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Elevated Tissue Plasminogen Activator Antigen and Stroke Risk

The Stroke Prevention in Young Women Study

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Background and Purpose—Abnormalities in endogenous fibrinolysis are associated with an increased risk for stroke in men and older adults. We tested the hypothesis that elevated plasma tissue plasminogen activator (tPA) antigen, a marker for impaired endogenous fibrinolysis, is an independent risk factor for stroke in young women.

Methods—Subjects were 59 nondiabetic females ages 15 to 44 years with cerebral infarction from the Baltimore-Washington area and 97 control subjects frequency-matched for age who were recruited by random-digit dialing from the same geographic area. A history of cerebrovascular disease risk factors was obtained by face-to-face interview. Plasma tPA antigen was measured by enzyme-linked immunosorbent assay.

Results—Mean plasma tPA antigen levels were significantly higher in stroke patients than control subjects (4.80 ± 4.18 versus 3.23 ± 3.67 ng/mL; $P=0.015$). After adjustment for age, hypertension, cigarette smoking, body mass index, and ischemic heart disease, there was a dose-response association between tPA antigen and stroke with a 3.9-fold odds ratio of stroke (95% CI, 1.2 to 12.4; $P=0.03$) for the upper quartile (>4.9 ng/mL) of tPA antigen compared with the lowest quartile. The dose-response relationship between tPA antigen and stroke was equally present in white and nonwhite women, and further adjustment for total and HDL cholesterol levels only modestly attenuated this association.

Conclusions—This population-based case-control study shows that elevated plasma tPA antigen level is independently associated with an increased risk for ischemic stroke in nondiabetic females 15 to 44 years of age. These findings support the hypothesis that impaired endogenous fibrinolysis is an important risk factor for stroke in young women. (*Stroke*. 1999;30:7-11.)

Key Words: cerebral infarction ■ fibrinolysis ■ risk factors ■ young adults ■ women

Abnormalities in endogenous fibrinolysis are increasingly recognized as independent predictors for increased risk of atherothrombotic events.^{1,2} In particular, elevations in tPA antigen have emerged as an important marker for impaired fibrinolysis associated with increased cerebral infarction risk in older populations.^{3,4} In a prospective study, Ridker et al found that elevated plasma tPA antigen levels were independently associated with an increased risk for stroke in adult males with a mean age of 62 years.⁵ Young adults, particularly women, are known to have better endogenous fibrinolysis profiles, lower atherosclerosis prevalence rates, and a more diverse profile of etiology for stroke than is typically found in older populations.⁶⁻⁸ The significance of impaired endogenous fibrinolysis as an independent predictor for

increased risk of stroke in the young adult population, and in women in particular, has not been established.

Abnormalities in fibrinolysis are now recognized in association with advancing age, male sex, and the extent of asymptomatic carotid atherosclerosis.⁷⁻¹⁰ Impaired fibrinolysis is also linked to selected cardiovascular disease (CVD) risk factors (including diabetes, hypertension, obesity, and dyslipidemia), elements of the insulin resistance syndrome that may elevate atherothrombotic risk by increasing plasminogen activator inhibitor-1 (PAI-1, the main circulating inhibitor for tPA).^{9,11,12} Prior case-control studies suggest that impaired fibrinolysis may be present in a substantial proportion of young stroke patients, including women.¹³⁻¹⁵ However, interpretation of these earlier studies is confounded by

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the nonspecific nature of fibrinolysis measures used and the limited covariate analysis for other CVD risk factors, which could also account for the impaired fibrinolysis findings. The present population-based study examined the hypothesis that elevated plasma tPA antigen is an independent risk factor for stroke in females aged 15 to 44 years.

Subjects and Methods

Subjects

The Stroke Prevention in Young Women Study is a case-control study within the defined geographic region of Maryland (except the far western panhandle), Washington, DC, and southern portions of Pennsylvania and Delaware. Case subjects included females aged 15 to 44 years with a diagnosis of first cerebral infarction identified by discharge surveillance at the 59 participating hospitals or by direct referral by regional neurologists. Recruitment within 1 year of stroke was required for participation. Methods for discharge surveillance, chart abstraction, and case adjudication have been previously described.¹⁶ Control subjects for the Stroke Prevention in Young Women Study were females without a history of stroke, frequency matched by age and geographic region, and recruited at a 2:1 ratio to the case subjects. For the tPA antigen study, consecutive ischemic stroke case subjects with citrate anticoagulated plasma available for measurement of tPA antigen were included, whereas controls included those women enrolled during the same time period with archived plasma similarly available for tPA antigen measurement. Stroke case and control subjects with a history of diabetes mellitus were excluded because of the known association between insulin resistance and impaired fibrinolysis, and because too few diabetic case subjects ($n=3$) were present to adjust for this important confounding variable.^{11,12}

A structured evaluation was used to characterize participant demographics, CVD risk factors, and other potential covariates affecting the relationship between tPA antigen and stroke. Hypertension, diabetes mellitus, and angina or myocardial infarction history were determined by asking study participants (or their proxy if participants could not answer) whether they had ever been diagnosed with such a condition or conditions by a physician. Smoking status was ascertained by determining whether participants had any cigarette usage in the 30 days preceding the index stroke, or before their interview for controls.

