Clinical characteristics of unknown symptom onset stroke patients with and without DWI-FLAIR mismatch

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Clinical characteristics of DWI-FLAIR-mismatch

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Abstract

Background – DWI-FLAIR mismatch was suggested to identify stroke patients with unknown time of symptom onset likely to be within the time window for thrombolysis.

Aims – We aimed to study clinical characteristics associated with DWI-FLAIR mismatch in patients with unknown onset stroke.

Methods – We analysed baseline MRI and clinical data from patients with acute ischemic stroke proven by DWI from WAKE-UP, an investigator-initiated, randomised, placebo-controlled trial of MRI based thrombolysis in stroke patients with unknown time of symptom onset. Clinical characteristics were compared between patients with and without DWI-FLAIR mismatch.

Results – Of 699 patients included, 418 (59.8%) presented with DWI-FLAIR mismatch. A shorter delay between last seen well and symptom recognition (p=0.0063), a shorter delay between symptom recognition and arrival at hospital (p=0.0025), history of atrial fibrillation (p=0.19) were predictors of DWI-FLAIR mismatch in multivariate analysis.

All other characteristics were comparable between groups.

Conclusions – There are only minor differences in measured clinical characteristics between unknown symptom onset stroke patients with and without DWI-FLAIR mismatch. DWI-FLAIR mismatch as an indicator of stroke onset within 4.5 hours shows no relevant association with commonly collected clinical characteristics of stroke patients.

Clinical Trial Registration – URL: http://www.clinicaltrials.gov. Unique identifier: NCT01525290; URL: https://www.clinicaltrialsregister.eu. Unique identifier: 2011-005906-32.

INTRODUCTION

Information on the time of symptom onset plays a critical role in acute stroke treatment. Intravenous thrombolysis is approved for treatment within 4.5 hours of symptom onset, and for mechanical thrombectomy unequivocal evidence is also only available for treatment within the first six hours (1). In about 20% of acute stroke patients however, information on time of symptom onset is not available, e.g. because of patients waking up with stroke symptoms (2).

Stroke MRI with diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) imaging has been suggested as biomarker of ischemic lesion age (3). The DWI-FLAIR mismatch, i.e. an acute ischemic lesion visible on DWI without corresponding parenchymal hyperintensity on FLAIR, was demonstrated to have a high positive predictive value in identifying patients within 4.5 hours of symptom onset in a multicentre study (4) as well as in several single centre studies from different groups (5-7). Case series using DWI-FLAIR mismatch to guide intravenous thrombolysis or mechanical thrombectomy in unknown unset stroke patients have previously been published (8, 9).

Using DWI-FLAIR mismatch as surrogate marker of lesion age relies on the assumption that time from symptom onset is the only relevant clinical factor influencing parenchymal hyperintensity on FLAIR and thus the presence or absence of DWI-FLAIR mismatch There is, however, hardly any data on potential clinical confounders of DWI-FLAIR mismatch in patients with unknown time of symptom onset. Thus, we aimed to identify possible clinical factors of influence on DWI-FLAIR mismatch by comparing clinical characteristics between patients with and without DWI-FLAIR mismatch in a large sample of patients with stroke of unknown onset.

METHODS

Study population

We analysed baseline data from the ongoing WAKE-UP trial (Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomised, double-blind, placebo-controlled trial; Clinicaltrials.gov identifier NCT01525290; EudraCT No.: 2011-005906-32) (10). In WAKE-UP MRI including DWI and FLAIR is used for screening stroke patients with unknown time of symptom onset, and patients presenting with DWI-FLAIR mismatch are randomized to treatment with intravenous thrombolysis or placebo. For this analysis we included baseline data of patients enrolled since the start of the trial on 22 September 2011 until 01 April 2016 meeting the following criteria: (1) information on symptom recognition and demographic characteristics available; (2) acute ischemic lesion visible on DWI indicating acute cerebral ischemia; (3) judgement of DWI-FLAIR mismatch available; (4) no signs of intracerebral haemorrhage on MRI.

DWI-FLAIR mismatch judgment

DWI-FLAIR mismatch was judged by trial investigators according to image analysis standards outlined in the trial protocol and in additional training material. DWI-FLAIR mismatch is defined as the absence of a marked parenchymal hyperintensity in FLAIR in the region of a clearly visible acute DWI lesion, while subtle FLAIR hyperintensities are disregarded (10). Imaging handbooks provide detailed documentation of the imaging critiera and numerous example cases of the application of the imaging criteria in the trial (see *figure* for examples). All investigators judging brain images in WAKE-UP have completed a software-based image analysis training and passed a certification exam.

