The rare coagulation disorders

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The rare coagulation disorders are inherited abnormalities of hemostasis.
Inheritance: autosomal recessive.

Overall frequency in general population is low:
1: 500 000 – 2 000 000.
It is found more frequently in areas of the world where marriage between relatives is common.

Diagnosis and management may be difficult.
Generally heterozygotes (factor level ~ 50%) have no significant clinical manifestations.

Common symptoms:

- **Epistaxis**
- **Easy bruising**
- **Menorrhagia**
- **Bleeding in the mouth (mostly after dental surgery or tooth extraction**
- **Bleeding during or after injury, surgery, or childbirth**
- **Rare symptoms: gastrointestinal-, central nervous bleeding, hematuria, umbilical cord bleeding at birth.**

Fibrinogen (FI) deficiency:

- ***Prevalence:*** **1: 1 000 000**
- ***Forms:***
  - **Afibrinogenemia: absence of fibrinogen**
  - **Hypofibrinogenemia: decreased level of fibrinogen**
  - **Dysfibrinogenemia: stucturally abnormal fibrinogen**
- ***Laboratory:*** **thrombin time ↑**
- ***Clinical picture:*** **very variable mucosal hemorrhage, umbilical bleeding, impaired wound healing. Thrombosis in some patient with dysfibrinogenemia!**
- ***Treatment:***
  - **fibrinogen concentrate /Haemocomplettan/ (half- life of infused fibrinogen is 3-5 days)**
  - **Dysfibrinogenemia: in individuals with thrombotic risk: anticoagulant prophylaxis may be indicated in addition to replacement therapy**

Prothrombin (FII) deficiency:

- ***Prevalence:*** **1: 2 000 000**
- ***Forms:***
  - **Complete deficiency may be incompatible with life**
  - **Hypoprothrombinemia (Type 1)**
  - **Dysprothrombinemia (Type 2)**
- ***Laboratory:*** **both prothrombin time (PT) and activated thromboplastin time (APTT) ↑, FII assay**
- ***Clinical picture:*** **variable**

  severe deficiency: hemarthros, hematoma, umbilical bleeding, intracranial hemorrhage
- ***Treatment:*** **Prothrombin complex concentrate (PCC)**

Factor V deficiency:

- ***Prevalence:*** **1: 1 000 000**
- ***Forms:*** **quantitative or qualitative defects**
- ***Laboratory:*** **both prothrombin time (PT) and activated thromboplastin time (APTT) ↑, FV assay**
- ***Clinical picture:*** **variable**

  moderately severe bleeding tendency which presents in childhood: easy bruising, mucous membrane bleeding, epistaxis, joint and muscle bleeding
- ***Treatment:*** **- Fresh frozen plasma (FFP) – FV-concentrate does not exist!**

  - Platelet transfusion may be benefit – FV in the platelet granules.

Combined deficiency of FV and FVIII:

- ***Prevalence:*** **1: 2 000 000**
  most cases in Israel, Iran, Italy.
- ***Laboratory:*** **both prothrombin time (PT) and activated thromboplastin time (APTT) ↑,**
  FV and FVIII assay
- ***Clinical picture:*** **spontaneous bleeding is rare**
  bleeding after surgery and dental extractions, menorrhagia, postpartum hemorrhage.
- ***Treatment:*** **- Fresh frozen plasma (FFP) + FVIII-concentrate**
  - Desmopressin (DDAVP)

Factor VII deficiency:

- ***Prevalence:*** **1: 500 000, the commonest of the rare bleeding disorders**
- ***Laboratory:*** **prothrombin time (PT) ↑, other tests: normal**
- ***Clinical picture:*** **relatively poor correlation between FVII level and bleeding manifestations.**

  Mucous membrane bleeding, menorrhagia.

  In severe deficiency: joint bleeding, intracranial hemorrhage (often in the neonatal period → at delivery of a potentially affected newborn is necessary to avoid instrumental delivery!)
- ***Treatment:***

  - Recombinant FVIIa concentrate (rFVIIa, NovoSeven)

  The half-life of FVII is short → treatment needs to be given every 2-4 hours!

  - Prothrombin complex concentrate (PCC) containing FVII

Factor X deficiency:

- ***Prevalence:*** **1: 1 000 000**
- ***Laboratory:*** **both prothrombin time (PT) and activated thromboplastin time (APTT) ↑, FX assay**
- ***Clinical picture:***

  - severe deficiency: severe bleeding, risk of intracranial bleeding in the neonatal period, epistaxis, menorrhoea, joint bleeding, spontaneous abortion at first trimester.

  - mild deficiency: no bleeding history, may be discovered incidentally.
- ***Treatment:***
  - **Prothrombin complex concentrate (PCC) /FIX concentrate does not exist./**

    (half- life of infused FX is 60 hours)

Factor XI deficiency (Hemophilia C):

- **It differs from Hemophilia A and B: inheritance: autosomal, no bleeding into joints and muscles.**
- ***Prevalence:*** **1: 1 000 000. Most common in Ashkenazi Jews.**
- ***Laboratory:*** **activated partial thromboplastin time (APTT) ↑, FXI assay**
- ***Clinical picture:*** **most people will have little or no symptoms at all. The relationship between the amount of FXI and the severity of symptoms is unclear. May be menorrhagia, bleeding after childbirth, bleeding after circumcision.**
- ***Treatment:*** **- Factor XI concentrate**
  - antifibrinolytic drugs (tranexamic acid)

Factor XIII deficiency:

- ***Prevalence:*** **1: 1 000 000**
- ***Laboratory:*** **diagnosis is difficult. All standard coagulation tests are normal. Urea solubility test (insensitive), FXIII assay (in specialized laboratory)**
- ***Clinical picture:*** **variable clinical severity. In severe deficiency: excessive bleeding from umbilical stump, risk of intracranial bleeding in the neonatal period, skin bruising, muscle and joint bleeding, spontaneous abortion, poor wound healing.**
- ***Treatment:***
  - **FXIII concentrate (Fibrogammin) - Because of the high risk of intracranial hemorrhage in severe deficiency, prophylactic treatment is offered. (Half- life of infused FXIII is long, enough to give every 4-6 weeks)**