Hematologic Measures

Nonfasting blood samples for tPA antigen were collected by antecubital venipuncture in citrate anticoagulated evacuated tubes (Vacutainer; Becton-Dickinson), placed immediately on ice, and transported to a central processing laboratory. Plasma was prepared by centrifugation (1520g at 4°C for 15 minutes) and stored at -70°C until measured in duplicate by enzyme immunoassay (American Bioproducts).⁷ Total cholesterol and HDL cholesterol levels were measured according to standard practice¹⁷; high total cholesterol and HDL cholesterol levels were defined as ≥ 240 and ≥ 35 mg/dL, respectively.

Statistical Analysis

t tests were used to compare the means between groups. Fisher's exact test was used to compare clinical and demographic features between patient and control populations. Wilcoxon rank sum tests were used to analyze the relationships between tPA antigen levels and selected clinical and demographic factors in controls, because the distribution of tPA antigen values was found to be skewed. For statistical analysis, age was categorized as less than or greater than 35 years, and body mass index (BMI, kg/m²) was evaluated by median split. Crude and adjusted odds ratios derived from logistic regression were used to determine whether the upper quartiles for tPA antigen were associated with an increased risk for stroke compared with the lowest quartile. Odds ratios for stroke were initially determined separately in white and nonwhite participants;

TABLE 1. Comparison of Clinical and Demographic Features in Stroke Patients and Controls

Factor	Patients, n (%)	Controls, n* (%)	<i>P</i>
Age			
<35 y	23 (39%)	43 (44%)	0.62
≥ 35 y	36 (61%)	54 (56%)	
Race			
White	33 (56%)	58 (60%)	0.74
Nonwhite	26 (44%)	39 (40%)	
Education			
≤ 11 th grade	4 (7%)	8 (8%)	1.00
≥ 12 th grade	55 (93%)	89 (92%)	
Current smoking			
No	29 (49%)	69 (71%)	0.01
Yes	30 (51%)	28 (29%)	
Median BMI, kg/m ²			
<25	29 (49%)	52 (54%)	0.62
≥ 25	30 (51%)	45 (46%)	
Hypertension			
No	45 (78%)	85 (88%)	0.12
Yes	13 (22%)	12 (12%)	
CVD history			
No	51 (86%)	91 (94%)	0.15
Yes	8 (14%)	6 (6%)	
Total cholesterol, mg/dL			
<240	49 (86%)	85 (88%)	0.81
≥ 240	8 (14%)	12 (12%)	
HDL cholesterol, mg/dL			
> 35	47 (82%)	91 (95%)	0.02
≤ 35	10 (18%)	5 (5%)	

CVD indicates coronary artery disease.

these groups were combined for subsequent models because there was no effect modification by race.

Results

There were 59 stroke patients and 97 control subjects with blood samples available for tPA antigen determination. Clinical and demographic features of study participants are shown in Table 1. There were no significant differences in age, education level, or distribution by race between patients and controls. Etiologic categories for stroke included 10 cardioembolic, 12 atherosclerotic, 1 small vessel (lacune), 15 indeterminate, and 21 "other" etiologies, based on the classification scheme previously described. Prevalence rates for current smoking status and low HDL cholesterol level (defined as < 35 mg/dL) were higher among stroke patients. There was a nonsignificant trend toward higher proportions of hypertension and coronary artery disease history among case subjects with stroke than control subjects.

The mean plasma tPA antigen levels were 4.80 ± 4.18 ng/mL in cases and 3.23 ± 3.67 ng/mL in controls, for a mean difference of 1.57 ($P=0.015$). Plasma tPA antigen levels measured in stroke patients from the acute period < 2 weeks after index cerebral infarction were not significantly different

TABLE 2. Univariate Relationship Between Selected Factors and Plasma tPA Antigen Levels in Controls Only

