Diagnostic Significance of Thrombin-Antithrombin III Complex (TAT) and D-Dimer in Patients With Deep Venous Thrombosis

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Thrombin-antithrombin III (TAT) and D-dimer were measured in 50 patients suspected of deep venous thrombosis (DVT) to assess the usefulness of these indicators in the diagnosis of DVT. DVT was diagnosed by ultrasonography (compression method and Doppler imaging). In patients who were negative for DVT (Group A), TAT was 3.8±2.36 μg/L (mean±SD) and D-dimer was 0.7±0.69 μg/ml, whereas in patients diagnosed with DVT (Group B), TAT was 20.4±19.10 μg/L (p<0.001) and D-dimer was 9.0±9.21 μg/ml (p<0.001). Thus, Group B had significantly higher levels of both markers. Moreover, 19 of the 23 cases in Group B had acute DVT, with symptoms appearing within 2 weeks of onset. When the cutoff for a positive diagnosis of DVT was set at TAT of 7.0 μg/L or more and D-dimer of 3.0 μg/ml or more, sensitivity was 84%, specificity was 96%, and accuracy was 90%. Based on these results, we concluded that TAT and D-dimer are extremely useful in screening for acute DVT.

(Jpn Circ J 1996; 60: 201–206)

The cause of pulmonary embolism (PE), a potentially fatal condition, is usually deep venous thrombosis (DVT) in the lower limbs or pelvis. However, two-thirds of all DVT cases are asymptomatic and difficult to diagnose clinically! so that often they are discovered only when a pulmonary embolism has occurred. The traditional method for confirming a diagnosis of DVT is through venography, but because this method is invasive and requires the use of radiographic contrast agents, it cannot be used for screening or with critically ill patients. Compression ultrasonography (C-US) is a new method that has been devised to replace venography in the diagnosis of DVT, and has been shown to be useful in DVT screening2–7. In addition, Kimura et al recently found that, within 2 weeks of an episode, patients with DVT have high levels of markers indicating activation of the plasma coagulation and/or fibrinolytic systems (thrombin-antithrombin III complex (TAT) and D-dimer)5.

In this present study, we assessed the usefulness of assays of TAT and D-dimer in the diagnosis of DVT.

SUBJECTS AND METHODS

The subjects consisted of 50 patients whose pulmonary embolism or edema of the legs had given rise to a clinical suspicion of DVT. C-US study was performed in all patients, who were then divided into two groups: 27 cases who were negative for DVT (Group A), and 23 cases who were diagnosed with DVT (Group B). Group A consisted of 15 men and 12 women (aged 44 to 80 years, mean 63±12.1 years), and Group
B consisted of 8 men and 15 women (aged 26 to 81 year, mean 66±13.1 years). Group A consisted of 8 cases of angina, 5 cases of acute myocardial infarction, 4 cases of heart failure, 3 cases of hypertension, 3 cases of lymphatic edema, and 4 others. Group B consisted of 2 cases of angina, 3 cases of heart failure, 5 cases of malignant tumor, 11 cases of idiopathic DVT, and 2 others. Pulmonary embolism had occurred in 12 of the cases in Group B. Moreover, 19 cases in Group B had symptoms within 2 weeks of onset and were classed as acute DVT, while the remaining 4 cases were considered as chronic DVT.

C-US and color Doppler imaging were used to diagnose DVT. We used a linear probe (7.5 MHz) to examine the common femoral and popliteal veins with the patient supine. The knee was then slightly flexed and the legs were spread to allow longitudinal and sagittal observation of the veins in the lower leg (the calf vein and the posterior tibial vein). The criteria for establishing the presence of DVT were as follows: (1) the echo in the vein was brighter than that from the parallel artery, (2) the venous diameter did not change in response to pressure and (3) color Doppler imaging revealed minimal or no flow of blood within the vein (Figs 1–3). In the 6 cases in which the diagnosis was inconclusive (1 case in Group A, 5
cases in Group B), venography was performed to clarify the findings from C-US.

