Inherited Thrombophilia in Ischemic Stroke and Its Pathogenic Subtypes

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Background and Purpose—One or more of the inherited thrombophilias may be causal risk factor for a proportion of ischemic strokes, but few studies have addressed this association or the association between thrombophilia and pathogenic subtypes of stroke.

Methods—We conducted a case-control study of 219 hospital cases with a first-ever ischemic stroke and 205 randomly selected community control subjects stratified by age, sex, and postal code. With the use of established criteria, cases of stroke were classified by pathogenic subtype in a blinded fashion. The prevalence of conventional vascular risk factors; fasting plasma levels of protein C, protein S, antithrombin III; and genetic tests for the factor V Leiden and the prothrombin 20210A mutation were determined in cases and control subjects.

Results—The prevalence of any thrombophilia was 14.7% (95% CI, 9.9% to 19.5%) among cases and 11.7% (95% CI, 7.4% to 17.0%) among control subjects (OR, 1.3; 95% CI, 0.7% to 2.3%). The prevalence of individual thrombophilias among cases ranged from 0.9% (95% CI, 0.1% to 3.4%) for protein S deficiency to 5.2% (95% CI, 0.3% to 9.1%) for antithrombin III deficiency; among control subjects, the prevalence ranged from 1.0% (95% CI, 0.1% to 3.6%) for protein S deficiency to 4.1% (95% CI, 0.2% to 7.8%) for antithrombin III deficiency. There were no significant differences in the prevalence of thrombophilia between cases and control subjects or between pathogenic subtypes of ischemic stroke.

Conclusions—One in 7 patients with first-ever acute ischemic stroke will test positive for one of the inherited thrombophilias, but the relation is likely to be coincidental rather than causal in almost all cases, irrespective of the pathogenic subtype of the ischemic stroke. These results suggest that routine testing for thrombophilia in most patients with acute ischemic stroke may be unnecessary. Whether the thrombophilias may still be important in younger patients with ischemic stroke or in predicting complications (eg, venous thrombosis) and stroke outcome remains uncertain.

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Key Words: cerebral infarction ■ stroke classification ■ thrombophilia

In recent years, an increasing number of largely inherited abnormalities of blood coagulation have been commonly associated with venous thromboembolism and sometimes arterial thrombosis.1–3 These conditions, the thrombophilias, include deficiencies of the natural anticoagulants such as antithrombin III,4,5 protein S,6,7 and protein C;8–12 and single point mutations in coagulation molecules such as factor V Leiden (1691G/A)13–16; or the 3’ untranslated region of the prothrombin gene (factor II) (20210 G/A).17,18

There is little doubt that inherited thrombophilias can cause venous thrombosis, but most individuals with a single genetic risk factor will not have a thrombotic event in the absence of circumstantial risk factors such as immobility or the oral contraceptive pill.19 Patients with ischemic stroke and TIA caused by arterial or heart disease are also sometimes found to have an underlying thrombophilic disorder.20,21 However, the difficulty in clinical practice is generally not in making the diagnosis of the underlying thrombophilia (it is often revealed from a routine blood test) but in knowing if thrombophilia is the cause of the ischemic stroke of TIA, particularly if another possible cause is also present (eg, carotid stenosis or atrial fibrillation); or if thrombophilia has exacerbated any cerebral ischemia caused by a coexistent pathogenesis (eg, atherothromboembolism); or if thrombo-
philia is unrelated and coincidental to the true underlying cause.

Previous studies have suggested that coagulation disorders are the major cause of only a minority (1% to 4%) of all ischemic strokes but that they may be relevant to the pathogenesis of subgroups of stroke patients such as strokes in young patients. We hypothesized that although inherited thrombophilias in isolation or combination may be important causal risk factors for only a small minority of patients with ischemic stroke, they may be pathogenically relevant to a greater minority of patients with specific pathogenic subtypes of ischemic stroke that involve thrombosis, such as large artery atherothrombosis and embolism of thrombus from the heart, and not other causes of ischemic stroke.

The objective of this study was to determine the role of the thrombophilias in the pathogenesis of ischemic stroke and particularly in certain pathogenic subtypes of ischemic stroke. We aimed to determine the prevalence of each of the known thrombophilias among patients with first-ever ischemic stroke compared with healthy community control subjects stratified by age, sex, and post code and to determine the relative prevalence of each of the thrombophilias among pathogenic subtypes of ischemic stroke.

