Practical Hematologist

Key Facts in Diagnosing and Managing VWD

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Introduction

Mary McGorray, MD, contributing author, had the pleasure of interviewing Dr. Angela Weyand, Clinical Assistant Professor of Pediatrics – Hematology/Oncology at the University of Michigan School of Medicine. Dr. Weyand shares her expertise regarding key facts in diagnosing and managing VWD.

Diagnosis delayed is management denied.

Frontline clinicians such as hospitalists, emergency room physicians, primary care physicians, OB/GYNs, and pediatricians are often the first people to evaluate patients living with von Willebrand disease (VWD). However, despite being the most common heritable bleeding disorder, diagnosis of VWD is often delayed. In a large metanalysis of commercial claims data, people living with VWD experienced an average delay in diagnosis of 669 days (1.83 years) [range 2 – 3369 days (8.99 years)].[1] For women, this delay can be 16 years between their first symptoms and diagnosis, with an average of 6 bleeding symptoms.[2] Patients ultimately diagnosed were discovered to have at least one bleeding episode (17.1%), or multiple bleeding episodes (21.4%), before receiving the correct diagnosis. Among these patients, even *after* the diagnosis of VWD, patients *still* demonstrated post-diagnosis bleeds, and only 27% received hematologic consultation.[1,3,4]

While experts report that 1 in 10,000 patients present with VWD severe enough to reach a tertiary care center, the true scope of untreated VWD patients is unknown.[5] These statistics suggest an unmet need for clinicians to become more facile with guideline-based diagnosis and management of VWD.[4] This is especially imperative in light of the modernized guidelines for diagnosis and management released by the American Society of Hematology (ASH),

International Society on Thrombosis and Haemostasias (ITSH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) in 2021.[6,7]

Dr. Weyand, why is von Willebrand disease frequently misdiagnosed or delayed in diagnosis?

Yes, I think there are several things that contribute to this. I think that bleeding symptoms, especially after surgery or mild bleeding symptoms, like nosebleeds or bruising are prevalent in the general population, even in those without a bleeding disorder. In primary care, you have many priorities to consider in your care—VWD is not necessarily one of them.

I think there is a lot of overlap between patients with VWD symptoms and those you see in the general population – like routine bleeding postoperatively. How does a primary care doctor really tease that out?

Also, I think there is a lot of stigma surrounding menstruation. One of the most common symptoms of VWD in women is heavy menstrual bleeding. But I think this is not discussed in a lot of patients and providers. Generally, society doesn't know what is normal and abnormal. My experience in primary care was that I didn't have the time or even knowledge to know that I should be asking more questions!

I see young women in my clinic, and I'll say, "How are your periods?" and they answer "Fine"—and then I look at their hemoglobin, and it's 4 g/dl. Then, when we delve further, they'll say "I bleed three weeks every month". This is all they have ever known, and often, the mother is present, and says "I have the same thing, I bled every month for most of the month, until I had a hysterectomy at age 25."

So, patients may not volunteer their symptoms, and providers may not have the time or the knowledge to elicit the symptoms. And then, as you get into the testing, the testing is very difficult.

We have done studies that have shown that the way a sample is processed, and if it's processed separately from where it was 'run', that these pre-analytical variables can affect the levels in both a positive and negative way. So, some people are misdiagnosed as having VWD or the opposite, missing the diagnosis.

As a primary care physician what is the likelihood that we are going to see a patient with VWD?

High, depending on how many patients you are following. The true incidence or prevalence of VWD is a bit difficult to know, because I think we miss a lot of diagnoses. It's estimated that up to 1 in 100 people may have lab values consistent with VWD. Probably, anywhere between 1 in a 100 and 1 in a 1000 people have VWD. It's likely that you'll have at least a couple patients.

In 2016, I gave several talks to general pediatricians and adolescent specialists—from those talks, one MD diagnosed 10 adolescents with VWD in her general pediatric clinic. Perhaps, some of those patients have been missed in the past because their primary care physician (PCP) or pediatrician has started that patient with heavy menstrual bleeding (HMB)—on OCPs—it's working, and they then think "Oh, nothing else needs to be done". It's difficult to know how many patients we are missing in that setting.

Does VWF activity differ among ethnic groups?

Historically the most widely available test is the ristocetin assay. There is a genetic polymorphism that's more frequently seen in African American patients that can make that assay somewhat unreliable—the results will read as lower levels on this ristocetin cofactor activity, but not necessarily portend any bleeding risk for those patients. You would want to do additional testing to tease that out. It can happen in any group, but it has been described in Black Hispanic and non-Hispanic Black populations.

How does the presentation of male patients with VWD differ from women and children?

Severe VWD, like Type 3 or some of the Type 2 subtypes, patients present early, similar to hemophilia, such as joint bleeds.

