Shortened Activated Partial Thromboplastin Time Is Associated With Acute Ischemic Stroke, Stroke Severity, and Neurological Worsening

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Background: The role played by hemostasis in the pathogenesis of ischemic strokes is still controversial. The activated partial thromboplastin time (APTT) measures the time necessary to generate fibrin from initiation of the intrinsic pathway. In the present study, we looked for a possible association of ischemic strokes with the shortened APTT. *Methods:* The study population consisted of 154 patients with acute ischemic strokes who had been admitted from December 2013 to December 2014 to the Department of Neurology, Chiayi Chang Gung Memorial Hospital, and 71 control subjects with no history of stroke. *Results:* In a univariate risk analysis, shortened APTT was associated with an odds ratio (OR) for acute ischemic strokes of up to 1.86 (95% confidence interval [CI], 1.06-3.29, $P = .031$). In a multivariate analysis using a logistic regression model including age, sex, hypertension, diabetes mellitus, and shortened APTT, shortened APTT was still found to significantly add to the risk of ischemic stroke (OR = 2.12 with 95% CI, 1.13-3.98, $P = .020$). Shortened APTT was also associated significantly with neurological worsening (OR = 3.72 with 95% CI 1.03-13.5, $P = .046$). As for stroke severity, shortened APTT was associated with an OR for moderate/severe stroke of up to 3.42 (95% CI, 1.53-7.61, $P = .003$). *Conclusion:* Shortened APTT is a prevalent and independent risk factor for ischemic stroke, stroke severity, and neurological worsening after acute stroke. **Key Words:** Stroke—ischemic—activated partial thromboplastin time—risk—association.

Introduction

The coagulation cascade is integral to the hemostatic process and serves to limit the amount of blood loss during trauma. However, derangements in this process can contribute to the development of thrombosis. Thrombosis is the major mechanism underlying acute complications of atherosclerosis. Coagulation can be activated by two principal mechanisms, the intrinsic and the extrinsic pathways, that converge to produce thrombin by a common pathway through a series of inter-related enzymatic reactions. These classical pathways form the basis of the two most frequently performed coagulation tests, the prothrombin time, that measures the extrinsic and common pathways, and the activated partial thromboplastin time

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(APTT), which measures the intrinsic and common pathways.

The intrinsic pathway significantly enhances thrombogenicity of atherosclerotic lesions after removal of the endothelial layer and exposure of smooth muscle cells and macrophages to blood flow.[1] The results with intrinsic pathway protease-deficient mice demonstrated that the reactions required for normal hemostasis are not identical to those involved in forming an occlusive arterial thrombus in the absence of bleeding.[2] Deficiencies of the intrinsic pathway proteases factor XII and factor XI are not associated with abnormal hemostasis in mice but impair formation of occlusive thrombi in arterial injury models, indicating that pathways not essential for hemostasis participate in arterial thrombosis.[3,4]

The APTT is a medical test that characterizes blood coagulation. Normal APTT times require the presence of the following coagulation factors: I, II, V, VIII, IX, X, XI, and XII. Dysregulation of intrinsic pathway would be expected to contribute to thromboembolic disease. In humans, correlations between plasma levels of factors VIII, IX, and XI and risk of venous thromboembolism have been demonstrated in large case-controlled population studies.[5-7] Factor XI activity more than the normal range was also identified as a risk factor for stroke and transient ischemic attacks in a retrospective analysis of patients younger than 55 years.[8]

Shortening of the APTT is considered to have clinical relevance with increased risk of thromboembolism.[9] Therefore, the aim of the present study was to assess the shortened APTT in acute ischemic stroke (AIS) and to determine whether shortened APTT is related to AIS with neurological worsening. Furthermore, shortened APTT has not been evaluated in ischemic stroke severity. In this study, we are going to evaluate if shortened APTT is associated with stroke severity according to the National Institutes of Health Stroke Scale (NIHSS).[10]

Materials and Methods

Subjects

The study population consisted of 154 AIS patients who had been admitted to the Department of Neurology, Chiayi Chang Gung Memorial Hospital, from December 2013 to December 2014 and 71 control subjects with no history of stroke (ischemic or hemorrhagic) or coronary artery disease. All enrolled subjects were Taiwanese. Patients with major renal, hepatic, and endocrinologic disorders, cancerous diseases, and recent infections were excluded. All patients were examined by a qualified neurologist. Stroke was defined as the sudden onset of nonconvulsive and focal neurologic deficits that persist for more than 24 hours. Hypertension (HTN) was defined as (1) previous diagnosis of HTN by a clinician or (2) systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more on two different occasions measured after the acute stage of stroke. Diabetes mellitus (DM) was diagnosed according to the National Institutes of Health revised criteria (1980).[11] Current cigarette smoking was defined as a risk factor if a patient smoked 10 or more cigarettes per day for more than 6 months before a stroke. All stroke patients underwent chest plain radiography, electrocardiography, a complete blood count panel (hemoglobin, hematocrit, platelet, and leukocyte), and tests for blood glucose, APTT, electrolytes, triglycerides, and cholesterol. In addition, all patients underwent brain computed tomography and/or brain magnetic resonance imaging to define the infarction area and to exclude any cerebral hemorrhage. Information on demographic features was collected using a structured questionnaire. The study protocol was approved by the ethical committee of our hospital.

Severity of stroke was assessed using the NIHSS at hospital admission and 48 to 72 hours later.[10] Videotapes and other clinical materials were used to train investigators in the application of the NIHSS. Neurological worsening of AIS was defined as an increase of 1 point or more on the NIHSS total score from hospital admission until 48 to 72 hours later. A subgroup of 106 patients with the NIHSS score less than 5 was classified as mild stroke, whereas the other 48 patients with NIHSS scores of 5 or more were classified as moderate/severe stroke.

Biochemical Analysis and Coagulation Factor Activity Assays

Samples of venous blood were drawn from each subject, after an overnight fast, at the time of enrollment. APTT, serum lipid levels, and other AIS risk factors were determined. APTT was assayed on the Sysmex CA1500 Analyzer (Sysmex Corporation, Kobe, Japan) with the instrument's accompanying APTT reagents (FSL actin; Dade Behring, Newark, DE). The normal plasma used as reference was prepared by pooling equal portions of fresh plasmas from the blood of 30 donors. The reference ranges are 23.3-39.3 seconds and the mean normal value is 28.4 seconds. Therefore, in this study, we defined shortened APTT as a specimen exhibiting an APTT of less than 28.4 seconds. Results for the APTT were expressed as a ratio of test to reference coagulation times.

Statistical Analyses

The data are expressed as the mean ± SD and were analyzed using the Statistical Package for Social Sciences, version 18.0 (Chicago, IL). The difference in demographic features between cases and controls was evaluated by the Student *t* test and chi-square test for continuous and categorical variables, respectively. The relationships between shortened APTT and AIS, stroke severity, and neurological worsening were evaluated by a forward