Subjects and Methods

The study was approved by the Institutional Review Board of Royal Perth Hospital, and informed consent was provided by all study participants.

Cases

Consecutive patients presenting to a university teaching hospital in Western Australia between March 1996 and June 1998 with first-ever ischemic stroke were approached for consent to participate in our study. Stroke was defined as a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, with symptoms lasting >24 hours or leading to earlier death, and with no apparent cause other than that of vascular origin. Ischemic stroke was defined as a stroke with either a normal CT brain scan or evidence of a recent infarct in the clinically relevant area of the brain on a CT or MRI brain scan, performed within 3 weeks of symptom onset, which is either normal or shows a small deep infarct in the basal ganglia, internal capsule, or brain stem; (3) cardioembolic disease: ischemic stroke with (a) atrial fibrillation, recent myocardial infarction [in the last 6 weeks], endocarditis, prosthetic heart valve), and (c) clinical opinion that the most likely cause of brain infarction was embolism from the heart; (4) other: ischemic stroke that did not meet the criteria for one of the categories outlined above (eg, periprocedural, hypoperfusion, dissection) or where there was more than one likely explanation (eg, concurrent large artery occlusive disease and major cardioembolic source).

Control Subjects

Control subjects were randomly selected from the Western Australian electoral roll, stratified by 5-year age group, sex, and postal code. A letter of invitation to participate, together with a stamped and self-addressed envelope, was sent to potential control subjects. Nonresponders were contacted by telephone. Control subjects who agreed to participate in the study were required to fast for a minimum of 8 hours before their appointment and were given the option of attending the hospital outpatient clinic or being visited at home by the study nurse. Baseline demographic data (age, sex), history of conventional vascular risk factors, and history of previous vascular events were obtained for each control subject. A fasting blood sample was obtained for coagulation and genetic analysis.

Laboratory Analyses

Blood samples were collected and processed with the use of a standardized protocol and were analyzed in the central core laboratory. Blood samples were collected into 1:10 volume of 3.8% sodium citrate (Greiner, Kremsmunster, Austria) and centrifuged at 1300 g for 10 minutes. The plasma was separated, centrifuged a second time at 1300g for 10 minutes, and stored at −80°C until assayed. Genomic DNA was isolated from nucleated blood cells by use of a Triton X-100 salt-precipitation method and was stored at −4°C until assayed.

Protein C and antithrombin III levels were measured with the use of chromogenic assays (Chromogenix). Plasma protein C was activated by a specific enzyme from Southern Copperhead snake venom, and the amount of activated protein C was determined by the rate of hydrolysis of a chromogenic substrate. Absorbance was measured in a spectrophotometer and plotted against a standard curve to determine protein S levels. For measurement of antithrombin III, plasma was incubated with an excess of factor Xa in the presence of heparin. The residual quantity of factor Xa was determined by the rate of hydrolysis of a chromogenic substrate. Absorbance was measured in a spectrophotometer and plotted against a standard curve to determine the plasma antithrombin III level. The intrabatch and interbatch coefficients of variation (CV) for each of these assays are <10%.

Bound protein S was precipitated with 25% polyethylene glycol and free protein S in the supernatant subsequently run on immunoelectrophoretic gel plates (Biopool) for 3 hours. After washing and staining with Brilliant Blue R (Sigma), the height of the protein S precipitation rockets was measured and results were calculated by comparison to standards. The intrabatch and interbatch CVs for this assay are <10%.

The prevalence of factor V Leiden and the 20210 G/A prothrombin mutations were determined by polymerase chain reaction, restriction enzyme digestion, and gel electrophoresis, according to the methods of Bertina et al and Poort et al, respectively.
Definitions of Thrombophilia

The diagnosis of a natural anticoagulant deficiency was based on established in-house laboratory reference ranges for protein C (70% to 149%), protein S (55% to 150%), and antithrombin III (82% to 105%). For the purpose of this study, patients with a single plasma level below the lower end of the reference range in the absence of concomitant anticoagulant therapy or other clear cause (eg, liver disease) were considered to have natural anticoagulant deficiency.

