Incidence of Von Willebrand Disease Among Patients presenting with Various Bleeding Tendency to Out-Patient Clinic of the National Center of Hematology

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Abstract
Background: Von Willebrand disease is frequent hereditary bleeding disorders with an incidence of about 1% in asymptomatic people. Previous Studies available around the Middle East displayed a prevalence ranged from 3 % to 34 % of Von Willebrand disease within the hereditary bleeding disorders. People with mucocutaneous bleeding represent a major subtype of hematologic clinical presentations but simultaneously present a substantial diagnostic challenge. On the other hand, bleeding symptoms are frequent in the general population, but their clinical relevance may be difficult to assess. The aim of this study was to estimate the incidence of Von Willebrand disease in patients presenting with various bleeding tendencies to out-patient clinic of the national center of hematology.

Methods: A total of 146 sequential patients referred to the national center of hematology between January 2011 and April 2012 were investigated. Tests performed for the diagnosis of Von Willebrand disease included complete blood count and blood film including platelet count, bleeding time, prothrombin time, activated partial thromboplastin time, Factor VIII:C assay, and von Willebrand Factor Antigen assay.

Results: Amongst 146 patients, 29 (19.8%) had Von Willebrand disease. Patients' age ranged from 1 year to 65 years, with 35 males and 111 females. Menorrhagia was the most common presentation. Amongst vWD patients, there were 7 male and 22 female. Positive family history in patients with VWD was found in 21 out of 29 patients (72.4 %) while positive family history in bleeding tendency other than VWD was found in 47 patients (40%). Statistical significant differences were found in prothrombin time, activated partial thromboplastin time, Factor VIII: C assay, and von Willebrand Factor Antigen assay between the studied groups.

Conclusions: Von Willebrand disease still among the most common cause of inherited bleeding tendency in patients presented with mucocutaneous or menorrhagia, yet many cases of vWD remain undiagnosed due to wide range of clinical presentations and lack in lab diagnosis.

Keywords: incidence, vWD, bleeding tendency

Introduction
Von Willebrand disease (vWD) is the most common, primarily autosomal dominant inherited bleeding disorder, which affects both male and female at equal level. It is estimated that about 1% of general population had vWD. 1,2 It is caused either by quantitative deficiency (Type 1 and Type 3) or qualitative defect (Type 2) of von Willebrand factor (vWF). The vWF is produced in the endothelial cells and megakaryocytes. It is kept in Weibel Palade bodies in the endothelial cells and alfa granules of thrombocytes.

The plasma level of vWF is equal to 10μg/ml. In the plasma it presents into the multimeric dimer configuration with different sizes ranging from small (500 kD) to very large (>10,000 kD) high molecular weight multimeric (HMWM) forms.

The larger molecules have greater sticky ability because of high number of individual adhesion positions. The vWF flows in the plasma in association with factor VIII: coagulant protein (FVIII: C) as vWF: FVIII: C complex. The two most significant roles of vWF are (i) it assists the adhesion of platelets to subendothelium at the position of damage, therefore contributing in primary hemostasis and (ii) it stabilizes FVIII:C in circulation and increases its half-life by five to 10 folds, therefore it as well takes part in secondary hemostasis. vWD is actually a heterogenous...
Incidence of Von Willebrand Disease Among Patients presenting disorder since it has different molecular mutations and variable penetrance. Within certain group of people there can be variety of phenotypes with different bleeding manifestations that may alter after a period of time. [3] There are many types of assays to be done by the laboratory specialists undertaking the investigations for vWD. Because of restrictions of each laboratory test, no single test technique is enough to allow detection of all types of vWD. [4] For all the reasons mentioned above, vWD continues to be an under diagnosed entity. Very few studies are available from Iraq or form Middle East pointing to prevalence of about 14% of vWD amongst all inherited bleeding disorders. [5, 6] that’s why this study was designed to estimate the incidence and of vWD in our center.

