiency of factors I, II, V, VII, X, XI and XIII, rare disorders, distributed worldwide

2. Treatment may be necessary during spontaneous bleeding episodes, during or after surgical procedures

3. In most deficiency states fresh frozen plasma replacement is used, but specific concentrates of factors are also available

4. The severity of the bleeding disorder usually relates to the severity of the factor deficiency