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Collateral circulation assessment within the 4.5 h time window in patients with and without DWI/FLAIR MRI mismatch

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ABSTRACT

Objectives: The aim of the present study was to assess the association between collateral status and DWI-FLAIR mismatch in patients with acute ischemic stroke within the 4.5 h time-window.
Methods: We analysed DWI, FLAIR, and PWI data in patients within 4.5 h after symptom onset from the I-KNOW European database. Collateral flow maps were graded by analyzing contrast 'staining' extent over the early, mid and late perfusion phases. ADC values, DWI lesion volume, and normalised perfusion parameters (CBV,Tmax) within DWI lesions were determined. Visibility of parenchymal hyperintensivty on FLAIR was evaluated ("FLAIR positive"), and DWI-FLAIR mismatch was assessed. Spontaneously reperfused regions were defined as voxels with Tmax < 6 s within the DWI lesion. Final infarct size was assessed on day-30 FLAIR images.
Results: Of the 168 patients included in I-KNOW database, 87 were eligible for this study. DWI-FLAIR mismatch was present in 69 patients. There was no difference between poor and good collaterals status according to age, sex, baseline NIHSS score, time to MRI and DWI lesion volume. Collateral status was significantly better in the FLAIR positive group ($p = .001$). Patients with poor collaterals had significantly increased Tmax ($p = .005$). Baseline DWI lesion volume and final lesion volume were significantly smaller in patients with good collateral status ($p < .001$ and 0.01, respectively).
Conclusions: We found that patients with early FLAIR lesion visibility have a better collateral status. This finding has implications for the management of stroke patients with unknown time-of-onset, and more widely should be considered in the current context of extending the therapeutic window.

In patients with unknown time of stroke onset, DWI-FLAIR mismatch may identify patients within the 4.5hr time window with high specificity and positive predictive value (PPV) [1–4]. The analysis of baseline data from WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke trial) showed that almost half of the patients with unknown time of stroke onset had DWI-FLAIR mismatch, making them likely eligible to thrombolysis. Few studies have documented the collateral status in DWI-FLAIR mismatch patients. Collateral supply plays an important role in the rate of infarct growth and response to reperfusion therapy [5–7]. Interestingly, it has been reported that the development of a FLAIR lesion is less dependent on time from symptom onset in patients with good collaterals as compared with

Abbreviations: ADC, apparent diffusion coefficient; AUC, area under curve; CBV, cerebral blood volume; CBF, cerebral blood flow; CI, confidence interval; DWI, diffusion weighted imaging; FLAIR, fluid attenuated recovery; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MTT, mean transit time; NIHSS, national institutes of health stroke scale; OR, odds ratio; PWI, perfusion weighted imaging; rt-PA, recombinant tissue plasminogen activator; TICI, thrombolysis in cerebral infarction; Tmax, time to maximum; VOI, volume of interest

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those with poor collaterals [8]. If true, this would imply that collateral status should be taken into account when assessing FLAIR positivity in patients with unknown time of onset. Dynamic susceptibility contrast (DSC) has emerged as a relevant method to assess collateral supply in acute ischemic stroke [9–11]. The present study aimed to assess the relationship between collateral status and FLAIR visibility in patients with or without DWI-FLAIR recruited within the 4.5hr time window from the I-KNOW European database.

1. Methods

1.1. Patients

We analysed patients from the I-KNOW multicentre prospective study, whose aim was to include patients with anterior circulation stroke who underwent both admission and follow-up MRI, to derive voxel-wise probabilistic maps of infarct prediction. Inclusion criteria were: (1) NIHSS score ≥ 4; (2) diffusion-weighted (DWI) and perfusion-weighted imaging (PWI) consistent with an acute anterior circulation ischaemic stroke; (3) admission MRI completed within 6 h or up to 12 h if, respectively, intravenous rt-PA or conservative treatment was suggested. Patients with lacunar or posterior circulation stroke, unknown time of onset, or intracerebral haemorrhage on MRI were excluded. Regional ethics committee approved the protocol and informed consent was obtained from all patients.

For the present study, patients who underwent admission MRI beyond 4.5 h after symptom onset were also excluded.

1.2. Acute MR imaging

At admission, all patients underwent DWI (3 or 12 directions; repetition time > 6000 ms, field of view 24 cm, matrix 128 × 128, slice thickness of 3 or 5 mm), FLAIR (repetition time 8690 ms; echo time 109 ms; inversion time 2500 ms; flip angle 150°; field of view 21 cm; matrix 224 × 256; 24 sections; section thickness of 5 mm; slice gap of 1 mm), T2-weighted gradient echo (repetition time 800 ms; echo time 28 ms; flip angle 20°; field of view 230 mm; matrix 512 × 512; 22 sections; section thickness of 5 mm), time of flight magnetic resonance angiography (MRA) and PWI (echo time 30–50 ms, repetition time 1500 ms, field of view 24 cm, matrix 128 × 128, 18 slices, thickness of 5 mm with gap = 1 mm; gadolinium contrast of 0.1 mmol/kg, intravenous injection of 5 ml/s followed by 30 ml saline). Final infarct size was evaluated at day 30 using FLAIR imaging.

