Acta Neurologica Scandinavica

Acta Neurol Scand 2014: 130: 338–345 DOI: 10.1111/ane.12272

ACTA NEUROLOGICA SCANDINAVICA

Predicting intracerebral hemorrhage by baseline magnetic resonance imaging in stroke patients undergoing systemic thrombolysis

Hobohm C, Fritzsch D, Budig S, Classen J, Hoffmann K-T, Michalski D. Predicting intracerebral hemorrhage by baseline MRI in stroke patients undergoing systemic thrombolysis.
Acta Neurol Scand 2014: 130: 338–345.

Objectives – Intracerebral hemorrhage (ICH) remains a serious complication in ischemic stroke patients undergoing systemic thrombolysis. Here, we examined whether the risk of treatment-associated hemorrhage can be predicted from magnetic resonance imaging (MRI) using fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) within 3 h after symptom onset. *Methods* – In this single-center observational study involving 122 ischemic stroke patients between January 2005 and December 2008, the incidence of FLAIR-positive lesions within diffusion-restricted areas was determined on baseline MRI, which was carried out prior to treatment with tissue plasminogen activator (Actilyse®) within 3 h from symptom onset. The rate of ICH was assessed by computed tomography performed within 24 h after treatment. Relationships between FLAIR-positive lesions, DWI lesion size, proportion of FLAIR/DWI-positive lesions, and occurrence of bleeding were explored. *Results* – Data from 97 patients were evaluated. FLAIR-positive lesions were present in 25 patients (25.8%) and ICH occurred in 32 patients (33.0%). FLAIR-positive lesions were associated with a bleeding rate of 80.0% compared with 16.7% in FLAIR-negative patients ($P < 0.001$; odds ratio 20.0, positive predictive value 0.8). DWI lesion size was significantly correlated with the rate of ICH ($P = 0.001$). In contrast, FLAIR/DWI proportion was not associated with ICH ($P = 0.788$). *Conclusions* – In ischemic stroke patients within 3 h from symptom onset, the existence of FLAIR-positive lesions on pretreatment MRI is significantly associated with an increased bleeding risk due to systemic thrombolysis. Therefore, considering FLAIR-positive lesions on baseline MRI might guide treatment decisions in ischemic stroke.

C. Hobohm[1], D. Fritzsch[2], S. Budig[1], J. Classen[1], K.-T. Hoffmann[2], D. Michalski[1]

[1]Department of Neurology, University of Leipzig, Leipzig, Germany; [2]Department of Neuroradiology, University of Leipzig, Leipzig, Germany

Key words: diffusion-weighted imaging; fluid-attenuated inversion recovery; intracerebral hemorrhage; ischemic stroke; magnetic resonance imaging; thrombolysis

C. Hobohm, Department of Neurology, University of Leipzig, Liebigstr. 20, 04103 Leipzig, Germany
Tel.: +49 3419724341
Fax: +49 3419724198
e-mail: carsten.hobohm@medizin.uni-leipzig.de

Accepted for publication May 20, 2014

Introduction

Systemic thrombolysis with tissue plasminogen activator (tPA) still represents the only approved treatment that has shown efficacy in randomized clinical trials (1, 2). In recent years, the usage of tPA has continuously increased (3), most probably related to the widening of the timeframe for

administration (4.5 h after symptom onset; 3), global information campaigns, increased availability of specialized treatment units (4), and increased confidence in drug safety. At the same time, magnetic resonance imaging (MRI) has increasingly been used for baseline imaging in stroke patients eligible to tPA, whereas requirements for licensed use of tPA require exclusion of hemorrhage typically by computed tomography (CT; 1, 2).

Previous studies indicated that MRI employing fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences may provide a useful tool for identifying recent symptom onset in patients in whom this important information cannot be determined clinically from history (5–11). Despite different techniques of visualization, MRI sequences had also been discussed to indicate structural brain damage after ischemia comparable with hypodensity on CT as an already established risk factor for secondary hemorrhage (1, 5, 11, 12). Consequently, a previous study had demonstrated that an increasing size of DWI lesions is associated with the risk of symptomatic intracerebral hemorrhage (ICH) after systemic or intra-arterial thrombolysis within 6 h after symptom onset (13). However, the usefulness of pretreatment FLAIR und DWI sequences captured within the very early hours as the striven time window for systemic thrombolysis remains to be further elucidated.

This study aimed to investigate the predictive impact of FLAIR- and DWI-positive lesions seen on baseline MRI in ischemic stroke patients undergoing systemic thrombolysis with tPA in a timeframe of 3 h after symptom onset. While focusing on ICH as probably most-serious complication of tPA treatment, relationships to both sole existence and size of detected lesions were explored.

