Prognostic Significance of Fibrinopeptide A in Survivors of Cerebral Infarction

Gianluca Landi, MD, Riccardo Barbarotto, MD, Alberto Morabito, PhD, Armando D’Angelo, MD, and Pier Mannuccio Mannucci, MD

We measured levels of fibrinopeptide A, β-thromboglobulin, and fibrinogen in the plasma of 27 patients 2 months after their first stroke. Concentrations of fibrinopeptide A, a sensitive index of in vivo hypercoagulability, were significantly higher in the 18 ischemic stroke patients than in 40 age- and sex-matched controls and in the six patients who experienced recurrence within 5 years than in the 12 who remained asymptomatic. On the contrary, fibrinopeptide A levels had no prognostic significance among the nine patients with hemorrhagic stroke. Concentrations of β-thromboglobulin, an index of platelet activation, were higher in the 27 stroke patients than in the 40 controls, but this index was not associated with stroke recurrence. Fibrinogen levels were not significantly higher in stroke patients than in controls. In a multivariate regression analysis of hemostatic and clinical variables, only fibrinopeptide A levels of >4 ng/ml were significantly related to cerebral infarction. Our results support the role of hypercoagulability in the recurrence of ischemic stroke and may allow identification of subjects at high risk for it. If confirmed in more patients, our results could provide a rationale for clinical trials of anticoagulant therapy in such patients.

Recurrence is common among survivors of cerebral infarction, with rates of >30% over 5 years.1,2 Correction of risk factors, such as hypertension and cardiac disease, has been advocated to improve prognosis,3,4 but the efficacy of this approach has not yet been firmly established. Several trials have assessed the prophylactic role of antiplatelet drugs after ischemic stroke and have reported no apparent benefit.5-7 Long-term anticoagulant therapy has also been evaluated,8-12 but as computed tomography (CT) was not available at that time, these trials probably also included patients with cerebral hemorrhage. The high rates of major (2-22%) and fatal (2-9%) bleeding complications, mainly cerebral hemorrhages, may account for the overall negative results in these trials. It has been estimated that, with a stroke rate of 8%/yr and a major bleeding rate of <2%/yr, a >50% reduction in the stroke rate is required for anticoagulant treatment to be beneficial.13 Besides optimal control of anticoagulation, this requirement can be fulfilled only by identifying a subgroup of patients who would gain maximal benefit from the treatment. With this aim, we measured sensitive indexes of platelet activation and coagulation (β-thromboglobulin [βTG], fibrinopeptide A [FPA], and fibrinogen concentrations) in stroke survivors and assessed the significance of the concentrations with regard to stroke recurrence.

Subjects and Methods

We evaluated 37 consecutive patients 2 months after their first stroke in a hemispheric distribution, as diagnosed by CT. We excluded 10 patients from the study since their neurologic status was too seriously compromised to allow outpatient visits. Eighteen patients suffered ischemic and nine suffered hemorrhagic strokes. We assessed the clinical variables age; sex; and the presence of hypertension (blood pressure of >160/90 mm Hg or regular use of antihypertensive drugs), cardiac disease (myocardial infarction, atrial fibrillation or other clinically important arrhythmias, or valvular disease), and neurologic impairment. The latter was scored on a 0-23-point scale evaluating motor function of the arm and leg (0, normal; 1, mild weakness; 2, severe weakness; and 3, paralysis), sensation of the arm and leg (0, normal; 1, mild hypesthesia; 2, severe hypesthesia; and 3, anesthesia), visual fields (0, normal; 1, mild hemianopsia; 2, moderate hemianopsia; and 3, severe hemianopsia), speech (0, normal; 1, mild receptive or expressive aphasia; 2, severe receptive or expressive apha-
TABLE 1. Clinical Variables and Results of Hemostatic Tests in Patients With Ischemic and Hemorrhagic Strokes

<table>
<thead>
<tr>
<th></th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>All (N=18)</td>
<td>All (N=9)</td>
</tr>
<tr>
<td>Mean</td>
<td>66.3</td>
<td>63.6</td>
</tr>
<tr>
<td>Range</td>
<td>38–81</td>
<td>46–74</td>
</tr>
<tr>
<td>Sex ratio (male:female)</td>
<td>15:3</td>
<td>3:6</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>%</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Neurologic score</td>
<td>Mean</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.0</td>
</tr>
<tr>
<td>Fibrinopeptide A concentration (ng/ml)</td>
<td>Geometric mean</td>
<td>3.85*</td>
</tr>
<tr>
<td></td>
<td>95% confidence interval</td>
<td>2.41–6.15</td>
</tr>
<tr>
<td>β-Thrombogulbin concentration (ng/ml)</td>
<td>Geometric mean</td>
<td>47.46†</td>
</tr>
<tr>
<td></td>
<td>95% confidence interval</td>
<td>33.98–66.28</td>
</tr>
</tbody>
</table>

*p<0.01, 0.001, respectively, different from controls by two-tailed t test for unpaired data.

