EVALUATION OF FACTOR VIII AS A RISK FACTOR FOR DEEP VEIN THROMBOSIS

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ABSTRACT

Background: Elevated factor VIII become increasingly an additional risk factor for thrombosis, many studies reported a 10% of normal population with elevated factor VIII more than 150iu/ml. Sustained increase in factor VIII level reported in response to acute phase reaction, malignancy, inflammation, pregnancy, Estrogen and in response to oral contraceptive pills. Many studies reported that elevated factor VIII reported in 25% in patients with DVT.

Objectives: This study was designed to assess the level of factor VIII in patients with deep vein thrombosis on warfarin therapy for more than 2 months.

Methods: Seventy on warfarin therapy for more than 2 months had been investigated for factor VIII level using one stage factor assay. This study done in the teaching laboratories of Baghdad medical city.

Results: 17 patients out of the 70 patients with DVT(24.3%) having factor VIII level more than 150% and 10 of them have recurrent DVT, 6 patients of later subgroup(60%) were found to have factor VIII more than 150%. Comparing mean factor VIII of those with recurrent DVT and normal healthy group is highly significant( p=0.0001) and with warfarinized control group( p=0.0002).

Conclusion: An impressive elevation of factor VIII level in patients with DVT make factor VIII as additional independent risk factor in the pathogenesis of deep vein thrombosis.

Key words: Venous thromboembolism (VTE), deep vein thrombosis (DVT), factor VIII level.

INTRODUCTION

Hypercoagulable states can be defined as a group of inherited or acquired conditions associated with a predisposition to venous thrombosis (including upper and lower extremity deep venous thrombosis with or without pulmonary embolism, cerebral venous thrombosis,
and intra-abdominal venousthrombosis), arterial thrombosis (including myocardial infarction, stroke, acute limb ischemia, and splanchnic ischemia), or both (1). Venous thromboembolic disease is the most common clinical manifestation resulting from hypercoagulable states. Although most inherited conditions appear to increase only the risk of venous thromboembolic events (VTEs). Classic acquired risk factors for venous thrombosis includetrauma, immobilization, pregnancy, surgery, malignancy, andinfection. These are all factors that may cause tissue damage, stasis of the blood, or changes in blood composition.

Inherited risk factors for venous thrombosis, most of which concern defects in the procoagulant and anticoagulant pathways, account for a substantial proportion of all thromboticevents (2). The inherited risk factors include factor V Leiden (resistance to activated protein C [APC]), prothrombin 20210A, deficiencies in antithrombin, protein C and S. Elevated fibrinogen, antiphospholipid antibodies, and hyperhomocysteinemia are examples of laboratory phenotypes associated with venous thrombosis. Some of these phenotypes have also been found to be associated with arterial thrombosis. Whether this is also true for genetic risk factors such as factor V Leiden or the prothrombin20210A allele is still uncertain (3,4,5,6,7,8). High levels of factor VIII are another common risk factor for venous thromboembolism. In the Leiden thrombophilia Study Factor VIII procoagulant activity levels in the upper quartile were associated with a 5-fold increase in the risk of venous thrombosis when compared to the risk in subjects with lower levels (9, 10). Similar findings have been reported in several independent studies. The high levels of factor VIII in patients with thrombosis persist over time, and are, in general, not caused by acute-phase reactions. In addition, O'Donnell et al. showed that only 50% of these persistently high factor VIII levels were associated with high vWF: Ag levels, indicating that vWF is not always responsible for high factor VIII plasma levels. Recently, it has been described that elevated plasma levels of factor VIII are a strong risk factor for venous thrombosis. As with the recent factor VIII study, the researchers adjusted for sex and age as well as other risk factors, including oral contraceptive use, protein C and protein S deficiencies, antithrombin deficiency, homocysteine, fibrinogen, factor VIII, and the factor V Leiden and G20210A mutation (11, 12). The regulation of plasma factor VIII levels is complex. Most factor VIII circulates as a complex with von Willebrand factor (vWF), the levels of which are known to be dependent on factors such as blood group, and endothelial stimulation. This highly complicates the study of the molecular basis of elevated factor VIII levels (13, 14). Factor VIII:C levels show a familial clustering, which remains after adjustment for the influence of vWF and blood group.
Analysis of familial aggregation of factor VIII levels $150 \text{IU/dL}$ in 12 large thrombophilic families identified blood group as the main determinant: 86% of the subjects with factor VIII levels $150 \text{IU/dL}$ had blood group non-O. However, after adjustment for blood group and age, factor VIII levels $150 \text{IU/dL}$ still aggregated in these families. Others have also observed a high concordance of factor VIII levels between first-degree relatives of patients with thrombosis with high factor VIII levels (15) O Donnell et al (2000) reported that 25.4% of those patients with unexplained thromboembolism had elevated factor VIII level more than 150% (11). The precise role of high factor VIII levels in defining venous thrombotic risk is still unknown. After its activation by thrombin, factor VIIIa dissociates from vWF to form a complex with factor IXa, which will result in marked acceleration of the activation of factor X. Activated factor X then converts prothrombin into thrombin, which in turn converts soluble fibrinogen into insoluble fibrin. It is possible that high factor VIII levels just increase the rate of thrombin and fibrin formation (in plasma, there is a large molar excess of factor IX over factor VIII) (16).

