Hypercoagulable States in Primary Upper-Extremity Deep Vein Thrombosis

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Background: There are very few data on the prevalence of coagulation abnormalities in primary deep vein thrombosis of the upper limbs.

Objective: To determine if coagulation abnormalities play a role in effort-related and/or idiopathic (non-effort-related) upper-extremity deep vein thrombosis (UEDVT).

Methods: Fifty-one consecutive patients (21 men and 30 women) who had effort-related (n = 20) or idiopathic (n = 31) UEDVT over an 18-year period (median age at diagnosis, 32 years; age range, 15-86 years) were routinely reexamined. Plasma was screened for antithrombin, protein C, and protein S deficiencies and for antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies). The DNA was screened for factor V Leiden and for prothrombin gene G20210A mutations.

Results: The median age (35 vs 28 years), the proportion of women (81% [25/31] vs 25% [5/20]), the proportion of patients with a personal and/or family history of thromboembolism (42% [13/31] vs 15% [3/20]), and the proportion of patients with at least 1 coagulation abnormality (42% [13/31] vs 15% [3/20]) were higher in the idiopathic UEDVT group than in the effort-related UEDVT group. The odds ratio of having a coagulation abnormality was 4.09 (95% confidence interval, 0.99-16.78; P = .06) in the idiopathic UEDVT group compared with the effort-related UEDVT group.

Conclusion: Hypercoagulable states appear to play a significant role in idiopathic but not in effort-related UEDVT.

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The role of hypercoagulability as a risk factor for lower-extremity deep vein thrombosis (DVT) has been shown in large epidemiological studies. The overall rate of the main clotting abnormalities (antithrombin, protein C, and protein S deficiencies; factor V Leiden; and antiphospholipid antibodies) in unselected patients with lower-extremity DVT is close to 30%,1,2 with the highest prevalence in patients with primary thromboses.2 There are very few data on the prevalence of coagulation abnormalities in primary upper-extremity DVT (UEDVT). Three recent studies3-5 provided estimates of the prevalence of clotting abnormalities in patients with primary UEDVT ranging from 8%3 to 43%3; these findings led to questions about the need for laboratory investigations in such patients. Primary UEDVT classically comprises effort-related thrombosis (Paget-Schroetter syndrome), which consists of axillary-subclavian vein thrombosis following strenuous activity of the affected arm; it also includes idiopathic UEDVT, in which no obvious associated disease or triggering factor is found. The dominant role of mechanical factors in the pathogenesis of effort-related UEDVT has been emphasized by the frequency of anatomical compressive abnormalities at the thoracic outlet in such cases.6 The aim of our study was to determine if coagulation abnormalities could be a significant contributing factor in effort-related UEDVT and/or idiopathic UEDVT, in which the role of mechanical triggering factors is less obvious.

Results: The median age (35 vs 28 years), the proportion of women (81% [25/31] vs 25% [5/20]), the proportion of patients with a personal and/or family history of thromboembolism (42% [13/31] vs 15% [3/20]), and the proportion of patients with at least 1 coagulation abnormality (42% [13/31] vs 15% [3/20]) were higher in the idiopathic UEDVT group than in the effort-related UEDVT group. The odds ratio of having a coagulation abnormality was 4.09 (95% confidence interval, 0.99-16.78; P = .06) in the idiopathic UEDVT group compared with the effort-related UEDVT group.

Conclusion: Hypercoagulable states appear to play a significant role in idiopathic but not in effort-related UEDVT.

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PATIENTS AND METHODS

PATIENTS

From April 1, 1980, through March 31, 1998, 51 consecutive patients were hospitalized in our department for primary UEDVT. None of these patients had a history of drug abuse or recent venous injections, central venous catheterization, pacemakers, major trauma, cancers, or heart failure, or evidence of liver or kidney disease. Of these patients, 21 were men and 30 were women, with a median age of 32 years (age range, 15-86 years). All but 2 patients (1 from the West Indies, 1 from Réunion) were from Europe. A total of 55 UEDVTs occurred in these 51 patients. Two patients had bilateral axillary-subclavian vein thromboses diagnosed at the first examination. 1 patient had a contralateral recurrence 2 years after the first event, and 1 patient had an ipsilateral recurrence 9 months after the first event. The diagnosis was confirmed by duplex ultrasonography in 23 cases and by phlebography in 32 cases. Phlebographic examination was performed when the ultrasonographic diagnosis was not definite (eg, when compressibility of the vein was not evaluable at the subclavian level) or when the head of the thrombus was not seen. The thrombi involved the axillary and/or subclavian veins in 54 cases, the brachial vein in 10 cases, the brachiocephalic trunk in 12 cases, the internal jugular vein in 3 cases, and the superior vena cava in 1 case. Screening for pulmonary embolism by lung scan, pulmonary angiography, or helicoidal computed tomography was performed in 26 cases, and results were positive in 11 (20%) of the 55 thromboses.