Factor	Median tPA, ng/mL	P
Age		
<35 y	1.7	0.00
>35 y	3.2	
Race		
White	2.7	0.19
Nonwhite	3.8	
Education		
≤11th grade	3.8	0.42
≥12th grade	2.5	
Current smoker		
No	2.3	0.26
Yes	3.1	
Body mass index, kg/m ²		
<25	1.4	0.00
≥25	4.1	
Hypertension history		
No	2.3	0.51
Yes	3.2	
Coronary artery disease		
No	2.2	0.03
Yes	4.5	
Total cholesterol, mg/dL		
<240	2.1	0.08
>240	4.0	
HDL cholesterol (mg/dL)		
<35 mg/dL	2.3	0.29
>35 mg/dL	3.5	

from those measured ≥2 weeks after index stroke (5.28 ± 4.7 [n=14] versus 4.66 ± 4.08 ng/mL [n=44]); $P=0.64$). Univariate relationships between selected conventional CVD risk factors, demographic factors, and plasma tPA antigen levels in controls are shown in Table 2. As expected, tPA antigen levels were higher in participants >35 years in age, in those with a history of ischemic heart disease, and in those with greater BMI by median split analysis. There was a nonsignificant trend toward higher tPA antigen levels in participants with elevated total cholesterol levels.

The odds ratios for stroke by increasing quartiles of tPA antigen are shown in Table 3. Overall, there was an unadjusted 4.4-fold increased risk for stroke associated with the upper quartile of tPA antigen values; this included crude odds ratios for stroke of 4.9 (95% CI, 1.4 to 17.4; $P=0.014$) in white women and 5.0 (95% CI, 0.8 to 29.6; $P=0.076$) in nonwhite women. After adjustment for age group, BMI by median split, hypertension, smoking status, and ischemic heart disease, there remained a strong dose-response association between tPA antigen and risk for cerebral infarction (Table 3). Lipoprotein lipid profiles were measured in 57 stroke patients and 96 control subjects. In these participants, the upper quartile of tPA antigen was associated with a 3.2-fold increased risk for stroke (95% CI, 0.097 to 10.7;

TABLE 3. Univariate and Adjusted Odds Ratios for Stroke by Quartiles of Plasma tPA Antigen Levels and for Age, Body Mass Index, Hypertension, Smoking, and Coronary Artery Disease History

Variable	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Body mass index, by median split	1.2 (0.63–2.3)	0.63 (0.28–1.4)
Age, < or ≥35 y	1.0 (0.99–1.1)	1.0 (0.97–1.1)
History of coronary artery disease	2.4 (0.86–8.0)	1.4 (0.36–5.1)
History of hypertension	2.0 (0.86–4.9)	1.6 (0.56–4.3)
Current smoking	2.5 (1.3–5.0)	2.5 (1.1–4.7)
1st quartile tPA antigen, <1.43 ng/mL	Reference	Reference
2nd quartile tPA antigen, 1.43–3.14	1.5 (0.5–4.1)	1.4 (0.5–4.1)
3rd quartile tPA antigen, 3.14–4.90	2.4 (0.9–6.2)	2.5 (0.8–7.3)
Upper quartile tPA antigen, >4.90	4.4 (1.6–11.8)*	3.9 (1.2–12.4)†

* $P<0.005$, † $p<0.03$.

$P=0.055$), even after further adjustment for total and HDL cholesterol levels.

Discussion

There are few hematologic factors that independently predict an increased risk for cerebral infarction in the young. Although factors such as elevated fibrinogen and impaired fibrinolysis are strongly associated with stroke, they also occur with advancing age and have been convincingly linked to stroke risk typically only in older stroke cohorts.^{5,7,18} In this population-based case-control study, we report an independent association between elevated plasma tPA antigen levels and risk for cerebral infarction in young women. The upper quartile of tPA antigen levels remained associated with an increased risk for stroke even after adjusting for age, BMI, history of angina or myocardial infarction, and conventional CVD risk factors, including total and HDL cholesterol levels. These findings provide the first evidence that impaired endogenous fibrinolysis is an independent predictor for increased risk of stroke in young women.

Some early studies suggest that impaired fibrinolytic capacity is present in young and middle-aged adults with stroke.^{13–15} Reduced fibrinolytic capacity determined with the fibrin plate method was reported in 70% of patients <55 years of age with a history of cerebral ischemia.¹⁵ Mettinger and Egberg¹³ later reported that “plasminogen activator” levels indexed by a peptide substrate method were lower in young women (<40 years of age) with a history of cerebral ischemia but not in men. Defective vessel wall fibrinolytic response or reduced euglobulin clot lysis time after a venous occlusion test was found in 38% of young adults (<45 years of age) with cerebral ischemia.¹⁴ In contrast, Sharma et al reported finding no abnormalities in resting euglobulin clot lysis time in young patients (mean age, 33 years) with a history of thromboembolic stroke.¹⁹ These studies are limited by their use of nonspecific fibrinolysis laboratory measures and inadequate consideration of other conventional CVD risk factors now recognized in association with impaired fibrinolytic capacity.^{9,11,12}