The aim of the study is to evaluate the prevalence of elevated factor VIII level in patients present with deep vein thrombosis compared to healthy normal individuals and patients warfarinized for cardiac diseases.

MATERIAL AND METHODS

Patients: Seventy patients diagnosed as DVT by aid of Doppler and another 2 control groups: study group, control healthy group and warfarinized control group.

Methods: All of patients were interviewed regarding age, sex, address, occupation, date of presentation, surgical history, history of pregnancy or abortion and drug intake. Blood samples were taken from patients and control groups by mixing 1.8 ml blood in 0.2 ml sodium citrate (0.11M). All samples (patients and 2 control groups) were tested for prothrombin time, activated partial thromboplastin time and factor VIII level by one stage assay. The cutoff point for factor VIII level is 150% (150 IU/100ml).

Statistical Analysis: The Statistical Analysis System–SAS (2010) was used to effect of different factors in study parameters. T-test was used for significant comparing between means in this study.
RESULTS
The study group included 70 unselected patients diagnosed as deep vein thrombosis mean age 43.5±13.3 years range (16-73) years (table 1). 37 were female and 33 male with M:F ratio 1:1.2. In this study 58 /70 patients are on warfarin and the rest 12 patients had already stopped this drug. The warfarin dose range 1.5-5mg/day with mean dose 3.5±1.2 mg and median 3mg/day.

The first control group includes 20 normal healthy individuals on no treatment with mean age 31±9.1 years range (17-56) and M:F ratio 1:1. The second control group includes 30 patients on warfarin for causes other than DVT with mean age(43.3±14.3) years and range (20-72), and warfarin dose range 1.5-5mg/day and mean dose 3.5±1.1mg.

The duration of warfarin in the study group (58 patients) range 2-36 months with mean duration 6.3±6 months and median of 3 months , while in warfarinized group the duration of drug range 2-250 months with mean of 65±71.2 and median of 36 months.

Table1 the distribution of age / year and sex for each study group

<table>
<thead>
<tr>
<th>Study Group</th>
<th>no</th>
<th>range</th>
<th>mean</th>
<th>median</th>
<th>M/F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT group</td>
<td>70</td>
<td>16-73</td>
<td>43.5±13.3</td>
<td>42</td>
<td>1:1.2</td>
</tr>
<tr>
<td>Healthy control group</td>
<td>20</td>
<td>17-56</td>
<td>31±9.1</td>
<td>30</td>
<td>1:1</td>
</tr>
<tr>
<td>Warfarinized Control group</td>
<td>30</td>
<td>20-72</td>
<td>43.3±14.4</td>
<td>46</td>
<td>1:1.3</td>
</tr>
</tbody>
</table>

Table2 the INR distribution for each study group

<table>
<thead>
<tr>
<th>Study group</th>
<th>no</th>
<th>Range</th>
<th>mean</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT group</td>
<td>70</td>
<td>1-7.1</td>
<td>2±1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>DVT on warfarin subgroup</td>
<td>58/70</td>
<td>1-7.1</td>
<td>2.2±1.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Healthy control</td>
<td>20</td>
<td>1-1.2</td>
<td>1.1±0.01</td>
<td>1</td>
</tr>
<tr>
<td>Warfarinized control group</td>
<td>30</td>
<td>1.2-6.2</td>
<td>2.8±1.2</td>
<td>2.2</td>
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</tbody>
</table>
The factor VIII level range 30-290% with mean value of 122.6±49.1% and median of 112.5% table3. 17 patients (24.3%) had factor VIII level in excess of 150% .In recurrent DVT (10 patients) had factor VIII level range 120-290% with mean of 181.5±55%, six of these patients (60%) had factor VIII level in excess of 150%.