Statistical Methods

Baseline differences between cases and control subjects were examined by means of the chi-square test for categoric data and an unpaired Student's t test for continuous data. Mean natural anticoagulant levels during the first 7 days and at 3 to 6 months of follow-up were compared by means of a paired t test, and the prevalence of natural anticoagulant deficiency at these two time points was compared by means of the McNemar test. The prevalence of inherited thrombophilia in pathogenic subtypes of ischemic stroke and control subjects was compared by means of a chi-square test.

The association between each of the thrombophilias (independent variables) and ischemic stroke (dependent variable) was examined with the use of a logistic regression model with and without adjustment for age, sex, and conventional vascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoker, history of previous vascular events). Results were expressed as odds ratios, together with their 95% CI. The SPSS for windows (version 8.0) statistical package was used for all analyses.

Results

Two hundred nineteen consecutive patients with ischemic stroke (140 men, 79 women; mean age, 66.1 years [SD, 12.4]), and 205 control subjects (131 men, 74 women; mean age, 67.0 years [SD, 11.8]) were studied.

Case-Control Differences

The 219 cases of ischemic stroke were characterized by a significantly higher prevalence of all conventional vascular risk factors, with the exception of hypercholesterolemia, compared with the control subjects (Table 1).

During the first 7 days after the acute stroke event, mean levels of protein S in the blood were significantly lower in cases compared with control subjects (118% versus 134%; mean difference, 16%; 95% CI, 7 to 25; P=0.001). Mean antithrombin III levels were significantly higher in cases compared with control subjects (119% versus 106%; mean difference, −14%; 95% CI, −20 to −8; P<0.001). There was no significant difference between cases and control subjects in the mean levels of protein C (Table 2).

Prevalence of Thrombophilia Among Cases

Among the 219 cases of first-ever ischemic stroke, the prevalence of thrombophilia ranged from 0.9% (95% CI, 0.1% to 3.4%) for protein S deficiency to 5.2% (95% CI, 0.3% to 9.1%) for antithrombin III deficiency. The prevalence of combined deficiency was 1.4% (95% CI, 0.3% to 4.1%) and any thrombophilia was 14.7% (95% CI, 9.9% to 19.5%) (Table 2).

Prevalence of Thrombophilia Among Control Subjects

Among the 205 community-based control subjects, the prevalence of thrombophilia ranged from 1.0% (95% CI, 0.1% to 3.6%) for protein S deficiency to 4.1% (95% CI, 0.2% to 7.8%) for protein C deficiency. There were no instances of combined deficiency (95% CI, 0% to 1.9%), and the prevalence of any thrombophilia was 11.7% (95% CI, 7.4% to 17.0%) (Table 2).

Association Between Thrombophilia and Ischemic Stroke

There was no significant association between any individual form of inherited thrombophilia and ischemic stroke, though trends for both factor V Leiden (OR, 2.1; 95% CI, 0.6 to 6.8) and the 20210 G/A prothrombin mutation (OR, 1.9; 95% CI, 0.5 to 6.2) were evident. There was no association between combined thrombophilia or any thrombophilia (OR, 1.3; 95% CI, 0.7 to 3.2) and ischemic stroke (Table 2). These results were unchanged when adjusted for age, sex, and conventional vascular risk factors.

Association Between Thrombophilia and Pathogenic Subtypes of Ischemic Stroke

There were no significant differences in the prevalence of individual causes of thrombophilia among the pathogenic subtypes of ischemic stroke, but the numbers of patients were small. There was also no association between combined thrombophilia or any thrombophilia and pathogenic subtypes of ischemic stroke (Table 3).
Natural Anticoagulant Levels During Acute Phase and at 3- to 6-Month Follow-Up

Repeat natural anticoagulant levels were obtained in 82 patients at 3 to 6 months of follow-up. There were no significant differences in plasma levels of protein C (120% versus 116%; mean difference, 4; 95% CI, –2% to 10%; P = 0.2), protein S (113% versus 101%; mean difference, 12; 95% CI, –1 to 25; P = 0.1), or antithrombin III (125% versus 123%; mean difference, 2; 95% CI, –12 to 15) during the acute phase and at 3 to 6 months (Table 4). Similarly, there

