CLINICAL VIGNETTE

Unexplained Familial Cryptogenic GI Bleeding

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Introduction

Von Willebrand Factor (VWF) is a crucial component of our ability to maintain hemostasis in two ways. VWF has many binding sites which allow it to bridge platelets to each other as well as to subendothelial structures at sites of injury. VWF also assists in fibrin clot formation by stabilizing and increasing the half-life of factor VIII. Von Willebrand's Disease (VWD), due to dysfunction or lack of VWF, is present in one percent of the population, and is the world's most common heritable bleeding disorder. However, the severity of Von Willebrand's disease in each patient depends heavily on the disease subtype, which in turn is classified by both the functional ability and number of Von Willebrand multimers. Prompt recognition of the presence of VWF as well as clarification of the subtype is crucial to the prevention and treatment of potentially life-threatening bleeding in a variety of situations.

Presentation

A 34-year-old female had episodes of spontaneous/cryptogenic lower GI bleeding for the past five years. She almost daily had hematochezia and reported a hemoglobin of 3ng/dl at an ED in New York, receiving four units of pRBCs. She saw a hematologist and was placed on IV iron intermittently, but no diagnosis established. Her GI evaluation showed internal hemorrhoids and a friable colon, but the findings were out of proportion to her level of bleeding. She relocated to Los Angeles two years ago and her symptoms recurred. She again underwent upper and lower GI endoscopy through an outside hospital with findings similar to what was found in New York. She continued to have intermittent bleeding and could not tolerate oral iron due to GI side effects. She never had any major surgeries or pregnancies. Her family history is significant for a similar undiagnosed bleeding disorder in her maternal uncle, who is also Ethiopian.

She transferred care and initial lab work with her new primary care physician showed a normal platelet count, a hemoglobin of 8.1ng/dl and a ferritin of 4mcg/L. She had a normal PT, PTT, as well as normal levels and activity of factors VIII, IX, XI, and XII. Her VWF antigen level was low at 43%, and her vWF activity low at 30%. She had a normal vWF multimeric distribution.

Her labs, family history and clinical picture were consistent with VWD. A Ristocetin-induced platelet aggregation (RIPA) test was done under fasting conditions to distinguish Type 1 vs. 2M VWD.

She was treated with Humate P (human derived VWF bound to factor VIII) and her bleeding stopped. However, she was not able to continue this due to cost. Aminocaproic acid was also used intermittently for minor bleeding as well as IV iron infusions for her iron deficiency anemia as needed.

Our patient became pregnant the following year. VWF actually increases during pregnancy, which can help ameliorate the condition, which was seen in our patient. However, there can be a steep drop in VWF levels after delivery, with >60% of patients experiencing postpartum hemorrhage, and >20% needing transfusion, critical care, or procedural intervention.[1] For this reason, our patient was hospitalized for induction of labor, and thankfully VWF levels remained normal and no prophylactic treatment was needed.

Discussion

Definition of VWD: The new guidelines and definition for Von Willebrand's Disease (VWD)[2] have two main criteria. People with 30-50% VWF levels who have a clinical history of bleeding are considered to have VWD. Our patient falls into this category. Those with or without a history of bleeding, but with VWF levels <30% are also considered to have VWD.

There are two main types of VWD:

Type I: reduced levels of VWF. In the Ristocetin Cofactor Test, there should be a parallel decrease between VWF activity and antigen.[3]

Type II: reduced VWF function.

a. Types 2a and 2b have decreased high molecular weight multimers due to decreased platelet binding. Since our patient had normal VWF multimers, this is not the case
b. Types 2N and 3 are very severe, and reduced VWF levels are accompanied by a reduced Factor VIII (as VWF acts as a carrier for Factor VIII), this is not the case for our patient who had normal factor VIII levels
c. Type 2M has decreased binding of VWF to platelet aggregation factor GpIb.[4] However, the binding sites for multimer aggregation are normal, so there are normal VWF multimers. The Ristocetin Induced Platelet Aggregation test (RIPA) is used to determine the whether the patient's VWF are able to functionally bind to the platelet glycoprotein (GP) Iba-V-IX

complex. Our patient has Type 2M VWD as determined by RIPA.

Treatments: Humate P or other formulations of normal VWF are very effective as it directly replaces the patient's own defective VWF (in function). The patient is theoretically also a candidate for DDAVP, as Desmopressin stimulates the release of endogenous VWF. However, since our patient had decreased levels as well as activity of VWF, the efficacy of DDAVP is dependent on the efficacy of her inherent VWF, which needs to be tested before it is used in urgent situations. Aminocaproic Acid was intermittently used for minor bleeding in our patient. This stabilizes the hemostatic plug by reducing fibrinolysis. This is especially helpful in mucous membranes that have higher fibrin activity, and therefore helpful for bleeding in sites such as nose, oropharynx or genitourinary tract.

Conclusion

Complaints of easy bruising and bleeding, including GI bleeding and hematochezia are exceedingly common in the primary care setting. A general understanding of when and how to screen for and treat this common bleeding disorder can minimize both potentially life-threatening cases of bleeding, and can help inform when specialty consultation is needed in high risk cases.

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