Coexixtence Type 1 and 3 Von Willebrand Disease in a Malaysian Child and Her Family

Malezyalı Bir Çocuk ve Ailesinde Coexixtence Tip 1 ve 3 Von Willebrand Hastalığı

Kimberly Fe Joibi[1,2], Noor Haslina Mohd Noor[1,2], Mohd Nazri Hassan[1,2], Wan Zaidah Abdullah[1,2], Salfarina Iberahim[1,2] Rosnah Bahar[1,2], Shafini Mohd Yusoff[1,2], Marini Ramli[1,2], Wan Suriana Wan Abdul Rahman[3], Zefarina Zulkafli[1,2]

[1]Department of Hematology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia
[2]Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
[3]School of Dental Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Von Willebrand disease (WVD) is a common inherited bleeding disorder due to a defect of von Willebrand factor (VWF). VWF is a glycoprotein that crucial for platelet adhesion to the subendothelium after vascular injury. VWD include quantitative defects of VWF, either partial (type 1 with VWF levels < 50 IU/dl) or virtually total (type 3 with undetectable VWF levels) and also qualitative defects of VWF (type 2 variants with discrepant antigenic and functional VWF levels). We report a case of an 11-month-old girl diagnosed with Type 3 VWD presented with mucocutaneous bleeding with von Willebrand factor antigen is < 1 IU/dl and positive family history of VWD. The family study was done and five other family members were also diagnosed with either Type 1 or Type 3 VWD with variable clinical presentations.

Key Words: Von Willebrand Disease, family, inherited bleeding disorder

Received: 12.24.2019 **Accepted: 02**.01.2021

ÖZET

Von Willebrand hastalığı (WVD), von Willebrand faktörünün (VWF) kusurundan kaynaklanan yaygın bir kalıtsal kanama bozukluğudur. VWF, vasküler yaralanmadan sonra subendotelyuma trombosit yapışması için çok önemli olan bir glikoproteindir. VWD, kısmi (VWF seviyeleri <50 IU / dl olan tip 1) veya neredeyse toplam (tespit edilemeyen VWF seviyelerine sahip tip 3) VWF'nin kantitatif kusurlarını ve ayrıca VWF'nin kalitatif kusurlarını (tutarsız antijenik ve fonksiyonel VWF seviyelerine sahip tip 2 varyantları) içerir. . Von Willebrand faktör antijeni ile mukokutanöz kanama ile başvuran Tip 3 VWD tanısı alan 11 aylık bir kız çocuğu <1 IU / dl ve VWD'nin pozitif aile öyküsünü bildiriyoruz. Aile çalışması yapıldı ve diğer beş aile üyesine de değişken klinik sunumlarla Tip 1 veya Tip 3 VWD teşhisi kondu.

Anahtar Sözcükler: Von Willebrand Hastalığı, aile, kalıtsal kanama bozukluğu

Geliş Tarihi: 24.12.2019 **Kabul Tarihi:** 01.02.2021

ORCID IDs: K.F.J. 0000-0002-8736-2631, N.H.M.N.0000-0001-8357-1850,M,N.H.0000-0003-4975-2038,W.Z.A.0000-0001-7113-475x,S.I. 0000-0002-6903-3519,R.B.0000-0003-4276-7288,S.M.Y.0000-0001-8950-5715,M.R.0000-0002-9104-7511,W.S.W.A.R.0000-0003-3878-208x,Z.Z.0000-0003-2029-2234

Address for Correspondence / Yazışma Adresi: Noor Haslina Mohd. Noor, MD Department of Hematology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia. E-mail: drhaslina@usm.my

doi:http://dx.doi.org/10.12996/gmj.2021.51

INTRODUCTION

VWD is one of the most common inherited bleeding disorders which commonly affects females and is characterised by the deficiency of VWF (1). VWF carries and protects factor VIII (FVIII) from degradation and helps in hemostasis. VWD is traditionally classified into Type 1 and Type 3, which describe mild to moderate and severe quantitative deficiencies of VWF, respectively, and Type 2, which is characterised by qualitative deficits in VWF (1). Depending on the classification, the mode of inheritance can be either of autosomal dominant or autosomal recessive. Each subtype of VWD involves different types and location of mutation of the VWF gene (2).

We report a case of an 11- months-old girl with possible of Type 3 VWD with five other family members with VWD but varies in clinical presentation.

CASE REPORT

An 11-months-old girl presented with continuous epistaxis after having a fall with her face in a prone position. Further history from the mother, revealed that she has multiple bruises at chest area since she was able to mobilise at the age of 5 months old. There was, however, no history of bleeding or haematoma post-vaccination. Physical examination revealed bruises at the left forearm, bilateral shin and left forehead. Her full blood count showed hypochromic microcytic anaemia with haemoglobin of 7.2 g/dl, leucocytosis with a white cell count of 22.2 x 10^3/uL and thrombocytosis. Her peripheral blood smear showed red cell features suggestive of iron deficiency anaemia. A von Willebrand study was done showed VWF Ag of <1 (UI/dl) with Ristocetin cofactor assay of <1 Ul/dl. Collagen binding assay was 4.5% and FVIII level was 8 Ul/dl.

