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Immune-inflammatory markers and arterial stiffness indexes in subjects with acute ischemic stroke

Antonino Tuttolomondo*, Domenico Di Raimondo, Rosaria Pecoraro, Antonia Serio, Gisella D'Aguanno, Antonio Pinto, Giuseppe Licata

Dipartimento Biomedico di Medicina Interna e Specialistica, Università degli Studi di Palermo, Italy

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ABSTRACT

No study has yet evaluated the relationship between arterial stiffness indexes and immuno-inflammatory pathway in patients with an acute cardiovascular or cerebrovascular event. The aim of our study was to evaluate in patients with acute ischemic stroke the relationship between immune-inflammatory markers and arterial stiffness indexes.

Methods: 107 subjects with acute ischemic stroke and 107 controls without stroke. We evaluated plasma levels of C-reactive protein (CRP), interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10), E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), von Willebrand Factor (vWF), tissue plasminogen activator (TPA), plasminogen activator inhibitor-1 (PAI-1). Carotid-femoral pulse wave velocity (PWV) and augmentation index (Aix) were evaluated.

Results: There was a significant positive relationship, corrected for age, and gender, between PWV and CRP, TNF-α, IL1β, VWF and IL-6. Aix was significantly related to VWF, IL-6 and TNF-α levels. Among Lacunar subtype PWV was significantly related to CRP, IL-1β, IL-6, TNF-α and vWF. In LAAS subjects PWV was significantly related to CRP, IL-1β, IL-6, TNF-α but not with vWF. Among CEI subtype, PWV was significantly and positively related to CRP, IL-1β, TNF-α and vWF.

Discussion: Our findings show that both aortic stiffness and wave reflection are related to the degree of systemic inflammation in stroke subjects, suggesting that circulating inflammation mediators can influence the stiffness of vessels distant to those involved in the disease process itself.

1. Introduction

Inflammation markers such as C-reactive protein (CRP) are predictive of stroke occurrence [1] and CRP has been reported elevated in stroke patients [2], whereas our group [3,4] and other authors [5,6] reported that some pro-inflammatory cytokines are systematically increased after ischemic stroke.

Although there are some inconsistencies, a number of recent studies have suggested that in a healthy population, there may be a significant relationship between CRP and measures of arterial stiffness. Yasmin et al. found CRP to be related to pulse wave velocity (PWV) but not to augmentation index (Aix) [9]. In contrast, Kampus et al. found CRP to be independently and significantly associated with Aix. Moreover in patients with systemic vasculitis, in which CRP levels are markedly elevated, they were positively correlated with PWV and Aix [11].

Arterial stiffness is increasingly recognized as an important determinant of cardiovascular risk [13–16] and may be directly involved in the process of atherosclerosis [17]. The factors underlying increased arterial stiffness are incompletely understood, but both functional and structural alterations in the vessel wall are thought to be important. Indeed, some investigators have shown that endothelial-derived nitric oxide (NO) regulates large artery stiffness in vivo [12,18–21]. This may explain why other cardiovascular risk factors such as diabetes mellitus and hypercholesterolemia, which are associated with endothelial dysfunction, are linked to premature arterial stiffening.

Few studies examined the relationship between arterial stiffness indexes and systemic inflammation markers such as pro-inflammatory cytokines [22], whereas no study has evaluated the relationship between these indexes and immune-inflammatory markers in patients with an acute cardiovascular or cerebrovascular event. Only one study [23] indirectly evaluated this relationship and only with regard to erythrocyte sedimentation rate (ESR).

* Corresponding author at: Dipartimento Biomedico di Medicina Interna e Specialistica, Università degli Studi di Palermo, P.zza delle Cliniche n.2, 90127 Palermo, Italy. Tel.: +39 091 6552197; fax: +39 091 6552285.
E-mail address: brunotutto@unipa.it (A. Tuttolomondo).

