Hemorrhaging at Menarche: A Case Report

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A 12-year-old girl presented with hemorrhaging at menarche and required multiple blood transfusions. She had a history of severe epistaxis. Bleeding studies indicated that the patient had type 1 von Willebrand's disease. Her three siblings were then screened and all tested positive for the disease.

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Family physicians see a large number of adolescents with heavy vaginal bleeding. These patients are usually treated for dysfunctional uterine bleeding. However, coagulation defects are present in about one fourth of women whose hemoglobin levels fall below 100 g/L (10g/dL) and in approximately one third of those who require transfusions for menorrhagia.[1] In women who do not respond to conventional therapy for dysfunctional uterine bleeding, a bleeding disorder should be suspected. The most common inherited bleeding disorder is von Willebrand's disease, and it often presents with menorrhagia.

Case Summary

A 12-year-old white girl presented at menarche with a 2-week history of heavy menstrual bleeding that had become increasingly heavy over the previous 24 to 48 hours. She was soaking a pad every 1 to 2 hours, felt lightheaded, and reported three near-syncopal episodes earlier that day. She denied being sexually active.

On examination, her skin was found to be pale and cool. Her pulse was 100 beats per minute and regular, and she was orthostatic. A pelvic examination was deferred. Her initial hemoglobin level was 91 g/L (9.1 g/dL).

The presumptive diagnosis was anovulatory bleeding. Therefore, she was given 25 mg of intravenous conjugated estrogen (Premarin), which had little effect. Within 3 hours, she was soaking a pad every 40 minutes, and her hemoglobin level had fallen to 63 g/L (6.3 g/dL). A pregnancy test was performed and was negative. A second dose of Premarin (25 mg) was administered intravenously, and the patient was admitted to the hospital.

During the next 24 hours she received a total of six doses of Premarin given intravenously, six units of packed red blood cells, and two units of fresh frozen plasma (FFP). Her menstrual flow did not slow, but her hemoglobin rose to 82 g/L (8.2 g/dL). A dilatation and curettage was then performed, which stopped her menstrual flow. A pelvic examination was performed with the patient anesthetized, but it was unremarkable. The pathology report showed proliferative phase endometrium.

Further history revealed that the patient, her father, and two of her sisters had had numerous episodes of severe epistaxis. Her father had required multiple blood transfusions for severe epistaxis.

A hematologist who was consulted recommended testing for von Willebrand's disease (Table 1). The blood for the patient's first von Willebrand's assay was drawn soon after receiving 2 units of FFP. FFP has a half-life of 2 to 3 days. Because the clotting factors in FFP can affect the results of the assay, a second assay was performed 16 days later. Marked differences were seen in the results (Table 2). The first assay gave no indication of von Willebrand's disease; however, antigen levels were borderline. The second assay indicated severe von Willebrand's disease.

This patient's multimeric study revealed type 1 von Willebrand's disease, thus making her a candidate for desmopressin therapy. Her second menstrual period occurred before this information was available, however, and she was treated with cryoprecipitate, 8 units administered intravenously every 12 hours for 5 days. The cryoprecipitate dosage was 3 bags per 10 kilograms of body weight per dose. This treatment adequately controlled her menstrual flow but exposed her to blood products from 80 different donors.

This patient was placed on a regimen of oral con-

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Table 1. Laboratory Terms Related to von Willebrand's Disease

von Willebrand's factor antigen (vWF:Ag): the plasma concentration of von Willebrand's factor, as determined by immunologic studies. Also called factor VIII-related antigen
Factor VIII coagulant (FVIII:C): the smaller glycoprotein in the factor VIII complex
Factor VIII complex: formed by linkage of vWF:Ag and FVIII:C
Ristocetin co-factor activity: ability of patient's plasma to agglutinate normal platelets in the presence of the antibiotic ristocetin
Multimer analysis: molecular weight of the multimeric forms of von Willebrand's factor glycoproteins, as determined by plasma electrophoresis

From Perry JJ, Alving BM.[2]

traceptives, which are often very effective in patients with von Willebrand's disease. To further reduce her menstrual flow, intranasal desmopressin was added to her treatment during her third menses. Her menstrual flow was slowed but not stopped. Her oral contraceptive was then changed to one with a higher level of progesterone, and her fourth period was light and short. Consequently, she did not require desmopressin during her fourth menstrual period.

The patient's sisters were screened for von Willebrand's disease (Table 3). The 14-year-old sister, who had a history of epistaxis, was diagnosed as having severe von Willebrand's disease. The 17-year-old sister, who had a history of both epistaxis and menorrhagia, was diagnosed as having moderate von Willebrand's disease. The 21-year-old sister, who had a history of having light periods and no epistaxis, also had von Willebrand's disease.

Discussion

The differential diagnosis for heavy vaginal bleeding in an adolescent can be divided into four categories: (1) anatomic abnormalities, (2) bleeding abnormalities, (3) hormonal abnormalities, and (4) pregnancy complications (Table 4).

An appropriate evaluation would include a detailed history and physical examination. A pelvic examination with direct visualization of the vagina and cervix should be included. If the patient is an adolescent, this examination may need to be done while the patient is under anesthesia.

Screening laboratory tests should include a complete blood count, platelet count, prothrombin time, partial thromboplastin time, and bleeding time. A serum pregnancy test should be considered.

