Atherosclerosis 226 (2013) 165–171

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Platelet derived growth factor-CC isoform is associated with hemorrhagic transformation in ischemic stroke patients treated with tissue plasminogen activator

Raquel Rodríguez-González [a,b], Miguel Blanco [a], Manuel Rodríguez-Yáñez [a], Octavio Moldes [a], José Castillo [a], Tomás Sobrino [a,*]

[a] Clinical Neurosciences Research Laboratory, Neurovascular Area, Department of Neurology, Hospital Clínico Universitario, IDIS, University of Santiago de Compostela, Santiago de Compostela, Spain
[b] Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain

ARTICLE INFO

Article history:
Received 16 July 2012
Received in revised form
15 October 2012
Accepted 30 October 2012
Available online 17 November 2012

Keywords:
Ischemic stroke
tPA
PDGF
Thrombolysis
Hemorrhagic transformation
Edema

ABSTRACT

Objective: Platelet derived growth factor-CC (PDGF–CC) isoform is activated by tissue plasminogen activator (tPA) regulating blood brain barrier permeability after ischemia. We aimed to study the association of PDGF isoforms serum levels with hemorrhagic transformation (HT) and edema after thrombolytic treatment in ischemic stroke.
Methods: We studied 129 patients with ischemic stroke treated with tPA within the first 4.5 h (h) from stroke onset. CT was performed on admission and at 24–36 h. On the 2nd CT, HT was classified according to ECASS II criteria, and severe brain edema was diagnosed if extensive swelling causing any shifting of the structures of the midline was detected. PDGF-AA, PDGF-AB, PDGF–BB and PDGF–CC serum levels were analyzed by ELISA on admission (before tPA bolus), at 24 and 72 h.
Results: Patients who developed HT showed only higher levels of PDGF–CC isoform on admission and at 24 h (all $p < 0.0001$). In the multivariate analysis, PDGF–CC levels on admission (OR, 1.02; CI 95%, 1.00 –1.04) and at 24 h (OR, 1.05; CI 95%, 1.02–1.08) were independently associated with HT after adjustment by confounding factors. On the other hand, patients with severe edema showed also higher levels of PDGF–CC on admission and at 24 h ($p < 0.0001$), but this statistical association was lost in the logistic regression analysis. PDGF–CC levels $\geq$ 175 ng/mL at 24 h predict the development of PH with a sensitivity of 90% and specificity of 88% (area under the curve 0.936; $p < 0.0001$).
Conclusion: Increased PDGF–CC levels after tPA treatment is associated with HT.

1. Introduction

Intravenous tissue-type plasminogen activator (i.v. tPA) within the first 4.5 h from symptom onset has demonstrated to be safe and effective in the treatment of acute ischemic stroke [1,2]. However, apart from its fibrinolytic properties, tPA also displays deleterious effects in the brain parenchyma that lead to neuronal death, including microglial activation, excitotoxicity and basal lamina degradation [3]. As a result, the most feared complication associated to tPA treatment is symptomatic intracerebral hemorrhage, which is associated with high mortality and limits the use of thrombolytic therapy in a large number of patients [4,5].

On the other hand, platelet derived growth factors (PDGFs) are a family of molecules involved in cell proliferation, acting as potent mitogens and regulating the survival and migration of cells of mesenchymal origin, including smooth muscle and glial cells. They also regulate the deposition of extracellular matrix and tissue remodeling factors, playing a significant role in angiogenesis and hematopoiesis. PDGF signaling family consists of four ligands, PDGF A to D, working all of them as secreted homodimers, except for PDGF-A and PDGF–B, which form the only functional heterodimer [6]. Importantly, it has been demonstrated that tPA activates PDGF–CC isoform in the neurovascular unit, leading to an increase of cerebrovascular permeability and indicating that blood–brain barrier (BBB) integrity may be regulated by PDGF signaling [7–9]. Moreover, the

* Corresponding author. Laboratorio de Investigación en Neurociencias Clínicas, Hospital Clínico Universitario, c/Travesa da Choupana s/n, 15706 Santiago de Compostela, Spain. Tel./fax: +34 981951098.
E-mail address: tomas.sobrino.moreiras@sergas.es (T. Sobrino).

