Where is the "clinical relevant" penumbra? A voxel-based analysis in acute stroke patients

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Background:

Middle Cerebral Artery (MCA) infarcts are a frequent type of ischemic stroke, and can be devastating especially when they are caused by proximal occlusion of the MCA trunk (M1 occlusion). In such case, the infarct volume increases gradually from the core of the ischemic focus into the ischemic "penumbra", a peripheral area that can be rescued by early arterial recanalization[1]. This mechanism explains the clinical efficiency of r-tPA thrombolytic treatment. The ischemic core is localized in the deep MCA arterial territory (i.e. basal ganglia and adjacent white matter tracts) and the ischemic penumbra is thought to be localized in the superficial MCA arterial territory[2] (i.e; the fronto-temporo-parietal cortico-subcortical areas of the lateral face of the cerebral hemisphere). This schema suggests that early recanalization improves prognosis by reducing infarct volume and extension into the superficial MCA territory. An alternative explanation is that the complexity of MCA arterial territory has been underestimated, and that areas of penumbra may occur in important white matter tracts such as the cortico-spinal pathway (CST) located within or close to the deep MCA territory. To test these hypotheses, we performed a SPM analysis of MRI studies obtained in 43 patients with initial M1 occlusion (< 6 hours post stroke onset-H6) and about 24 hours later (D1). The analysis was made on apparent Diffusion Coefficient (ADC) maps, which are quantitative biomarkers of ischemic injury directly derived from DWI sequences. We have focused on the localization of infarct growth between the initial and follow-up MRI. We also analyze the impact of MCA recanalization on the localization of final ADC-defined infarct areas and the relationship with key regions associated with poor outcome.

Material and Methods:

ADC maps were generated from DWI acquired at 1.5-T in acute stroke patients with MCA trunk occlusion examined within the first six hours of stroke onset (H6) and with a follow-up DWI at day one (D1). ADC maps were normalized into the MNI T2 template. MCA recanalization was assessed on follow-up MRA and rated as 0 for complete, 1 for partial recanalization, and 2 for persistent occlusion. Stroke outcome was assessed at three months by the modified Rankin Scale (mRS) and good outcome was defined by a mRS 0 to 2.

First, SPM analysis (SPM5 package) was performed to find regions associated with infarct growth between ADC maps of H6 and D1. Then, we compared at D1 the ADC maps of recanalized and non-recanalized patients to identify regions saved by MCA recanalization using ANCOVA with age as a confounding variable (height threshold $p<0.001$). Clusters were superimposed on a CST template for interpretation[3]. Finally, relationship between arterial recanalization and stroke outcome was explored by correlation analysis and SPM analysis to find key regions associated with poor outcome.

Results:

Forty-three patients (mean age: 62 years, mean baseline NIHSS: 16) had an initial DWI/ADC map before H6 (mean time to MRI: 2.6 hours) and a follow-up MRI at day one (mean time to follow-up MRI: 1.2 days).The D1 *vs.* H6 ADC maps comparison shows a significant reduction in ADC values in an area including part of the caudate nucleus, the corticospinal tract and the perisylvian regions (figure 1, T-score>4), suggesting that consistent infarct growth occurs in the insular region and in the deep MCA territoriy.. At D1, the comparison of recanalized and non recanalized patients shows that in the latter ADC-defined infarct consistently involved the internal capsule and the lenticular nucleus, overlapping with the CST template (Figure 2, T score>5).

Concerning stroke outcome, MCA recanalization was significantly correlated with the Rankin scale (ρ: 0.529, p:0.01) and regions associated with poor outcome with ADC voxel-based analysis had a high overlap with infarcted regions in non recanalized patients. (Figure 3).

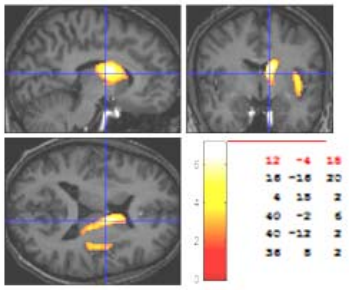

Figure 1.

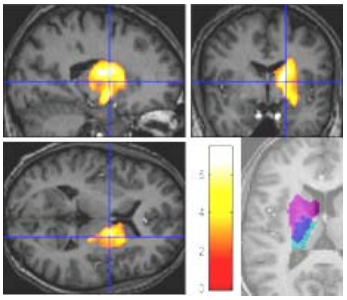

Figure 2.

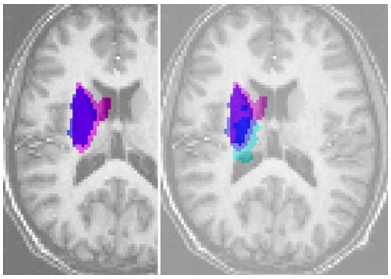

Figure 3.

Figure 1. Areas of decreased ADC value in the SPM comparison of the follow-up (D1) *versus* initial (H6) ADC maps superimposed of the T1-anatomical images. MNI coordinates (x, y, z) of the significant peaks are indicated.

Figure 2. Areas of decreased ADC value in the SPM comparison of the ADC maps (D1) of recanalized *vs.* non recanalized patients superimposed of the T1-anatomical images. Overlap of this region (pink) with the CST template (cyan).

Figure 3. Left: Overlap of the ADC decrease in the SPM comparison of recanalized *vs.* non recanalized patients (pink) and the good *vs.* poor outcome group (blue) at D1. Right: with the CST template (cyan).

Conclusion:

This study suggests that ischemic penumbra consistently persists during the therapeutic window in or close to the deep MCA territory especially in the CST, which appears to be "salvaged" by early arterial recanalization. Therefore, the clinically relevant penumbra may be located in the deep white matter tracts rather than in the superficial MCA territory. This finding may have important implications for neuroprotection research[4], which may needs to be refocused on deep white matter tracts rather than on cortical infarct volume reduction.

References

1- Rha et al, Stroke, 2007
2-Humpich et al, Cerebrovascular diseases, 2006
3- Bürgel et al, NeuroImage, 2006
4- Savitz et al, Annals of Neurology, 2007