Data analysis

In order to identify clinical characteristics associated with the presence of DWI-FLAIR mismatch, univariate analysis was performed comparing patients with and without DWI-FLAIR mismatch regarding the following clinical characteristics: age, sex, time between last seen normal and symptom recognition, delay between symptom recognition and hospital

arrival, reason for unknown time of symptom onset, neurological deficit on admission assessed by the National Institutes of Health Stroke Scale (NIHSS), medical history and vascular risk factors, current medication, presence of clinical exclusion criteria for thrombolysis. Fisher's exact test or the Chi-square test was used for categorical variables, and non-parametric Kruskal-Wallis test was used for continuous variables. $P<0.05$ was considered significant in exploratory analysis without correction for multiple tests. Additionally, we performed a multivariate analysis using logistic regression model to predict the odd of DWI-FLAIR mismatch including all covariates with a p-value ≤0.15 in univariate analysis. Finally, only parameters with $p<0.05$ were retained. SAS software, version 9·3 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Overall, 699 patients met the inclusion criteria. Of those 418 (59.8%) presented with DWI-FLAIR mismatch and 281 (40.2%) hat no DWI-FLAIR mismatch. Results of group comparison are shown in the table. Patients with DWI-FLAIR mismatch had a shorter delay between last seen well and symptom recognition (median 7.5 vs. 8.0 h, p=0.0030). A history of atrial fibrillation was more frequent in patients with a DWI-FLAIR (10.6% vs. 4.9%, p=0.0098). In multivariate analysis, both shorter delay between last seen well and symptom recognition with odds ratio (OR) 0.94 (95% confidence interval 0.91-0.98) and history of AF with OR 2.36 (1.11-5.02) were retained as significant predictors of DWI-FLAIR mismatch (see table). In addition, delay between symptom recognition and hospital arrival remained a significant predictor with OR 0.74 (0.62-0.90). All other characteristics were comparable between groups.

DISCUSSION

In this sample of acute stroke patients with unknown time of symptom onset, patients with DWI-FLAIR mismatch indicating symptom onset within 4.5 hours were comparable to

patients with no DWI-FLAIR mismatch with regards to the vast majority of clinical characteristics. There were no differences in age or severity of neurological symptoms reflected by the NIHSS score. There were also no differences concerning the majority of vascular risk factors, current medication, or the reason why symptom onset was not known. Two parameters differed between groups: the delay between last seen well and symptom recognition was shorter, and history of atrial fibrillation was more frequent in patients with DWI-FLAIR mismatch.

This is the first analysis of clinical characteristics in a larger group of stroke patients with unknown time of symptom onset assumed to qualify for reperfusion treatment based on DWI-FLAIR mismatch, and the results confirm the assumption that DWI-FLAIR mismatch as surrogate marker of lesion age is not strongly influenced by clinical characteristics of patients. This is in line with previous studies of DWI-FLAIR mismatch in patients with known symptom onset. In a large multicentre study, patients with DWI-FLAIR mismatch were mismatch were older but otherwise comparable to patients without a DWI-FLAIR mismatch(4). This, however, was discussed as a potential confounding effect of leukoaraiosis being more frequent with higher age and interacting with the visibility of acute ischemic lesions on FLAIR in the elderly. In WAKE-UP, severe leukoaraiosis interacting with the judgement of DWI-FLAIR mismatch is considered an exclusion criterion, which may obscure the indirect effect of age observed previously.

With regards to the observed differences between the groups, findings have to be interpreted with caution as they only apply to patients eligible for this analysis which excluded patients with poor quality of MRI or severe leukoaraiosis precluding proper judgement of DWI.FLAIR mismatch.. However, the association of DWI-FLAIR mismatch with shorter delays between last seen well and symptom recognition and between symptom recognition and hospital arrival appears biologically plausible considering the visibility of acute ischemic lesions on FLAIR as a function of time. In all previous studies of DWI-FLAIR mismatch instroke patients with known onset, shorter time from symptom onset was the strongest predictor of DWI-FLAIR mismatch (3-7). Although we do not know the time of stroke onset in our patients, it

may be reasonable to assume that a longer delay between last seen normal and symptom recognition may to a certain extent correlate with a longer delay between stroke onset and symptom recognition.

