Finding the right clues

Hereditary Bleeding Disorders

By Mary-Frances Scully, MD, MRCPI, FRCP

In this article:

1. How to manage hereditary bleeding disorders.
2. Who and how to screen?
3. What are the treatment options?

Case

A 36-year-old woman finds it difficult to cope with work and the demands of a toddler at home. She is fatigued. Blood work confirms iron deficiency anemia. Her menstrual flow has always been very heavy and she is unable to function well for two to three days per month due to problems with flooding. Her mother had a hysterectomy at 40 years of age. Her pelvic exam is normal.

Laboratory testing shows:

- Hemoglobin: 95 g/L
- Mean corpuscular volume: 76 femtolitres
- White cell count (WCC): 8.2 x 10^9/L
- Platelets: 220 x 10^9/L
- Smear: Normal
- Prothrombin time (PT): Normal
- Activated partial thromboplastin time (APTT) = 40 sec (Normal range 21.9-35.1sec)
- Bleeding time: Six minutes normal
- Factor VIII: 0.48 IU/mL
- von Willebrand assay: 0.30 IU/mL
- Ristocetin cofactor assay: 0.30 IU/mL

Why Screen?

Recurrent bleeding can be associated with significant morbidity and even mortality. In mild bleeding disorders bleeding tends to be episodic and hence is frequently ignored by patients, families, and health-care providers. There is very effective treatments available for hereditary bleeding disorders. Early diagnosis combined with effective education and counselling can have a very positive impact.

Background Information

Epidemiologic studies suggest that mild hereditary bleeding disorders are relatively common. Von Willebrand's disease (vWD) has been reported to occur in 1% to 2% of the Caucasian population, and some studies suggest that mild

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Practice Pointer

There are 3 subtypes of vWD:

- Type I is an autosomal dominant disorder with a wide hereditary heterogeneity of clinical expressions.
- In Type II vWD, there is a qualitative defect leading to the production of an abnormally functioning vWF.
- Type III vWD is associated with very severe clinical disease. There is almost a total absence of vWF in the blood.

platelet function disorders may also be quite common, particularly in individuals whose ethnic background is from the Middle East and Central Asia.[1,2]

Von Willebrand's disease is divided into three basic subtypes. Type I vWD affects approximately 70% of all patients.[3] It is an autosomal dominant disorder with a wide hereditary heterogeneity of clinical expressions. In Type I vWD, there is a mild to moderate reduction in von Willebrand factor (vWF), immunologic and functional levels. Type II vWD makes up about 15% to 20% of all patients.[3] In Type II vWD, there is a qualitative defect leading to the production of an abnormally functioning vWF. Type III vWD is extremely rare. There are approximately 50 cases reported in Canada.[4] In Type III vWD, there is almost a total absence of vWF in the blood, which is associated with a very severe clinical disease.

Dr. Scully is associate professor, child health and internal medicine, faculty of medicine, Memorial University, director of the Hemophilia Program Newfoundland and Labrador, and staff hematologist at Health Sciences Centre, St. John's, Newfoundland.

With the advent of home infusion therapies in the late 1970s, comprehensive care hemophilia programs were developed at 24 centres across Canada for patients with hemophilia A and B.[5] These programs were so successful in managing severe complications of hemophilia A and B that they have become a model for the management of patients with all hereditary bleeding disorders. Registry data from Canada and other countries with access to care for hereditary bleeding disorders suggest that most patients with severe bleeding disorders are registered with hemophilia treatment centres and receive appropriate therapy. Such cases include patients with moderate and severe hemophilia A and B and almost all patients with severe rare coagulation disorders, such as, deficiencies of factor V, VII, and XII. By contrast, less than 5% of the estimated number of patients with vWD and platelet functional disorders are currently registered.[6] This suggests that there is a tremendous under diagnosis of mild hereditary bleeding disorders in Canada and, indeed, elsewhere in the world.

Who to Screen?

Severe bleeding disorders tend to present in the first year of life. Hemophilia A and B have the same clinical presentation. Less than 1% of patients with moderate to severe hemophilia present with an intracranial bleed at birth. Such bleeding can be fatal and is frequently associated with significant morbidity. To optimize care, early referral to a specialized obstetric unit is important for pregnant women who are known to be carriers of hemophilia or other bleeding disorders.

