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BRIEF COMMUNICATION

Presentation and diagnosis of patients with type 3 von Willebrand disease in resources-limited laboratory

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KEYWORD
Type 3 von Willebrand disease

Abstract
Von Willebrand disease (VWD) is a bleeding disorder that results from decreased von Willebrand factor (VWF) activity <0.30 iu/mL. Therefore, the diagnosis of type 3 VWD in patients with bleeding requires finding a VWF:Ag and/or VWF:platelet ristocetin cofactor (RiCof) <0.03 iu/mL, no further testing is usually necessary. This is a cohort study that included 64 patients with type 3 VWD who were presented and diagnosed at the National Center of Hematology (NCH) from October 2014 to October 2016. In this study the sensitivity of VWF:Ag is only 78%, the sensitivity of VWF:RiCof is 92% of diagnosed cases. From our results it can be concluded that patients with type 3 VWD are usually presented with moderate/severe mucocutaneous bleeding that is associated with prolonged bleeding time test of >10 min and a family history of similar type of bleeding. This fact was frequently utilized to provisionally diagnose several members of the same family, forming a cohort of patients that is larger than the number of objectively-diagnosed patients included in this study, when they cannot afford to be all tested with VWF:Ag/VWF:RiCof.

Background

Von Willebrand disease (VWD) is an inherited bleeding disorder that results from decreased von Willebrand factor (VWF) activity <0.30 iu/mL [1].

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VWF is a large complex multimeric glycoprotein that has two essential roles in primary hemostasis, (a) by promoting platelet adhesion to the subendothelium at the site of vascular injury under high shear rate, and (b) it is a carrier of Factor VIII (FVIII) and this association protects FVIII from rapid proteolysis.

VWF concentration is lower in individuals with blood group O than other blood groups [2], however, a VWF activity <0.30 iu/mL is usually associated with bleeding symptoms and with a mutation in VWF gene [1].

In practice, VWF activity is assessed using the measurement of VWF:antigen (VWF:Ag) by ELISA, and VWF:Ristocetin cofactor (VWF:RiCof) by functional assay, mostly by light transmission aggregometry (LTA).

In the National Center of Hematology (NCH), the diagnosis and classification of patients with VWD is based on the latest British Committee for Standards in Haematology (BCSH) guidelines that were published in 2014 [1]. The diagnosis of type 3 VWD in patients with bleeding requires finding a VWF:Ag and/or VWF:RiCof <0.03 iu/mL, no further testing is usually necessary. Type 3 VWD is either an autosomal recessive bleeding disorder, due to null VWF alleles that shows virtually complete deficiency of VWF, or it results from a codominant inheritance of mutant alleles [3]. Type 3 VWD often occurs in several members of families with a history of consanguinity.

The aim of this study is to describe the cohort of patients with type 3 VWD from Iraq, features of bleeding, and the findings of coagulation assays in these patients that were essential for diagnosis.

Patients and methods

This is a cohort study that included 64 referred patients with type 3 VWD who were diagnosed at the NCH from October 2014 to October 2016.

Patients were interviewed with history taking concentrating on bleeding events and whether occurring spontaneously or induced, if medical intervention or blood component transfusion was required, consanguinity, and family history of bleeding.

A brief medical examination for signs of bleeding was done, including conducting a template bleeding time. Blood was withdrawn before starting specific treatment or replacement therapy and sent for the following tests: full blood count (FBC), reticulocyte percentage, blood smear, prothrombin time (PT, Stago, France), activated partial thromboplastin time (APTT, Stago, France), VWF:Ag (Stago, France) using ELISA, FVIII assay (one-stage clotting assay, Stago, France), VWF:RCo (vW Factor Assay, Bio/Data, USA) using platelet LTA (PAP-8E, Bio/Data, USA), according to manufacturer's leaflet.

Assessment of presence and severity of bleeding was performed according to Bowman's bleeding score, as this score was created [4] and further examined [5] by assessing bleeding mostly in pediatric patients with VWD, and that we were already using at the NCH.

Results

The male to female ratio in this study is 1.37:1. Other findings are presented in Tables 1–3 and Fig. 1.