Methods

Study setup and patients

We screened our internal database containing patients admitted to the stroke unit of the University of Leipzig between January 2005 and December 2008 for eligible candidates. Inclusion criteria were the following: (i) Sudden onset of a focal neurological deficit related to the anterior, middle or posterior cerebral artery territory (e.g., hemiparesis, aphasia or hemianopia); (ii) Systemic treatment with tPA (Actilyse®; Boehringer-Ingelheim, Ingelheim, Germany) in a total dose of 0.9 mg/kg body weight according to the guidelines of the European Stroke Organization (www.eso-stroke.org) and ECASS II study (1), initiated within 3 h after symptom onset; (iii) cerebral MRI containing at least DWI, FLAIR and T2* performed prior to tPA administration, including the presence of a DWI-positive lesion in the anterior, middle or posterior cerebral artery territory, and ruling out primary hemorrhage by the absence of T2*-positive lesions; and (iv) cerebral CT performed within 24 h after treatment initiation. Cranial CT was typically carried out on the following day after tPA administration.

From all patients included, the following characteristics were recorded: Sex, age, cardiovascular risk factors (arterial hypertension, diabetes, hyperlipoproteinemia and nicotine abuse), history of previous stroke, preexisting disability (modified Rankin scale, mRS), severity of stroke symptoms prior to tPA treatment as assessed by the National Institute of Health stroke scale (NIHSS) and time from symptom onset to tPA administration. Additionally, stroke etiology/subtype was classified according to the TOAST criteria (14).

This study was approved by the ethics committee of the University of Leipzig (reference number 149-13-03062013).

Study endpoints and assessment

Two neurologists examined – independently from each other and in a blinded manner – the pretreatment MR images for presence and size of FLAIR-positive lesions located within the area of restricted DWI also demonstrating lowered ADC values. Patients were consequently allocated into a FLAIR-positive and FLAIR-negative group. Further, control CTs were screened for bleeding complications, classified first in the existence or non-existence of any ICH and second according to the ECASS II criteria: Hemorrhagic infarction 1 (HI-1, small petechiae), hemorrhagic infarction 2 (HI-2, confluent petechiae), parenchymal hemorrhage (PH-1, blood clots up to 30% of infarcted area) and parenchymal hemorrhage (PH-2, blood clots in more than 30% of infarcted area; 1). In subsequent analyses, CT-based data were added by information on the clinical course within the first 24 h after hospital admission. Clinical deterioration of at least four points at the NIHSS according to the ECASS III trial (2) was considered indicative of symptomatic ICH. An independent neuroradiologist – also blinded to further patients' characteristics – reevaluated MRI or CT scans in cases of inconsistent ratings from the two neurologists.

Imaging protocols for baseline MRI and control CT

Magnetic resonance imaging was performed on a 1.5 Tesla scanner (Siemens Symphony; Siemens, Erlangen, Germany) using a standardized time-saving scanning protocol including FLAIR, DWI, T2* and perfusions-weighted imaging (PWI) in an axial plan, as well as time-of-flight MR-angiography (ToF-MRA) for intracranial and contrast-enhanced MRA for visualization of extracranial vessels (total time about 11 min). We used a 240 mm FOV with an acquisition matrix of 256 × 128 and a slice thickness of 5 mm. *B*-values of 0, 500 and 1000 s/mm² served for DWI including isotropic trace images and ADC images. As this study focused on FLAIR and DWI, data on PWI and vessel's condition were not considered.

The follow-up CT scan – primarily intended to address tPA-related hemorrhage – was performed as a 5 mm slice axial scan (kV: 120, mAs: 370, CTDIvol: 62, 76 mGy) without contrast medium on a 64-slice CT scanner (Brilliance 64; Philips, Amsterdam, The Netherlands).

Statistical analyses

All calculations were performed with the standard software package PASW Statistics (Version 18; SPSS Inc., Chicago, IL, USA). After obtaining descriptive values, statistical significance was verified either by the Mann–Whitney *U*-test in case of non-categorical variables, or the Pearson's chi-squared test as well as Fisher's exact test for categorical variables. Further, multiple regression analysis was utilized to identify potential confounder for the addressed MR imaging parameters. The inter-rater agreement for MR and CT imaging acquisition was evaluated by Cohen's κ. Generally, $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics and incidence of FLAIR-positive lesions

