Practical Hematologist

Treating Pediatric and Young Adult Patients Living with VWD

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Introduction

Mary McGorray, MD, contributing author, had the pleasure of interviewing Dr. Sarah O'Brien, MD, MSc. Dr. O'Brien is a pediatric hematologist at Nationwide Children's Hospital and an Associate Professor of Pediatrics at The Ohio State University College of Medicine. She serves as the Director of Experimental Therapeutics for the Division of Pediatric Hematology/Oncology/BMT and leads a multi-disciplinary young women's hematology clinic at Nationwide Children's Hospital. Her clinical and research interests include the evaluation and diagnosis of bleeding disorders and the intersections between hematology and women's health.

In Part II, Dr. O'Brien answers questions regarding the treatment of pediatric and young adult patients who are living with von Willebrand disease (VWD). She helps frontline clinicians understand the role of prophylaxis in this population of patients, as well as special circumstances to consider when evaluating children for bleeding disorders.

How much bleeding and what type of bleeding should we tolerate in our patients before we commit them to long term prophylaxis?

When we say prophylaxis in bleeding disorders, I think that the image that most people think of is a patient with hemophilia who is receiving regular factor infusions to prevent the development of joint bleeds or other bleeding. I think with von Willebrand disease, it's quite different. Certainly, there is Type 3 VWD, which is a rare and severe form of the disorder very similar to hemophilia in terms of clinical presentation. Many of those patients are on regular factor prophylaxis.

The good news is that most of our patients with mild VWD—the large majority of patients with VWD—do not need to use prophylactic factor. Because contraceptive agents and IUDs work so well for many of our patients, especially those with heavy menstrual bleeding, we don't need to resort to using factor replacement for those patients.

When we do consider prophylactic therapy, it is based on quality of life. Are the bleeds severe enough and frequent enough that they are impacting our patient's ability to attend school, participate in their activities, and to feel confident about themselves? Quality of life issues should be weighed carefully to consider prophylaxis. Similarly, the 2021 guidelines from ASH/ISTH/NHF/WFH for the management of von Willebrand disease recommend considering prophylactic factor for patients with severe and frequent bleeding as well, which is a rather general recommendation.

Let's talk about our patients with severe Type 1 VWD who have never had to use prophylaxis before. In those patients, it depends on the pattern of their menses. We almost never do this in isolation. It is usually a patient who is also on some type of hormonal medication that is not completely controlling their heavy bleeding. In that case, we will give them a dose of factor at the time that their menses begins. Then depending on the pattern of their menses, we tailor patient therapy. Some patients may have heavy bleeding for a day or two, and that single dose of factor replacement is sufficient. Other patients may need two or three doses, depending on how low their VWF levels are and what their pattern of bleeding is. The factor replacement is something they would only take at the time of their menses.

I would also add that hormonal management with oral medication is usually our first line. We are using more and more IUDs in the adolescent population. A lot of concerns I hear from families is that that IUDs will impact their daughters' fertility later in life—I dispel these worries for them.

Patients harbor perceptions that you cannot have an IUD if you're not sexually active or if you haven't given birth. Some people still worry that IUDs are associated with pelvic infections. These are long conversations where I review those parents' fears and dispel their concerns. Many children's hospitals, including ours, also allow for young women to have IUDs placed in procedure centers—under sedation— if they are patients who are not sexually active and have never had a pelvic exam. This also reduces barriers to IUDs as an effective therapy for our patients.

Are these IUDs infused with contraceptive hormones?

Yes, that is an important distinction. We use the levonorgestrel IUDs that contain progestin medication. We do not use copper IUDs in our patients because they don't help to reduce blood flow.

Is prophylaxis therapy worth it to our patients?

The literature for prophylactic factor in von Willebrand disease is a lot smaller than it is in hemophilia. For patients with Type 3 von Willebrand disease, I think we can clearly correlate their experience with that of patients with hemophilia. Prophylactic factor treatment makes a lot of sense for those patients to prevent joint bleeds, and other complications.

We consider these interventions for patients with moderate to severe von Willebrand disease. Those are patients with factor levels less than 30 IU/dL, the minority of my patients. Most of our patients are those with VWF levels between 30 IU/dL and 50 IU/dL.

How real is the risk of joint bleeding in a VWD patient and what types of VWD?

Certainly, with Type 3, it is a frequent finding. I think that for the bulk of our patients with VWF levels between 30 to 50 IU/dL, it is pretty rare for me to see patients with these symptoms in practice. Typically, if I have a patient who has experienced a joint bleed who has milder von Willebrand disease, there's usually trauma involved or some other kind of inciting factor. It is not a spontaneous event.

What does a joint bleed look like in a child? Is it very dramatic?

Typically, it is pain, warmth, and swelling. It depends on the child. In hemophilia, I've seen very dramatic joint bleeds. In Von Willebrand disease it may not be as dramatic. I think one study that's helpful now and much more available are ultrasounds—to see what's going on inside of a joint.

If you do have a patient with Von Willebrand disease who is in the ER with a joint complaint, I think it is worthwhile to try to do that imaging to assess whether there might be any bleeding involved. Because even if it is a trauma, they may be having more bleeding than expected, which may require different intervention than the ER would normally perform.

What type of follow-up testing do you do to assess treatment response, Dr. O'Brien? Do you continually measure Von Willebrand factor level, FVIII levels, platelets, PT, and PTT?

We don't measure von Willebrand factor levels routinely because we expect those to stay stable over time. In assessing treatment response, we monitor our patients' clinical symptoms. One exception would be when our patients are hospitalized after a major surgery. In that setting, we do follow von Willebrand and FVIII levels to help guide the timing and dosing of our factor replacement.