The higher rate of atrial fibrillation in patients with DWI-FLAIR mismatch is less easily explained and may simply be due to chance. On the other hand, a circadian variation of atrial fibrillation with peak incidence in the morning hours (11) is known, and there are observations of a higher frequency of atrial fibrillation in wake-up stroke (12, 13). This might provide an explanation for a higher frequency of atrial fibrillation in those patients from our sample with stroke onset in the morning hours shortly before symptom recognition and thus more likely to show DWI-FLAIR mismatch. On the other hand, rates of atrial fibrillation were comparable between patients with wake-up stroke and those with unwitnessed daytime-onset stroke (8.5% vs. 7.0%, p=0.16 Fisher's exact test).

Previous case series have reported on the rates of DWI-FLAIR mismatch in smaller samples with stroke of unclear onset as compared to patients with stroke of known onset, but they did not report on clinical characteristics of patients with DWI-FLAIR mismatch as compared to those without (14, 15). The proportion of patients with DWI-FLAIR mismatch in our population was slightly higher than in these two previous studies (59.8% as compared to 43.7% and 50.0%), which may result from the fact that in within the context of WAKE-UP being a thrombolysis trial MRI may have been performed more rapidly, and that patients being clearly beyond the time window for thrombolysis, e.g. because of admission to hospital >4.5 hours of symptom recognition, were a priori excluded. The decreasing rate of DWI-FLAIR mismatch with time passing appears to parallel decreasing proportions of patients with penumbral pattern with time from stroke onset (16). Although by concept DWI-FLAIR mismatch and penumbral imaging, e.g. perfusion-diffusion mismatch, address a different pathophysiological phenomenon, i.e. lesion age on the one hand and metabolic tissue status on the other hand, both imaging parameters appear to show a certain association independent from time fo stroke onset (17, 18). Future analyses of the subgroup of patients with perfusion MRI available in the WAKE-UP trial may further improve the understanding of

this association.To conclude, the MRI pattern of DWI-FLAIR mismatch was not associated with different clinical characteristics except for a longer delay and more frequent atrial fibrillation in the first 699 patients from our trial of intravenous thrombolysis in stroke with unknown symptom onset. Thus, DWI-FLAIR mismatch as indicator of stroke onset of less than 4.5 hours does not seem to be confounded by clinical characteristics of stroke patients beyond time from symptom onset and appears well suited as a surrogate marker of lesion age in patients with unknown time of symptom onset. The question of efficacy and safety of intravenous thrombolysis in unknown symptom onset stroke patients with DWI-FLAIR mismatch will be answered in the final analysis of the WAKE-UP trial.

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AUTHOR CONTRIBUTIONS:

Götz Thomalla – study concept and design, acquisition of data, analysis and interpretation of data, study supervision, drafting/revising the manuscript for content

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Pascal Roy – analysis and interpretation of data, study supervision

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CONFLICTS OF INTEREST

Götz Thomalla received fees as a consultant or lecture fees from Acandis, Bayer Vital, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daichii Sankyo, GlaxoSmithKline, and Stryker.

