HEMOPHILIA: A X-LINKED RECESSIVE BLEEDING DISORDER

Amy Renyue
Stuyvesant High School
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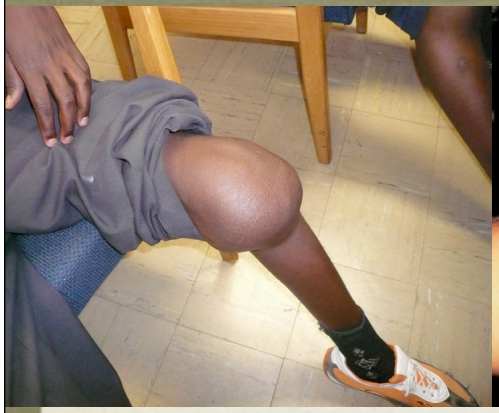
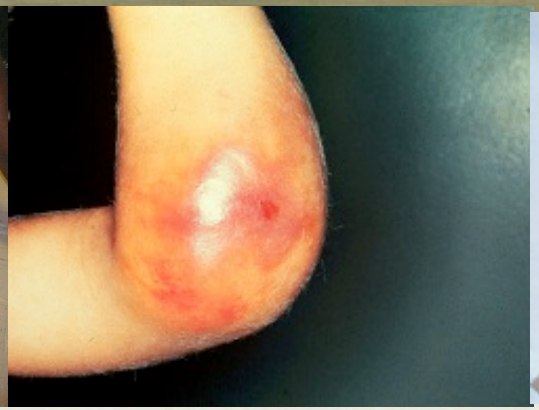
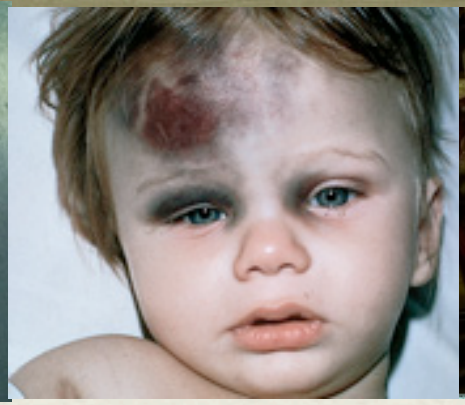
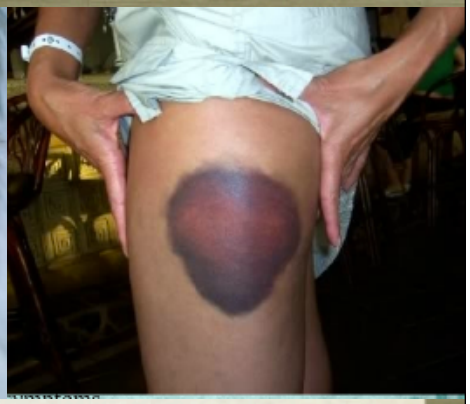
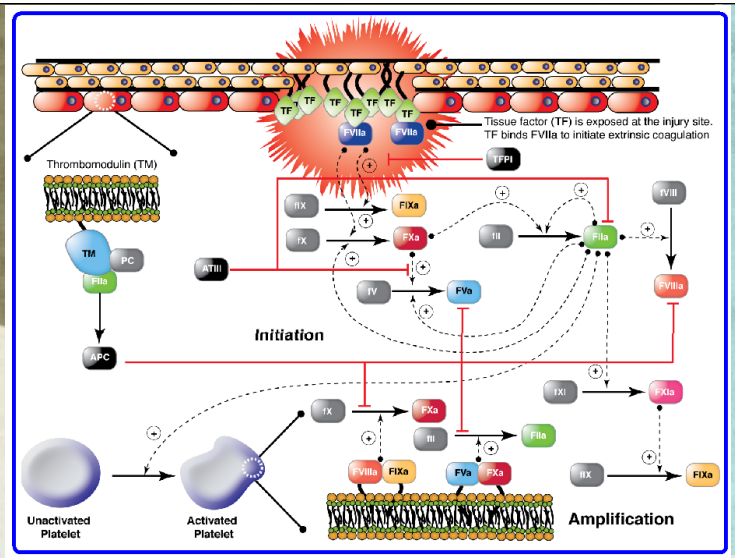
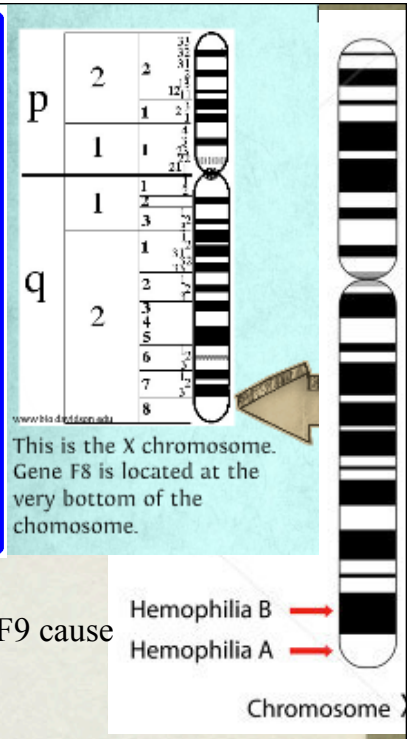
PHYSIOLOGY

