Chronic thrombotic scarring in patients with acute deep venous thrombosis of the lower limbs

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Abstract
Some patients with acute deep venous thrombosis of the lower limbs may present risk factors for recurrent disease. Aims: To analyze the most important conditions related to recurrent deep venous thrombosis of the lower limbs, other than thrombophilies. Patients and methods: We examined 88 consecutive patients (47 males-53.41%, average age 64.9±13.9 years) admitted to a Medical Clinic in 2007. Duplex ultrasonography was performed to assess acute deep venous thrombosis and post-thrombotic syndrome. Anamnesis and physical examination were used to detect risk factors for recurrent disease. The 28 subjects with acute deep venous thrombosis and post-thrombotic syndrome were included in group A (31.82%). Group B comprised 60 patients (68.18%) with acute deep venous thrombosis without post-thrombotic syndrome. Results: Risk factors for recurrent disease in groups A and B were the following: personal history of deep venous thrombosis of the lower limbs (17 subjects versus 7, p<0.0001), varicose veins (14 vs 24, p=0.51), obesity (13 vs 18, p=0.21), malignancy (6 vs 8, p=0.25), chronic obstructive lung disease (5 vs 6, p=0.24), prolonged immobilization (1 vs 7, p=0.21), major surgery (1 vs 1, p=0.54), stroke (0 vs 3, p=0.62), family history of deep venous thrombosis, immobilizing plaster cast, and congestive heart failure (0 vs 1, p=0.54). Location of thrombi in patients in groups A and B was as follows: 18 patients in group A vs 25 subjects in group B on the left side and 13 patients in group A vs 20 patients in group B on the right side (p=0.02). Conclusion: Post-thrombotic syndrome correlated with personal history of deep venous thrombosis and previous deep venous thrombosis located in the left lower limb.

Keywords: deep venous thrombosis, post-thrombotic syndrome, recurrence, risk factors for thrombosis

Introduction
Venous thromboembolism is defined by the existence of deep venous thrombosis (DVT) and/or pulmonary embolism. There are many environmental or acquired risk factors (RF) associated with the development of DVT [1,2]. These factors are classified into three categories: strong, moderate and weak. Fractures, hip or knee replacements, major surgery and major trauma are strong
RF - odds ratio (OR) greater than 10. Moderate RF (OR 2-9) include personal history of thromboembolism, thrombophilia, cancer, chemotherapy, paralytic stroke, congestive heart failure, respiratory failure, arthroscopic knee surgery, oral contraceptives, hormone replacement therapy, and postpartum period. Some diseases and conditions are weak RF such as increasing age, immobility, obesity, laparoscopic surgery, varicose veins, and antepartum period [3].

Post-thrombotic syndrome (PTS), recurrence of thrombosis and pulmonary embolism are the main complications of DVT [4]. The following modifications of the deep veins characterize the PTS: thickened wall, decreased caliber, nonocclusive intraluminal material (thrombus), and reflux [5,6].

In many cases, older thrombi and deep-vein reflux are detected by ultrasonography in patients with clinical suspicion of acute DVT. Recurrence depends on predisposing factors (e.g., personal history of thromboembolism, cancer and inherited blood clotting diseases as moderate RF) so re-thrombosis may occur in subjects with PTS [7-9].

Aims

We investigated the major diseases and conditions (location of thrombi and predisposing factors for venous thromboembolism other than thrombophilias) associated with recurrent thrombosis.

Patients and methods

This study was conducted at the Internal Medicine Department of the Municipal Hospital „Iuliu Hatieganu” University of Medicine and Pharmacy Cluj-Napoca, Romania between January and December 2007. The study protocol was approved by the local Ethics Committee.