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REFERENCES

1. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke* 2016;11(1):134-47.
2. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and treatment option - an update. *Front Neurol* 2014;5:35.
3. Thomalla G, Rossbach P, Rosenkranz M, et al. Negative fluid-attenuated inversion recovery imaging identifies acute ischemic stroke at 3 hours or less. *Ann Neurol* 2009;65(6):724-32.
4. Thomalla G, Cheng B, Ebinger M, et al. 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. *Lancet Neurol* 2011;10(11):978-86.
5. Aoki J, Kimura K, Iguchi Y, Shibazaki K, Sakai K, Iwanaga T. FLAIR can estimate the onset time in acute ischemic stroke patients. *J Neurol Sci* 2010;293(1-2):39-44.
6. Petkova M, Rodrigo S, Lamy C, et al. MR imaging helps predict time from symptom onset in patients with acute stroke: implications for patients with unknown onset time. *Radiology* 2010;257(3):782-92.
7. Ebinger M, Galinovic I, Rozanski M, Brunecker P, Endres M, Fiebach JB. Fluid-attenuated inversion recovery evolution within 12 hours from stroke onset: a reliable tissue clock? *Stroke* 2010;41(2):250-5.
8. Aoki J, Kimura K, Iguchi Y, et al. Intravenous thrombolysis based on diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch in acute stroke patients with unknown onset time. *Cerebrovasc Dis* 2011;31(5):435-41.
9. Wei XE, Zhou J, Li WB, Zhao YW, Li MH, Li YH. MRI based thrombolysis for FLAIR-negative stroke patients within 4.5-6h after symptom onset. *J Neurol Sci* 2016.
10. Thomalla G, Fiebach JB, Ostergaard L, et al. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). *Int J Stroke* 2014;9(6):829-36.
11. Viskin S, Golovner M, Malov N, et al. Circadian variation of symptomatic paroxysmal atrial fibrillation. Data from almost 10 000 episodes. *Eur Heart J* 1999;20(19):1429-34.
12. Kim YJ, Kim BJ, Kwon SU, Kim JS, Kang DW. Unclear-onset stroke: Daytime-unwitnessed stroke vs. wake-up stroke. *Int J Stroke* 2016;11(2):212-20.
13. Riccio PM, Klein FR, Pagani Cassara F, et al. Newly diagnosed atrial fibrillation linked to wake-up stroke and TIA: hypothetical implications. *Neurology* 2013;80(20):1834-40.
14. Huisa BN, Liebeskind DS, Raman R, et al. Diffusion-weighted imaging-fluid attenuated inversion recovery mismatch in nocturnal stroke patients with unknown time of onset. *J Stroke Cerebrovasc Dis* 2013;22(7):972-7.
15. Kim BJ, Kim HJ, Lee DH, et al. Diffusion-weighted image and fluid-attenuated inversion recovery image mismatch: unclear-onset versus clear-onset stroke. *Stroke* 2014;45(2):450-5.
16. Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. *Lancet Neurol* 2009;8(3):261-9.
17. Wouters A, Dupont P, Norrving B, et al. Prediction of Stroke Onset Is Improved by Relative Fluid-Attenuated Inversion Recovery and Perfusion Imaging Compared to

the Visual Diffusion-Weighted Imaging/Fluid-Attenuated Inversion Recovery Mismatch. *Stroke* 2016;47(10):2559-64.

18. Wouters A, Dupont P, Ringelstein EB, et al. Association between the perfusion/diffusion and diffusion/FLAIR mismatch: data from the AXIS2 trial. *J Cereb Blood Flow Metab* 2015;35(10):1681-6.

TABLE

Table: Group comparison of clinical characteristics

	DWI-FLAIR-mismatch (n=418)	**No DWI-FLAIR-mismatch (n=281)**	**Group comparison *p*-value**	**Multivariate analysis *p*-value ‡**
Age [years], median (IQR)	68 (59-74)	67 (58-74)	0.39	-
Sex = female, n (%)	147 (35.2)	117 (41.6)	0.095	0.12
Reason for unknown time of symptom onset Nigh-sleep wake-up stroke Daytime unwitnessed stroke	 368 (88.0) 50 (12.0)	 240 (85.4) 41 (14.6)	0.15	0.93
Delay between last seen well and symptom recognition [h], median (IQR)	7.5 (5.0-9.0)	8.0 (6.0-10.0)	0.0030	0.0063
Delay between symptom recognition and hospital arrival [h], median (IQR)	1.6 (1.1-2.3)	1.8 (1.1-2.6)	0.11	0.0025
Medical history / risk factors * Arterial hypertension, n (%) Diabetes mellitus, n (%) Hypercholesterolemia, n (%) Atrial fibrillation, n (%) Ischemic stroke, n (%) Transient ischemic attack, n (%) Intracranial haemorrhage, n (%) Gastrointestinal bleeding, n (%)	 200/415 (48.2) 62/410 (15.1) 120/391 (30.7) 43/406 (10.6) 59/415 (14.2) 15/409 (3.7) 0 6/413 (1.5)	 134/266 (50.4) 45/269 (16.7) 68/259 (26.3) 13/266 (4.9) 26/270 (9.6) 11/269 (4.1) 0 5/270 (1.9)	 0.58 0.59 0.25 0.0098 0.077 0.84 - 0.76	 - - - 0.019 0.47 - - -
Smoking Never smoked, n (%) Ex-smoker, n (%) Current smoker, n (%)	 176/401 (43.9) 108/401 (26.9) 117/401 (29.2)	 98/245 (40.0) 60/245 (24.5) 87/245 (35.5)	0.25	-
Current medication * Antiplatelets, n (%) Anticoagulants, n (%) Antihypertensives, n (%) Antidiabetics, n (%) Statins, n (%)	 142/414 (34.1) 4/415 (1.0) 199/416 (47.8) 54/416 (13.0) 124/415 (30.0)	 72/264 (27.3) 2/264 (0.8) 141/264 (53.4) 40/462 (15.2) 76/264 (28.8)	 0.063 1.00 0.18 0.43 0.80	 0.26 - - - -
NIHSS on admission, median (IQR)	6 (4-11)	6 (4-12)	0.68	-
Clinical exclusion criteria for IV-tPA treatment present, n (%)	8 (1.9)	10 (3.6)	0.22	-