Material and method
The study was carried on at the national center of hematology/ Almustansiriya University, Baghdad, Iraq. Patients attended out-patient clinic or referred form other hospitals because of bleeding tendency like prolonged bleeding from injuries, following tooth extraction, epistaxis, menorrhagia, gum bleeding, ecchymosis, hemarthrosis, etc., were tested for vWD. There were two groups in this study. Group 1 included 146 sequential patients, while group 2 includes 60 apparently healthy persons. The study period was between January 2011 and April 2012. The study was approved by the Institutional Ethics Committee.

Oral informed consent was obtained from the patients or parents for participation in the study prior to collection of blood samples. A detailed questionnaire containing the nature of the bleeding episodes, age at the onset, frequency of bleeding, family history, mode of inheritance and history of prior medication including blood transfusion was filled along with detailed physical examination.

Complete blood count and platelets were analyzed on whole blood containing EDTA by Cell counter, (Cell Dyne,USA). Coagulation tests were examined on fresh blood containing 3.2% sodium citrate anticoagulant centrifuged with 2500 G rpm for 15 minutes. [7]

Then coagulation tests were performed on platelet poor plasma. Bleeding time was performed by a laboratory technician using IVY technique. In this method, the blood pressure cuff is placed on the upper arm and inflated to 40 mmHg and after making an incision with appropriate size and depth on the forearm, the bleeding time was measured with a filter paper. PT (Prothrombin time) was measured with STAGO kit and the STA compact analyzer with clotting method and 3 units above control PT was considered abnormal. Also, aPTT was measured with STAGO kit and the STA compact analyzer with clotting method and 5 units above control PTT was considered abnormal. vWF: antigen levels were estimated by ELISA using commercial kits (Diagnostica Stago, France).

Results
A total of 146 patients were examined for abnormal bleeding manifestations. Out of 146 patients, 29 (19.8%) patients were diagnosed as von Willebrand disease by appropriate tests done for them. The age of overall patients ranged from 1 year to 65 years with median age of 33.7 years. There were 35 males and 111 females with M: F ratio of 0.31. Amongst vWD patients, there were 7 male and 22 female. Positive family history in patients with VWD was found in 21 out of 29 patients (72.4 %) while positive family history in bleeding tendency other than VWD was found in 47 patients (40%).

Table (1) shows that mean age ± SD of patient with bleeding tendency and control group were 18.26±14.23 years, 23.11±14.1 years respectively . There was slight significant difference in the age of the studied groups(p < 0.05). Statistical
significant differences were also found in PT, PTT, BT, VonWillebrand factor and factor VIII between the studied groups.

Table (2) shows the percent of the clinical manifestations in 146 patients in which menorrhagia (33.5%) was the most common presentation followed by epistaxis (31.5%), and ecchymosis (28%) in patient with or without von Willebrand disease.

Table (3) shows no significant statistical difference in age and PT between patients with VonWillebrand disease with bleeding tendency and those without (p>0.05).while Significant statistical differences found in PTT, BT, factor V111 and vWF between the two groups.

Table 1: Distribution of variables between the two studied groups

<table>
<thead>
<tr>
<th>variable</th>
<th>Bleeding tendency group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>146</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Male: female</td>
<td>35:111</td>
<td>14:46</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (yr.)</td>
<td>18.26±14.23</td>
<td>23.11±14.1</td>
<td>0.02</td>
</tr>
<tr>
<td>PT second (Mean ±SD)</td>
<td>13.34±1.2</td>
<td>12.32±1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>PTT second(Mean ±SD)</td>
<td>37.32±12.44</td>
<td>29.12±12.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>BT minute(Mean ±SD)</td>
<td>5.26±4.0</td>
<td>3.2±0.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>VWF Ag %</td>
<td>78</td>
<td>116</td>
<td>0.0001</td>
</tr>
<tr>
<td>Factor 8 %</td>
<td>61</td>
<td>124</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