Von Willebrand's disease is the most common inherited bleeding disorder. It is typically transmitted in an autosomal dominant manner, and has a prevalence of as high as 0.82%.[3] Patients often present with epistaxis, excessive bleeding after dental or surgical procedures, or menorrhagia.[2]

Von Willebrand's disease involves an abnormality in the factor VIII clotting complex. This complex is composed of two known glycoproteins controlled by genes on different chromosomes. The larger of the two is the von Willebrand's factor antigen. It is inherited under the influence of an autosomal gene and is produced by endothelial cells. The factor VIII coagulant is a much smaller glycoprotein produced under the influence of the X chromosome gene and is possibly produced by a cell in the liver. The release of the von Willebrand's antigen from endothelial cells induces the production or release of factor VIII coagulant. These two glycoproteins then link and circulate as a complex.[4]

At least 21 types and subtypes of von Willebrand's disease have been identified, with type 1 being the most common.[3,5] Both the composition and quantity of the circulating complex determine the subtype of the disorder and the severity of bleeding. A multimeric determination analysis is used to classify the subtypes.

All affected members within a family carry the same subtype, but the severity of the condition is variable.[4] Some members who carry the gene may have no hemorrhagic symptoms. Because the concentration of von

Table 2. Assay Results of a 12-year-old Patient with von Willebrand's Disease

Timing of Assay	Factor VIII* (50%–150%)†	Template Bleeding Time (1–8 min)†	Factor VIII–Related Antigen (50%–150%)†	Ristocetin Co-factor (50%–140%)†
Drawn soon after receiving 2 units of fresh frozen plasma	163	>15	54	77
Drawn 16 days after receiving fresh frozen plasma	61	>15	<1	<1

**A measurement of overall factor VIII clotting process.*
†Normal range.

Table 3. Assay Results of Patient's Sisters Tested for von Willebrand's Disease

Age of Sisters (y)	Factor VIII* (50%–150%)†	Template Bleeding Time (1–8 min)†	Factor VIII-Related Antigen (50%–150%)†	Ristocetin Co-factor (50%–140%)†
14	79	>15	15	<1
17	62	>15	16	27
21	55	5	Undetectable	<1

**A measurement of overall factor VIII clotting process.*
†Normal range.

Willebrand's factor tends to increase with age, individuals may become phenotypically normal as they grow older.[6]

Until recently, fresh blood products were the only available treatment for von Willebrand's disease. Despite the screening of blood products for viral contamination, the current risk of developing human immunodeficiency virus after receiving blood is 1 in 40,000 units, and the risk of developing non-A non-B hepatitis is 1 in 160 units. Consequently, blood products carry a significant risk of disease transmission.[3]

The development of pharmacologic agents that can be substituted for blood products is a significant advance in the treatment of von Willebrand's disease. One of the most useful agents is desmopressin, a synthetic analog of vasopressin. An intravenously administered dose of .03 mg/kg induces an increase in factor VIII coagulant, which reaches a maximum level in 30 to 120 minutes and then decreases over 6 hours. The drug should be given slowly to prevent flushing, tachycardia, and transient hypotension. Intranasal desmopressin at doses of 2 to 4 mg/kg produce a similar increase in factor VIII coagulant.[3]

Desmopressin appears to mediate the release of factor VIII coagulant and von Willebrand's antigen from vascular endothelial cells. The medication is effective for 24 to 48 hours, after which a decreased response is seen. A delay in the use of desmopressin for 24 to 48 hours allows reestablishment of the original response.[7] Dosing intervals for use in von Willebrand's disease have not been well established.

The response to desmopressin therapy in patients with type 1 is usually good.[6] However, desmopressin is contraindicated in type 2 and pseudo-von Willebrand's disease because it can increase platelet aggregation and cause thrombocytopenia.[7] Consequently, it is important to know which type of von Willebrand's disease is present so that safe and effective therapy can be given.

Table 4. Differential Diagnosis of Menorrhagia in an Adolescent

- Anatomic abnormality
  - Genital neoplasm (sarcoma botryoides)
  - Genital trauma or laceration
  - Severe vaginitis (especially streptococcal)
  - Foreign body
  - Prolapsed urethra
- Bleeding abnormality
  - Platelets
    - Platelet dysfunction
    - Thrombocytopenia
  - Clotting disorder
    - Hemophilia A
    - von Willebrand's disease
    - Afibrinogenemia
    - Hypoprothrombinemia
    - Dysfibrinogenemia
  - Induced disorder
    - Ingestion of antiplatelet drugs (aspirin)
- Hormonal abnormality
  - Anovulatory bleeding
- Pregnancy complication
  - Threatened abortion

Conclusions

In the adolescent with menorrhagia who does not respond to conventional therapy for dysfunctional uterine bleeding and who has a history of epistaxis or other bleeding abnormalities, a bleeding disorder such as von Willebrand's disease should be considered. Often the only abnormal screening test result will be a prolonged bleeding time. If the patient has received clotting factors before the von Willebrand's assay is drawn, results may be misleading and the test may need to be repeated 1 to 2 weeks later.

After a patient has been diagnosed with von Willebrand's disease, family members should be screened. The family physician has the vital role of coordinating the family's medical care. The family should be offered genetic counseling. Patients with von Willebrand's disease should be instructed to avoid aspirin and nonsteroidal antiinflammatory drugs. These medications affect platelet cyclo-oxygenase and increase the risk of serious bleeding in patients with the disease.

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