<table>
<thead>
<tr>
<th>Inherited Thrombophilia (Reference Range)</th>
<th>Cases (n=219)</th>
<th>Control Subjects (n=205)</th>
<th>Mean Difference OR 95% CI P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C (70% to 149%)</td>
<td>119 (24)</td>
<td>117 (23)</td>
<td>–2</td>
</tr>
<tr>
<td>Protein C deficiency (&lt;70%)</td>
<td>3</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>1.4% (0.3% to 4.1%)</td>
<td>2.0% (0.6% to 5.1%)</td>
<td></td>
</tr>
<tr>
<td>Protein S (55% to 150%)</td>
<td>118 (47)</td>
<td>134 (44)</td>
<td>16</td>
</tr>
<tr>
<td>Protein S deficiency (&lt;55%)</td>
<td>2</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>0.9% (0.1% to 3.4%)</td>
<td>1.0% (0.1% to 3.6%)</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III (82% to 105%)</td>
<td>119 (41)</td>
<td>106 (17)</td>
<td>–13</td>
</tr>
<tr>
<td>Antithrombin III deficiency (&lt;82%)</td>
<td>11</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>10</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>4.6% (2.2% to 8.4%)</td>
<td>2.0% (0.6% to 5.1%)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>8</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>3.7% (0.2% to 7.2%)</td>
<td>2.0% (0.6% to 5.1%)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>3</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>1.4% (0.3% to 4.1%)</td>
<td>0% (0% to 1.9%)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>31</td>
<td>22</td>
<td>1.3</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>14.7% (9.9% to 19.5%)</td>
<td>11.7% (7.4% to 17.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*χ² test for categoric variables, unpaired Student’s t test for continuous variables.

TABLE 3. Prevalence of Thrombophilia in Pathogenic Subtypes of First-Ever Ischemic Stroke and Control Subjects

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Control Subjects (n=205)</th>
<th>Cases (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Large Artery (n=63)</td>
<td>Small Artery (n=68)</td>
</tr>
<tr>
<td>Protein C</td>
<td>4 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Protein S</td>
<td>2 (1.0%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>8 (4.1%)</td>
<td>5 (8.1%)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>4 (2.1%)</td>
<td>4 (6.5%)</td>
</tr>
<tr>
<td>Prothrombin 20210 G/A</td>
<td>4 (2.1%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Combined*</td>
<td>0</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Any</td>
<td>22 (11.7%)</td>
<td>11 (17.7%)</td>
</tr>
</tbody>
</table>

*Any two defects.
were no differences in the prevalence of natural anticoagulant deficiency during the acute phase and at 3 to 6 months (Table 4).

Discussion
This is the first study, to our knowledge, which examines the association between all the major causes of inherited thrombophilia (in isolation and combination) and pathogenic subtypes of acute ischemic stroke. Our study reveals no association between any or all of the thrombophilias combined and any of the pathogenic subtypes of ischemic stroke. Even among all patients with first-ever ischemic stroke, the prevalence of isolated thrombophilias is low (0.9% [95% CI, 0.1 to 3.4%] to 5.2% [95% CI, 0.3% to 9.1%]) and not significantly greater than in the general population. Furthermore, the prevalence of any of the thrombophilias is as high as 1 in 7 (14.7% [95% CI, 9.9% to 19.5%]) among patients with first-ever ischemic stroke, the prevalence is not significantly higher than in the general population (11.7% [95% CI, 7.4% to 17.0%]; OR, 1.3 [95% CI, 0.7 to 2.3]). Inherited thrombophilia is therefore unlikely to be relevant to the pathogenesis of the majority of, if not all, cases of first-ever ischemic stroke. The implications of these results, if verified in larger studies, are that laboratory testing for the thrombophilias in all patients with acute ischemic stroke is unwarranted, and treatment of the thrombophilias after acute ischemic stroke may be unnecessary unless any or all of the thrombophilias are shown in other studies to be causally associated with important complications after stroke (eg, pulmonary embolism) or a poorer outcome.

The majority of prior studies demonstrating an association between inherited thrombophilia and any cause of ischemic stroke have been small, uncontrolled, or failed to measure natural anticoagulant levels in the acute and convalescent phases after an acute ischemic event. Our findings of a lack of association between inherited thrombophilia and any ischemic stroke are consistent with the findings from 3 major prospective studies examining the role of factor V Leiden,13 20210 G/A prothrombin,18 and protein C or antithrombin III20 in ischemic stroke. Meanwhile, the only prior study, to our knowledge, examining the prevalence of inherited thrombophilia in pathogenic subtypes of ischemic stroke also failed to find an association with factor V Leiden.29

