血和骨髓(BBM)

新型血友病因子基因多态性导致紫斑

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案例报告

摘要

血友病(血友病)是最常见的遗传性出血疾病。它是由于血友病因子(VWF)的缺乏和/或异常合成，由内皮细胞和巨核细胞合成。编码VWF的基因已被克隆并位于12p13.2染色体上。粘膜出血是所有血友病病例的典型表现。在这里，我们描述了一个以前未在文献中报告的VWF基因变异。

一位67岁的白人女性，有月经过多和骨关节炎病史，因抓伤后紫斑和皮下瘀斑出现在双臂。她否认鼻出血或近期严重出血，但正在服用阿司匹林和布洛芬。家族病史中偶尔有鼻出血。她的初步血液检查，包括凝血和补体因子，正常。然而，VWF基因分析在其中一例c. 1280T>C (p. Ile427Thr)变异的外显子11检测到了一种新型多态性。根据我们所知，这种新型多态性尚未在文献中报告。

这个病例说明了一个新的、独特的VWF基因多态性，以一种轻微增加的出血倾向出现。由于家庭拒绝检测，我们无法确定这种变异是遗传的还是偶然的。这种条件可以预测在重血手术或创伤事件中可能出现的严重出血。我们不知道长期使用抗血小板药物对这名患者的风险。

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KEYPOINTS:

1. Von Willebrand disease is often missed and neglected in clinical practice as it may present as minor bleeding.
2. We are reporting a novel Von Willebrand factor gene mutation that could predict future risk of bleeding in trauma or surgery.

INTRODUCTION

VWF is a multimeric multidomain adhesive protein that plays an important role in primary hemostasis by promoting platelet adhesion to the subendothelium at sites of vascular injury and platelet-platelet interactions in high shear-rate conditions. It is also the carrier of factor VIII (FVIII), and thus indirectly contributes to the coagulation process.\[^{1}\]

Molecular biology techniques have been used to map the VWF gene. The VWF gene is highly polymorphic and a number of single nucleotide polymorphisms have been found that contribute to large variation in “normal” VWF levels.

VWD is a bleeding disorder caused by a dysfunctional VWF and is the most common inherited disorder of the coagulation proteins in humans. VWD has a prevalence of about 1% in the general population, but the true incidence of clinically relevant cases is lower (about 100/million inhabitants). Bleeding manifestations are heterogeneous; and mucosal bleeding is typical of all VWD cases, but hemarthrosis and hematomas may also be present when FVIII levels are low.\[^{2}\] Patients with VWD can become symptomatic at any age.

VWD is associated with mutations on chromosome 12 in the p13.2 region that encode VWF, which is synthesized in endothelial cells and megakaryocytes.\[^{3}\] It is either inherited as an autosomal dominant trait or acquired due to several different pathophysiological mechanisms. An array of tests is usually required to characterize VWD type and to establish the best treatment modality.

CASE DESCRIPTION (MATERIALS/METHODS)

A 67-year-old post-menopausal Caucasian female was referred to the MountainView Hospital Division of Hematology and Oncology for evaluation of persistent purpuric lesions on both arms. Her medical history was significant for knee osteoarthritis and menorrhagia during her reproductive years. Her home medications were multivitamins, baby aspirin and naproxen for pain as needed. She denied recent trauma or any other bleeding. She was a current daily smoker. Family history was significant for occasional epistaxis in both of her sisters and her daughter. On physical examination scratch purpura and multiple old and new non blanching ecchymoses of variable size were seen on both arms.

