Thrombosis & Haemostasis: Research

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Case Report

A Novel Mutation Case of Type 3 Von Willebrand Disease Misdiagnosed as Hemophilia A

Zheng X[1], Liang S[2], Wang D[1], Lin W[1], Zhang J[1], Ye M[1], Dong L[1] and Zhang S[1]*

[1]Department of Laboratory Medicine, The First Affiliated Hospital, Sun Yat-sen University, China

[2]Department of Internal Medicine, Life Share Blood Center, 8910 Linwood Ave Shreveport, USA

***Corresponding author:** Shihong Zhang, Department of Laboratory Medicine, The First Affiliated Hospital, Sun Yat-sen University. No.58 Zhongshan Second Road, Guangzhou, 510080 China

Received: September 22, 2022; **Accepted:** October 22, 2022; **Published:** October 29, 2022

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VWD is reported as the most common inherited bleeding disorder worldwide, found in approximately 1% population [1-4]. It can be divided into 3 subtypes: type 1, type 2 and type 3, caused by quantitative or qualitative defects of VWF. VWF is a complex plasma protein essential for primary hemostasis and coagulation. VWF helps to bind and stabilize blood clotting FVIII from rapid breakdown within the blood stream. Any defect in VWF can also cause reduction of FVIII levels [5].

Type 3 VWD is the rarest and most severe type due to virtual absence of VWF and very low levels of FVIII, another protein involved in blood clotting. Hemophilia A is another type of genetic bleeding disorder characterized by deficiency in clotting FVIII, usually affecting males. Type 3 VWD can be difficult to diagnose due to its rarity. Symptoms, hemostatic challenge and bleeding history may become more apparent with increasing age. Since type 3 VWD also exhibits very low levels of FVIII resembles hemophilia A and it can be misdiagnosed if based on FVIII levels only.

We report a rare case here, a 34 years old Chinese male visited a local hospital with persistent nasal bleeding without obvious inducement lasting 10 days. He was diagnosed with Hemophilia A at birth and had experienced countless repeated bleeding from the right knee joint in his lifetime. No personal or family history of bleeding tendencies or any underlying autoimmune disorder. He was the offspring of a consanguineous marriage. He was treated with nasal packing but his bleeding symptoms did not resolve.

The patient was admitted to the general medicine department of our hospital for further testing and investigations. Nasal endoscopy showed a large amount of active hemorrhage occurred after removal of the packed Vaseline gauze. A complete blood count examination indicated low red blood cell (2.72×10^{12}/L) and hemoglobin level (82 g/L), slightly elevated platelet (335×10^{9}/L) and white blood cell (15.49×10^{9}/L) counts. The biochemical examination showed high ferritin concentration (102.8 μg/L), and normal liver and renal functions.

Routine coagulation tests revealed normal PT, APTT, and elevated fibrinogen and D-Dimer level. Further special coagulation tests were performed as screening for both thrombophilia and bleeding diathesis (Table 1). Eventually the results of all thrombophilia tests were found to be normal.

We were surprised to discover that his FVIII level was normal (99.5%) since the patient was diagnosed with hemophilia A, had been bleeding over 10 days. It was expected that his FVIII level should have been significantly decreased. This led us to order a full VWD panel. Simultaneously the patient developed GI bleeding, his hemoglobin level dropped to 52g/L, and he received 2 units of RBC. We also discovered that his normal FVIII level was due to recent infusion of FVIII concentrate at another hospital. Surprisingly, his von Villlebrand factor antigen was 6% (normal range is 50%-160%) and the VWF activity was <15%. His FVIII dropped to 2% after 7 days and despite treatment with DDAVP and recombinant Human Coagulation Factor VIII injection his von Villlebrand factor antigen level remained low (3%). The results of Thromboelastography were normal (Figure 1), which further indicated the probable misdiagnosis of Hemophilia A.

Hence, he was transfused with cryoprecipitate (0.2U/kg) until bleeding symptoms stopped (VWF concentrates are unavailable in China). Homozygous VWF c.4743_4747del (p.Leu 1582fs) was found in the patient, and his parents were confirmed to be heterozygous carriers (Figure 2).

Type 3 VWD is a rare condition which is characterized by the most severe bleeding disorder mainly due to little or complete deficiency of von willebrand factor [6]. It manifests with severe bleeding including both excessive mucocutaneous bleeding and musculoskeletal [4]. In populations with frequent consanguineous partnerships, the rate of recessive forms of VWD may be elevated and type 3 VWD comprises a larger proportion of affected individuals. VWD type 3 affects 0.5-6% million population, increasing with the rate of consanguinity [7]. Homozygous or heterozygous mutations in the von willebrand factor gene which affects the synthesis of glycoprotein or allele silencing causes the disease.

Our case is interesting due to a novel mutation homozygous VWF c.4743_4747del (p.Leu 1582fs) in exon 28, which has not been previously reported. This mutation led to his very low VWF level and serious bleeding manifestations. His misdiagnosis of hemophilia A since birth was probably based on FVIII levels only. Consequently, he was not reevaluated for other bleeding disorders, we eventually reevaluated the patient because of his persistent bleeding symptoms and mismatched FVIII levels. It's important to make the appropriate diagnosis because the patient's treatment will be affected greatly. Our patient was initially treated with DDAVP, however, it didn't work. DDAVP is used to help stop bleeding in patients with VWD and hemophilia A. It causes the release of von willebrand antigen from

Citation: Zheng X, Liang S, Wang D, Lin W, Zhang J, Ye M, et al. A Novel Mutation Case of Type 3 Von Willebrand Disease Misdiagnosed as Hemophilia A. Thromb Haemost Res. 2022; 6(3): 1083.

platelets and the cells that line the blood vessels where it is stored, but DDAVP is not effective for patients with type 3 VWD [8]. Besides, our patient was repeatedly transfused with FVIII whenever he had bleeding symptoms. As a result, he appeared to have made anti-FVIII. There is no exact cure for this type of disease, symptomatic treatment can be given based on the conditions.

In conclusion, our case was caused by consanguineous marriage leading to a novel homozygous VWF c.4743_4747del (p.Leu 1582fs) mutation in exon 28. This variant has not been previously reported, which makes our case is interesting. Additionally, our patient had been misdiagnosed with hemophilia A since birth. We report this occurrence to raise clinicians' awareness. We also suggest that a VWF assay should be included when evaluating hemostasis disorders.

Conflict of Interest

All authors are staff of the First Affiliated Hospital of Sun Yat-sen University. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Author Contributions

Sandra was involved in preparation of the manuscript, SHZ and XHZ analyzed and diagnosed the case, they were also involved in patient management and assisted in compiling clinical data. DW and WBL carried out the laboratory testing. LJD and JQZ assisted in data compilation and analysis. MMY assisted in statistical analysis.

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