Blood was withdrawn from the antecubital vein via a 21-gauge needle under early morning fasting conditions, and coagulation and thrombolytic markers were assayed immediately. Serum TAT concentration was determined by enzyme immunoassay based on the EIA sandwich method (TAT-test, Teijin Ltd, Osaka, Japan). The D-dimer and fibrin degradation product (FDP) titers were measured by latex agglutination turbidimetry (Latron Laboratories Inc, Tokyo, Japan). The antithrombin III (AT-III) concentration was assayed by the chromogenic synthetic substrate method (Chromogenix, Sweden), and fibrinogen was assessed by thrombin coagulation time, using Sysmex Fbg II (Toa Medical Electronics Corp, Kobe, Japan). The 7 PE patients in Group B were tested at 1- and 2-week intervals in order to observe time-course changes in TAT and D-dimer.

RESULT

The mean TAT was 3.8±2.36 μg/L in Group A and 20.4±19.10 μg/L in Group B (p<0.001). The mean D-dimer was 0.7±0.69 μg/ml in Group A and 9.0±9.21 μg/ml in Group B (p<0.001). The mean FDP was 3.0±2.97 μg/ml in Group A and 10.5±10.15 μg/ml in Group B (p<0.001). The mean fibrinogen was 308.5±85.15 mg/dl in Group A and 410.8±159.51 mg/dl in Group B (p<0.01). Thus, Group B had significantly higher levels of all of the markers except for antithrombin-III, for which there was no difference between the groups (Table I). The values for TAT and D-dimer in particular showed very little overlap between the two groups: the 4 patients with TAT of less than 7.0 μg/L and D-dimer of less than 3.0 μg/ml were all cases of chronic DVT (Fig 4).

Regarding the accuracy of diagnosis, a cutoff for TAT of 7.0 μg/L provided 82% sensitivity, 93% specificity, and 87% accuracy. A similar evaluation of D-dimer with a cutoff of 3.0 μg/ml provided 78% sensitivity, 96% specificity, and 87% accuracy. When the two markers were combined, ie, TAT of 7.0 μg/L or more and D-dimer of 3.0 μg/ml or more were both required for a positive diagnosis of DVT, sensitivity was 84%, specificity was 96%, and accuracy was 90% (Table II).

The study of time-course changes in TAT showed that TAT remained high in the first two weeks after the onset of DVT and returned to normal levels thereafter (Fig 5).

DISCUSSION

DVT, together with its frequent complication by PE, used to be a rare condition in Japan. However, in step with the Westernization of the Japanese lifestyle, the frequencies of both conditions are on the rise. The incidence of acute PE is particularly high after surgery in the lower limbs or abdomen? Since the death rate is extremely high in unexpected or sudden cases of PE, it is very important to use caution in daily clinical practice to prevent it.
### TABLE I COAGULATION AND FIBRINOLYTIC MARKERS IN GROUPS A AND B

<table>
<thead>
<tr>
<th></th>
<th>TAT</th>
<th>D-dimer</th>
<th>FDP</th>
<th>Fibrinogen</th>
<th>AT-III</th>
</tr>
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<tbody>
<tr>
<td>group A (n=27)</td>
<td>3.8 ± 2.36</td>
<td>0.7 ± 0.69</td>
<td>3.0 ± 2.97</td>
<td>308.5 ± 85.15</td>
<td>97.1 ± 15.75</td>
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<tr>
<td>group B (n=23)</td>
<td>20.4 ± 19.10</td>
<td>9.0 ± 9.21</td>
<td>10.5 ± 10.15</td>
<td>410.8 ± 159.51</td>
<td>99.2 ± 15.60</td>
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<tr>
<td>p-value (A vs B)</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.01</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data are means ± SD. TAT: thrombin-antithrombin III complex, FDP: fibrin degradation product, AT-III: antithrombin-III.

