

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on “**Hemophilia.**” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Hemophilia

Developed by Adam Neufeld, Brendan Lee, and Dr. Roona Sinha for PedsCases.com.
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Introduction:

Hello, and welcome to this podcast on pediatric hemophilia. My name is Adam Neufeld, and my colleague’s name is Brendan Lee. Both of us are third year medical students at the University of Saskatchewan. This podcast was supervised by Dr. Roona Sinha, a pediatric hematologist and oncologist at the University of Saskatchewan. Special thanks to Dr. Sinha for her contributions and expert guidance on the making of this podcast.

We would like to cover several important objectives to help solidify the important concepts regarding the management of hemophilia. At the end of this podcast, we’ll finish with a summary of the key learning points to help bring it all together.

Objectives:

The objectives of this podcast are to:

1. Review the pathophysiology, inheritance, and epidemiology of hemophilia
2. Discuss how hemophilia presents clinically
3. Outline disease sequelae and severity
4. Review the diagnostic tests for hemophilia
5. Discuss the management of a child with hemophilia, and
6. Outline the benefits and risks associated with physical exercise and sports

Before we dive into covering the objectives, however, let’s first start with a case.

Case:

You are working in a family medicine clinic and are seeing Daniel, who is an 18-month-old boy who presents with a 1-day history of worsening right elbow swelling. His parents are with him.

While playing at daycare, Daniel tripped and banged his arm into the corner of a wall. Within minutes, his elbow began to hurt and swell. Concerned for Daniel, his daycare worker informed his parents at the end of the day, who noticed some bruising but little else. There were no signs of swelling or bruising anywhere else, no fever or signs of illness, and Daniel’s energy was still up, so they figured he’d just recover and put him back into daycare the next day, as per routine. Over the next day, however, Daniel’s arm continued to swell until his elbow range of motion was sufficiently decreased to the point he could not extend his arm. At this point, Daniel was displaying significant signs of pain and discomfort. His caretaker called his parents, who came to pick him up from daycare, and brought him to clinic.

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On a systematic review of Daniel's presenting illness, there was no sign of fever or malaise, no changes in his energy or appetite, bowel or urinary habits, and no nausea or vomiting. Upon further questioning, the parents explained his elbow had never swollen up like this before, although they always noticed Daniel, who was an active child, bruised quite easily. There was no family history of bleeding disorders known.

On physical exam, Daniel looked well and vitals were all within normal range. There were no signs of reduced mentation, no pallor or jaundice, nor any indications of physical abuse. On an MSK exam of his upper and lower limbs, there was a swollen bruised right elbow, with reduced range of motion on passive extension, which caused significant discomfort. The joint was warm to the touch, with a moderate effusion present.

Given the obvious bruising and inflammation of the elbow, you tell Daniel's parents that he has a right elbow hemarthrosis, and that you will order some blood work to help sort out the diagnosis.

Pathophysiology, inheritance, and epidemiology

Now, with this case in mind, let's move into the definition of hemophilia, and start by discussing the pathophysiology, inheritance pattern, and a little bit about the epidemiology.

First off, to understand what hemophilia is, it's important to first understand the basic principles of hemostasis.

Clotting factors are proteins in the blood which control bleeding. There are many different clotting factors, made by the liver and the body's endothelial cells, which work together in a series of chemical reactions to stop bleeding when it occurs. Hemophilia is a condition in which the ability of the blood to clot is severely reduced. The diminished capacity is usually caused by a hereditary lack of a coagulation factor.

Hemophilia is an x-linked or "sex linked" recessive inherited bleeding disorder, caused by absence, deficiency, or dysfunction of plasma coagulation factor VIII (in hemophilia A), or factor IX (in hemophilia B). Thus, hemophilia primarily only occurs in males, while other clotting disorders can occur equally in males and females. Affecting approximately 1/5,000 people, it is estimated to affect over 400,000 people worldwide. Unfortunately, only 25% of those affected receive adequate treatment and care for their condition.