The patient was evaluated for persistant ecchymoses that was out of proportion to her aspirin and nonsteroidal anti-inflammatory drug (NSAID) use. Complete blood count (CBC), coagulation profile, serum and urine protein electrophoresis, iron studies, total complement (CH 50), serum beta-2 microglobulin, concentration of VWF antigen (VWF: Ag), Ristocetin induced platelet agglutination (RIPA) and ANA were normal. However, VWF gene analysis detected a novel polymorphism in one copy of a c. 1280T>C (p. Ile427Thr) variant in exon 11 which has not been previously reported in the literature. Her aspirin and naproxen were stopped. During a follow-up visit, the patient reported spontaneous resolution of her lesions. She was also found to have diffuse atherosclerosis in the abdominal aorta with greater than 50% hemodynamically-significant stenosis of the proximal right common iliac
artery. Of note, her total cholesterol was 183 mg/dl, LDL 73 mg/dl and triglycerides were 275 mg/dl. Her blood pressure throughout her office visits was between 110/70 mmHg to 147/93 mmHg. She is being evaluated by her cardiologist for long-term antiplatelet therapy. She was counseled about getting her siblings and children tested for the same polymorphism, but two sisters declined testing, while the daughter who agreed was awaiting for approval from her insurance carrier. The patient has been lost to followup for the last couple of months.

**DISCUSSION**

VWD was first described by Erik von Willebrand in a Scandinavian family in 1923. There are three major subtypes of VWD. These are classified as: a partial quantitative deficiency of VWF (type 1 VWD) with variable bleeding tendency; a qualitative deficiency (type 2 VWD) with more homogeneous dysfunctional VWF; or virtually complete deficiency (type 3 VWD). Type 1 and type 2 VWD have an autosomal dominant pattern of inheritance, while type 3 is inherited as a recessive trait. The diagnosis of VWD, especially type 1, is difficult since the laboratory phenotype is highly heterogenous and is compounded by factors outside the VWF gene (including age, race, blood group specially blood group O, pregnancy, stress, hormones and smoking) that influence VWF levels. Diagnosis is usually made by reviewing the patient’s personal and family history of bleeding and by clinical evaluation for more common reasons for bleeding, which is then supplemented with laboratory tests. Assessment may be used to determine bleeding risk before surgery and other invasive procedures, and to diagnose reasons for unexplained bleeding. Acquired forms of WVD are most frequently described in patients with clonal lymphoproliferative and autoimmune diseases (e.g., systemic lupus erythromatosis). Nonimmune mechanisms that have been described include adsorption of VWF onto tumor cells (Wilms’ tumor, multiple myeloma and Waldenstrom’s macroglobulinemia), VWF multimers degradation (decompensated cirrhosis, pancreatitis, myeloproliferative disorders and disseminated intravascular coagulation) and reduced levels in heart diseases (noncyanotic congenital heart diseases and high-grade aortic stenosis).

VWF is a large multimeric and multidomain glycoprotein that mediates the attachment of platelets to damaged endothelium and also serves as the carrier protein for coagulation factor VIII (FVIII), protecting it from proteolytic degradation. It circulates in plasma at a concentration of 0.5-1.0 mg/dl; 15% of which is contained within the platelets. Larger VWF multimers (as high as 10,000-20,000 kDa) are targeted to endothelial cytoplasmic storage granules, the Wiebel-Palade bodies. In platelets, VWF is stored in a-granules. VWF is synthesized by endothelial cells and megakaryocytes. Synthesis of VWF is regulated in part by hormones because VWF production in endothelial cells is increased by estrogen and thyroid hormones.

The gene coding for VWF has been cloned and located at chromosome 12p13.2. It is a large gene composed of about 178 kilobases and contains 52 exons. There is also a noncoding pseudogene located in chromosome 22.2, spanning the gene sequence from exon 23 to exon 34.2. The primary product of the VWF gene is a 2,813 amino acid protein made of a signal peptide of 22 amino acids (also called a pre-peptide), a large pro-peptide of 74 amino acids (also called von Willebrand antigen II) and a mature VWF molecule containing 2,050 amino acids. Different protein regions, corresponding to four types of repeated domains (D1, D2, D’, D3, D4, A1, A2, A3, B, C1, C2) are responsible for the different binding functions of the molecule (Figure 1).
Figure 1: Schematic illustration of VWF protein structure with the functional domains and VWD mutations as reported in the VWD database (http://www.vwf.group.shef.ac.uk/).[11]

These multiple domains deliver the unique hemostatic abilities of VWF, including the localization of platelet-binding sites in the A1, C1, and C2 domains, collagen binding in the A1 and A3 domains, and a FVIII-binding site in the D’, D3 domains. The high-molecular-weight multimers are the most effective forms of VWF that mediate platelet adhesion at sites of vascular injury.