Umbilical cord bleeding is highly suggestive of factor XIII defi-

ciency — an extraordinarily rare and very treatable disorder. Patients with a severe hereditary bleeding disorder most commonly present in the first year of life with easy bruising, occasional lip or tongue bleeds, or characteristic bleeding into muscles and joints. Historically, many patients with hemophilia A or B have presented due to prolonged bleeding post circumcision or tonsillectomy.[7] As circumcision and tonsillectomy are performed far less frequently today, and as dental health improves, many individuals with a bleeding disorder will experience their first real hemostatic challenge much later in life.

Epistaxis is a very common symptom in childhood. Some studies have suggested that it is a useful predictor for the presence of a hereditary bleeding disorder, however, it has a low specificity.[8,9] Certainly, patients who experience frequent or prolonged episodes of epistaxis should be screened for a hereditary bleeding disorder.

What is the Family History?

Hemophilia A and B are classic examples of sex-linked recessive disorders. Mild vWD, the most common form of vWD, is autosomal dominant. The majority of other rare bleeding disorders are autosomal recessive. A positive family history is an indication for referral to an adult or pediatric hematologist or to a hemophilia treatment centre for screening. However, a negative family history does not rule out a hereditary bleeding disorder. From the mid-1980s to the 1990s, patients and families with hereditary bleeding disorders in Canada were severely affected by the epidemic of blood borne viruses. This started in the early 1980s with human immunodeficiency virus (HIV), followed by the hepatitis C epidemic. Patients, particularly those in rural areas, are very concerned about the possibility of being stigmatized by the association between hereditary bleeding disorders and viral infections. As a result, many individuals may not be forthcoming about a family history of a bleeding disorder (Figure 1). The absence of a family history is often due to the family's lack of knowledge about the correct medical diagnosis. The coagulation system is a complex and confusing topic. Frequently, patients who have been told as children they have vWD will present as adults asking that their own children be screened for hemophilia or *vice versa*. If a new patient comes to your practice who has not been evaluated in a hemophilia program for several years, it is worthwhile to re-refer him/her, at least to reconfirm or refute the diagnosis. In 30% of patients, the diagnosis of hemophilia is made because of the occurrence of a new mutation, and there is no previous family history.[10]

Practice Pointer

Patients most commonly present in the first year of life with the following:

- Easy bruising.
- Occasional lip or tongue bleeds.
- Characteristic bleeding into muscles and joints.

Bleeding After Surgery and Dental Work

Characteristically, patients with bleeding disorders do not bleed more profusely than the general population, however, they do bleed more persistently. Delayed bleeding after dental work and surgery is typically six to eight hours post procedure, particularly for patients with coagulation

Bleeding Disorders

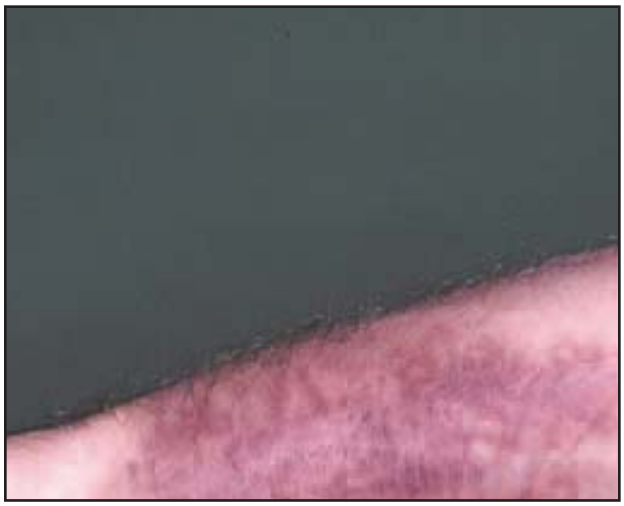

Figure 1. Severe bruising on a patient with severe hemophilia A who had stopped home infusion. He was discouraged coping with his HIV and hepatitis C infection.

factor deficiencies. Surgical hemostatic techniques have improved tremendously, therefore, it is quite possible for a child or an adult with a mild bleeding disorder to undergo a surgical procedure with no unusual bleeding. The patient, however, may develop significant bleeding complications, such as hematoma, after another procedure. This episodic or intermittent bleeding problem is characteristic of mild disorders and is probably a major reason for a delay in diagnosis.