In terms of inheritance, when a father has hemophilia but the mother does not, none of their sons will have it, and all the daughters will carry the hemophilia gene. If a woman inherits a copy of the altered gene from either of the parents, she is said to be a "carrier". Therefore, she'll have 1 normal and 1 altered gene, and can pass either onto her children. For each child, there's a 50% chance that a son will have hemophilia, and a 50% chance that a daughter will carry the gene.

On average, carriers of the hemophilia gene will have about 50% of the normal clotting factor, but some carriers have far lower levels. Therefore, depending on the genetic predisposition to factor levels, a carrier may in fact have symptoms of hemophilia.

Rarely, hemophilia can be acquired, typically later in life, often involving middle aged or elderly people, or young women who have recently given birth or are in later stages of pregnancy. This condition often resolves with treatment. Hemophilia can occur when there is no family history.

This is called 'sporadic hemophilia', and about 30% of those with hemophilia acquire it through a sporadic mutation. However, as inherited forms of hemophilia A and B are most common, those will be the primary focus of this podcast.

Clinical presentation

Next, let's cover the clinical presentation of hemophilia and its symptoms. Hemophilia is characterized not by faster bleeding, but by bleeding that can occur for longer than others, typically internally, into muscles and joints. However, most patients with hemophilia present with a family history – therefore testing at birth is recommended if suspected.

The signs and symptoms are essentially the same for hemophilia A and B, which include bruising, hemarthroses (or bleeding into joints), spontaneous bleeding, prolonged bleeding (e.g. after circumcision, after getting a cut, a tooth removed, or during/after surgery), and bleeding for a long time after an injury.

While other medications or conditions can cause easy bruising or bleeding (e.g. patients on anti-coagulation drugs like aspirin, Warfarin, Heparin, etc.) can cause bleeding, bleeding disorders are important to keep on your working differential diagnosis, especially in young males and if there's a family history!

Disease sequelae and severity

It is necessary to treat hemophilia, especially if it is severe. Left untreated, bleeding into muscles and joints can cause severe joint damage. For example, repeated hemarthroses can lead to synovitis, which is inflammation of the synovial membrane that lines the joint, which is painful, especially when moved. Chronically, this can lead to joint degeneration and arthropathy. Over longer periods of time, this can also lead to joint contractures, limited range of motion, and chronic pain – where the elbows, knees, and ankles are the most affected. If severe, life-threatening bleeding can also occur (e.g. intracranial, vital organs, airway) requiring emergent treatment.

Importantly, treatment is generally effective in controlling these symptoms, and thus presentations like the ones mentioned typically only present in patients who are either not being treated, and/or who are presenting for the first time.

As mentioned, severity is an important consideration of hemophilia, which can vary from asymptomatic to mild to severe. The severity of the condition and its subsequent symptoms depends primarily on the amount of clotting factor a patient has. Typically, those with mild hemophilia have been shown to have between 5-40% of the normal clotting factor amount. Those with moderate hemophilia have between 1-5%. Those with severe hemophilia often have less than 1-2% of the normal level of clotting factor, and these individuals can have spontaneous bleeding even without trauma. As a reference, those without hemophilia commonly have between 50-150% of these clotting factors present at any time.

Now, if hemophilia and its severity is based on clotting factor availability, you can already guess how the diagnosis is made.

Diagnosis

Diagnosis of hemophilia is made by taking a blood sample and confirming the level of blood clotting factor present (like factor VIII and IX in hemophilia A and B, respectively), as well as ordering coagulation studies like partial thromboplastin time (PTT). In this case, factor levels would be reduced, and the PTT would be increased.

As an aside, it would be important to rule out other bleeding disorders like Von Willebrand's Disorder, which is the most common bleeding disorder, often presenting with milder, mucocutaneous bleeds (e.g. epistaxis). VWD factor antigen can be measured in the blood.

Finally, if a mother is a known carrier, testing can be done before a baby is born. Prenatal diagnosis can be done at 9-11 weeks by chorionic villus sampling, or be fetal blood sampling at a later stage (e.g. 18 or more weeks). Otherwise, a cord blood sample after delivery can be used to determine if a male baby has hemophilia or not. Prenatal tests can be done at a hemophilia testing center, which are available in most major cities in Canada.