The algorithm for diagnosis of DVT was based on the determination of pre-test probability of DVT, D-dimer test and compression ultrasonography [10]. Predicting pre-test probability means the calculation of the Wells’ score by adding the points given to different clinical characteristics and by subtracting two points if there is an alternative diagnosis such as Baker’s cyst. The main clinical characteristics which are awarded one point are swelling of the whole leg, personal history of DVT, collateral non-varicose superficial veins, plaster immobilization, paralysis, bed rest more than three days, and active cancer. Possible score is between -2 and 9. Score of 2 or higher means that DVT is likely. Thrombosis is unlikely if the score is less than 2. Compression ultrasonography was performed in patients with score greater than or equal to 2 and in those with score less than 2 associated with positive D-dimer test [10-12].

The main ultrasound criterion for detecting acute DVT was the lack of compressibility in at least one deep vein. Other acute DVT criteria were: increased cross-sectional diameter, absence of Doppler signal and collateralization. Thickened venous wall, decreased cross-sectional diameter, small echogenic thrombus and valvular insufficiency characterized the PTS [5,13].

We used two duplex ultrasound machines: General Electric Logiq 500 with a 7.5 MHz linear transducer and Aloka Prosound SSD 4000 equipped with a linear transducer with variable frequency between 7 and 10 MHz.

A total of 88 consecutive inpatients met the inclusion criteria for this study. Depending on the presence of PTS and DVT criteria patients were divided into two groups: A (acute DVT patients with known or unknown PTS) and B (DVT subjects without PTS).

Following parameters were analyzed in all patients: demographic data (gender, age), anamnestic data (personal history of DVT, laparoscopic or major general surgery, arthroscopic knee surgery, malignancy, chemotherapy, bed rest of more than three days, hormone replacement therapy, oral contraceptives, and pregnancy), physical exam data (obesity, varicose veins, stroke, respiratory insufficiency, congestive heart failure) hematologic tests (complete blood count, coagulation, D-dimer test), biochemical tests (fasting blood glucose and lipid profile, serum creatinine), morphological data (thrombus location, echogenicity and caliber, venous wall thickness and compressibility and collateralization) and functional data (spontaneous flow, Valsalva response, augmentation, reflux).

Venous system of the lower limbs was analyzed bilaterally on segments: inferior vena cava and iliac veins, femoral veins (common, superficial and deep), popliteal vein and calf veins (posterior tibial, peroneal and anterior tibial veins, gastrocnemius and soleal veins).

We performed an observational transversal study. Statistical analysis was done using Epi Info computer package, version 3.3.2. We performed univariate analysis ($\chi^2$ test, ANOVA test with a p-value less than 0.05 as selected level of statistical significance) and logistic regression (to characterize parameters related to location of thrombi when p-value was less than 0.10 in univariate analysis)

Results

Eligible patients age was between 23 and 86 years (mean 64.9±13.9 years). Patients’ distribution by age was as follows: under 40 years (10 – 11.4%), 41-59 years (22
Chronic thrombotic scarring in patients with acute deep venous thrombosis of the lower limbs

- 25%), 60 – 74 years (34 – 38.6%) and over 75 years (22 – 25%). There were 47 men (53.4%) and 41 women (46.6%).

Some RF were encountered in many patients: varicose veins (38 subjects – 43.1%), obesity (31 patients – 35.2%), personal history of DVT (24 – 27.2%), cancer (14 – 15.9%), respiratory failure (11 – 12.5%) and bed rest more than three days (8 – 9%).

We found 183 occluded venous segments in the 88 patients included in our study: tibioperoneal (49 – 55.6%), soleo-gemelar (47 – 53.4%), popliteal (39 – 44.3%), femoral (38 – 43.1%) and iliac (10 – 11.3%).

Thrombi location was in the left lower limb in 43 cases (48.8%) and in the right lower extremity in 33 subjects (37.5%). Only 12 patients (13.7%) had bilateral thrombosis.

Chronic thrombotic scarring and deep vein reflux were found in 28 patients (31.8%) with acute DVT criteria.

The figures 1-3 illustrate the acute DVT diagnosis while the figures 4-7 present the changes encountered in the PTS.

