PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Von Willebrand Disease.**" 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.

Von Willebrand Disease

Developed by Chen Jin and Dr. Mia Lang for PedsCases.com
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Introduction:
Hello everyone, my name is Chen Jin and I am a medical student at the University of Alberta. With the help of Dr. Mia Lang, a pediatrician at the University of Alberta, I have created this podcast to provide an approach and management of pediatric von Willebrand disease (VWD).

Clinical case:
You are a medical student working in the emergency department when a 3 year-old male presents with epistaxis for two hours. After initial packing to stop the bleeding, you take a detailed history and perform a physical exam. The patient's mom is very concerned and reports that this is his second episode of nose bleeding in the past 6 months where she has needed to bring him to the hospital. His vital signs are stable, but on physical exam you do notice there is quite excessive bruising over his knees and ankles. The parent mentions that he does bruise easily and has prolonged oozing from immunization injection sites. She denies a family history of bleeding/clotting disorders. She is very anxious about his symptoms and is concerned that this may affect his ability to participate in physical activities. You suspect a bleeding disorder. In the emergency department setting, what are you next steps?

The objectives for this podcast will include the following:
1. Review the epidemiology, etiology and pathophysiology of VWD
2. Recognize clinical manifestations VWD and other differential diagnosis that may have a similar presentations
3. List pertinent laboratory investigations and abnormalities
4. Discuss the management of VWD as well as patient education

Epidemiology
VWD is caused by a decreased level of functioning von Willebrand factor (VWF), which plays a crucial role in primary hemostasis. Most forms of VWD follow an inherited autosomal dominant pattern that affects males and females equally.
VWD is the most common inherited bleeding disorder and affects approximately 1% of the general population but only 1% of affected individuals may have symptomatic presentations. In the pediatric population, the prevalence of VWD is approximately 0.11% when it comes to presentation to the primary care setting.

Etiology and pathophysiology
VWF plays an important role in the formation of the platelet plug at sites of endothelial damage.

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It functions by binding to platelet glycoprotein 1b to cause platelet aggregation and bridging platelets to the injured vascular sites. In the circulatory system, VWF is generally found in multimers. This particular formation allows for multiple binding sites for platelets as well as injured endothelial sites. In addition, VWF also acts as a protein carrier for factor VIII, the latter of which plays an important role in the formation of the fibrin clot. When factor VIII is not bound to VWF, the half-life of factor VIII is reduced by half.

VWD can manifest with different levels of severity depending on the classification of disease. This can be largely grouped into the 3 major types. Type 1 VWD is the most common type and accounts for approximately 75% of patients with VWD. These patients have a reduced level of functioning VWF and severity of disease could vary depending on the level of factor deficiency. Type 2 and 3 VWD are classified based on underlying pathophysiology and are less common. (Additional details can be found in the appendix section)

Another type of VWD is acquired VWD which is associated with hematologic malignancies, autoimmune diseases such as systemic lupus erythematosus, Wilm's tumour, hypothyroidism and cardiovascular disease such as congenital heart disease and aortic stenosis.
It is interesting to note that the ABO blood group could also affect disease severity. In individuals with type O blood, plasma circulating levels of VWF may be 25-35% lower than individuals from other blood groups, thus explaining the lack of reported family history in certain individuals presenting with VWD.

Clinical manifestations of VWD
Patients with VWD, especially those with mildly decreased levels of VWF, may not seek medical attention due to mild symptoms. A diagnosis of VWD should be considered in individuals who do present with concerns including frequent epistaxis, easy bruising, oral mucosa bleeding, heavy menstrual cycles in females of reproductive age, bleeding from the gastrointestinal tract as well as prolonged bleeding after surgical interventions.

There have been data collection methods developed to assist the diagnosis of VWD including the Pediatric Bleeding Questionnaire (PBQ). The questions are focused on symptoms of mucocutaneous bleeding including frequency and/or duration of spontaneous bleeding as well as difficulties with prolonged bleeding post-trauma and post-surgical procedures. In patients with a lack of family history and presenting with symptomatic bleeding later on in life, always consider the possibility of acquired VWD and treat the underlying cause.

Additionally, it is always important to keep in mind a list of differential diagnosis that may have similar presentations including, but not limited to:
- Hemophilia A, B, C
- Bernard Soulier Syndrome
- Platelet disorders
- Antithrombotic therapies
- Intentional injuries in pediatric populations

Investigations
When considering VWD as a potential differential diagnosis, initial investigations could include CBC which may show a low hemoglobin from bleeding. In addition, patients should be investigated with INR, aPTT, plasma VWF antigen levels, VWF activity levels, and factor VIII levels. Bleeding time may be ordered as it could support the diagnosis of a bleeding disorder if it is abnormal.

For a diagnosis of VWD, a VWF activity and/or antigen level of 30 IU/dL or less is needed. Normal ranges from 50 to 200 IU/dL and the mean level of population is 100 IU/dL.
If these initial investigations are abnormal, additional tests could be done to help distinguish the subtype of VWD including a VWF multimer distribution using gel electrophoresis and a Ristocetin-induced platelet aggregation test.

Treatment and Management options:
For patients who seek medical attention with an active bleeding process, interventions should be initiated to stop the bleeding and ensure hemodynamic stability is achieved.
VWD can present in different types and thus, have different responses to treatment. Pediatric hematology should be involved in patient care when it involves specific treatments.

For patients with a severe deficiency in VWF in a seriously bleeding condition where other interventions trialed have failed, VWF replacement therapy should be considered.
For patients seeking advice for a previous history of excessive bleeding and bruising, management could differ based on disease severity. All patients with a diagnosis of VWD should be advised to minimize trauma and avoid medications that could worsen bleeding symptoms such as antiplatelet agents. For long term pharmacological intervention, desmopressin, an antidiuretic hormone analogue, has been shown to increase plasma VWF and factor VIII levels.

In addition to VWF replacement therapy for an active bleeding process, it is also indicated for short term prophylaxis for patients who have planned surgeries. VWF replacement therapy has not generally been recommended for long term use prophylactically. Cryoprecipitate and fresh frozen plasma is generally not recommended due to the lack of viral inactivation process. In addition, fresh frozen plasma, although does contain VWF in minor quantities, would necessitate large amounts of transfusion to obtain targeted VWF levels.
Other therapies that have been suggested include antifibrinolytic agents, such as tranexamic acid, prophylactically for dental procedures and estrogen therapy for females with menorrhagia.
In severe forms of VWD, patients could consider wearing medical alert devices.

Take home points
● VWD is the most common inherited bleeding disorder affecting approximately 1% of the general population
● Disease severity could vary depending on subtype of disease and not all patients may seek medical attention
● Common presentations include excessive and prolonged mucocutaneous bleeding and easy bruising
● Diagnosis of VWD is made when there is a VWF activity and/or VWF antigen level of 30 IU/dL or less
● Consider acquired VWD as a possible diagnosis in patients with other medical comorbidities such as hematologic malignancies and systemic lupus erythematosus
● Treatment options include VWF replacements on an as-needed basis and desmopressin

References
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Appendix

Other types of VWD

In addition to Type 1 VWD and acquired VWD, there are other types of VWD classified based on pathophysiology. Type 2 VWD is less common than type 1 and the pathophysiology can vary from having decreased of multimer formation of VWF, reduced platelet glycoprotein ib binding, and reduced binding to factor 8. Type 3 VWD is the most rare form of the disease that affects approximately 1 in 1 million but is also the most severe in terms of symptoms. Patients with type 3 VWD have a marked decrease or even absence of VWF that may present with severe mucocutaneous bleeding.

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