CIRCUMSTANCES OF THE THROMBOTIC EVENT

Detailed information on the patients’ occupational and recreational activities and on any unusually strenuous efforts made before the thrombotic event was obtained from February 1996 through March 1998 by combining a careful analysis of medical records (the only source for 2 patients who were lost to follow-up) and a new interview at a follow-up visit (or by telephone in 2 cases). The patients who had made an unusually strenuous effort within 7 days prior to the thrombosis or whose regular occupational or recreational activities involved vigorous use of the arms composed the effort-related UEDVT group. If no strenuous use of the arms had occurred during the week before the thrombosis or in daily life activities, the UEDVT was classified as idiopathic. A personal or family (parents, children, brothers/sisters, or grandparents) history of venous thromboembolism was also recorded. The circumstances of the event (effort-related vs idiopathic) were assessed immediately after each patient interview, before the test results were obtained in our laboratory (3-4 weeks later).

LABORATORY TESTS

Laboratory investigations were performed in the absence of anticoagulant therapy for at least 21 days. Blood samples were collected from February 1996 through March 1998 at the time of the follow-up visit, or later if the patients were receiving anticoagulant therapy. Venous blood was collected on 0.129-mmol/L trisodium citrate (1:10), and plasma was kept at −40°C until use. The DNA was isolated from leukocyte cells by standard methods and stored at 4°C. Plasma antithrombin activity was measured using the Coatest antithrombin kit (Chromogenix, Uppsala, Sweden), and protein C and protein S anticoagulant activity were measured using the STA Staclot PC or PS kit on an STA analyzer (Diagnostica Stago, Asnieres, France). Free protein S levels were measured by enzyme-linked immunosorbent assay (ELISA) using the Asserachrom free PS kit (Diagnostica Stago). Lower limits of normal antithrombin and protein C activities were 0.80 and 0.65 IU/mL, respectively. The lower limit of normal protein S (free or activity) was 0.70 IU/mL in men and in women older than 50 years and 0.60 IU/mL in women younger than 50 years. We screened for lupus anticoagulant using activated partial ristocetin aggregation, 7 levels of immunoglobulin G anticardiolipin antibodies were measured with an ELISA kit (Biomedical Diagnostics SA, Marne la Vallée, France). The upper limit of normal for anticardiolipin antibody values was 10 IgG phospholipid units (UGPL). The DNA was screened for factor V Leiden after polymerase chain reaction amplification of exon 10 of the factor V gene and digestion by restriction enzymes, and for the prothrombin gene G20210A transition, as described elsewhere.

STATISTICAL ANALYSIS

Statistical tests in 2 × 2 tables were done using the Fisher exact test. Continuous variables were compared with the nonparametric Mann-Whitney test. The proportion of pregnant patients was calculated among nonmenopausal women who were not taking oral contraceptives. The proportion of oral contraceptive users was calculated among women who were both nonpregnant and nonmenopausal.
ing a third course of human gonadotrophin (Neopergonal; Ares-Serono International SA, Geneva, Switzerland) for ovarian stimulation, a treatment carrying a risk of thromboembolism.13 None of these 4 women had a coagulation abnormality. Fourteen (38%) of the 24 nonpregnant, nonmenopausal women in the study group took oral contraceptives. The small number of women with effort-related UEDVT ruled out a between-group comparison of risk factors for thrombosis specific to women, such as estrogen use and pregnancy.