Treatment

Treatment for hemophilia is very effective, but it can be complicated. It is therefore important to have a multidisciplinary bleeding disorder care team, including a hematologist, on board. It is recognized that access to this level of specialized care may vary worldwide.

Basically, there are two types of treatment: prophylactic, and treatment of bleeds. In general, treatment often requires the use of treatment products, of which numerous are available.

In developed countries, factor concentrates are the treatment of choice for hemophilia. These are made from plasma-derived human blood products, or manufactured using genetically engineered products that carry a human factor gene, which is referred to as a recombinant product.

Cryoprecipitate is another option, which is derived from blood and contains a high level of clotting factor VIII (but not IX). However, it is ineffective for joint and muscle bleeds, has a poorer safety profile compared to concentrates, and is more difficult to store and administer.

Fresh frozen plasma (FFP) is a product in which the red blood cells have been removed, leaving the blood proteins, including factors VIII and IX. It is less effective than cryoprecipitate, but does have some benefit for treatment of hemophilia B. However, large volumes of plasma must be transfused, which can lead to circulatory overload.

Although FFP and cryoprecipitate would not be the treatment of choice in developed countries, these are still the only products available for treatment of hemophilia A and B in some countries, and can be beneficial.

Desmopressin (DDAVP) is another alternative in the treatment of hemophilia, which is a synthetic hormone that stimulates the release of the body's intrinsic factor VIII. However, it is only effective for mild to moderate cases, and is most effective for treating hemophilia A.

In terms of treatment, the missing clotting factor(s) is injected into the bloodstream using a syringe, and bleeding ceases when enough factor reaches the bleeding site. Bleeding should be treated as quickly as possible, as this will help reduce pain, as well as damage to joints, muscles, and organs. If treated promptly, less blood products are required, as well. Importantly, for life threatening bleeds, it is crucial for physicians to give a first dose of factor immediately and then investigate further afterward.

With adequate quantity of treatments, people with hemophilia can live perfectly normal and healthy lives. Without adequate treatment, however, disability and mortality are known to be higher, and can significantly affect quality of life. In terms of treatment and quality of life, self-

treatment is the primary goal, and home IV therapy programs exist to help parents and children cope and deal with injecting factor, ideally to empower and make self-treatment a viable option most can do. This has been shown to be cost saving to the healthcare system.

An important aspect of treatment is not only what is needed for treatment, but what to avoid. In terms of medications and herbal remedies, there are a number of contraindications. First of all, avoiding aspirin (ASA) as well as other non-steroidal-anti-inflammatories (NSAIDS) is highly important. Examples are Ibuprofen, Ketorolac, or Naproxen. These interfere with the stickiness of platelets and can exacerbate bleeding problems. Acetaminophen (Tylenol) is a perfectly safe alternative to ASA for pain relief. Lastly, certain herbal remedies should also be avoided. Examples include ginkgo biloba, garlic in large amounts, ginger (although dried is OK), Asian ginseng, saw palmetto, and willow bark. Though this list is not exhaustive, these are some of the most common ones to consider.

For all medications, it is simply recommended to clear it with a pediatric hematologist.

There is currently extensive hemophilia research being conducted on more targeted therapies such as gene therapy (e.g. monoclonal antibodies), and bypass therapy (e.g. targeting inhibitors), that will continue to modify and shape treatment regimens and improve patient outcomes.

Benefits/risks of hemophilia in exercise/sports

A common concern for parents of children with hemophilia is, “what can my son or daughter not do?” The consensus, in general, is that provided treatment is being properly managed, exercise is highly encouraged and has numerous benefits, albeit some risks as well, which we will discuss.

Fitness, anaerobic power, and muscle strength are lower in those with hemophilia. Therefore, they are at higher risk for injury, which can cause bleeding and a higher frequency of medical visits. Affected children and their parents, in anticipation of an injury, or due to pain, may restrict physical activity out of fear. While this is understandable, unfortunately it tends to precipitate social isolation or exclusion, and can contribute to subsequent mental disturbances in conjunction with lack of needed physical exercise. Although hemophilia does not directly negatively affect athletic performance, chronic hemophilic arthropathy can lead to impaired neuromuscular function, diminished muscle strength, and reduced endurance and deconditioning.

