

Identification of early onset strokes using multiparametric MRI as a witness

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Introduction: For approximately 25% of ischemic stroke patients, the onset of stroke symptoms is unwitnessed¹. Many of these patients are rapidly brought to the hospital within 3 h of symptom discovery, but current FDA guidelines, which use the time they were “last known well” (LKW) as the presumed stroke onset time, exclude them from consideration for intravenous (IV) thrombolysis. It is suspected, however, that many of these patients have a stroke duration of < 4.5 h and could receive alteplase under current AHA expanded time window guidelines² if onset time could be clearly established. It has long been posited that imaging can be used to inform on the age of a stroke lesion. We sought to investigate whether MRI-based parameters can be used to predict stage of ischemic injury.

Methods: Acute stroke patients imaged within 12h from LKW with diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and FLAIR were retrospectively analyzed. Analysis was limited to patients whose difference between when found with symptoms and LKW was ≤ 0.5 h. Patients exhibiting bilateral lesions or imaged post-thrombolysis were excluded. ADC maps were calculated from the slope of the linear regression fit of the log of the DWI (b-value=1000 s/mm²) and b-zero (b-value=0 s/mm²) images. The low b-value (b=0 s/mm²) and high b-value (b=1000 s/mm²) images were used as the T2-weighted image (T2WI) and isotropic DWI (iDWI) maps respectively. CBF, CBV and mean transit time (MTT) maps were calculated as previously described³. Tmax maps were measured as the peak time of the residue function⁴. All acute images were coregistered (MNI Autoreg)⁵. Relative signal intensities were calculated by normalizing each parametric map with its mirror image. Lesions were outlined on acute iDWI, superimposed on the normalized images and median value calculated. Patients were dichotomized as early (LKW \leq 4.5 h) or late. Differences in imaging parameters as a function of time were compared (two-sided Wilcoxon-rank sum test). Backward step-wise multivariate logistic regression was performed to investigate the relationship between imaging parameters and stroke duration (JMP, version 8).

Results: A total of 175 patients met our inclusion criteria. All results are provided as median [interquartile range] or mean \pm standard deviation. Age was 68 \pm 17 years old, admission NIH Stroke Scale (NIHSS) score was 6 [2–13], and 55% of the patients were male. Stroke subtypes were cardioembolic (46%), large vessel (21%), small vessel (6%) or undetermined (18%) or other determined cause (8%). Acute DWI and Tmax volumes were respectively 7.9 [1.8–29.1] cm³ and 27.7 [3.5–118] cm³. LKW was 4.8 \pm 2.3 h. There was 94 patients imaged early and 81 imaged late. There was no significant difference between NIHSS score, stroke subtype distribution, DWI or Tmax lesion volumes between patients seen early or late. In regions that were DWI abnormal, there was a significant difference in relative T2WI (P=0.04) and FLAIR (P=0.003) values between patients seen early and late. Relative ADC tended to be higher (P=0.10) while CBF lower (P=0.08) for patients imaged earlier. Multivariate logistic regression found relative T2WI (P=0.002), ADC (P<0.001), and CBV (P=0.02) to be 80% [71-88%] specific and 48% [37–59%] sensitive for identifying which patients have early LKW.

Discussion: Our results demonstrate that imaging can be used to identify patients that are relatively early with respect to stroke onset, and therefore potentially eligible for therapeutic intervention. Early hyperintensity changes on T2WI or FLAIR are likely indicative of vasogenic edema, which has been shown by several experimental studies to occur at subacute stages^{6,7}. A recent study of 120 patients has shown that patients seen within 3 h present with minimal abnormalities on FLAIR imaging⁸. Fink et al found ADC to be negatively correlated with stroke onset, similar to our findings⁹. Our multivariate logistic regression results show that early stage stroke patients tend to exhibit preserved CBV in combination with normal T2WI, and not too reduced ADC. This is consistent with earlier reports that showed only reduced CBV was specific for infarction, suggesting reduced CBV may be a death knell for tissue outcome. The significance of our findings suggests that imaging can be potentially used as a surrogate eyewitness when a human witness is not available to verify stroke duration. Cross-validation of our results with an independent data set needs to be performed.

References: 1. Barreto AD, et al. *Stroke*. 2009; 40, 827-32. 2. del Zoppo GJ, et al. *Stroke*. 2009; 40, 2945-8. 3. Østergaard L, et al. *Magn. Reson. Med*. 1996; 36, 715-25. 4. Wu O, et al. *Magn Reson Med*. 2003; 50, 164-74. 5. Collins DL, et al. *J. Comput. Assist. Tomogr*. 1994; 18, 192-205. 6. Knight RA, et al. *Stroke*. 1994; 25, 1252-61; discussion 61-2. 7. Matsumoto K, et al. *AJNR. Am. J. Neuroradiol*. 1995; 16, 1107-15. 8. Thomalla G, et al. *Ann. Neurol*. 2009; 65, 724-32. 9. Fink JN, et al. *Stroke*. 2002; 33, 988-93.