Holy C.O.W.!

It's…

Clinical Question of the Week #25
December 15th, 2008 through December 22nd, 2008

Welcome to the Winter Holidays version of Holy C.O.W.! Please e-mail your answers to Kuo, Tim, Wendy, and Kevin (klian@mednet.ucla.edu; tprovias@mednet.ucla.edu; wsimon@mednet.ucla.edu; kbreger@mednet.ucla.edu) by 0800 on Monday, December 22nd, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize! **This will be the final Clinical Question of the Week for 2008 – see you next year!**

Case: A 27-year-old man presents to the Emergency Department with acute onset of right knee pain and swelling. He was in his usual state of health until the day of presentation when he developed sudden onset of warmth sensation in his knee followed immediately by swelling and severe pain. Earlier in the day, he had gone on a walk through the woods Griffith Park and felt his knee to be somewhat stiff, but had no significant trauma. His past medical history is notable for some sort of left ankle injury as a young child. Family history is notable for similar injuries. Physical examination reveals a diffusely tender and swollen right knee with slightly decreased range of motion. An MRI is obtained, and PACS also has a knee radiograph from an office visit four months ago.

Prior radiograph and T2-weighted MRI (right) obtained on presentation of the patient's right knee.

Questions:

1. **What is the diagnosis? Describe the genetic basis of this condition.**
   Hemophilia A (Factor VIII deficiency) and hemophilia B (Factor IX deficiency, also known as **Christmas Disease**) are part of a group of inherited disorders of coagulation and platelet function (the most common of which is von Willebrand disease). Hemophilia A (also known as classic hemophilia) and hemophilia B are X-linked disorders, affecting 1:5,000-10,000 males and 1:25,000-30,000 males, respectively. In each of these disorders, approximately 2/3 of A individuals and 1/2 of B individuals those affected have severe disease, with factor activity <1% of normal – this severity is also inherited. While the disease is predominantly seen is males, females may be affected via de novo mutations or when a carrier female and affected male mate and produce female offspring (1:2 affected).

   Interestingly, a subgroup of B individuals have the Leyden phenotype, in which a mutation occurs in the hepatocyte nuclear factor 4 (HNF-4) binding site, and results in a severe disease during childhood that gets milder after puberty – possibly due to the fact that the adjacent site for the androgen response element on the gene is not affected. Also, coinheritance of a Factor V mutation or other prothrombotic markers occurs in a small population of A individuals, resulting in milder disease as well.

   If genetics/family history are not already known, the initial presentation usually manifests as a bleeding:
   Perinatal – subgaleal/intracranial hemorrhage, circumcision
   Children – excessive bruising, hemarthroses (seen with hematocrit level in MR image above), hematomas
   Adult – in milder disease, excess bleeding with trauma or surgery
   In addition to the above, sites of bleeding also include muscular hematoma, naso/oropharyngeal bleeding, GI bleeding, and GU bleeding. (1, partial credit for vWD)

2. **Name two other manifestations of the disease.**
   Late manifestations of the disease include:
   1. Hemophilic arthropathy due to joint destruction in patients with hemarthroses (seen in the radiograph above), including dense fibrosis and decreased mobility of the joint.
   2. Infection due to contamination of blood products (traditionally the hepatidities and HIV in the past, however this is becoming vanishingly rare given the screening). Given the multiple donors involved in producing factor in the past, the risk of becoming infected with a contaminated product was relatively high. However, with the advent of recombinant factor and high-grade purification techniques, viral transmission via infected blood products is becoming more a thing of the past.
   3. Factor inhibitor development due to the production of specific IgG, occur in 25-30% of A individuals and 3-5% of B individuals, leading to decreased response during bleeding episodes. Presence of factor inhibitors have also been associated with a maturational delay in children.
   4. Finally, individuals who are affected or carriers of hemophilia appear to have a reduced CHD risk, not accounted for by usual cardiac risk factor adjustment (1)

3. **What tests are used for diagnosis?**
   Diagnosis is made mostly via family history and genetic testing, however no family history is present in up to 1/3 of cases, thought due to de novo mutation, or maternal fetal loss of affected individuals resulting in a line of carrier females with negative family history. Laboratory analysis will reveal normal platelet count, normal prothrombin time, but prolonged activate partial thromboplastin time. Mixing study will correct with hemophilia but will not correct in the presence of factor inhibitor. Specific factor VIII and IX levels are also obtained. In contrast, von Willebrand disease is diagnosed with the ristocetin cofactor assay (plasma vWF activity), bleeding time, and platelet function assays. (0.5)

4. **What is the treatment?**
   Treatment involves comprehensive preventative care, including consideration for holding circumcision if applicable, giving deep IM vaccinations via subcutaneous route, routine careful dental care, and appropriate genetic counseling. Replacement therapy for bleeding episodes includes plasma derived products including cryoprecipitate, but when available specific factor replacement is used, including specific recombinant factor when available. (0.5)

**Christmas disease was named such in 1952, when it was discovered that when the blood of two hemophiliacs were able to clot when mixed. One of the patients, Stephen Christmas, was found to have a variant form of hemophilia, subsequently named Hemophilia B. Other notable individuals with hemophilia include Prince Leopold, son of Queen Victoria, and Alexei, son of Russia's Tzar Nicholas II.