The strengths of our study are that we prospectively assembled an inception cohort of more than 200 patients with ischemic stroke and more than 200 community-based control subjects selected at random from the electoral roll. The diagnosis of stroke and pathogenic subtype of ischemic stroke was made by a single neurologist who specializes in stroke medicine, on the basis of predefined and established criteria while remaining blinded to the results of the blood tests. The blood tests were measured within a consistent and narrow time frame (7 days) of the acute stroke event and in the fasting state in all subjects. Confirmatory levels performed in a subset of patients at 3 to 6 months revealed no significant difference in the prevalence of natural anticoagulant deficiency during the convalescent phase, which suggests that the consumption of natural anticoagulants is not an important cause of false-positive thrombophilia tests in the setting of acute stroke. Meanwhile, the results of the genetic analyses are not likely to be affected by acute illness.

Our study has several potential limitations. First, although cases were classified prospectively and recruited consecutively and control subjects were randomly selected from the community, potential confounding can never be entirely eliminated in an observational study. Second, the small

### TABLE 4. Mean Levels and Prevalence of Natural Anticoagulants (Protein C, Protein S and Antithrombin III) in Cases During First 7 Days After the Acute Event Compared With at 3 to 6 months of Follow-Up

<table>
<thead>
<tr>
<th>Natural Anticoagulant</th>
<th>0 to 7 d</th>
<th>3 to 6 mo</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C (70% to 149%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>120 (25)</td>
<td>116 (26)</td>
<td>4</td>
<td>−2 to 10</td>
<td>0.2</td>
</tr>
<tr>
<td>Protein C deficiency, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>0</td>
<td>3</td>
<td>...</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>0% (0% to 4.4%)</td>
<td>3.7% (0.8% to 10.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S (55% to 150%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>113 (51)</td>
<td>101 (37)</td>
<td>12</td>
<td>−1 to 25</td>
<td>0.1</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>1</td>
<td>3</td>
<td>...</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>1.2% (0% to 6.6%)</td>
<td>3.8% (0.8% to 10.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III (82% to 105%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>125 (49)</td>
<td>123 (46)</td>
<td>2</td>
<td>−12 to 15</td>
<td>0.8</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>3</td>
<td>3</td>
<td>...</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>3.7% (0.8% to 10.3%)</td>
<td>3.7% (0.8% to 10.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*McNemar test for categoric variables, paired t test for continuous variables.
number of cases among the pathogenic subtypes of ischemic stroke may have limited the power of our study to detect potentially important differences in the prevalence of thrombophilia between these groups. Third, the inclusion of control subjects irrespective of whether they had a history of vascular disease may have reduced the power of our study to detect a significant difference between cases and control subjects. However, the number of control subjects with vascular disease was small (26 of 205, or 13%), and it is very unlikely that this would have significantly altered the prevalence of thrombophilia among the cases. Finally, estimates of the prevalence of a natural anticoagulant deficiency (particularly antithrombin III) in our control group were higher than might be expected, based on previous reports in the general population, suggesting that our laboratory assay may be overestimating the incidence of antithrombin deficiency. Antithrombin III levels decline with increasing age, and is possible that the reference range needs to be modified in older populations, such as included in our study. Meanwhile, the clinical significance of a borderline low level is uncertain that the reference range needs to be modified in older populations, such as included in our study. Meanwhile, the clinical significance of a borderline low level is uncertain.

Our results suggest that 1 in 7 patients with a first-ever ischemic stroke will be found to have a thrombophilic disorder, but it is unlikely to be relevant to the pathogenesis of the stroke except perhaps in a very small proportion of patients. We were not able to support our hypothesis that affected patients may be at increased risk of one or more particular pathogenic subtype of ischemic stroke. These findings may have implications for the treatment of patients with acute stroke and an associated thrombophilic disorder. These patients are often treated empirically with anticoagulants, based on the assumptions that the association between the stroke and the thrombophilia is likely to be causal and that anticoagulants are the most effective therapy. However, neither of these assumptions are evidence-based, and the most appropriate prophylactic antithrombotic treatment for these patients may still be antiplatelet therapy. Our study also raises questions about the need to test for thrombophilias in patients with first-ever acute ischemic stroke. This issue may be resolved by follow-up studies that aim to determine whether any or all of the thrombophilias may be significant independent predictors of complications after stroke and a poor outcome.

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References


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