LABORATORY EVALUATION

The results of laboratory tests are shown in Table 2. Testing was incomplete in 4 patients (2 had been lost to follow-up and 2 could not return to the laboratory for new blood sampling). Technical problems accounted for the absence of anticardiolipin antibody measurements in 6 cases. The overall proportion of patients with at least 1 clotting abnormality was 31% (16/51 patients) and was higher in the idiopathic UEDVT group than in the effort-related UEDVT group (42% [13/31] vs 15% [3/20]; P = .06). Abnormal laboratory data are detailed in Table 3. The risk of having a clotting abnormality, estimated by the odds ratio, was 4.09 (95% confidence interval [CI], 0.99-16.78) for all the abnormalities combined, and 5.43 (95% CI, 0.60-48.70) for protein S deficiency and/or factor V Leiden. In the effort-related UEDVT group, a young tennis player had factor V Leiden and a negative personal and family history of venous thrombosis. In the idiopathic UEDVT group, the factor V Leiden mutation was found in a 49-year-old woman (negative personal and family history), a 54-year-old man (positive personal history), an 86-year-old woman (positive personal and family history), and a 30-year-old woman (positive family history, together with low levels of total and free protein S). In the same group, protein S deficiencies were found in a 38-year-old woman (positive family history) and a 17-year-old girl (negative family history). Plasma protein S deficiencies were confirmed in a second blood sample in all patients, but no family investigation could be performed. Increased anticardiolipin antibody titers (11-196 UGPL) were found in 10 patients (20%), of whom 8 were in the idiopathic UEDVT group. A 30-year-old man had idiopathic UEDVT that was followed 2 years later by spontaneous lower-extremity DVT, leading to the diagnosis of a primary antiphospholipid antibody syndrome; he had both lupus anticoagulant and a high anticardiolipin antibody titer (196 UGPL). None of the other 9 patients with slightly to moderately increased anticardiolipin antibody titers (11-37 UGPL) had recurrent thromboembolism, except for an 86-year-old woman with the factor V Leiden mutation. The DNA samples from 37 patients were analyzed for the 20210A mutation of the prothrombin gene; all the patients had the wild-type 20210G/G genotype.

Table 3. The risk of having a clotting abnormality, estimated by the odds ratio, was 4.09 (95% confidence interval [CI], 0.99-16.78) for all the abnormalities combined, and 5.43 (95% CI, 0.60-48.70) for protein S deficiency and/or factor V Leiden. In the effort-related UEDVT group, a young tennis player had factor V Leiden and a negative personal and family history of venous thrombosis. In the idiopathic UEDVT group, the factor V Leiden mutation was found in a 49-year-old woman (negative personal and family history), a 54-year-old man (positive personal history), an 86-year-old woman (positive personal and family history), and a 30-year-old woman (positive family history, together with low levels of total and free protein S). In the same group, protein S deficiencies were found in a 38-year-old woman (positive family history) and a 17-year-old girl (negative family history). Plasma protein S deficiencies were confirmed in a second blood sample in all patients, but

Primary UEDVT is a rare condition, with an incidence of approximately 2 per 100 000 persons per year14; this rarity explains the unresolved questions regarding its pathogenesis, treatment, and prognosis.15 An association between UEDVT and clotting abnormalities was not routinely sought until 1997, the year of publication of 3 studies in which coagulation abnormalities were found in 6 (43%) of 14 patients,6 6 (26%) of 23 patients,4 and 3 (8%) of 36 patients3 with this disease. Differences in the results of these studies may be explained by the limited size of the patient population (at least in 2 of them), small differences in recruitment from center to center, and differences in the coagulation tests used. In particular, lupus anticoagulant or anticardiolipin antibodies were found in 1 (7%) of 14 patients and in 4 (17%) of 23 patients with spontaneous UEDVT in 2 studies3,4 and in none of the patients in the third study4 (in this study, the tests used to screen for antiphospholipid antibodies were not specified).