P value from student t-test

Table 2: Bleeding manifestation in vWD

<table>
<thead>
<tr>
<th>Bleeding manifestations</th>
<th>No.of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menorrhagia</td>
<td>49</td>
<td>33.5</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>46</td>
<td>31.5</td>
</tr>
<tr>
<td>ecchymosis</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Bleeding from minor cut</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding after trauma</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>GIT bleeding</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Table (3): Distribution of variables between patients with bleeding tendency according to the diagnosis of VonWillebrand disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bleeding tendency with VWD</th>
<th>Bleeding tendency without VWD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>29 (19.8%)</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>7:22</td>
<td>28:89</td>
<td></td>
</tr>
<tr>
<td>Mean age±SD (yr)</td>
<td>16.25±18.58</td>
<td>18.76±12.98</td>
<td>0.397</td>
</tr>
<tr>
<td>PT second (Mean±SD)</td>
<td>13.07±1.1</td>
<td>13.41±1.3</td>
<td>0.196</td>
</tr>
<tr>
<td>PTT second (Mean±SD)</td>
<td>43.59±13.11</td>
<td>35.76±11.82</td>
<td>0.002</td>
</tr>
<tr>
<td>BT minute (Mean±SD)</td>
<td>8±4.6</td>
<td>4.58±3.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>VWF Ag %</td>
<td>4</td>
<td>93</td>
<td>0.0001</td>
</tr>
<tr>
<td>Factor 8 %</td>
<td>10</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

P value from unpaired t test

Discussion

Von-Willebrand disease is most frequent inherited bleeding disease. It is estimated that about 1% of general population had vWD.\(^{1,2}\) This study revealed that 19.8% of patients with bleeding tendency had VonWillebrand disease, this high figure is consistent with that of recent studies by Kadir et al\(^{(8)}\) and Woo et al\(^{(9)}\). These studies were similar to our study including patients presented with menorrhagia. They excluded patients with uterine pathology. All these raised the importance of screening for Von-Willebrand disease as a part of routine investigation in any patient presented with bleeding tendency in the presence of other normal coagulation profiles.

Other studies stated that women with VonWillebrand disease appear to be at high risk in developing menorrhagia. In this study other bleeding symptoms like bruising, epistaxis, bleeding after surgery and dental extraction were statically significant, this goes with other studies\(^{(9, 10)}\). Family history of bleeding was significantly associated with increased incidence of VonWillebrand factor, in patient with bleeding tendency. This may be attributed to the fact that Von-Willebrand disease is inherited as autosomal dominant\(^{(10)}\).

Although vWD is a heterogenous disease in which the association between platelets, coagulation factor deficiency, and mucocutaneous bleeding is much more frequent than coagulation type of bleeding like hemarthrosis and hematomas in these patients. In this study Menorrhagia was the most common manifestation and it found in 33.5%. mucocutaneous bleeding like epistaxis, ecchymosis, gum bleeding and bleeding from minor cuts were most common clinical presentation. Females were affected more than males which agree with most of other published studies.\(^{(5, 6, 11, 12)}\) Further, it is pertinent to mention that almost all of these studies are hospital based and therefore disease is identified only in those patients who presented themselves for investigation thus giving a higher prevalence of disease. In contrast, most of the studies done in Western countries are epidemiological studies done in general population giving an overall prevalence of vWD ranging from 0.7% to 1.6% with an average prevalence of ≈ 1% and a very high prevalence of Type 1 disease.\(^{(13, 14, 15)}\) Identification of Type 1 vWD (mild form) is very important as these patients are either asymptomatic or suffer from mild and infrequent bleeding episodes.
which make them to consider their bleeding tendencies as normal. If they are not identified, they may bleed profusely after getting major hemostatic challenges like surgery and trauma. In Iraq, characterization of vWD is difficult in general population because of financial constraints, inadequate awareness and lack of support for these patients from health care system. The complexities involved in its diagnosis requiring a series of tests which are not widely available even in major hospitals, need of the tests to be repeated for correct diagnosis, make this disease an underestimated entity in many countries. Efforts are needed to develop national registries and to make basic services for diagnosis widely available so that patients of vWD could be managed properly avoiding morbidity and mortality during major hemostatic challenge or after any invasive procedure done on them.

In conclusions Von Willebrand disease still among the most common cause of inherited bleeding tendency in patients presented with mucocutaneous or menorrhagia, yet many cases of vWD remain undiagnosed due to wide range of clinical presentations and lack in lab diagnosis.

References

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