1.3. MRI qualitative analysis

Blinded to clinical information, two raters analysed independently anonymised DWI and FLAIR sequences pairs that were randomly presented on a dedicated workstation. They were allowed to modify window and level for optimal contrast. Then, the two reading grids were compared and a consensus session was carried in case of disagreement. FLAIR images were analysed with knowledge of the DWI findings: “FLAIR-negative” was defined as no FLAIR hyperintensity or subtle FLAIR hyperintensity on the DWI lesion (Fig. 1A) and “FLAIR-positive” as obvious hyperintensity (Fig. 1B) [3,12]. Arterial FLAIR hyperintensities were disregarded. The level of occlusion was assessed in each case on baseline MRA data.

1.4. MRI quantitative analysis

After motion correction, maps of the time-to-maximum of the residue function (Tmax) were computed by circular singular value decomposition of the tissue concentration curves with an automatic selection of arterial input function based on brain tissue clustering using Olea Sphere® (Olea Medical, La Ciotat, France). ADC mean value, cerebral blood volume (CBV) and Tmax were measured within the DWI lesion masks. The relation between baseline DWI volume and Flair positivity was also assessed. The final infarct was measured on FLAIR sequences obtained on the day-30 MRI and the difference between baseline DWI ischemic core and final lesion volume taken to reflect lesion growth. Spontaneously reperfused voxels within the DWI lesion were defined as voxels with Tmax < 6 s. The relative volume of reperfused DWI lesion at H0 was defined as the ratio between the volume of DWI lesion and voxels with Tmax < 6 s.

1.5. Generation and grading of MR-based collateral flow maps

Collateral maps were automatically generated from the raw DSC-PI according to the methodology previously described of Kim et al. [9,11]. Inter-frame rigid registration was performed to correct for patient motion, and non-brain tissue was removed from each time frame (FSL v5.0, FMRIB, Oxford, UK). As in DSA, to enhance the visualization of the contrast agent, the first frame was used to subtract the anatomical structures from all consecutive frames. Next, each time-frame was collapsed into a single summated signal intensity value for the whole brain. To partition the DSC-PI into physiologically driven phases, the summated signal intensity was plotted against time and a set of six consecutive frames with the lowest signal intensity was identified. As in Kim et al. [9], we assumed that these frames corresponded to the mid phase of the collateral flow map. This phase was used as reference to generate the rest of the collateral flow maps by summing up the adjacent images. Thus, the DSC-PI was divided into an early, mid, and late phase by summing an increasing number of frames (four, six, and eight, respectively). A dichotomized classification was used: grades 0 to 2 were considered as poor collaterals, and grades 3 and 4 as good collaterals. Representative collateral flow maps for each collateral grade are summarized in Fig. 2.

1.6. Statistical analysis

Interrater agreement (percentage) and reliability analysis (Kappa statistic) of FLAIR findings were performed to determine consistency between two evaluators. Continuous variables were described using median and interquartile range; categorical variables were described with number and percentage. Clinical and imaging variables were matched to collateral status dichotomized as good versus poor. Parametric tests, chi-square test for categorical variables and t student test were used for continuous variables. Variables with p values < 5% were considered as statistically significant. Analyses were performed with SPSS software.

2. Results

Of the 168 patients included in I-KNOW, 87 were eligible for this study. Thirty-five (41.4%) were female, median age was 71 yrs. (interquartile range [IQR], 62–78 years). Causes for exclusion were time from symptom onset to MRI > 4.5 h in 28 patients, and other reasons in 53 patients (listed in the flowchart in Fig. 3). Interobserver agreement for FLAIR assessment was 73.2% with Kappa = 0.602 (p < .001), 95% confidence interval (0.548–0.659). The kappa value for inter-rater agreement in grading MRI-based collateral maps was 0.85 (95% CI: 0.79–0.92). Clinical and imaging data according to collateral status are described in Table 1.

There was no difference between groups regarding age, sex, NIHSS and onset-time to MRI. Baseline DWI lesion volume were not significnatly different (p-value 0,41) between FLAIR negative (10.1 ml) and FLAIR positive group (11.1 ml). Baseline DWI lesion volume and final infarct volume were significantly smaller in patients with good collaterals (p-value < .001 and 0.01, respectively). On follow-up MRI there was no difference between-groups regarding lesion growth. Collateral status was significantly better in the FLAIR positive group (p-value 0.02). Patients with poor collaterals had a significantly higher