Another time that we check von Willebrand levels is during pregnancy because we know that pregnancy increases von Willebrand levels. In that third trimester, we will check our patients to see if they've normalized. If they haven't normalized, then we put a plan into place of what they may need to receive, especially if they want to get an epidural with their pregnancy.

So a woman with VWD could receive an epidural?

Yes, she absolutely can. I always tell my patients to plan early so that your hematologist, anesthesiologist, and obstetrician/gynecologist are all prepared and know what the plan is around the time of delivery.

When preparing to give an epidural to a woman living with VWD, we give either a factor infusion or an antifibrinolytic about 30 to 60 minutes before the epidural is going to be placed. Then, we also provide these medications after delivery to prevent prolonged postpartum bleeding.

When I am concerned about non-accidental trauma (NAT) in a patient, should I always do a bleeding workup first?

That's what we do here at Nationwide Children's Hospital for patients admitted to the hospital for suspected non-accidental trauma. There are a few reasons for that. Unfortunately, these patients have a high mortality rate, and so there may not be an opportunity to do the testing later if this question arises.

It is also typically a very young population. Often these are shaken babies or toddlers. These young patients may not have yet had time to express bleeding symptoms. They may not have had any surgical

challenges that would give us a clue that these patients have an underlying bleeding tendency. I think from a medico-legal standpoint, it's important to do this testing routinely. We have a protocol at Nationwide Children's Hospital that is immediately initiated when these patients are admitted to the hospital. Hematology is automatically consulted, and we perform screening tests on all of the patients.

For our readers, would you mind defining what non-accidental trauma (NAT) is?

Typically, a common scenario is an infant who presents to our emergency room with a severe head bleed, and a story from the caregiver that doesn't match the pattern or severity of the intracranial bleed. Or a patient may come in with really unusual bruising. The ER physicians may perform a skeletal survey and see that a young patient has evidence of old fractures; rib fractures or suggestions that they've been abused as a child. These are the two most common scenarios that we see.

Routine screening for bleeding disorders is important because when these cases go to court, what often comes up as a possible defense is that the patient had a bleeding disorder as the cause of their symptoms.

What clinical differences can help me make a good decision about taking the time for a bleeding disorder work-up in a pediatric case of non-accidental trauma?

I really think we should do it for everybody. I always make a point of saying that, in most cases, we're ruling out bleeding disorders. We've just crossed that off the list of possibilities. It is also important to understand that, in the rare event that a patient turns out to have a bleeding disorder, almost always the pattern of injuries is still not consistent with the bleeding disorder. In those cases, the bleeding disorder probably exacerbated the bleeding. In the end, it was still trauma—a non-accidental trauma—that was caused by a caregiver to the child.

What does non-patterned bleeding mean?

For example, let's say that we perform this evaluation, and the patient turns out to have mild von Willebrand disease. Patients with mild VWD do not experience spontaneous subdural hematomas or retinal hemorrhages. In those cases, we have to explain to the court that even though the patient has a mild bleeding disorder, the clinical picture of their injuries and their bleeding is not explained solely by the von Willebrand disease.

Dr O'Brien, is there anything you would like to add?

I like to emphasize the importance of getting a menstrual history. Even if you only have time to ask those four questions highlighted in Part I of this Newsletter, that's so helpful.

Menstrual History Questions:

- How many days is the period lasting?
  — More than seven days should be a flag.
- How often are they having to change their soaked menstrual product.
  — If that is less than two hours, that would be a flag for us.
- Do they have to get up at night to change a product?
- Are they passing large clots in their flow? We define large clots as those larger than the size of a grape.

I think the other major point for frontline clinicians is looking for iron deficiency—and knowing what the definition of that is—a ferritin level of <15.

Also, I always emphasize to primary care providers that you don't need to have a set of labs or abnormal labs, to refer a patient to a hematologist. If you are worried about a patients' bleeding symptoms, that alone is reason enough to refer to us. A clinician may be practicing in an area where you don't have access to great coagulation testing. And there are also patients with bleeding disorders that have normal labs. For example, patients who have joint bleeding due to joint hypermobility.

We sometimes follow patients with 'bleeding disorders of unknown cause' because they bleed after every surgery, but we don't know what they have. But we know that we want to be involved with their next surgery, so we can give them medications, so they don't bleed. Another example are hemophilia carriers or other patients who have normal labs, but still have bleeding symptoms. They need to be followed by hematologists**.**

Should every primary care physician do a bleeding assessment tool for each patient. What bleeding assessment tools (BATs) do you recommend?

I don't think a BAT needs to be done for each patient. I think they are helpful if you have a patient with one bleeding symptom so that you can help assess the severity of the symptom. This also gives you a guide of what other symptoms to ask about. The one I like the most is the one that the ISTH (International Society of Thrombosis and Hemostasis) developed—the ISTH Bleeding Assessment Tool. That has been validated for children and adults, which makes it helpful. It is 'one-stop shopping'.

I advise providers: if you open up the survey, it seems very overwhelming. It has many pages of questions, but really everything you need to know is at the very end. The table at the end describes all the different symptoms and what score you would get. So, I just look at the table and go through it—it's very quick. Once you've done it a few times; the BAT asks about 14 symptoms. In reality, most of us only

see a few common symptoms in our day-to-day practice, and it's pretty easy to get comfortable with how the scoring table looks for those symptoms that you tend to see!

Summary

The Practical Hematologist sincerely thanks Dr. Sarah O'Brien for her generous and elucidating interview regarding the nuances of treating children and young adults with VWD. Collaborating with hematologists, frontline and community physicians can enhance quality of life for patients and their caregivers living with von Willebrand disease.

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