Table 1 Demographic features of patients with type 3 Von Willebrand disease.

Parameter		*N*	%
Sex	Male	37	57.8
	Female	27	42.2
Current age (y)	Birth–5	21	32.8
	6–10	12	18.8
	11–15	9	14.1
	16–20	9	14.1
	≥ 21	13	20.3
Age at presentation (y)	Birth–5	61	95.3
	6–10	2	3.10
	11–15	1	1.60
Consanguinity	Yes	60	93.7
	No	4	6.30
Family history of bleeding	Yes	56	87.5
	No	8	12.5
Residence	Baghdad & Central Iraq	46	72.0
	South to Baghdad	14	22.0
	North to Baghdad	4	6.30

Note. y = year.

Table 2 Type and severity of bleeding in patients with type 3 von Willebrand disease.

Parameter		*N*	%
Type of bleeding	Mucocutaneous	64	100
	Other types	2	3.1
[a]Severity of bleeding	Mild	2	3.1
	Moderate	17	26.6
	Severe	45	70.3
Bleeding time	Normal (<4 min)	3	4.7
	Markedly prolonged (≥10 min)	61	95.3

Note. NCH = National Center of Hematology.

[a] Classified according to local policy at the NCH into mild with only scores 0–1 in all bleeding categories, moderate with scores up to 3 in all bleeding categories, and severe with score 4 in one or more of the bleeding categories according to Bowman's score.

Table 3 Laboratory findings in patients with type 3 VWD.

Parameter		Range	Median (SD)
Hb concentration (g/dL)	Males	7.2—14	10.95 (2.19)
	Females	7.6—13.2	10.67 (1.99)
Platelet count (*10^9/L)		Normal	
PT (s)		Normal	
PTR		Normal	
APTT (s)		34—82	55.97 (9.47)
Normalized APTT		1—2.34	1.6 (0.27)
FVIII (%)		0.1—25	5.63 (13.1)
[a]VWF:Ag (iu/mL)		0.25 — 17.6	3.3 (3.56)
[b]VWF:RiCof (iu/mL)		0 — 9	0.39 (1.57)

Note. APTT = activated partial thromboplastin; Hb = hemoglobin; NCH = National Center of Hematology; PT = prothrombin time; SD = standard deviation; VWF = von Willebrand factor.

[a] Sensitivity for diagnosis of type 3 VWD was: 94% for APTT, 88% for normalized APTT, 78% for VWF:Ag, and 92% for VWF:RCo.

[b] Sensitivity of other parameters were not presented as they were irrelevant to diagnosis (Hb concentration), with normal findings (platelet count, PT, PTR), or abnormal in all patients (FVIII).

