UKE Paper of the Month October 2011

Lancet Neurol. 2011 Nov;10(11):978-986. Epub 2011 Oct 4. (PMID:21978972)

DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study

Thomalla G, Cheng B, Ebinger M, Hao Q, Tourdias T, Wu O, Kim JS, Breuer L, Singer OC, Warach S, Christensen S, Treszl A, Forkert ND, Galinovic I, Rosenkranz M, Engelhorn T, Köhrmann M, Endres M, Kang DW, Dousset V, Sorensen AG, Liebeskind DS, Fiebach JB, Fiehler J, Gerloff C; for the STIR and VISTA Imaging Investigators

Abstract: *Background:* Many patients with stroke are precluded from thrombolysis treatment because the time from onset of their symptoms is unknown. We aimed to test whether a mismatch in visibility of an acute ischaemic lesion between diffusion-weighted MRI (DWI) and fluid-attenuated inversion recovery (FLAIR) MRI (DWI-FLAIR mismatch) can be used to detect patients within the recommended time window for thrombolysis. *Methods:* In this multicentre observational study, we analysed clinical and MRI data from patients presenting between Jan 1, 2001, and May 31, 2009, with acute stroke for whom DWI and FLAIR were done within 12 h of observed symptom onset. Two neurologists masked to clinical data judged the visibility of acute ischaemic lesions on DWI and FLAIR imaging, and DWI-FLAIR mismatch was diagnosed by consensus. We calculated predictive values of DWI-FLAIR mismatch for the identification of patients with symptom onset within 4.5 h and within 6 h and did multivariate regression analysis to identify potential confounding covariates. This study is registered with ClinicalTrials.gov, number NCT01021319. *Findings:* The final analysis included 543 patients. Mean age was 66·0 years (95% CI 64.7-67.3) and median National Institutes of Health Stroke Scale score was 8 (IQR 4-15). Acute ischaemic lesions were identified on DWI in 516 patients (95%) and on FLAIR in 271 patients (50%). Interobserver agreement for acute ischaemic lesion visibility on FLAIR imaging was moderate (κ=0.569, 95% CI 0.504-0.634). DWI-FLAIR mismatch identified patients within 4.5 h of symptom onset with 62% (95% CI 57-67) sensitivity, 78% (72-84) specificity, 83% (79-88) positive predictive value, and 54% (48-60) negative predictive value. Multivariate regression analysis identified a longer time to MRI (p<0·0001), a lower age (p=0.0009), and a larger DWI lesion volume (p=0.0226) as independent predictors of lesion visibility on FLAIR imaging. *Interpretation:* Patients with an acute ischaemic lesion detected with DWI but not with FLAIR imaging are likely to be within a time window for which thrombolysis is safe and effective. These findings lend support to the use of DWI-FLAIR mismatch for selection of patients in a future randomised trial of thrombolysis in patients with unknown time of symptom onset. *Funding:* Else Kröner-Fresenius-Stiftung, National Institutes of Health.

Statement: Our work opens up the perspective for effective treatment for a large group of stroke patients (i.e. patients waking up with stroke symptoms), which is currently excluded from treatment only due to the fact that the onset of stroke symptoms is unknown. This affects approximately 400.000 patients in the EU per year. The study overcomes the limitations of previous smaller single-centre studies in selected patient populations in an international multicentre study and thus provides conclusive evidence for the use of the tested imaging pattern (DWI-FLAIR mismatch) as an imaging surrogate marker of lesion age in acute stroke. By this, the study paves the way for the use of (DWI-FLAIR mismatch) as a criterion to enrol patients with wake-up stroke into a randomized controlled trial. This trial will be funded by the European Commission as FP7 collaborative project. It will be coordinated by Christian Gerloff and Götz Thomalla (Klinik und Poliklinik für Neurologie, UKE) which also were the Principal Investigators of the PRE-FLAIR study and first and last author of the paper submitted.

This work was coordinated by the interdisciplinary Clinical Stroke Imaging Group at the Departments of Neurology, Neuroradiology, and Computational Neurosciences at UKE headed by Götz Thomalla. His study group has a strong interest in the use of multiparametric MRI in acute stroke both to improve the understanding of the pathophysiology of acute cerebral ischemia and to guide acute stroke treatment in individual patients. The study reported in the paper was conducted as a joined effort of an international team of stroke MRI researchers (STIR and VISTA Imaging). It was funded by grants from the Else Kröner-Fresenius-Stiftung and the National Institutes of Health.