Prevalence of Hereditary Von Willebrand Disease among Saudi Students

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Abstract

Background: Von Willebrand disease (vWD) is the most common inherited bleeding disorder, with a prevalence ranging between 0.7-1.6%, globally.

Materials and methods: Our study was conducted between January 2014 and February 2016 on adolescents in Riyadh, trained interviewers surveyed had contacted 2,000 university students between 17 to 22 years, using the standardized questionnaire based on Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease (MCMDM1-VWD). All blood samples were tested for complete blood count (CBC), prothrombin time (PT), Partial thromboplastin time (PTT), and platelet function analyzer (PFA-100). Samples had abnormal result of PTT and/or PFA100 were tested for Factor VIII (FVIII) Activity, von Willebrand factor (vWF): antigen, vWF: activity.

Results: Out of these students 730 (36.5%), had reported bleeding symptoms, 326(44.6%) had agreed to give blood samples, 116 (35.5%) samples had prolonged PTT (>41 sec), 39 (11.9%) had prolonged PFA -100 epinephrine (EPI), 48 (14.7%) had prolonged PFA-100, adenosine diphosphate (ADP), and 72 (22.0%) had abnormal results in both PTT and PFA-100. Out of 275 samples tested for vWF (Ag and activity) and FVIII.13 (3.9%) had low levels or impaired function of vWF and 5 (1.6%) had low FVIII levels. After correlation with ABO blood group, only 5 (1.6%) cases were confirmed for vWD, the prevalence of vWD among Saudi Adolescents in the selected student population was 1.5%.

Conclusion: This is initial results of the epidemiological survey of bleeding disorders in Arab ethnicity. We are continuing to survey more areas in the country and increase the sample size of this survey.

Keywords: Bleeding disorders; Arabs; Epidemiology; Adolescents; Survey

Introduction

Von Willebrand disease (vWD) has been reported worldwide as one of the most common hereditary bleeding disorders. It was first described in 1926 by Dr. Eric von Willebrand from Finland. vWD associated with a qualitative or a quantitative defect in von Willebrand factor (vWF). VWF is a multifunctional adhesive protein that plays an important role in both primary and secondary hemostasis. It is essential for platelet adhesion to damaged endothelium as well as platelet interactions at high shear stress [1-3]. VWF has a direct role in thrombin and fibrin generation, acting as a carrier molecule for the cofactor, factor VIII (FVIII) [4]. Patients are classified as type 1, type 2 or type 3, depending on the qualitative and quantitative defects in the vWF antigen [5]. The laboratory diagnosis of vWD can be difficult as the disease is heterogeneous. This heterogeneity stems from different molecular defects that can occur in more than one of the functional domains of the multimeric glycoprotein, so an array of assays is required to characterize the phenotype [6,7].

The method used to estimate the prevalence of vWD is of major importance to the accuracy of the estimation, the referral-based prevalence method based on the number of symptomatic patients seen at hemostasis centers or hospitals, and is dependent on several factors, such as diagnostic facilities, the subtyping of vWD based on laboratory evaluation, severity of bleeding patients in those centers. The alternative method of population-based prevalence (i.e., prevalence of VWD in the general population) is employs standard criteria for assessing bleeding symptoms, family history and laboratory values. In such a survey, asymptomatic subjects and those with less severe bleeding (like bruises or ecchymosis and menorrhagia which is generally considered as familial), are more likely to be detected [8]. In this study, our purpose was to estimate the prevalence of vWD among students at KSA and identify students with bleeding who are either not diagnosed or misdiagnosed of vWD.

Material and Methods

This study was performed as a part of a larger project, which studies the prevalence of bleeding disorders among adolescents in Riyadh city, Saudi Arabia [9]. This study was conducted between January 2014 and February 2016. Each student had signed a consent after approval by the ethical committees of participating institutes.

First phase

Trained interviewers surveyed 2,000 preparatory and first-year university students (male and female) at King Saud University (KSU) in Riyadh city, Saudi Arabia. The age range of students was between 17 to 22 years. The questionnaire was developed using the Molecular and Clinical Markers for the Diagnosis and Management of Type 1
Second phase

A total of 730 (36.5%) of the 2000 students interviewed, Potential candidates for bleeding disorders identified in the first phase were contacted for blood sampling. Only 326 (44.6%) had agreed to have blood testing to investigate for the bleeding tendency, the other 404 (55.4%) students did not participate: 217(54%) of them refused sampling, and 187 did not respond (46%) (Figure 1).

Sample collection

Venous blood collection was performed at students’ locations and samples delivered to the Center of Excellence in Thrombosis and Hemostasis (CETH) laboratory within four hours of collection. For each participant, 2 mL of blood was collected in a 3.2% sodium citrate tube and centrifuged at 3500 rpm for 10 min to obtain plasma. PT and PTT performed by plasma (STAGO Compact* system, France) according to the manufacturer’s recommendation. A sample of EDTA was collected for CBC (UniCel ® DxH 800 COULTER) and ABO grouping. PFA100 testing (Siemens-Dade International, USA) by both cartridge EPI and ADP, which was performed immediately and results were reported as Closure Time (CT) in seconds. Each subject who had abnormal results for PFA-100 EPI or ADP or PTT or both was tested for vWF: Ag, VWF: activity and FVIII using STAGO Compact® system and reagents.

