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Atherosclerotic intracranial internal carotid artery calcification and intravenous thrombolytic therapy for acute ischemic stroke

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ABSTRACT

Background and aims: Intracranial internal carotid artery calcification (IICAC) is a frequent and readily available finding in acute stroke patients treated with intravenous (IV) tissue plasminogen activator (tPA). We aimed to investigate the effects of IICAC subtype (medial and intimal) on the response to IV tPA.
Methods: In this retrospective study, 91 (57% female, age 69 ± 13 years) consecutive acute anterior circulation stroke patients treated with IV tPA were included. IICAC were diagnosed and classified according to Kockelkoren's methods.
Results: IV tPA was effective at 24 h in 48% of patients with no IICAC (n = 27), 60% of intimal IICAC (n = 50) and 43% of medial IICAC (n = 14) (p=0.408). Presence of medial IICAC tended to be linked negatively to early dramatic response to IV tPA (p=0.052). IICAC status had no significant effect on the third month good (mRS≤2; 48% in no IICAC, 36% in intimal IICAC and 29% in medial IICAC; p=0.189) and favorable outcome (mRS≤1; 56% in no IICAC, 48% in intimal IICAC, 43% in medial IICAC, p=0.411). Frequency of symptomatic post-tPA cerebral hemorrhage was marginally higher in patients with non-intimal IICAC (21% *vs.* 4% in no-IICAC, 4% in intimal-IICAC, p=0.052). Exploratory multivariate analysis documented that this effect was stable (p=0.004) after adjustment for age, admission NIHSS and door-to-needle time.
Conclusions: Medial type IICAC has been associated with numerical increase of symptomatic intracerebral hemorrhage and decrease of early dramatic response in stroke patients receiving IV tPA. Acknowledging that these preliminary observations should be replicated in larger cohorts, it is currently reasonable to say that "the treatment" is still useful in these patients and the presence of medial IICAC does not justify withholding IV tPA.

1. Introduction

Calcification in the intracranial segments, namely cavernous and siphon, of internal carotid artery [ICA] is a highly prevalent finding in non-contrast enhanced head computerized tomography [CT] scans in patients with acute ischemic stroke. Frequency of intracranial ICA calcification [IICAC] increases with atherosclerosis burden and its risk factors, and understandably differs significantly in etiological subtypes of stroke [1].

There is a recent interest on the interaction between presence of IICAC and results of acute stroke treatments. However, studies focusing on the modifying effect of various acute stroke treatments by the presence and load of IICAC disclosed highly conflicting results. For example, one study showed that the presence of severe IICAC corresponded to poorer functional outcome because of lower success rate in terms of post-procedural arterial recanalization after thrombectomy [2]. Another study replicated the connection with poorer outcome, but not with worse interventional success [3]. A third one failed to show any link between the presence/burden of IICAC and outcome/recanalization measures [4]. These notable differences can be attributed to the design of the studies, such as size and characteristics of the study population, and imaging parameters used. Another contributor may be the type of calcification, which was not distinguished in any of these studies.

IICAC has two subtypes: intimal and medial calcification. Their pathophysiology is highly different. Until recently, the two types of calcification could only be differentiated by post-mortem histopathology. However, Kockelkoren and his colleagues, in their very recent article [5], documented that this distinction could be

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attained with CT angiography. The discrimination score system they defined therein is quite convenient for incorporation into clinical settings. We used this scale to determine whether these two subtypes of IICAC modify the therapeutic efficacy of intravenous (IV) tissue-plasminogen activator (tPA) in patients with acute ischemic stroke of embolic origin.

2. Patients and methods

In this retrospective study, 91 (57% female, mean ± SD age 69 ± 13 years) consecutive acute anterior circulation stroke patients treated with IV tPA, from 2009 to 2017, were included. Clinical and imaging data were obtained from our prospectively gathered, local ethical committee approved, institutional database utilizing a predefined etiology and outcome detection protocol. Etiology search protocol included transthoracic echocardiography, angiography of cervicocerebral arteries, 24-h Holter's monitoring, and diffusion-weighted magnetic resonance (MR) imaging in all subjects. Patients with ICA occlusion, posterior circulation stroke, treated with thrombectomy or not studied with CT angiography, were not included into the current analyses.