Women and Bleeding

Since the early 1990s, there has been an increased recognition of the effect of bleeding disorders on women. Ten per cent of women experience menorrhagia, and 5% of women aged 30 to 49 consult a physician for this symptom.[11,12] Menorrhagia makes up 12% of referrals to gynecologists, and 10% to 20% of those referred are found to have a definable bleeding disorder. Meanwhile, 50% to 75% of women diagnosed with hereditary bleeding disorders are affected by menorrhagia.[11,13] Numerous studies have shown that menorrhagia has a very negative impact on quality of life, and adolescents with menorrhagia tend to have difficulty participating in sports and lose more time in school.[12,14] Equally so, adult women may lose more time from work, especially if flooding is a problem. Woman with hereditary bleeding disorders have an increased risk of post-coital bleeding, miscarriage, infertility and primary and secondary postpartum hemorrhage (Table 1).

Always take a thorough family history, checking if bleeding symptoms have occurred in first-degree relatives (*i.e.*, parents, siblings, *etc.*) It is important to ask whether any female relatives have undergone a hysterectomy or experienced miscarriage or infertility. Many medications, particularly non-steroidal anti-inflammatories, affect platelet function. Anti-inflammatory agents are used as first-line therapy to control dysmenorrhea. Some studies show that patients subsequently diagnosed with a hereditary bleeding disorder reported increased menorrhagia by using anti-prostaglandin. Other medical diseases which should be screened for, include systemic erythematosis, Cushing's syndrome, chronic liver disease, chronic renal failure, and thyroid disorders, as hypothyroidism is a cause of menorrhagia.

It is also important to inquire about migraine headaches or frequent headaches. DDAVP, an analogue of vasopressin, is a standard and very effective therapy for a majority of patients with mild bleeding disorders, as well as for many patients with platelet function disorders. However, this medication can cause headaches.

What to Look For?

During the physical examination, it is important to check the skin. Bruises should be measured to obtain a baseline status, and the mouth, lips and

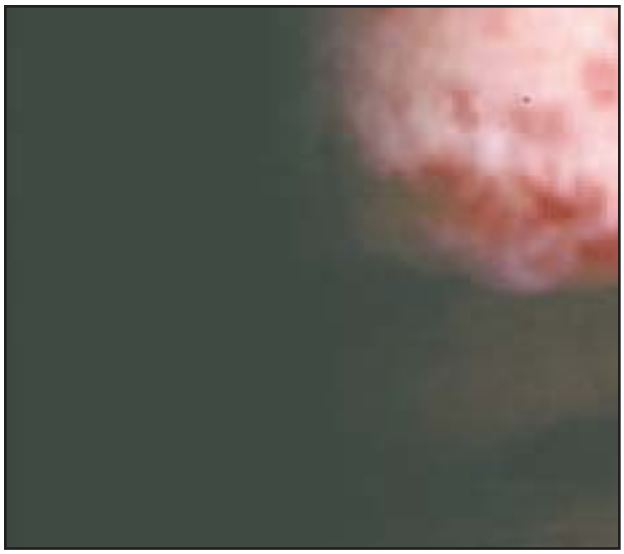

Figure 2. Buccal telangiectasia in a patient presenting with massive epistaxis and hemoptysis.