Fig 1. Short-axis view of the right common femoral vessels. Heterogenous hypoechoic intraluminal material dilating the common femoral vein. vfc: common femoral vein; afc: common femoral artery. dr: right lower extremity

Fig 2. Longitudinal and transverse images of the right popliteal vessels. Dilated popliteal vein with heterogenous intraluminal deposition of thrombotic material. vp: popliteal vein; ap: popliteal artery.

Fig 3. Short-axis view of the right calf. Increased cross-sectional diameter of a posterior tibial vein. VTP: posterior tibial vein; ATP: posterior tibial artery.

Characteristics of patients included in our study are presented in Table I.

Some patient characteristics had a p-value less than 0.1: personal history of DVT (p<0.001), left side of lesions - acute thrombus and chronic thrombotic scarring (p=0.08), iliac vein involvement (p=0.09), femoral location of thrombi (p=0.1) and male gender (p=0.1). We performed unconditional logistic regression with these five factors (Table II).

As can be seen in Table II, only two features showed a statistically significant correlation with the presence of chronic thrombotic scarring in patients with acute DVT: personal history of DVT (p<0.0001) and thrombosis located in the left lower extremity (p=0.0244).

Discussion

The mean age of our patients was approximately 65 years. It is known that incidence and prevalence of DVT increases with increasing age [14]. For example, in people over 80 years, the incidence of DVT can reach a value of 10‰/year [15,16]. Caprini [17] has developed a useful tool in determining thrombotic risk score (Total Risk Factor Score) according to which DVT prophylaxis should be performed. According to age, each patient receives one, two or three points, as follows: one point (age between 41 and 60 years), two points (age between 60 and 74 years) and three points (age over 75 years). For example, the three points characterize the DVT high risk so that patients require prophylaxis with heparin [17].

Of the 88 patients included in the study, 47 were men. The male-to-female ratio in our sample was 1.14. Bauersachs et al [18] examined 1388 outpatients (658 men and 730 women) with confirmed DVT. They found that prevalence of DVT was higher in men and proximal DVT was more frequent in men than in women (59.6% vs 44.5%, p<0.001). Andreou et al [19] examined 1838 outpatients and found that the prevalence of DVT was higher in men compared to women (14.4% vs 9.4%, p=0.001).

The most common RF were varicosis and obesity (found in more than one third of patients), personal history of DVT (27.2%) and active cancer (15.9%). Caprini [17] gave one point for varicose vein and obesity, two points for cancer and three points for DVT personal history. In patients with cancer, thromboembolic disease is the second leading cause of death [20].
In our study, more than half of the thrombi were located in the calf. A total of 106 of the 239 patients examined by Pennell et al [21], representing 44.4%, had calf thrombosis. Calf thrombosis is important because it is known that calf vein thrombosis involves the proximal veins in 25% of patients [1].

The left side-to-right side ratio was 1.30. Virchow (1851), cited by Ludwig et al [22], found that DVT occurs five times more frequently in the left leg versus right leg.

Thrombi were located bilaterally in 13.7% of our patients. Bilateral thrombosis was encountered in 19.7% of symptomatic cases of Pennell et al [21]. Clinically silent contralateral thrombosis was diagnosed in 34% of their patients.

PTS frequency in our patients was 31.8%. Labropoulos et al [23] followed 153 patients for 5 years after acute episode of DVT. Recurrence rate was 26.1% in these patients. Brandjes et al [7] found a frequency of 20%. Percentage of Hennerici et al [5] is at least double - 40-50%. A total of 50 of the 490 patients included in the PROLONG Study had recurrent DVT (12.2%) [24].

