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Mini-Review

Von Willebrand's Disease

Jennifer E. Dietrich, MD, MSc
Division of Pediatric and Adolescent Gynecology, Department of Obstetrics, Gynecology and Women's Health, University of Louisville, Louisville, Kentucky, USA

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Objectives

1. To understand the prevalence of von Willebrand's Disease
2. To understand the pathophysiology of the disease
3. To understand diagnosis and treatment modalities

Introduction

Over 2 million women in the United States have an underlying bleeding disorder.[1] Among women with menorrhagia specifically, bleeding disorders as a group have a prevalence of 20%.[2] Von Willebrand's disease (VWD) is the most common of these disorders in women with menorrhagia, with a reported prevalence of 5−15%. VWD appears to be more prevalent among Caucasians with menorrhagia symptoms.[3] In one study, Caucasians were found to have VWD 15.9% of the time compared to African Americans, whose prevalence was 1.3%.[4] Even among people with a positive family history or bleeding symptoms, the population prevalence has been estimated at 0.6−1.3%.[2,5] VWD is more common in women compared to men, by a ratio of 7:3.[6]

Von Willebrand's disease is an autosomally inherited congenital bleeding disorder in which a deficiency of von Willebrand's factor exists. Von Willebrand's factor (VWF) is critical to the process of hemostasis. First, VWF serves as a bridge between platelets and injury sites in the vessel walls, and ultimately it plays a role in platelet adhesion. Finally, VWF protects Factor VIII, another important player in the intrinsic pathway of the coagulation cascade, from rapid proteolytic degradation.[7]

VWD is a complex genetic disorder in which three subtypes have been described. These include both quantitative and qualitative defects. Type 1 accounts for 70% of cases, and is the mildest form of the disease. Type 1 cases are caused by a partial deficiency of VWF.[7,8] Type 2 cases are more difficult to diagnose due to the qualitative nature of the defect. These defects range from absence of certain protein multimers for binding during hemostasis to improper binding and decreased affinity. This Type 2 sub-group accounts for approximately 20−30% of cases.[7,8] Fortunately, the most severe form, Type 3, is rare. Type 3 accounts for $<5\%$ of cases overall. However, in some Swedish communities with prevalent disease, 1/200,000 people may have the severe form.[5,7,8]

Hallmarks of the Disease

The most commonly reported symptoms among individuals with a diagnosis of VWD or suspected bleeding disorder include epistaxis, gingival bleeds, easy bruising, and menorrhagia.[9−11] Among women with a diagnosis of VWD, 48% reported easy bruising, 44% reported epistaxis, 51% reported gingival bleeding, and 84% presented with menorrhagia. In addition, a case control study in 2003 revealed that women with Von Willebrand's disease were much more likely than controls to experience menorrhagia (95%), ovarian cysts (52%), endometriosis (30%), fibroids (32%), endometrial hyperplasia (10%), polyps (8%), and hysterectomy (26%).[12,13]

Diagnosis

History is very important in consideration of an initial work-up. Many assays have been described, but a great deal of variability exists. In general, many recommend that an initial evaluation include the following: CBC,

Address correspondence to: Pediatric and Adolescent Gynecology, Department of Obstetrics, Gynecology and Women's Health University of Louisville, Louisville, KY 40202.; E-mail: jediet01@louisville.edu

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PT, PTT, INR, platelet function assay (PFA-100), blood type, bleeding time, and VWF assays. The specific VWF assays involve evaluation of Factor VIII, VWF, and Ristocetin cofactor activity. These tests allow for initial evaluation of potential quantitative or qualitative defects that may be present.[8]

However, there are limitations of certain tests. First, not all tests are routinely available in all laboratories. It is important to check with a laboratory prior to ordering these tests, because certain tests also have limitations, and may rule in or rule out a diagnosis. Furthermore, many of these assays are affected by hormones, stress, chronic disease states, pregnancy and even blood type. Therefore, if one set of tests seem to rule out the condition, but symptoms are still present, it is worthwhile rechecking the assays and consulting with a hematologist.[8]

Treatment

A variety of treatments exist. In cases of mild disease, oral contraceptives or hormones are first-line treatments. In a study involving women with a diagnosis of VWD, 88% reported improvement in menorrhagia with oral contraceptives alone.[10,13] In addition, the levonorgestrel-releasing intrauterine system has been proven effective for the reduction of menorrhagia symptoms in adult women with bleeding disorders.[14] Other contraceptives have not yet been studied in this population.

In non-responders or cases of more severe disease, specific hematologic therapies are required. Two commonly used monotherapies include Stimate and Humate P.[8] Stimate releases Factor VIII, VWF, and Plasminogen activators from storage sites called Weibel-Palade bodies in the endothelial cells. In contrast, Humate P works by replacing diminished or absent factor and factor complex.[8]

Newer hemostatic agents have included anti-fibrinolytics. One such anti-fibrinolytic is Amicar. Amicar prevents plasmin formation by inhibiting plasminogen activator.[8]

Other blood products, such as cryoprecipitate and fresh frozen plasma, have not been advocated as first-line due to the risk of infection transmission, but rather are encouraged for use only in emergency situations.[8] A hematologist or specialist in the field are key to long-term management of these patients. Patients should also be reminded that products that prevent platelet adhesion, such as aspirin or ibuprofen, should be avoided once diagnosed.[8]

Resources

Because this is a common condition among adolescent females and adult women, any patient presenting with clinical signs or symptoms should be evaluated. The American College of Obstetricians and Gynecologists has recommended the first gynecological visit occur at the age of 13 to 15. This gives many providers an opportunity to inquire about menstrual history early.[15]

A variety of resources exist for patients and providers through the Centers for Disease Control, National Hemophilia Foundation, and Project Red Flag Campaign.[16] Educating patients, families, and providers is critical to the health and well-being of these patients in the future.

Although recommendations for treatment are presently in place for several European countries, formal recommendations in North America are limited to Canada. These guidelines were developed by multidisplinary groups who care for women with bleeding disorders.[17] The National Heart Blood Lung Institute from the NIH is now formalizing guidelines for the care of patients with VWD, and soon these recommendations for clinicians will be available.[18]

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