0021-9150/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2012.10.072

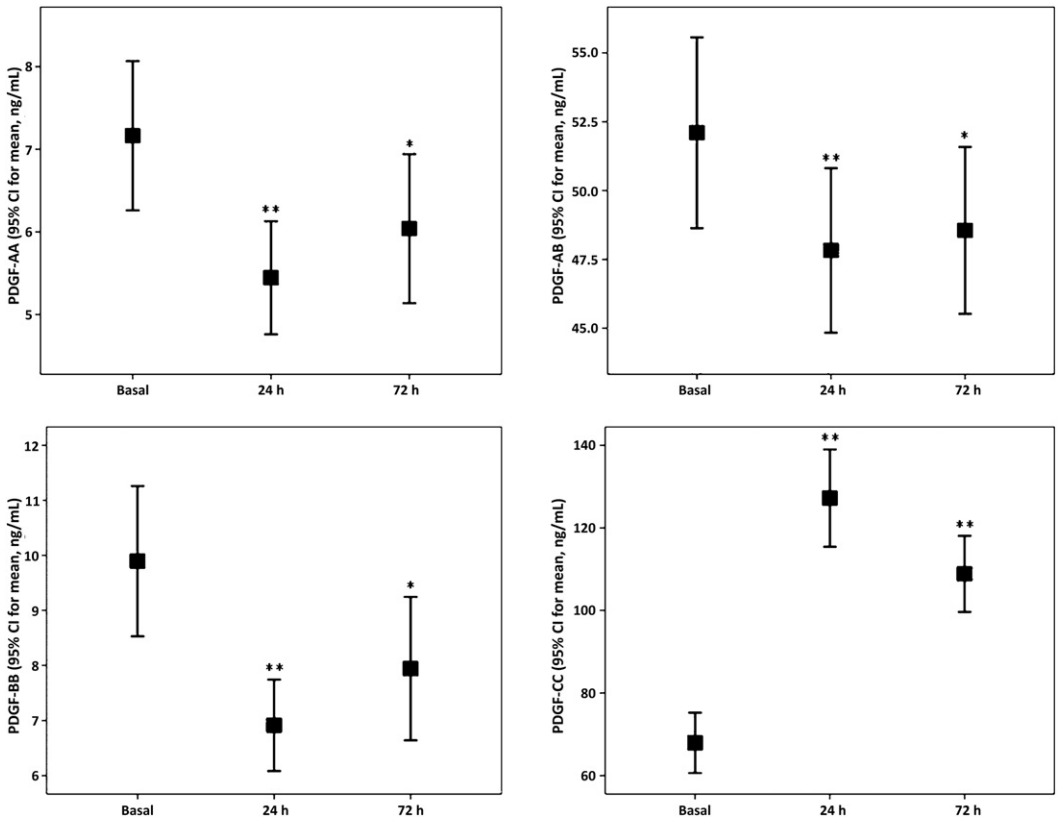

Fig. 1. Temporal profile of PGDF isoforms levels during the first 72 h from stroke onset. Charts showing mean values and 95% confidence intervals (CI) of serum levels of PDGF isoforms; $^{*}p < 0.01$; $^{**}p < 0.0001$compared to basal levels. See text for details.

blockade of PDGF receptor α attenuates tPA-associated complications in mice models of brain ischemia [10].

Since PDGF isoforms have been involved in all these aforementioned processes mediated by tPA, our aim was to study the association of blood levels of PDGF isoforms with hemorrhagic transformation (HT) and brain edema in patients with acute ischemic stroke treated with tPA.

2. Methods

2.1. Study population and patients characteristics

We prospectively studied 129 consecutive patients with acute ischemic stroke and middle cerebral artery (MCA) occlusion (as shown by Transcranial color-coded sonography (TCCS)) treated with i.v. tPA within 4.5 h from symptoms onset. All patients were prospectively evaluated by using cranial CT, TCCS, neurological and functional scales during a follow-up period of 90 days. Patients with prior disability (modified Rankin Scale (mRS) > 1) and known infectious, inflammatory or cancer diseases at the time of treatment were excluded. The sample size was calculated with a precision level of 5%, confidence level of 95% and test strength of 80% in order to ensure reliability of the results and that they could be translated to the population under study using an incidence for hemorrhagic transformation according to SITS-MOST (Safe Implementation of Thrombolysis in Stroke - Monitoring Study) registry. Sample size was determined using EPIDAT software (http://dxsp.sergas.es/ApliEdatos/Epidat/cas/default.asp). This research was carried out in accordance with the Declaration of Helsinki of the World Medical Association (2000) and approved by the Ethics Committee of the Servizo Galego de Saúde. Informed consent was obtained from each patient or their relatives after full explanation of the procedures.

2.2. Transcranial color-coded sonography (TCCS)

TCCS assessments were performed on admission to asses MCA occlusion according to the methods described elsewhere [11]. General Electric Vivid 7 Pro (GE Vingamed Ultrasound, Horten, Norway) and Aplio 50 Toshiba SSA-700 devices equipped with multi-frequency transducers were used by investigators with extensive experience in TCCS monitoring.

2.3. Clinical variables

All patients were admitted to an acute stroke unit and treated following the European Stroke Organization guidelines [12]. Medical history recording potential vascular risk factors, blood and coagulation tests, 12-lead ECG, chest x-ray, and carotid ultrasonography were performed on admission. Stroke subtype was classified according to the TOAST criteria [13] and stroke severity was assessed by an internationally certified neurologist using the National Institute of Health Stroke Scale (NIHSS) [14] at admission, just before tPA administration, and at 24 and 72 h. Functional outcome was evaluated at 3 months and good functional outcome was defined as a mRS score ≤ 2 [15].

2.4. Neuroimaging variables

CT scans were carried out immediately before treatment, and at 24–36 h after thrombolytic therapy. Early CT signs of infarction were evaluated on admission, and hypodensity volume and HT were assessed at 24–36 h. HT was classified as hemorrhagic infarction type 1 (HI1) and 2 (HI2), and parenchymal hematoma type 1 (PH1), type 2 (PH2), and remote (rPH) according to ECASS