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### Table I. Patient characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A N=28</th>
<th>Group B N=60</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>19</td>
<td>28</td>
<td>2.41</td>
<td>0.86-6.91</td>
<td>0.1</td>
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<tr>
<td>Age (mean ± standard deviation, median, range)</td>
<td>65.5±13.3</td>
<td>64.6±14.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>41-59 years</td>
<td>7</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>60-74 years</td>
<td>9</td>
<td>25</td>
<td>0.77</td>
<td>0.2-2.93</td>
<td>0.89</td>
</tr>
<tr>
<td>≥75 years</td>
<td>9</td>
<td>13</td>
<td>1.48</td>
<td>0.36-6.13</td>
<td>0.75</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>1</td>
<td>1</td>
<td>2.19</td>
<td>0.0-83.72</td>
<td>0.54</td>
</tr>
<tr>
<td>Personal history of DVT</td>
<td>17</td>
<td>7</td>
<td>11.7</td>
<td>3.49-41.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6</td>
<td>8</td>
<td>1.77</td>
<td>0.47-6.56</td>
<td>0.25</td>
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<tr>
<td>Respiratory diseases</td>
<td>5</td>
<td>6</td>
<td>1.96</td>
<td>0.46-8.28</td>
<td>0.24</td>
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<tr>
<td>Stroke</td>
<td>0</td>
<td>3</td>
<td>0.7</td>
<td>0.03-8.21</td>
<td>0.62</td>
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<tr>
<td>Chemotherapy</td>
<td>3</td>
<td>0</td>
<td>0.7</td>
<td>0.03-8.21</td>
<td>0.62</td>
</tr>
<tr>
<td>Arthroscopic knee surgery</td>
<td>0</td>
<td>1</td>
<td>2.19</td>
<td>0.0-83.72</td>
<td>0.54</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>14</td>
<td>24</td>
<td>1.5</td>
<td>0.55-4.08</td>
<td>0.51</td>
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<tr>
<td>Obesity</td>
<td>13</td>
<td>18</td>
<td>2.02</td>
<td>0.73-5.66</td>
<td>0.21</td>
</tr>
<tr>
<td>Immobilization &gt; three days</td>
<td>1</td>
<td>7</td>
<td>0.28</td>
<td>0.01-2.49</td>
<td>0.21</td>
</tr>
<tr>
<td>Tibioperoneal</td>
<td>18</td>
<td>31</td>
<td>1.68</td>
<td>0.61-4.71</td>
<td>0.38</td>
</tr>
<tr>
<td>Muscular (soleo-gemelar)</td>
<td>18</td>
<td>29</td>
<td>1.92</td>
<td>0.7-5.38</td>
<td>0.24</td>
</tr>
<tr>
<td>Popliteal</td>
<td>14</td>
<td>25</td>
<td>1.4</td>
<td>0.52-3.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Femoral</td>
<td>16</td>
<td>22</td>
<td>2.33</td>
<td>0.84-6.37</td>
<td>0.12</td>
</tr>
<tr>
<td>Iliac</td>
<td>6</td>
<td>4</td>
<td>3.82</td>
<td>0.84-18.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Left-sided DVT</td>
<td>18</td>
<td>25</td>
<td>2.52</td>
<td>0.91-7.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Right-sided DVT</td>
<td>13</td>
<td>20</td>
<td>1.73</td>
<td>0.63-4.79</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* 95% confidence interval

### Table II. Unconditional logistic regression with five factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.1081</td>
<td>0.6778-6.5571</td>
<td>0.1977</td>
</tr>
<tr>
<td>Personal history of DVT</td>
<td>20.3202</td>
<td>4.8501-85.1343</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Femoral</td>
<td>0.9677</td>
<td>0.2759-3.3949</td>
<td>0.9591</td>
</tr>
<tr>
<td>Iliac</td>
<td>2.0399</td>
<td>0.3310-12.5696</td>
<td>0.4423</td>
</tr>
<tr>
<td>Left side DVT</td>
<td>5.0128</td>
<td>1.2313-20.4076</td>
<td>0.0244</td>
</tr>
</tbody>
</table>
unprovoked DVT (relative risk 2.9) and age more than 65 years (relative risk 1.5).

Limitations

There were no patients with the following RF: pregnancy, oral contraceptives, hormone replacement therapy, polycythemia vera, total hip or knee replacement, arthroscopic procedures, laparoscopic surgery, spinal cord injuries and major trauma.

We could not evaluate thrombophilia.

Conclusion

In our study, PTS correlated with personal history of thromboembolism and previous left lower leg thrombosis.

Competing interest

No conflict of interest.

References