Results

The 5-year recurrence rate was the same (33%) for patients with ischemic and hemorrhagic stroke (Table 1). Only one patient with hemorrhagic stroke suffered a new hemorrhagic stroke, whereas all other recurrent strokes were ischemic. Among the 18 ischemic patients, strokes recurred 9, 17, 22, 35, 42, and 54 months after the first stroke. As shown in Table 1,
prevalence of clinical risk factors did not differ significantly between the ischemic and hemorrhagic subgroups nor between those with and without recurrent stroke.

The geometric mean (and 95% confidence interval) for βTG concentration in the control group was 26.05 (21.96–30.89) ng/ml; for FPA, 1.97 (1.53–2.54) ng/ml; and for fibrinogen, 337 (312–365) mg/dl. The within-assay coefficient of variation was 8% for βTG and 10% for FPA, and the between-assay coefficients of variation were 10% and 9%, respectively. Mean (and 95% confidence interval) fibrinogen level in the 27 stroke patients (365 [324–411] mg/dl) was not significantly higher than that in the 40 controls. On the contrary, levels of both FPA and βTG were significantly (p<0.05 and p<0.001) higher in the 27 stroke patients than in the 40 controls. Compared with the controls, however, only the 18 patients with ischemic strokes had significantly elevated FPA levels (p<0.01, Table 1). This was due to significantly higher values in patients with recurrent stroke than in those without (p<0.01). On the contrary, βTG levels were higher than control in both ischemic and hemorrhagic patients, and the concentrations were not related to stroke recurrence (Table 1). Although hemorrhagic patients had higher mean βTG levels than those with ischemic stroke, the difference was not significant.

Among the 18 patients with ischemic stroke, FPA levels of >4 ng/ml were associated with recurrence, with a sensitivity and a positive predictive value of 66.6%, whereas specificity and negative predictive value were 83.3% (Figure 1). Multivariate regression analysis including all variables listed in Table 1 demonstrated that only FPA levels of >4 ng/ml were associated with recurrent stroke among our ischemic patients (z = 1.99, p<0.05). The cumulative 5-year probability of surviving free of recurrence was significantly reduced in patients with ischemic stroke who had FPA levels of >4 ng/ml (χ² = 3.96, p<0.05).

**Discussion**

The role of the hemostatic system in the pathogenesis of cerebral infarction is still debated. In a prospective study of asymptomatic individuals, an increased fibrinogen concentration was associated with later stroke, but other coagulation parameters were not. Several authors have reported abnormalities of different hemostatic variables after acute cerebral ischemia, but surprisingly few have evaluated the prognostic significance of these variables, with inconclusive findings. Our prospective study provides the first demonstration that among patients surviving 2 months after ischemic stroke, elevated FPA levels (which result from in vivo thrombin activity on fibrinogen and are thus regarded as a reliable index of hypercoagulability) are significantly related to recurrence of cerebral infarction within 5 years. On the contrary, we found that the concentration of βTG, a sensitive marker of in vivo platelet activation, is equally elevated in patients with ischemic and hemorrhagic strokes but is not associated with stroke recurrence. Although the number of our patients was relatively small, they represent an unselected population of stroke survivors suitable for inclusion in a therapeutic trial. On the other hand, the methodologic variability of our assay was sufficiently low to indicate that our sample size was adequate.

Our results are consistent with those of a previous study in which βTG levels did not predict recurrence of cerebral infarction. Stewart et al reported an association between elevated βTG (but not FPA) and subsequent vascular events in a group of patients with transient ischemic attacks (TIAs). However, most of these patients had recurrent TIAs rather than a stroke, and the only subject who suffered a later stroke had a normal βTG concentration, suggesting that platelet hyperactivity is involved in the pathophysiology of TIAs but not permanent vascular occlusions giving rise to cerebral infarction. This hypothesis is further supported by the results of a recent trial showing no benefit from antiplatelet treatment with aspirin on the incidence of recurrent cerebral infarction.

In conclusion, hypercoagulability (as manifested by elevated FPA levels) appears to be an independent risk factor for recurrent cerebral infarction in patients with at least partial preservation of neurologic function. The good predictive value of FPA levels of >4 ng/ml allows identification of a subset of high-risk patients for whom long-term anticoagulant therapy would appear rational. However, owing to the few end points in our study, examination of more

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**FIGURE 1. Scatterplot. Distribution of fibrinopeptide A (FPA) levels in subgroups of patients who survived 2 months after stroke.**
patients appears appropriate before testing the efficacy of this treatment in a clinical trial.

References


KEY WORDS • blood coagulation • cerebral infarction • fibrinogen • beta-thromboglobulin
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