~Hemophilia A is most common, around 1 in 5,000 males worldwide are born with this disorder
~Hemophilia B more rare: 1 in 20,000 new born males
~There is also the very rare condition of hemophilia C (F11 gene mutation; on chromosome 4)
~Hemophilia A and B are caused by mutations on the F8C and F9 genes, respectively
~ Onset at birth
~Symptoms: spontaneous bruising, bleeding in the bowel, the brain and soft tissues, which can lead to throwing up blood or passing blood in feces or urine; sudden severe pain in the joints or limbs; bleeding into the soft tissues of the arms and legs which lead to nerve damage
~ The symptoms vary depending on whether the person has the mild, moderate, or severe form, which is caused by the lack of clotting factors. Patients often have some level of working clotting factor.
~Severe hemophilia have less than 1% active factor. Spontaneous joint bleeding, bleeding in brain
~Moderate hemophilia 1-5% active factor. Longer bleeding after small injuries
~Mild form of hemophilia (5-30% active factor), do not have spontaneous bleeding, longer bleeding may still result after surgery, teeth removal or major injuries

MOLECULAR CAUSE





~Transmission: X-linked recessive; Spontaneous mutation can happen.
~Mutations of F8C cause deficiency/ dysfunction of clotting factor VIII (hemophilia A); mutations of F9 cause deficiency/ dysfunction of clotting factor IX (hemophilia B)
~Factor IX functions as a protease and factor VII functions as a cofactor.
~Hemophilia A and B have similar clinical manifestations because both factor VIII and factor IX are required to form the X-activating complex (the lack of either leads to a similar lack of platelet X-activation activity, thrombin/coagulation factor II generation is decreased)
~ In about 20% of all cases, hemophilia is caused by a spontaneous gene mutation
~The position of FVIII gene is Xq28 and of FIX is Xq27.1 location on distal long arm of chromosome X
~On about half of the patients who suffer from severe hemophilia A, there is a large inversion in intron 22 of their FVIII mRNA which it is repeated
~Detected some gene mutations on FVIII as insertion, deletions or point mutations which involved in the reduced or cut up in FVIII activation
~Common F9 mutation for hemophilia B is a promoter defect which is caused by point mutation

TREATMENTS

~ Treatments vary depending on the severity of the disease.
~For mild hemophilia , treatment may involve slow injection of the hormone desmopressin (DDAVP) into a vein (or given as a nasal medication) to stimulate a release of more clotting factor to stop bleeding
~ For moderate to severe hemophilia, bleeding may stop only after an infusion of clotting factor derived from donated human blood or from genetically engineered recombinant clotting factors. Repeated infusions may be needed if internal bleeding is serious
~ The basic treatment to stop or prevent bleeding in people with hemophilia A and B is factor replacement therapy.
~This is the infusion/ injection into the bloodstream of factor VIII or IX concentrates to prevent or control bleeding. This replacement of the congenitally deficient factor VIII or IX through plasma-derived or recombinant concentrates is the mainstay of treatment.
~ These concentrates come from either human plasma (a component of blood) or a genetically engineered cell line made by recombinant DNA technology
~However, the replacement of the missing clotting factors needs to be done often
~Half of the clotting factor activity which was infused is removed by the body every 12 to 24 hours. This means that within 2 or 3 days almost none is left.
~Depending on the patient/ the severity of the disease, factor concentrates are given from day-to-day bases to only in cases of an accident or surgery. (This preventative therapy should be considered in all severely affected patients)
~Complications of replacement therapy include the developing antibodies (proteins) that attack the clotting factor and developing viral infections from human clotting factors. Antibodies can destroy the clotting factor before it has a chance to work, which prevents replacement therapy from working. These antibodies, aka inhibiters, develop in about 20 percent of people who have severe hemophilia A and develop in about 1 percent of people who have hemophilia B.

PROPOSED CURE/LIMITS

~The immune system tend to kills all the delivery viruses that carry the intact copies of Factor XIII and IX to replace with the defective one before the genes have an effect on the body.
~Researchers discovered more effective delivery virus and steroids that prevent the immune system from killing the viruses.
~The virus used in the treatment is called ‘adeno-associated virus-8’. This virus functions better in the treatment that other kinds of viruses can randomly invade into chromosomes, making a change in a gene, whereas ‘adeno-associated virus-8 only stays outside the chromosomes’
~ Additionally, factor IX is generally produced by liver cells, which are targeted by this virus, it helps the therapy efficient. The negative aspect, however, is that as liver cells do not last eternally the length of time the therapy lasts really depends on liver cells.

~Technically speaking, the only real cure for hemophilia is liver transplant, because clotting factor is made in the liver.
~But it only makes sense to do liver transplants with end-stage liver diseases because it will be lifesaving.
~Propose instead, perhaps only using parts of the liver, as in cells that line the liver might be useful. For example, transplanting healthy liver cells into patients with hemophilia may allow them to produce missing clotting factors.

~Propose to use the adeno-associated virus-8 as delivery in combination with the transplanting of liver lining.

~This still have some risks of danger, and might not be worth it because replacement therapy is a great choice.

REFERENCES

- Physiology Slide

Images and Content:

Swollen Knee (figure 1), Bruised Knee (figure 4):
--->http://www.glogster.com/hvonallman14/hemophilia-hannah-von-allman/g-6lp1908md279somecki1ga0

Internal Bleeding in Arm (figure 2)
--->http://biol1020-2012-1.blogspot.com/2012/03/hemophilia-b.html

Bruised Child (figure 3)
--->http://www.accessmedicine.ca/search/searchAMResultImg.aspx?rootterm=contusions&rootID=17135&searchType=1

Molecular Cause Slide:

Images and Content:

Chromosome (figure 7)
--->http://www.shutterstock.com/g/alila/sets/22221-molecular-cell-biology-genetics

Chromosome (figure 6)
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Molecular Pathway (figure 5)
--->http://www.varnerlab.org/coagulation

--->http://www.mayoclinic.com/health/hemophilia/DS00218/DSECTION=symptoms

Treatment, Proposed Cure/Limits Slides

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--->http://www.nhlbi.nih.gov/health/health-topics/topics/ hemophilia/treatment.html

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