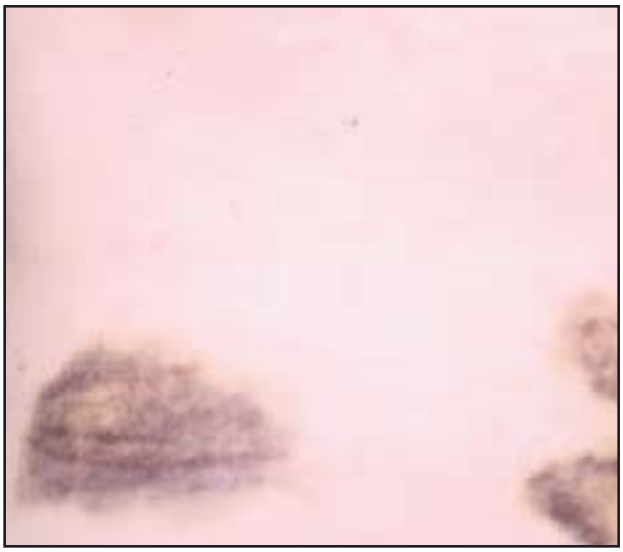

Figure 3. Severe bruising at the site of injection with a low molecular weight heparin in a patient with storage pool disease on treatment for a deep venous thrombosis.

hands should be examined for classic signs of other hereditary causes of upper gastrointestinal (GI) bleeding, such as hereditary telangiectasia (Figure 2). Skin and joint movement should be examined for elasticity to screen for a connective tissue disorder, such as Ehlars-Danlos. Patients presenting with menorrhagia should also have a pelvic examination and ultrasound to screen for fibroids or ovarian cysts. Patients with anovulatory menstrual cycles require an endometrial biopsy or dilatation and curettage (D and C) with hysteroscopy to rule out endometrial cancer and endometrial proliferation with breakdown. Vaginal swabs and chlamydial swabs are also an important part of the investigation for sexually active patients who report pelvic pain with menorrhagia.

All patients with unusual or unexplained bruising, GI bleeding, or bleeding while taking anticoagulants (Figure 3) should be evaluated by personal and family history and physical examination for a possible hereditary bleeding

Table 1

What to Ask the Patient Presenting With Menorrhagia

Question	Typical Answer
Were your periods heavy when you first started to menstruate?	YES
Have you experienced flooding or staining of your clothes or undergarments during menstruation?	YES
Have you ever lost time from school or work or been unable to participate in sports because of a heavy period?	YES
Do you need to use more than one tampon or pad at the same time?	YES
Have you been told you were low in iron or had a low blood count?	YES
Do you use a super absorbent tampon or pad?	YES
On the heaviest day of your period, would you need to change your tampon or pad more frequently than every two hours?	YES

Adapted from: Kouides PA: Menorrhagia from a hematologist's point of view. Part 1: Initial evaluation. Haemophilia 2002; 8:330-8.

disorder. For example, a woman with mild vWD may present with severe, uncontrollable menorrhagia, as she has now also developed fibroids. Alternatively, a mild platelet function disorder may contribute to rectal bleeding in a patient with an inflammatory bowel disease or colorectal cancer. All patients who present with joint or muscle bleeds need to have a factor VIII and IX level measured to screen for hemophilia A and B.

How to Screen?

If you suspect a hereditary bleeding disorder, the following laboratory evaluation should be performed: A complete blood count, including, blood smear and ferritin levels to screen for iron deficiency. The PT and APTT should be performed, as these tests are readily available. However, these tests are very insensitive and rather ineffective in diagnosing mild hereditary bleeding disorders. Bleeding time has been the gold standard test to screen for disorders of platelet function, such as vWD and hereditary platelet function disorders, for many years. In many laboratories in North America, this test is being replaced by analysis with platelet function analyser (PFA)/100. In one study of 60 patients known to have vWD, the sensitivity and specificity were 96% and 95% respectively.[15] This instrument may be very helpful in screening patients for hereditary bleeding disorders, especially in rural areas.