In children, whether they are females or males, I think it's incredibly difficult, because most of them haven't gone through hemostatic challenges, and they are not menstruating yet. Especially, when it comes to bruising, I think people are generally unaware of what is normal versus abnormal bruising. People say like "Oh, I bruise easily, but what does that really mean?" Males are more likely to have epistaxis versus the heavy menstrual bleeding observed in females.

Surprisingly, the claims data reveal the men are diagnosed earlier.

There is a big lag between when females first have symptoms and when they get diagnosed. By the age of 12, I think 50% of females are not diagnosed versus 76% of males that are diagnosed by age 10. Why? I think epistaxis tends to be more outwardly visible and abnormal. I think a lot of females get diagnosed later because of the stigma around menstruation.

For every patient with a GI bleed, should they have a bleeding score, bleeding assessment tool, and a workup for VWD?

The key is really to try to tease out what is typical versus atypical GI bleeding. Even with VWD, GI bleeding is not super common. I think if you are seeing a patient with a GI bleed, and they

have a clear setup, and it responds appropriately to your standard of care and then goes away, I don't think those patients need a workup for bleeding disorders.

Both in adults and pediatrics, is it usually an upper GI bleed or can it be colonic as well?

It can be colonic. With specific subtypes of VWD, it's more common. That's because von Willebrand factor (VWF) is important with angiogenesis. Angiodysplasia will form where you have abnormal vessels—that type of GI bleeding with VWD is not subtle. It is something that is incredibly hard to treat. Those are patients that typically get started on prophylaxis and need it for a long time, because angiogenesis doesn't happen in a short time. You replace that VWF in a chronic way where you can allow for some remodeling and repair of that abnormal vasculature.

Should every patient with iron deficiency anemia have an evaluation for VWD?

Often, I'd say "Yes!" For adults, you need to consider a colonoscopy and ask yourself '*Do they have a good reason to have iron deficiency anemia.'*

In pediatrics, when I see iron deficiency, it is commonly in tiny toddlers and has to do with their diet. In menstruating adolescents, that *does* signal they should have some workup, whether it's a bleeding assessment tool, or just going straight to labs. When a menstruating adolescent is iron deficient without other cause, studies show it's a signal that they are more likely to have a bleeding disorder and warrant testing. How people respond to treatment for iron deficiency anemia can guide you as to the need for further evaluation.

What about the timing of testing? If someone had epistaxis yesterday, should you wait a few weeks to do testing for VWD because of the stress that bleeding causes?

We know that in patients presenting to the ER with heavy menstrual bleeding, that their VWD levels are elevated. Test them again once their iron is replete and they have resolved anemia. Then, outside of that acute bleeding stress, their levels are more reflective of their true baseline.

So, we should test when we're suspicious and keep an open mind if those results are normalized that we are very likely going to need to retest, especially if we have a suspicious bleeding score?

Exactly. The normal values are 50 IU/dL to 150 IU/dL. Some of the literature that we've published has shown that above 100 IU/dL, **if your levels are above 100, acutely or otherwise, that's pretty good for being able to rule VWD out**,[8] but in that 50 IU/dL to 100 IU/dL range, that's probably not the case.

What tests do you recommend frontline clinicians perform when they have a positive bleeding assessment tool?

I think a lot depends on where you are. Typically, at minimum for VWD, we would send a VWF antigen level, some assessment of platelet binding activity. In most places this is going to be VWF Ristocetin Cofactor assay, and then, a Factor VIII level.

What about glycoprotein 1b levels?

Yes, GP1bM. That is what is now being recommended, over the VWF Ristocetin Cofactor assay – like the most recent guideline panels published in 2021, but GP1BM is not widely available, so you may not be able to order that.

So if, after their diagnosis, the hematologist recommends prophylaxis for VWD, are PCPs able to guide my patient in giving prophylaxis or should we rely on the specialist?

I would say that even hematologists not specializing in hemostasis and thrombosis would find that challenging. I think a hub-and-spoke system is a good option for that. The specialist should be able to help you develop a plan, follow up monitoring correctly, for doing the prophylaxis that can then be done locally.

What labs should PCPs do for follow up in a patient who is established on prophylactic therapy?

Ideally, we would check those same three tests: a Factor VIII, a VWF antigen, and a VWF Ristocetin level, which the dosing for factor prophylaxis is based on.

Dr. Weyand, what else would you add that frontline physicians should be aware of in VWD?

Don't be convinced by the labs. In VWD, considering VWF levels, there are many different things that can affect it. And there are bleeding disorders outside of VWD. If your index of suspicion for a bleeding disorder is high and your testing is normal, then I think that's a completely appropriate referral – because specialized testing is indicated in those patients.

I'm amazed by the variety and breadth of what primary care physicians observe: Because you see so much, I think, '*Listen to that little voice, when something doesn't seem typical!'* Use your perspective. For example, when you see a GI bleed—you've seen a million GI bleeds—but '*There's something off about this one'*, listen to that voice—and always feel comfortable reaching out to hematology. We really want to be able to help primary care doctors to manage this and do what is right for patients.

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