Clinical stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) [6] at admission, at the end of the first day and at discharge. Functional outcome was assessed with modified Rankin's scale (mRS) at 90th day after stroke onset [7]. "Effective" response to IV PA was defined as a decrease in the score by ≥ 4 points and/or attaining a score of 0 or 1 at the end of the first 24 h after treatment. "Dramatic" response to IV tPA was described as a decrease of at least 8 points in NIHSS at the end of the first day. An mRS score of 0–2 was accepted as "good" outcome at the end of the third month after stroke, while mRS less than 2 was defined as "favorable" outcome. The Causative Classification of Stroke method was used to classify stroke etiology [8]. Fiorelli's type 2 intracerebral hemorrhages detected within 36 h after IV tPA administration were considered as significant hemorrhagic complications [9].

2.1. Imaging

CT angiography source images were used for the analyses. CT angiography was performed with a commercially 16-slice available multi-detector row scanner (SOMATOM Sensation 16, Erlangen, Germany). Details of the technique were previously described [10,11]. In brief, a single bolus injection (up to 130 cc of nonionic iodinated contrast medium into the antecubital vein at a rate of 3–5 cc/sec via automatic injector), with dynamic contrast bolus detection for timing of acquisition followed by helical scanning technique, was used. Parameters were 120 kV, aortic arc to vertex, 2-m slice thickness and 0.75 mm collimation.

The images were reviewed in all planes (axial, coronal and sagittal). Window level and width were adjusted to optimize the differentiation between calcification and luminal contrast media. IICAC were diagnosed and classified according to Kockelkoren's methods (summarized in Fig. 1) [5]. This method scores three characteristics of IICAC: the first is "circularity", which scores "1" in the presence of isolated calcific dots, "2" calcification line extending less than 90° the ICA wall, "3" from 90° to 270°, and "4" for greater than 270°. The second is "thickness" of calcification, which is scored as "1" when there is a thick calcification with a perpendicular

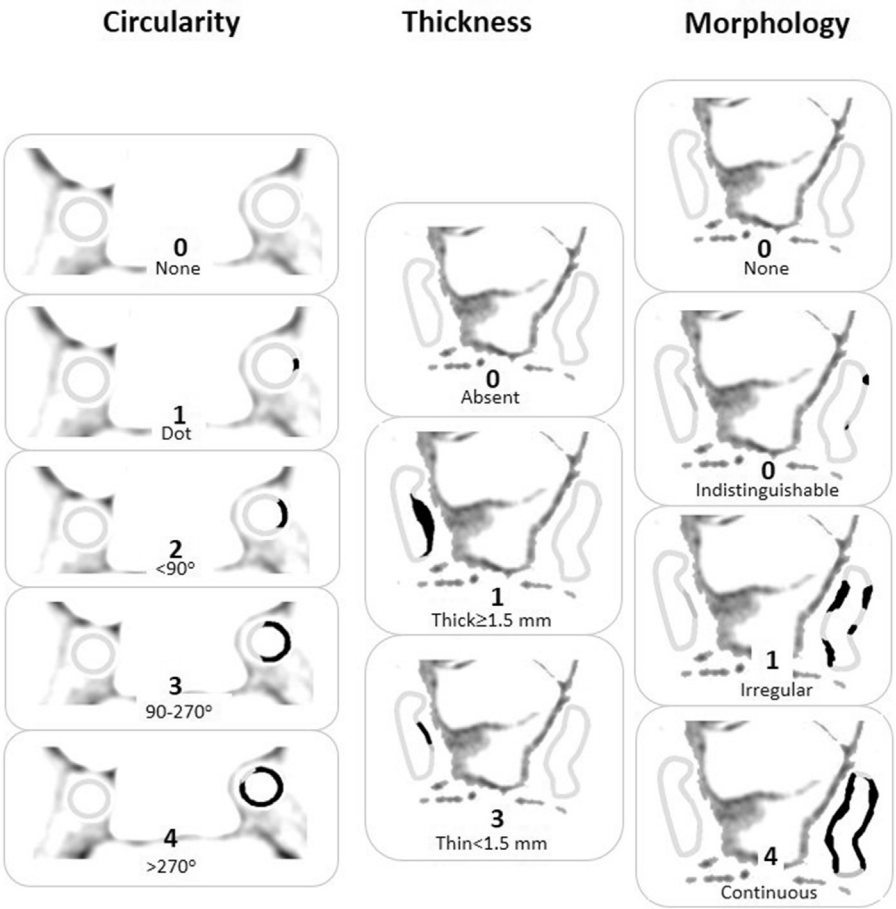

Fig. 1. Intracranial internal carotid artery calcification score: graphical summary of the criteria.