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**Fig 4.** Coagulation and fibrinolytic markers in Groups A and B.
Variabilities are expressed as the standard error of the mean (SEM).
TABLE II  ACCURACY OF TAT AND D-DIMER IN DIAGNOSING DVT

<table>
<thead>
<tr>
<th></th>
<th>sensitivity</th>
<th>specificity</th>
<th>accuracy</th>
</tr>
</thead>
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<tr>
<td>TAT 7.0 μg/L ≤ positive</td>
<td>82%</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td>D-dimer 3.0 μg/ml ≤ positive</td>
<td>78%</td>
<td>96%</td>
<td>87%</td>
</tr>
<tr>
<td>TAT 7.0 and D-dimer 3.0 ≤ positive</td>
<td>84%</td>
<td>96%</td>
<td>90%</td>
</tr>
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</table>

Since most episodes of PE arise from DVT in the lower limbs, screening and an accurate diagnosis of DVT in high-risk patients is very important in its prevention. Venography was once the test of choice for diagnosing DVT, but more recently compression ultrasonography (C-US) has been found to be more convenient and reliable, and is increasingly seen as an alternative to venography. This method is especially effective in the diagnosis of DVT proximal to the popliteal vein, which makes C-US comparable to venography. For these reasons, we chose to use C-US to confirm our diagnoses of DVT in the present study. In our experience, the use of C-US alone is adequate for establishing a diagnosis of DVT in the area ranging from the common femoral vein to the popliteal vein, while the use of color Doppler to examine the flow of blood in the veins allows for a still more reliable diagnosis. The greatest drawback of C-US is that sometimes it cannot be used to diagnose DVT in the veins of the lower leg. The calf vein in particular is too small, making diagnosis by C-US difficult. Fortunately, however, the incidence of DVT in this part of the leg is fairly low.

Remarkable advances have been made in the study of coagulation and thrombolytic factors, but much more needs to be done to understand the significance of these factors in cases of thrombosis. In this country, the only report that we are aware of which addresses these factors in DVT is that of Kimura et al, who studied 20 cases of acute DVT for the first 2 weeks after onset, and compared TAT and D-dimer levels with venography results. Their method had a sensitivity of 100% and a specificity of 88%. Since a similar accuracy was demonstrated in the present study, it seems clear that the combination of thrombolytic markers and imaging studies is most useful in screening for acute DVT.

TAT is a complex consisting of thrombin and antithrombin-III which serves as an indicator of thrombin production and accurately reflects the activation of coagulation. In contrast, D-dimer is a byproduct of the breakdown of stabilized fibrin, so that levels of D-dimer indicate whether or not clot dissolution is in progress; i.e., D-dimer is an indicator of secondary fibrinolysis. In the present study, TAT was markedly higher in patients with DVT. Thus, although it is possible that the aggravated levels were secondary to thrombus formation, it is more reasonable to assume that they had some effect on thrombogenesis. TAT and D-dimer levels are also known to be raised during disseminated intravascular coagulation (DIC), in the presence of malignant tumors, and during highly invasive surgery. These potential factors should be borne in mind when screening for DVT.

Another factor to keep in mind when using TAT and D-dimer for DVT screening is the time elapsed since the DVT episode. We conducted a follow-up study of the 7 patients who had had DVT to measure time-course changes in TAT and D-dimer, and found that these levels were significantly elevated for 2 weeks after DVT, but then the markers lost almost all of their diagnostic value. This also reflects the fact that, of the 23 cases in Group B, the 4 patients with chronic DVT had very low TAT and D-dimer.
In conclusion, measuring TAT and D-dimer is an extremely useful for diagnosing acute DVT, since a sensitivity of 84%, a specificity of 96%, and an accuracy of 90% can be achieved by setting a cutoff value of 7.0 μg/L or more for TAT and 3.0 μg/ml or more for D-dimer. This method may be especially useful in screening for acute DVT, not only in symptomatic, but also in asymptomatic patients, after surgery in the lower abdomen and legs or after invasive imaging procedures such as vascular catheterization.

REFERENCES