According to CPS’s statement on physical activity recommendations for children with hemophilia, participation in collision or contact sports can be especially dangerous, as it can cause life-threatening situations, depending on the severity of the child’s hemophilia. In general, risk factors vary based on individual hemorrhagic tendencies, prophylactic treatment adherence, and sport participation, etc. Careful assessment prior to new physically demanding or rigorous exercise is especially warranted in sports like martial arts, hockey, or football. Consultation with both a sport medicine physician and a hematologist would be recommended.

With those caveats and risks addressed, there are definitely numerous benefits of exercise for those with hemophilia. For example, regular activity has been shown to reduce bleeding episodes, and this is thought to occur due to the increased muscle strength and mass around joints, which provides some added protection against hemarthrosis, as well as increasing stability of joints. Together, these can contribute to reducing injury risk. Weight bearing exercise, especially in children with severe hemophilia, is also highly beneficial for improving bone

mineral density, which they tend to be deficient in. Beyond strengthening, aerobic exercises uniquely benefit coagulation as well. Studies have shown that vigorous exercise can directly modify coagulation parameters in those with mild to moderate hemophilia, and reduce their risk of bleeding.

General recommendations for participation in exercise/sports

In terms of exercise, prophylactic factor replacement is recommended to prevent the risk of bleeding. It is important for the child, and the family, to work with their care team to discuss physical activity and develop a plan. Further, those with hemophilia who partake in sports should undergo regular assessment of joint and muscle function, especially prior to engaging in any new sport or major activity. If restrictions are required, physicians should counsel parents and children and help recommend alternatives.

Importantly, parents of children with hemophilia, especially if they intend to participate in sports, are encouraged to coordinate with school teachers and sport coaches, to prevent or treat bleeds if they occur. This is often facilitated by written strategies, emphasizing use of protective equipment, undergoing physical therapy, and/or taking prophylactic factor replacement therapy. Further, if acute bleeds do occur, factor replacement should be readily available, as well as splinting, ice, and rest protocols. If injured, physical activity should be avoided until joint pain or swelling has resolved, and return to sport requires individualized assessment and appropriate rehabilitation.

Conclusion:

Now, that's quite a bit of information about hemophilia in a short amount of time! We've discussed the pathophysiology and inheritance, the clinical presentation and disease sequelae if untreated, the diagnosis and management, and some information around the risks, benefits, and guidelines to participating in sports/activities. To summarize this PedsCases podcast on hemophilia, here are the most important key concepts:

Key learning points:

1. Hemophilia is an x-linked recessive bleeding disorder which is generally inherited, and is caused by a deficiency of plasma coagulation factor VIII in hemophilia A or factor IX in hemophilia B. Therefore, it primarily only occurs in males. If a female carrier gives the gene to a male, he will have hemophilia, and if she gives it to a female, she will be a carrier.
2. Hemophilia most commonly presents with a family history. For this reason, testing at birth is generally recommended. This is done with blood testing for clotting factor amounts and bleeding time, with coagulation studies.
3. Treatment essentially breaks down into two categories: prophylactic or treatment of bleeds. As treatment is generally very effective in controlling and preventing symptoms, most patients presenting with symptoms are typically not being treated, and/or are presenting for the first time.
4. With life threatening bleeds, it is crucial to give a first dose of factor immediately, and then investigate further afterward. Investigations should not impede this step, in management.
5. Having a multidisciplinary bleeding disorder care team including a hematologist, is important. They work with and involve the parents and the affected child, to empower them to live a full and healthy life. Home IV therapy programs exist and are valuable resources. The goal is to make self-treatment a viable option that most can do safely and comfortably, which has been shown to be cost saving to the healthcare system.

6. Once treatment is in place, there is nothing preventing kids with hemophilia from taking part in regular exercise and sports activities, although rough contact sports are considered higher risk. Therefore, careful precautions and holistic care, including parents, teachers, and coaches should be undertaken.

Well, that's it for our PedsCases podcast on hemophilia. We hope you enjoyed listening and that it was beneficial to your learning. Stay tuned for more PedsCases podcasts!"

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