Table 3 factor VIII % activity level in each study group

<table>
<thead>
<tr>
<th>Study group</th>
<th>no</th>
<th>Range</th>
<th>mean</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT group</td>
<td>70</td>
<td>30-290</td>
<td>122.6±49.1</td>
<td>112.5</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>10/70</td>
<td>120-290</td>
<td>181.5±55</td>
<td>182</td>
</tr>
<tr>
<td>Healthy control group</td>
<td>20</td>
<td>55-160</td>
<td>101.5±32.1</td>
<td>100</td>
</tr>
<tr>
<td>Warfarinized control group</td>
<td>30</td>
<td>45-260</td>
<td>117±50.6</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4 the prevalence of elevated factor VIII in each study group

<table>
<thead>
<tr>
<th>Study group</th>
<th>no</th>
<th>prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT GROUP</td>
<td>70</td>
<td>17(24.3%)*</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>10/70</td>
<td>6(60%) **</td>
</tr>
<tr>
<td>Control1</td>
<td>20</td>
<td>2(10%) *</td>
</tr>
<tr>
<td>Control2</td>
<td>30</td>
<td>7(23.3%)</td>
</tr>
</tbody>
</table>

DISCUSSION
The incidence of deep vein thrombosis (DVT) in general population has been reported to be about 1/1000 people/year. The pathogenesis of DVT is quite complex hyperactive coagulation pathway, hypoactive anticoagulant pathway or hypoactive fibrinolysis being all implicated. DVT appear to be multicausal disease, that is, more than single risk factor need to be present simultaneously to cause thrombosis (17). The risk factors incriminated include acquired and genetic factors. Known acquired risk factors include immobilization, surgery, trauma, pregnancy, puerperium, lupus anticoagulant, malignant disease and female hormones.
Among the genetic factors causing tendency to DVT are anti-thrombin III deficiency, protein C deficiency, protein S deficiency, factor V Leiden, prothrombin 20210 A mutation and hyperhomocysteinemia (3,4,5,6,7,8). However, in about 30% of patients with family tendency of DVT, no underlying genetic disease is found.

Recently elevated factor VIII level was proposed as an additional risk factor in development of DVT (18).

This study demonstrated that factor VIII level were in excess of 150% in 24.3% of those with DVT, compared to 10% of normal healthy control (p<0.0001). These findings is similar to those of Koster et al (1995) who found that 25% of those with first DVT attack had increased factor VIII level more than 150% compared to 11% of healthy controls (16). The increased risk of thrombosis in patients with elevated factor VIII level is most likely due to an imbalance between procoagulant factor VIII and that of anticoagulant as protein C, such imbalance lead to thrombosis in a similar to that seen in protein C deficiency and activated protein C resistance. Furthermore, there may be an imbalance between high factor VIII level and fibrin lytic system.

Significantly higher level of factor VIII was obtained in those with recurrent DVT (60%) than in healthy control 10% and in those with single DVT attacks 18.33% (p<0.0001). More over such observation was shared by study of Kraaijenhagen (2000) who found elevated factor VIII level > 175% in 10% of healthy control compared to 19% in those with single DVT attack and 33% of those with recurrent DVT attack. Furthermore, another study by O Donnell (2000) confirmed that elevated factor VIII level is found in patients with unexplained thromboembolism with absence of markers of ongoing acute phase reaction. In this study patients with history of DVT of less than two months duration were excluded to reduce any chance of acute phase reaction, since it’s well known that acute phase reaction will usually subside within six weeks.

Although high frequency of elevated factor VIII level in warfarinized group (23.3%) table 4, but no significance in comparison with DVT group p=0.878 or with healthy control p=0.141.

REFERENCES


