Hemophilia A

Genetics

-Gene: F8 (Coagulation factor VIII; Xq28)

-XLR

Clinical findings/Dysmorphic features

-Deficiency in factor VIII clotting activity --> prolonged oozing after injuries, tooth extractions, surgery; delayed or recurrent bleeding prior to complete wound healing; excessive bruising

-Severe: diagnosed during first two years; bleeding from minor mouth injuries and large "goose eggs" from minor head bumps; spontaneous joint bleeds or deep-muscle hematomas; hemarthrosis or intracranial bleed with mild or no trauma

-Moderate: seldom spontaneous bleeding; prolonged or delayed oozing after relatively minor trauma; usually diagnosed before age 5-6 year

-Mild: no spontaneous bleeding episodes; abnormal bleeding with surgery or tooth extractions

Etiology

-Birth prevalence of hemophilia A in the United States is approximately 1:6,500 live male births

Pathogenesis

-Normal Factor VIII circulates as an inactivated clotting cofactor; gets activated by thrombin

-Severe: absent protein, mild-mod: abnormal protein

Genetic testing/diagnosis

-Decreased factor VIII clotting activity and normal von Willebrand factor level (severe: <1%, moderate: 1-5%, mild: 6-35%); prolonged activated partial thromboplastin time (aPTT)

-Severe: F8 intron 22 gene inversion (48%)/F8 intron 1 gene inversion (3%)/F8 gene del, rearrangement, frameshift, splice, nonsense mutations (40%)/missense mutation (10%)

-Mild-moderate: missense mutation (97%), no intron inversions

Others

-Approximately 30% of heterozygous females have clotting activity below 40%

-Intravenous infusion of factor VIII concentrate