Based on the results of laboratory investigation, Type 3 VWD was suspected in this patient. Family history revealed a non-consanguineous marriage between her parents. Pedigree analysis of the family showed that the patient's father, mother and siblings were also suffering from VWD. (Table 1 & Figure 1).

Table 1: Summary of Clinical Presentations and Laboratory Results of Family Members

	Father	Mother	Sister 1	Brother	Sister 2	Sister 3	Sister 4	Patient
Clinical symptoms	No	No	No	No	No	Easy bruising, gum bleeding, bleeding from immunization site, continuous bleeding post trauma	No	Epitaxis and easy bruising
aPTT (secs)	34.6	42.5	47.1	38.4	42.7	**83.5**	37.2	**49.6**
Blood Group	NA	A+	NA	NA	NA	A+	NA	O+
VWF Ag (UI/dl)	61.5	**30.6**	**49.1**	108	65.4	**<12**	107	**<1**
VWF Activity (UI/dl)	82.6	**46.6**	70.4	156	96.2	Not done*	104	Not done*
Ristocetin Cofactor Assay (UI/dl)	53.02	**45.68**	**48**	98.29	66.54	Not done*	81	**<1**
Collagen binding assay (%)	Not done*	Not done*	Not done*	Not done*	Not done*	**2**	95.5	**4.5**
FVIII level (UI/dl)	122	73	108	137	98	**2**	115	**8**
Impression	Unable to exclude mild Type 1	VWD Type 1	VWD type 1	Normal VWD study	Unable to exclude VWD Type 1	Most probably VWD Type 3	Normal VWD study	Most probably VWD Type 3

*Test was not performed as reagent was not available

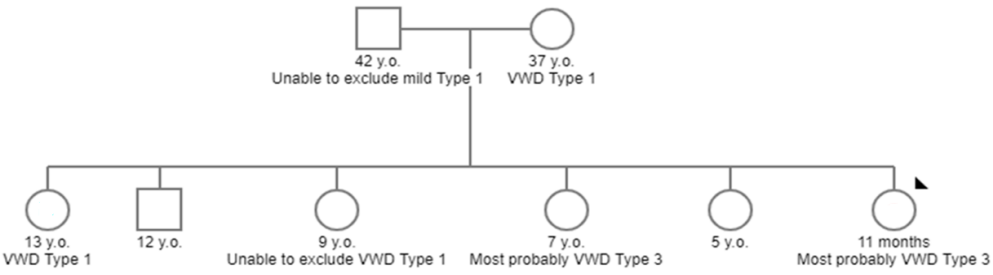

Figure 1: Patient's family pedigree.

DISCUSSION

VWF is a large complex multimeric glycoprotein that has two essential roles in primary hemostasis. VWD is characterised by the abnormal quantity or quality of VWF. It is further divided into a few subtypes with different modes of inheritance and mutation for each subtype (1).

Here we present a child with type 3 VWD and several other family members exhibiting possible both Type 1 and Type 3 VWD, based on bleeding symptoms and laboratory investigations, VWD itself is a rare disease in Malaysia, accounting for 0.002% among Malaysian populations. Majority of cases were Type 1 VWD accounting for 77.2% of cases, while Type 3 VWD accounts only a small percentage of 2.1% of all VWD cases (3). The prevalence of VWD depending on the method used to identify patients, either by population screening of persons at risk or actual patients seen at medical centres. (4).

Current standard practice in the laboratory diagnosis for VWD relies on two VWF-specific tests that evaluate (1) the quantity of VWF that is present in plasma, and (2) the efficacy of this plasma VWF in its ability to bind platelets in the presence of the antibiotic Ristocetin. A combination of these tests, plus the measurement of FVIII activity (FVIII:C), allows for the classification of patients into the classic groupings of VWD type 1, type 2, or type 3. The basic VWF assays remain essential to make an accurate diagnosis (1).

Type 3 von Willebrand disease is inherited as an autosomal recessive disorder which is associated with a severe quantitative defect and more severe bleeding tendencies compared to the other types of VWD. Type 3 accounts for about 1% of patients with VWD. Bleeding usually starts in infancy and can include epistaxis, recurrent mucocutaneous bleeding, bleeding after surgery and haemarthroses. (4).

Laboratory characteristics of type 3 VWD include undetectable VWF:Ag and VWF:RCo (ristocetin cofactor assay), accompanied by very low FVIII:C and absent VWF multimers. (5). No further testing is usually necessary for the diagnosis of type 3 VWD in patients with bleeding and VWF: Ag and/or VWF: RCo of <0.03 IU/mL (6).