The VWF gene polymorphism that we are reporting is located on exon 11, corresponding to domain D2. Amplification was done for more common splice junction sites on selected exons (exons 11, 12, 14, 15, 16, 18, 19, 20, 24, 27 and 52). This does not include any comprehensive evolution for other less frequent variations that may be detected using mRNA splicing and protein synthesis. At this time we are unsure of the underlying pathogenetic mechanisms leading to this polymorphism. The cleavage of ultra-large-molecular-weight multimers leads to the production of smaller, lower-molecular-weight multimers that are inherently less hemostatically active.[11]

Although low laboratory values are common in VWD patients, only a fraction of such patients seek medical attention due to bleeding symptoms. The low incidence of bleeding is due to the mild nature of the disease in many patients and due to the lack of bleeding challenges and/or lack of recognition of excessive bleeding (e.g., heavy menstrual bleeding) in others. In addition, the highly heterogeneous phenotype and presence of factors outside the VWF gene make diagnosis of VWD difficult and is almost always delayed, which could have been the case in our patient.

The laboratory tests used to evaluate and screen for VWD include prothrombin time, activated partial thromboplastin time, VWF antigen (VWF: Ag), VWF activity as ristocetin cofactor (VWF: RCo) or as collagen binding (VWF: CB) activity and FVIII activity (FVIII: C). VWF levels may vary at different time points. Physiological and disease states should be taken into account while interpreting tests. In patients with borderline laboratory tests,
the diagnostic testing should be repeated on two or more occasions separated by 4-6 weeks, as was done with our patient. There is no single straightforward diagnostic test available to either confirm or exclude the diagnosis. Newer assays of VWF function are becoming more available and are useful in determining the laboratory diagnosis of VWD. [12]

VWF is synthesized with a very large propeptide (VWFpp) that is critical for the intracellular processing of VWF through dimerization and multimerization for optimal functioning. We believe that the gene polymorphism we are reporting here might perhaps lead to a hypoproduction of protein product. The routine use of aspirin and NSAID may have unmasked this prior undetected gene polymorphism, which then became clinically apparent. This variant has not been reported earlier in the VWF database. [13]

Our patient also had peripheral arterial disease with hemodynamically significant stenosis. Due to her current bleeding, aspirin was stopped. At this point we are uncertain about the risks and benefits of starting antiplatelets or anti-coagulants in this patient. A review of data did not show any studies done to date on the safety of long-term antiplatelet therapy in patients of VWD and peripheral arterial disease, with the exception of acute coronary syndromes where patients underwent percutaneous coronary intervention with adjuvant antiplatelet and antithrombotic therapy for short periods without significant bleeding complications [14, 15]

RESULTS/CONCLUSION

This case illustrates a new and unique heterozygous variant of VWF gene polymorphism presenting with a mild increased incidence of bleeding. Recent advances have illuminated the ways in which VWF contributes to both kinds of hemostatic emergency, whether minor or major life threatening, often through disturbances in VWF synthesis or catabolism.

It is essential to conduct a future comprehensive study, including clinical, basic, and special testing, laboratory tests, in order to establish a correct diagnosis, develop new therapeutic approaches, and offer appropriate medical care and genetic counselling to our patients.

It is possible to determine if this is inherited or sporadic by testing family members for the same gene mutation, which could predict the possibility of serious bleeding in the event of a major surgery or trauma. For now, we do not know what the risk would be of using long-term antiplatelet agents for vascular stenosis in these patients.

DECLARATION OF CONFLICTING INTEREST

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