* Percentage calculated with reference to number of patients with information available;

† intracerebral haemorrhage, subarachnoid haemorrhage, intraventricular haemorrhage, hemorrhagic transformation;

‡ parameters with p≤0.15 in univariate analysis were entered into multivariate logistic regression model

IQR = interquartile range; NIHSS = National Institutes of Stroke Scale;

FIGURE

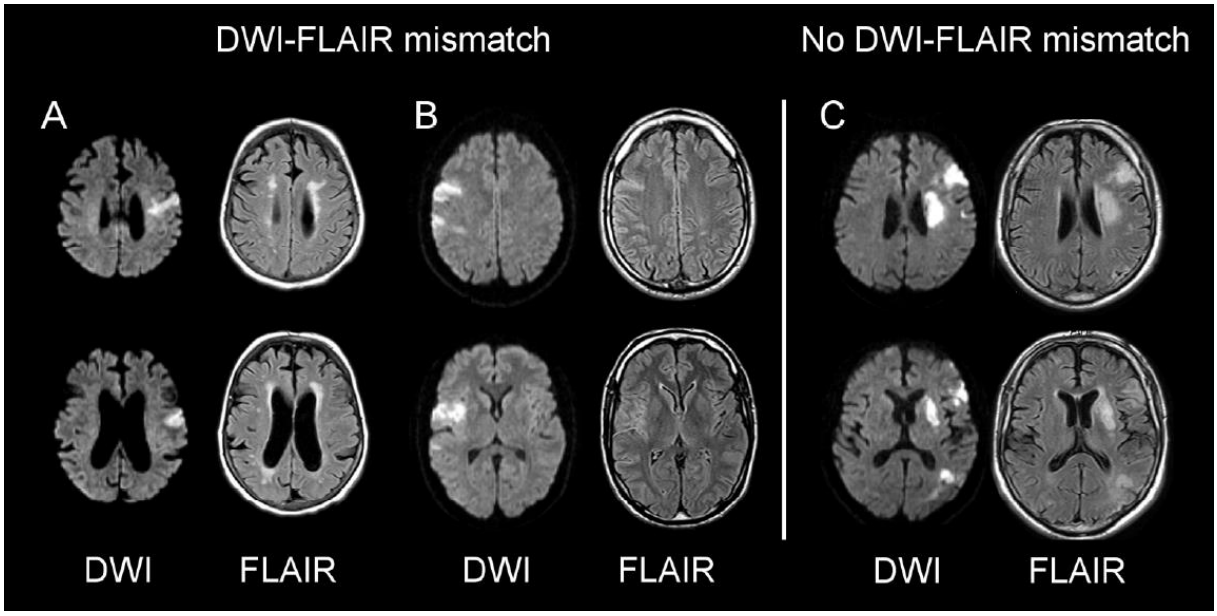

FIGURE LEGEND

Examples of DWI-FLAIR mismatch and No DWI-FLAIR mismatch.

The figure shows three cases from the study sample. For each case, two representative slices of diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) are shown. (A) DWI-FLAIR mismatch – no parenchymal hyperintensity visible on FLAIR in the region of the acute DWI lesion, patient was randomized; (B) DWI-FLAIR mismatch – subtle parenchymal hyperintensity visible on FLAIR in the region of the acute DWI lesion considered as “negative” FLAIR according to the image judgement criteria in WAKE-UP, thus imaging criteria of DWI-FLAIR mismatch are met, patient was randomized; (C) No DWI-FLAIR mismatch – clear parenchymal hyperintensity visible on FLAIR in the regions of acute DWI lesion, patient was not randomized.