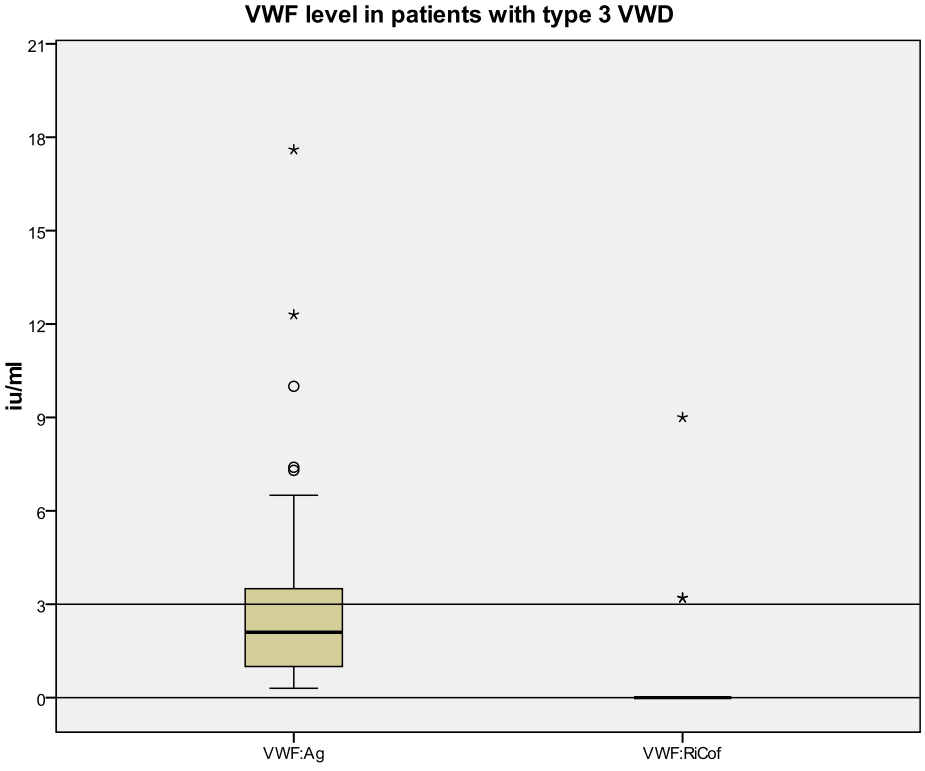

Fig. 1 VWF level in patients with type 3 VWD. N.B.: All patients had either or both VWF:Ag and VWF:RCo below the cut-off value of 3 iu/ml that is required for diagnosis of type 3 VWD. Small circles and stars refer to values that lie outside the middle 95% and 99% of examined data respectively.

Discussion

In this study, we evaluated a population of patients, and some of their relatives, with type 3 VWD from Iraq. There were slightly more males with type 3 VWD than females. There was a significant difference between current age of patients and age of patients at first presentation with relevant bleeding history. This can be largely attributed to absence of diagnostic facilities for type 3 VWD before the start of this study. Most of the patients presented with history of significant bleeding at a very young age and this is expected in type 3 VWD.

There was a very high incidence of consanguinity, and this can explain the high incidence of family history of bleeding and type 3 VWD in Iraq.

We believe that the distribution of patients according to residence shows some bias as it basically reflects limited

and/or easy access to our service more than being a real geographic distribution of patients.

From our results it can be concluded that patients with type 3 VWD usually show moderate/severe mucocutaneous bleeding symptoms that is associated with markedly prolonged bleeding time test of >10 min and a family history of similar type of bleeding. This fact was frequently used to provisionally diagnose several members of the same family, forming a cohort of patients that is larger than the number of objectively-diagnosed patients included in this study, when they cannot afford to be all tested with VWF:Ag/VWF:RiCof. Response to the same lines of treatment is taken as further evidence to confirm the diagnosis.

Classically the normal range for VWF and FVIII was presented according to blood group of patients, as both tend to be much lower in patients with blood group O than other types of blood groups. However, as the latest BCSH guidelines recommend against the use of reference ranges according to blood group, we prefer to use the cut-off values of VWF activity of 0.30 iu/mL and 0.03 iu/mL to diagnose VWD and type 3 VWD respectively [1]. The demographic distribution of patients according to blood group and the comparison of patients with O blood group with other patients with non-O blood group was omitted as it became irrelevant from the diagnostic point of view.

In this study the sensitivity of VWF:Ag is only 78%, and the sensitivity of VWF:RiCof is 92% to diagnose patients with type 3 VWD, Therefore, both tests should be included in assessment of patients with VWD to avoid misdiagnosis of some type 3 VWD as type 1 or 2 VWD.

The majority of patients showed mild to moderate anemia that was compatible with their history of chronic moderate to severe bleeding and with the nature of their final diagnosis of type 3 VWD.

Platelet count, PT, and Prothrombin time ratio (PTR) were normal in all patients included in this study, and this was in harmony with the diagnosis of type 3 VWD. APTT and normalized APTT are prolonged in most patients with type 3 VWD, in keeping with the marked reduction of FVIII in the same cohort of patients.

From this study we can recommend the following:(a) to follow the BCSH guidelines to diagnose and classify patients with VWD, as the technical requirements are not exhaustive, (b) testing all first degree relatives of patients with type 3 VWD, especially those with history of mucocutaneous bleeding and family history of consanguinity can probably identify more patients; and (c) using both VWF:Ag and VWF:RiCof to study the VWF, as none has ideal sensitivity to detect all potential patients with type 3 VWD.

Conflicts of interest

The authors have no conflicts of interest to declare.

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