Statistical analysis

Data were analyzed using IBM Statistical Package for Social Sciences (IBM-SPSS for Windows Ver. 20). Median with minimum and maximum values are preferred over mean and standard deviation where data were not in conformity with the normality assumptions tested using Shapiro-Wilk’s Test. P-values less than 0.05 were considered to be statistically significant.

Results

A total of 730 (36.5%) of the 2000 students interviewed, whereas 550 (75%) female and 180 (25%) male, answered 2 or more questions with "yes" and were suspected to have bleeding disorders. Only 326 from suspected subjects who agreed to continue in the study. This studied cohort was consisted of 206 (63%) females and 120 (37%) males with median age of 19 years whereas maximum age was 22 years and minimum age was 17 years. Out of the responders, 128 (39.7%) had gum bleeding, 100 (30.3%) had epistaxis, and 98 (30.0%) had ecchymosis (Table 1).

Out of 326 blood samples were tested for CBC, PT, PTT, and PFA-100. 275 Samples had abnormal results whereas 116 (35.5%) samples had prolonged PTT (>41 sec), 39 (11.9%) had prolonged PFA100 EPI, 48 (14.7%) had prolonged PFA100 ADP, and 72 (22.0%) had abnormal results in both PTT and PFA-100 by both cartridge EPI and ADP. Out of 275 samples that have abnormal results (PTT, PT, PFA-100) tested for vWF: Ag, VWF: activity and FVIII, 13 (3.9%) had low levels or impaired function of vWF (Ag and activity) and 5 (1.6%) had low FVIII levels. After correlation with ABO blood group, only 5 (1.6%) cases were confirmed for vWD. The medians and ranges of vWF antigen, vWF activity and FVIII activity were (101.5) 25-178 (U dL)-1, (102.5) 27-178 (U dL)-1 and (183) 31-335% respectively (Table 2).
Discussion

This study was performed to estimate prevalence of vWD among Saudi Adolescents in the selected student population. vWD was reported worldwide as one of the most common Hereditary Bleeding Disorder [12]. Our results showed 13 (3.9%) cases met criteria for possible vWD, they had low levels or impaired function of vWF. Many study revealed that levels of vWF correlate with ABO blood type O individuals have significantly (approximately 25%) lower than those of people with non-O blood groups [13,14].

After correlation with ABO blood group, only 5 (1.6%) cases were confirmed for vWD, so the prevalence of vWD was 1.5%. Our study, which is, to the best of our knowledge, the first epidemiological screening study of bleeding disorders based on a validated questionnaire and confirmed by specialized tests for suspected cases. The prevalence of vWD in our study is similar to other global studies [15,16]. Two paediatric studies, one involving the screening of 1218 otherwise healthy Italian children [15] and another involving 600 American children [16], found 10 (0.82%) Italian and 8 (1.3%) American children with vWD. All affected children had at least one significant bleeding symptom and a family member with bleeding symptoms, in addition to fulfilling the laboratory criteria.

Various investigations have been conducted on the prevalence of vWD in Turkey. The prevalence was found in 2 separate investigations to be 0.7% in the Ankara region [17], and 0.9% in the Edirne region [18]. New study was conducted on adolescents in the city of Izmir between October 2006 and March 2007. A total of approximately 1339 high school students were vWD type-1 was diagnosed in 14 individuals for a prevalence of 1.04% [19] compared to a previous study in the Izmir region the prevalence of vWD was 0.4% [20].

The prevalence of vWD has also been studied in other ethnic groups (A total of 315 subjects were white, 212 were black, 16 were Hispanic, 10 were from other groups, and 47 were biracial. Eight subjects (four black, four white) met the criteria for vWD, for a prevalence of 1.3% [15].

Unfortunately, no other similar local studies were evaluated for comparison, because they aren’t available. There are few reports from Saudi Arabia and the Middle East are old and hospital-based, small population sizes and were this not large enough to establish an accurate prevalence estimate of vWD in Saudi Arabia. Zaher and Adam [21] did an 11-year retrospective analysis in the Western Province of the KSA. They found that 18 out of 64 studied patients where they already suspected to have vWD. AlFawaz et al. [22] 15 reported clinical characteristics and types of Hereditary Bleeding Disorder in one institute of KSA. Out of 168 patients where they already suspected to have vWD, 25 (14.8%) from 15 different families had vWD. Kumar et al. [23] reported a vWD prevalence of 40 (17.4%) in 230 patients with known inherited bleeding disorders. Type 2 and 3 were the most common. Other findings have been reported from Iran: 39 (7%) of 545 patients with inherited bleeding disorders had vWD with a greater predominance of type 2 and 3 [24].

Conclusion

The data presented herein will serve as a basic reference that can help to establish the prevalence of vWD in KSA and will pave the way for further research into diagnosing and treating this disorder.

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References