Relationship between Cardiac Troponin and Thrombo-Inflammatory Molecules in Prediction of Outcome after Acute Ischemic Stroke

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Background: In patients with acute ischemic stroke (AIS) without cardiovascular complications, we investigated the association of serum concentration of cardiac troponin (high-sensitivity cardiac troponin T [hs-cTnT]) with thrombo-inflammatory markers. *Methods:* Thirty-five patients with first-ever AIS were prospectively examined. Serum hs-cTnT was measured 6 and 24 hours after stroke, whereas S100B, high-sensitivity C-reactive protein (hsCRP), soluble CD40 ligand, tissue plasminogen activator (tPA), monocyte chemoattractant protein-1 (MCP-1), and P-selectin were measured 6 and 72 hours after stroke. Severity of stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS) on admission, 24 hours later, and at discharge. *Results:* Concentration of MCP-1 at 6 hours was higher in the serum of patients with worsened NIHSS by 24 hours ($P = .009$). Concentration of hs-cTnT at both 6 and 24 hours was higher, if NIHSS worsened by discharge ($P = .026$ and $P = .001$). A cutoff value for hs-cTnT measured at T24 greater than or equal to 9.4 predicted worsened NIHSS on discharge with a sensitivity of 81% and a specificity of 74% (area: .808, $P = .002$). Concentration of hs-cTnT at both 6 and 24 hours was also higher in nonsurvivors compared with survivors ($P = .03$, respectively), and correlated with (1) tPA levels at 6 hours ($P = .001$ and $P = .002$, respectively); (2) MCP-1 concentration at 6 hours ($P = .01$ and $P = .015$, respectively); and increased hsCRP levels at 72 hours ($P = .01$, respectively). Concentration of hs-cTnT at 24 hours was an independent predictor of worsened NIHSS at discharge (odds ratio: 1.58, 95% confidence interval: 1.063-2.370, $P = .024$). *Conclusions:* Elevated concentration of hs-cTnT measured 24 hours after AIS is an independent predictor of progressing neurologic deficit in patients without apparent myocardial damage, and also correlates with acute elevation of tPA and MCP-1. **Key Words:** Acute ischemic stroke—outcome—monocyte chemoattractant protein-1—high-sensitivity troponin t—S100B.

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Received August 16, 2017; revision received October 11, 2017; accepted October 31, 2017.

Grant support: This study was supported by a grant from the University of Pecs AOK-KA- 34039/10-17 to T. Molnar.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.10.040

Introduction

Cerebrovascular and cardiovascular diseases are major causes of death and disability worldwide. Elevated levels of cardiac troponin (cTn) in the serum reflect myocardial damage and also predict poor prognosis in acute ischemic stroke (AIS).[1] Ischemic stroke is a frequent complication in cardiac diseases, and cardiac complications commonly cause early clinical worsening and death after stroke.[2] In addition, acute myocardial infarction is a common complication of AIS.

Increased cTn concentrations in the serum in patients with acute coronary syndrome (ACS) indicate ongoing myocardial necrosis. Beyond ACS, it implies an increased risk for adverse outcome in patients with various cardiovascular conditions such as heart failure, stroke, myocarditis, Takotsubo cardiomyopathy, aortic dissection, arrhythmias, valvular diseases.[3] The prognostic value of high-sensitivity cardiac troponin T (hs-cTnT) in a low-risk outpatient population also provided excellent risk stratification on all-cause mortality, acute myocardial infarction, and stroke.[4]

However, the reason of cTn elevation in stroke patients without apparent cardiovascular damage is not yet explored. Recently, the association between poststroke mortality and abnormal results of cardiac troponin/echocardiogram was evaluated in a large number of patients with AIS, who presented to an emergency department: elevated troponin concentration was associated with increased mortality at 1 and 3 years even in the absence of concomitant myocardial infarction.[5]

Several blood biomarkers have been proposed to be associated with AIS. S100B in the peripheral blood is a sensitive marker of both blood–brain barrier dysfunction and ischemic brain damage and predictor of stroke outcome.[6,7] Increased high-sensitivity C-reactive protein (hsCRP) in the subacute stage is an independent predictor of death.[8] Thrombo-inflammatory molecules (tissue plasminogen activator [tPA], soluble CD40 ligand [sCD40L], P-selectin, interleukin-6, interleukin-8, monocyte chemoattractant protein-1 [MCP-1]) connect the prothrombotic state, endothelial dysfunction, and systemic/local inflammation in acute vascular events such as myocardial infarction or ischemic stroke.[9,10] Besides other factors, MCP-1 plays a crucial role in atherogenesis.[11] On the other hand, shear stress-induced overexpression of MCP-1 contributes significantly to the development of protective collaterals in the heart, but little is known about its role in the cerebral vasculature.[12]

The aim of this study was to explore the associations among hs-cTnT, S100B, hsCRP and thrombo-inflammatory markers such as MCP-1, tPA, sCD40L, and P-selectin.

Materials and Methods

The study protocol was approved by the Local Ethics Committee at University of Pecs, Faculty of Medicine, and informed consent was obtained from each patient.

Subjects

Thirty-five patients were enrolled within 6 hours after onset of first-ever AIS at the Department of Neurology, University of Pecs. Initial assessment of each patient, including cardiac anamnesis, 12-lead electrocardiogram recording, and physical examination, was performed to enroll only patients without acute cardiovascular event into this prospective study. Severity of stroke was measured by the National Institutes of Health Stroke Scale (NIHSS) on admission and on a daily basis until discharge or death.[13]

Inclusion and Exclusion Criteria

Inclusion criteria were (1) first-ever ischemic stroke; (2) onset of AIS within 6 hours; (3) duration of neurologic symptoms over 24 hours; (3) computed tomography or magnetic resonance result showed infarction in the brain area corresponding to the clinical symptoms and signs. The enrolled patients were conservatively treated; therefore, we were exclusively assaying the circulating levels of endogenous tPA after stroke. Exclusion criteria were (1) hemorrhagic stroke; (2) patients with ACS, myocardial infarction, stable angina, or the presence of clinical symptoms indicating acute infections, and other chronic infectious diseases; (3) patients with immune disorders, liver or kidney dysfunction, myopathy, and tissue injury outside of the brain; (4) recent use of both prescribed and over-the counter anti-inflammatory drugs.

Biomarkers

Venous blood samples were taken for the measurement of hs-cTnT within 6 hours after onset of first neurologic symptoms and 24 hours later. P-selectin, MCP-1, sCD40L, and tPA, hsCRP, and S100B were measured within 6 hours after onset and at 72 poststroke hours. Blood samples were centrifuged at $3000 \times g$ for 10 minutes. Supernatants were frozen and stored at –80°C until analysis. hs-cTnT concentrations were measured by a fully automated solid phase electrochemiluminescence immunoassay (Roche), (Roche Diagnostics, GmbH, Mannheim, Germany) using a Cobas e 411 analyzer (Roche). Serum levels of S100B were examined by automated electrochemiluminescent immunoassay (Liaison Sangtec 100 system, DiaSorin, Bromma, Sweden). Serum levels of hsCRP were examined by automated fluorescence immunoassay (BRAHMS Kryptor, Berlin, Germany). Concentration of P-selectin, MCP-1, sCD40L, and tPA were examined by immunoassay (BMS711F, Bender Gmbh, Campus Vienna Biocenter 2, Vienna, Austria).