Abbas et al. observed the sensitivity of VWF: Ag is only 78%, and the sensitivity of VWF: RCo is 92% to diagnose patients with type 3 VWD. Therefore, both tests should be included in the assessment of patients with VWD to avoid misdiagnosis of some type 3 VWD as type 1 or 2 VWD (6).

Study by Bowman et al. reported Type 3 VWD disease with complete absence of VWF:Ag and VWF:RCo with severe deficiency of FVIII:C, they are commonly associated with deletions, insertions, nonsense mutation which often leads to a null allele and classically are inherited in autosomal recessive manner and can either consists of homozygous or compound heterozygous states (2).

A Canadian cohort study reported that though most obligate carriers of Type 3 VWD is phenotypically silent, 48% of the obligate carriers have been diagnosed with Type 1 VWD (2). Bleeding history, FVIII:C and VWF:Ag levels in obligate carriers of Type 3 VWD was found to have worse manifestation than normal control, however, better than an obligate carrier for Type 1 VWD (7).

The prevalence of type 1 VWD may be under-reported due to various reasons. One of the most likely causes of under-reported is due to mild disease in type 1 VWD. Type 1 VWD is difficult to diagnose in many cases due to plasma levels of VWF are close to the normal range (4).

Laboratory characteristics of type 1 VWD include a mild to moderate decrease in both VWF:Ag and VWF:RCo with normal or borderline low FVIII:C. Bleeding symptoms in type 1 VWD range from mild mucosal bleeding to more severe surgical haemorrhage. Other influences on VWF levels such as blood type, ethnicity and modifier genes have all been implicated. Repeat testing should be considered in symptomatic patients with borderline normal levels as exercise and stress can also elevate VWF levels (5). Mutations in Type 1 VWD are commonly missense mutations (8). However, genetic testing is not usually helpful in type 1 VWD as not all patients have a sequence variation in VWF and mutation status is not currently predictive of either clinical symptoms or response to treatment (5).

CONCLUSION

Patients with Type 3 VWD usually meet all three main criteria required for the diagnosis of VWD: a history of bleeding episodes since childhood, reduced plasma VWF and autosomal recessive inheritance. Clinical markers are very important and include a negative history of bleeding in parents in most families because of the autosomal recessive inheritance and moderate to severe bleeding episodes in most cases. The measurement of VWF: Ag and VWF: RCo are key components in the diagnostic algorithm for VWD. The molecular pathology of type 3 VWD has been well characterized, with an array of different mutation; however, its utility is currently limited.

Von Willebrand study for the patient and other family members was planned to be repeated in future; however, due to logistic and lost of follow up, these cases were not available for repeat samples.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1.Christopher Ng DGM, and Jorge Di Paola**.** Diagnostic approach to von Willebrand disease. Blood. 2015; (125(13)):2029–37.

2.M. Bowman AT, C. Notley, C. Brown, S. Tinlin†, M. Deforest, J. Leggo†, V.S. Blanchette, D. Lillicrap, and P. James† The Genetics of Canadian Type 3 von Willebrand Disease (VWD): Further Evidence for Co-dominant Inheritance of Mutant Alleles. J Thromb Haemost. 2013 11(3):512–20.

3.Periayah MH HA, Saad AZM, Yaacob NS, Karim FA**.** Report on von Willebrand Disease in Malaysia. Open Access Maced J Med Sci. 2016;4(1):112-7.

4.J. E. Sadler UB, J. C. J. Eikenboom, E. J. Favaloro, F. G. H. Hill, L. Holmberg, J. Ingerslev, C. A. Lee, D. Lillicrap, P. M. Mannucci, C. Mazurier, D. Meyer, W. L. Nichols, M. Nishino, I. R. Peake, F. Rodeghiero, R. Schneppenheim, Z. M. Ruggeri, A. Srivastava, R. R. Montgomery, A. B. Federic**.** Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. Journal of Thrombosis and Haemostasis 2006; 4:2103–14.

5.Roberts JC FV**.** Laboratory diagnosis of von Willebrand disease. . Int J Lab Hematol. 2015;37(Suppl 1):11-7.

6.Abbas Hashim abdulsalam YG, Nidhal Alrahal**.** Presentation and diagnosis of patients with type 3 von Willebrand disease in resources-limited laboratory. Haemato oncol stem sell ther. 2019;12:211-4.

7.Castaman G RF, Tosetto A, Cappelletti A, Baudo F, Eikenboom JC, et al**.** Hemorrhagic symptoms and bleeding risk in obligatory carriers of type 3 von Willebrand disease: an international, multicenter study. Journal of thrombosis and haemostasis. 2006;4(10):2164-9.

8.I. Peake AG**.** Type 1 Von Willebrand Disease. Journal of thrombosis and haemostasis. 2007;5:7-11.