Recent case-control studies further support a relation between impaired fibrinolysis, indicated by elevated plasma tPA antigen, and increased risk for stroke in selected populations. In older men and women attending a metabolic ward, elevated plasma tPA antigen levels were a strong predictor of ischemic stroke status, more reliable than plasma PAI-1 antigen levels.⁴ Jeppeson et al found that there were elevated plasma tPA antigen levels in older women with ischemic stroke (mean age, 76 years) but not older men and that tPA levels were related to stroke severity and infarct size only in women.²⁰ In the only prior study of fibrinolysis and stroke in young adults, Chancellor et al reported that tPA antigen levels were not elevated in male and female patients (mean age, 27 years) with stroke of undetermined etiology.²¹ Taken together, these studies suggest that sex- and age-specific differences may exist for the significance of fibrinolytic markers as predictors of increased stroke risk.

In a prospective study, Ridker et al found that plasma tPA antigen levels elevated beyond the 95th percentile (>19.7 ng/mL) were independently associated with a fourfold increased relative risk for thromboembolic stroke in adult males (mean age, 62 years).⁵ Similarly, we observed a dose-response relationship between the tPA antigen level and the adjusted odds ratio for thromboembolic stroke in young women, with the upper quartile of tPA antigen levels associated with a 3.8-fold increased risk. Furthermore, the odds ratios for stroke were of similar magnitude in white and nonwhite women. The mechanisms underlying cerebral infarction in young adults are diverse and fundamentally differ from those in older populations by virtue of reduced atherosclerosis rates.⁶ Thus, it is remarkable that we observed the same dose-response relationship between tPA antigen and stroke risk in young women as that described in older men by Ridker and colleagues.⁵ These results extend the hypothesis that impaired endogenous fibrinolysis is an important mechanism underlying increased risk for cerebral infarction across gender, race, and a broad age range.

Plasma tPA antigen levels constituting the upper quartile in young women (>4.9 ng/mL) were much lower than those in older stroke cohorts.³⁻⁵ This is consistent with studies showing reduced fibrinolytic capacity in men and with studies of advancing age.⁷⁻⁹ Results of this study indicate that even these low levels of tPA antigen are associated with an increased risk for stroke in young women. A number of conventional CVD risk factors that have been linked to the insulin resistance syndrome and those in which prevalence increases with advancing age are also related to impaired fibrinolysis.^{9,11,12} To account for these potential covariates we excluded diabetic patients, adjusted for age, BMI, and other conventional CVD risk factors in a multiple regression model. This analysis may underestimate the true importance of fibrinolysis abnormalities to stroke risk, because these factors may foster atherothrombosis in part by impairing fibrinolysis.^{9,11,12} That further adjustment for cholesterol levels modestly attenuates the association between tPA antigen level and stroke risk is consistent with this hypothesis. These results underscore a need for age-sex dependent adjustment and consideration of other CVD risk factors as covariates when interpreting the clinical significance of fibrinolytic markers.

Our results are limited by the retrospective study design. We cannot rule out the possibility that elevated tPA antigen was a consequence rather than a precursor to stroke. However, it is unlikely that the elevated tPA antigen levels were due to an acute phase response after stroke. There were no significant differences in mean plasma tPA antigen levels between those women whose blood was sampled before and those sampled >2 weeks after index stroke. These findings corroborate observations in older stroke patients that tPA antigen levels are similar in acute and convalescent phases.³ Plasma tPA antigen is a measure of inactive and free-active tPA; the majority is bound to PAI-1 as an inactive circulating complex.^{7,22} Findings of elevated tPA antigen are interpreted as reduced net fibrinolytic capacity with relative excess in PAI-1.²²⁻²⁴ Because we did not directly measure tPA and PAI enzyme activities, we cannot distinguish whether the elevated tPA antigen is a marker for premature atherosclerosis, impaired fibrinolysis, or both.

In summary, our findings suggest that elevated plasma tPA antigen level is an independent risk factor for cerebral infarction in young women, supporting the hypothesis that impaired endogenous fibrinolysis is an important predictor for increased risk of stroke across gender and a broad age range.^{4,5,20} This relationship is similar in white and black women and persists in a dose-response fashion even after adjustment for age and conventional CVD risk factors. The magnitude of increased risk, a 3.9-fold adjusted odds ratio for stroke with the upper quartile of tPA antigen levels, was more robust than those observed for hypertension and smoking. Further studies are needed to differentiate genetic from environmental determinants of elevated tPA antigen level and to investigate the potential health benefits of interventions aimed at improving endogenous fibrinolysis in high-risk populations.²⁵⁻²⁷

Appendix

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