The laboratory diagnosis of vWD is challenging. Testing requires a bleeding time or platelet function analysis, measurement of factor VIII levels and measurement of the vWF antigen immunologically and functionally, using either von Willebrand ristocetin cofactor assay, or, in some countries, a von Willebrand collagen binding assay. If screening APTT is prolonged, a factor VIII, IX and XI assay is mandatory. Factor VIII

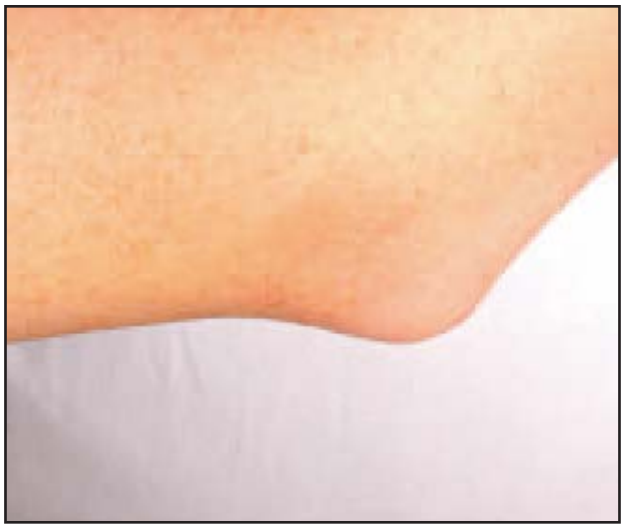

Figure 4. Bleeding into the olecranon bursa due to minor trauma in a patient with mild hemophilia A.

and IV levels must be measured in all patients presenting with minimal muscle or joint bleeds (Figure 4). If these baseline tests are entirely normal and the history is very convincing it is important to refer the patient to a specialized hematology centre for further laboratory analysis.

For a good move see page 100

How to Manage?

All patients diagnosed with hereditary bleeding disorders should be referred to the nearest hemophilia treatment centre for confirmation and education. Patients should be advised to either wear a medical identification bracelet or obtain a Factor First card or patient identification sheet from their hemophilia treatment centre. First-line therapy for all patients with mucosal bleeding is with an antifibrinolytic agent. These drugs, currently available in Canada, are tranexamic acid and aminocaproic acid. The standard oral dose for tranexamic acid is approximately 25 mg per kg. It is generally effective on an as-needed (p.r.n.) basis and can be given up to three to four times per day for serious bleeding. It is also available in an intravenous form at a maximum dose of 10 mg per kg given intravenously (IV) q.6.h. Oral dose aminocaproic acid is 70 mg q.6.h. p.r.n. This medication is available in syrup form. Tranexamic acid is not currently available in syrup form, however, it can be crushed and is quite soluble. Some centres use a soluble mixture of tranexamic acid with lidocaine to treat persistent mouth and gum bleeding.

Antifibrinolytic agents are absolutely contraindicated in patients with bleeding through the urinary tract and in patients with advanced severe atherosclerotic disease. There have been active reports of retinal vein and sagittal vein thrombosis in relatively young patients receiving high doses of antifibrinolytic therapy with tranexamic acid. Therefore, high doses should be used with great caution, especially if there is a personal or family history of thrombophilia. DDAVP can be used to treat over 85% of patients with mild hemophilia A and some patients with platelet function disorders. The standard dose is 0.3 mcg/kg up to a maximum dose of 20 mcg/kg.

DDAVP is contraindicated in children under two years of age. Seizures have been reported in children in this age group who also have an electrolyte imbalance and received DDAVP. DDAVP is most frequently administered as a once off treatment prior to invasive procedures or minor surgery. Complications include facial flushing, headache and electrolyte disturbances. DDAVP can be given every 12 hours for up to three days,

Case Discussion

The test results confirm a diagnosis of Type I vWD. A regimen of iron repletion and a combination of 1-deamino-8-D-arginine vasopressin (DDAVP) and tranexamic acid improves the patient's quality of life. She prefers not to use an oral contraceptive as she wishes to conceive a second child.

however, the maximum effect occurs with the first dose. The majority of patients with mild vWD can be managed with a combination of DDAVP and an antifibrinolytic agent. Eighty-five per cent of patients with mild hemophilia A can also be treated with this combination. Safe, effective replacement factor concentrates are provided by Canadian blood services. These products are extremely expensive and are not routinely stocked in blood banks. Hemophilia treatment centres across Canada co-ordinate necessary factor replacement therapy for patients registered in their program. Patients are currently counselled about emergency therapy and are given a Factor First card when seen in a clinic. There is firm evidence that rapid infusion of products in emergency situations reduces morbidity, mortality and is cost-effective. CME

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