In our study, the only inherited clotting abnormality in the effort-related UEDVT group was factor V Leiden in 1 patient (5%), which corresponds to the mean prevalence of this allele in European populations13; the percentage of patients with anticardiolipin antibodies (10%
[2/20]) was close to that observed in unselected blood donors (5.6%). Thus, the frequency of coagulation abnormalities in patients with effort-related UEDVT appears to be similar to that in apparently healthy populations. By contrast, in the idiopathic UEDVT group, 19% of patients (6/31) had factor V Leiden and/or protein S deficiency, and 26% (8/31) of them had anticardiolipin antibodies (together with lupus anticoagulant in 1 case). The overall proportion of patients with idiopathic UEDVT who had at least 1 coagulation abnormality (42% [13/31]) was similar to that observed in primary lower-extremity DVT.12 Interestingly, 3 of the 4 carriers of the factor V Leiden mutation in the idiopathic UEDVT group were at least 49 years old (ie, much older than the median age of the group), a finding consistent with the observation that the risk of thromboembolism attributable to the factor V Leiden mutation increases with age.15 Causes of transient hypercoagulability were also observed in 15 of the 25 women with idiopathic UEDVT (estrogen use, n = 11; pregnancy, n = 3; ovarian hyperstimulation, n = 1). Two of the 3 pregnancies followed in vitro fertilization procedures, and 1 of these 2 women had massive pulmonary embolization before UEDVT was diagnosed. The upper venous system seems to be an elective site of thrombosis associated with ovarian stimulation, particularly when accompanying in vitro fertilization9,16-18 and clinicians should pay particular attention to this possible complication in women engaged in such procedures.

This study is necessarily limited by the definition of the term effort-related UEDVT. This term has little descriptive validity, since the limit between strenuous effort and scant effort is arbitrary, and mechanical factors (such as thoracic outlet syndrome) probably play a role in a certain number of upper-limb thromboses that do not follow strenuous effort. However, the distinction between effort-related and idiopathic UEDVT has been recognized for a long time and has proven useful in clinical studies. There is a possibility of recall bias when patients reported triggering factors several years after the event; but the possibility appears limited in this young population, as indirectly shown by the excellent agreement between medical records and patient interviews on the evidence of unusually strenuous effort during the week before the thrombosis. In addition, the type of UEDVT (effort-related vs idiopathic) was assessed before the test results were available, thus avoiding a potential observation bias.

We conclude that hypercoagulability does not play a role in the pathogenesis of effort-related UEDVT, while it seems to be a frequent factor in the idiopathic forms of both UEDVT and lower-extremity DVT. This may have important implications in the future (for example, if the forthcoming Prevention of Recurrent Venous Thromboembolism [PREVENT] trial shows a benefit of long-term low-dose warfarin therapy for idiopathic lower-extremity DVT in hypercoagulable patients).

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Effort-Related UEDVT (n = 20)</th>
<th>Idiopathic UEDVT (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women, No. (%)</td>
<td>15/5 (75/25)</td>
<td>6/25 (19/81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median age at thrombosis (range), y</td>
<td>28 (15-56)</td>
<td>35 (17-86)</td>
<td>.06</td>
</tr>
<tr>
<td>Personal and/or family history of lower-extremity venous thrombosis, No. (%)</td>
<td>3 (15)</td>
<td>13 (42)</td>
<td>.06</td>
</tr>
<tr>
<td>Use of oral contraceptives, No. (%)</td>
<td>3 (75) [n = 4]</td>
<td>11 (58) [n = 19]</td>
<td>NA</td>
</tr>
<tr>
<td>Pregnancy or hormonal treatment to induce ovulation, No. (%)</td>
<td>0 [n = 1]</td>
<td>4 (33) [n = 12]</td>
<td>NA</td>
</tr>
<tr>
<td>Coagulation abnormality, No. (%)</td>
<td>Factor V Leiden</td>
<td>1 (5)</td>
<td>4 (15) [n = 27]†</td>
</tr>
<tr>
<td></td>
<td>Protein S deficiency</td>
<td>0</td>
<td>2 (7) [n = 27]</td>
</tr>
<tr>
<td></td>
<td>Protein C deficiency</td>
<td>0</td>
<td>0 [n = 27]</td>
</tr>
<tr>
<td></td>
<td>Antithrombin deficiency</td>
<td>0</td>
<td>0 [n = 30]</td>
</tr>
<tr>
<td></td>
<td>Lupus anticoagulant antibodies</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Anticardiolipin antibodies</td>
<td>2 (10) [n = 19]</td>
<td>8 (26)</td>
</tr>
<tr>
<td></td>
<td>Patients with at least 1 abnormality</td>
<td>3 (15)</td>
<td>13 (42)‡</td>
</tr>
</tbody>
</table>

*NA indicates P value not available. †Associated with protein S deficiency in 1 case. ‡One patient had both the factor V Leiden and anticardiolipin antibodies, and another patient had lupus anticoagulant and anticardiolipin antibodies.

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REFERENCES