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On this basis the aim of our study was to evaluate the relationship between arterial stiffness and cytokine, selectin, adhesion molecule and von Willebrand Factor plasma levels in subjects with acute ischemic stroke.

2. Methods

2.1. Patient selection

We enrolled all consecutive patients with a diagnosis of acute ischemic stroke admitted to the Internal Medicine Department at the University of Palermo between November 2006 and January 2008, and hospitalized control patients without a diagnosis of acute ischemic stroke. Control subjects were patients admitted, in the same period, to our Internal Medicine Department, for any cause other than acute cardiovascular and cerebrovascular events.

Stroke was defined by focal neurological signs or symptoms thought to be of vascular origin that persisted for >24 h confirmed by brain CT and/or MRI in baseline conditions and brain CT with contrast medium after 48–72 h [9].

In order to match patients with acute ischemic stroke and controls for cardiovascular risk and previous cardiovascular morbidity, controls were included if they had vascular risk factors or a history of myocardial infarction or cerebrovascular disease or peripheral vascular disease, but they were excluded if they had either current or recent (within 6 months) cerebrovascular disease or one of the exclusion criteria (see above).

Cardiovascular risk factors were evaluated for both cases and controls on the basis of the criteria shown below. Hypercholesterolemia was defined as the presence of total cholesterol blood levels $\geq$200 mg/dl. Hypertension was defined as present if subjects had been previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy. Patients were defined as type 2 diabetics if they had known diabetes treated by diet, oral hypoglycaemic drugs or insulin before stroke.

Previous coronary artery disease was determined on the basis of a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by a questionnaire.

Previous cerebrovascular disease (TIA/ischemic stroke) was assessed by history, specific neurologic examination performed by specialists, and hospital or radiological (brain computer tomography or brain magnetic resonance) records of definite previous stroke.

Subjects were classified as having previous peripheral artery disease (PAD) when they had an history of ABI <0.9 and/or of intermittent claudication or of critical limb ischemia or when they had undergone a peripheral arterial bypass or amputation.

The study protocol was approved by the local ethics committee, and all participants gave written informed consent Every subject with ischemic stroke was matched for age ($\pm$3 years), sex, and cardiovascular risk factor prevalence with one control subject.

The type of acute ischemic stroke was classified according to the TOAST classification [24]: (1) Large Artery AtheroSclerosis (LAAS); (2) CardioEmbolic Infarct (CEI); (3) LACunar infarct (LAC); (4) stroke of Other Determined Etiology (ODE); (5) stroke of UnDetermined Etiology (UDE).

2.1.1. Large Artery AtheroSclerosis (LAAS)

These patients have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism.

2.1.2. CardioEmbolic Infarcts (CEI)

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism. At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. Stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

2.1.3. LACunar infarct (LAC)

The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated.

2.1.4. Stroke of Other Determined Etiology (ODE)

This category includes patients with rare causes of stroke, such as non-atherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies.

2.1.5. Stroke of UnDetermined Etiology (UDE)

In some cases, the cause of a stroke cannot be determined with any degree of confidence. Some patients have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory.

All the ischemic stroke patients underwent: medical history with recording of potential stroke risk factors, blood and coagulation tests, 12-lead ECG, 24 h electrocardiography monitoring, trans-thoracic echocardiography, carotid ultrasound, brain CT or MRI at admission (*repeated between the third and seventh days of stroke onset*).

Neurological deficit score on admission was evaluated by Scandinavian Stroke Scale (SSS). SSS assesses neurological deficit through an evaluation of consciousness level, eye movement, strength in arms, hands, and legs, orientation, language, facial weakness and gait, giving rise to a score ranging from 58 (*absence of deficit*) to 0 (*death*).

2.2. PWV measurement

Carotid-femoral PWV was measured in the supine position using the automatic device (SphygmoCor version 7.1) that measured the time delay between the rapid upstroke of the carotid and femoral artery pulse waves. The distance between the 2 arterial points was measured on the surface of the body using a tape measure. PWV