MR imaging was performed in 122 acute stroke patients, all treated with intravenously applied tPA within 3 h from symptom onset. Data from 25 patients had to be excluded because of poor quality of DWI and/or FLAIR sequences in baseline MRI (mostly motion artifacts), which prevented determination of existence or lesion size of affected brain tissue. Therefore, this study based on data from 97 patients (42 females, 55 men) with a mean age of 70.7 (±11.7) years, a medium baseline NIHSS of 13.2 (±7.1) and a medium baseline mRS of 0.4 (±0.9). Systemic thrombolysis was conducted within the first 90 min after symptom onset in 21.6% and from 1.5 to 3 h after symptom onset in 78.4% of patients. The overall inter-rater agreement for evaluation of cerebral imaging was similarly high for FLAIR status (0.76) as for secondary hemorrhage (0.75). According to the study protocol, all 97 patients exhibited DWI-positive lesions. In contrast, FLAIR-positive lesions in diffusion-restricted areas were detected in only 25 patients (25.8%), while the remaining 72 patients (74.2%) were FLAIR-negative. To test for possible influencing factors, baseline characteristics were analyzed between the FLAIR-positive and FLAIR-negative group (Table 1). Neither arterial hypertension nor diabetes, hyperlipoproteinemia or nicotine abuse were found to be associated with the occurrence of FLAIR-positive lesions. Likewise, no significant differences between FLAIR-positive and FLAIR-negative patients were found for history of previous stroke, preexisting disability as indexed by mRS, time from symptom onset to tPA administration,

Table 1 Patients characteristics ($n = 97$)

		FLAIR-negative ($n = 72$)	FLAIR-positive ($n = 25$)	*P*-value
Age	*M* (SD)	71.3 (11.7)	68.9 (12.1)	0.153†
Gender				
Male	*n* (%)	39 (54.2)	16 (64.0)	0.485‡
Female	*n* (%)	33 (45.8)	9 (36.0)	
History of drugs influencing the coagulation system				
None	*n* (%)	43 (59.7)	19 (76.0)	0.320*
Antiplatelets	*n* (%)	26 (36.1)	5 (20.0)	
Oral Anticoagulation	*n* (%)	3 (4.1)	1 (4.0)	
Cardivascular risk factors				
Arterial hypertension	*n* (%)	60 (83.3)	20 (80.0)	0.763‡
Diabetes	*n* (%)	20 (27.8)	10 (40.0)	0.683‡
Hyperlipoproteinemia	*n* (%)	28 (38.9)	16 (64.0)	0.934‡
Nicotine abuse	*n* (%)	15 (20.8)	3 (12.0)	0.906‡
Previous stroke	*n* (%)	11 (15.3)	2 (8.0)	0.807‡
Pre-existing disability				
Modified Rankin scale	*M* (SD)	0.40 (1.0)	0.24 (0.52)	0.841†
Time from symptom onset to tPA treatment				
≤1.5 h	*n* (%)	17 (23.6)	4 (16.0)	1.000‡
>1.5 h	*n* (%)	55 (76.4)	21 (84.0)	
Stroke severity prior to tPA treatment				
National Institutes of Health stroke scale	*M* (SD)	12.7 (7.1)	14.9 (6.9)	0.086†
Stroke subtype according to the TOAST classification				
Large artery atherosclerosis	*n* (%)	16 (22.2)	4 (16.0)	0.441*
Cardioembolism	*n* (%)	26 (36.1)	10 (40.0)	
Small vessel occlusion	*n* (%)	27 (37.5)	9 (36.0)	
Stroke of other determined etiology	*n* (%)	1 (1.4)	2 (8.0)	
Stroke of indeterminate etiology	*n* (%)	2 (2.8)	0 (0)	

FLAIR, fluid-attenuated inversion recovery; *M*, mean; SD, standard deviation; tPA, tissue plasminogen activator.
*Chi-square test.
†Mann–Whitney *U*-test.
‡Fisher's exact test.

history of drugs influencing the coagulation system and stroke severity as indicated by the NIHSS. Stroke subtype was comparably distributed between both groups (Table 1). These findings were verified by multiple regression analysis (*P*-values ranging from 0.061 to 0.786).

Intracerebral hemorrhage after systemic thrombolysis

Out of 97 patients, ICH was detected in 32 patients (33.0%) based on findings in the control CT. Thereby, the distribution of cerebral bleeding complications were as follows: HI-1 occurred in seven patients (21.9%), HI-2 in five patients (15.6%), PH-1 in nine patients (28.1%), and PH-2 in 11 patients (34.4%). In relation to the overall study population (97 patients), we found HI-1 in 7.2%, HI-2 in 5.1%, PH-1 in 9.2%, and PH-2 in 11.3%. Subsequent analyses addressed the rate of symptomatic ICH yielding a proportion of 34.4% (11 of 32 patients).

To test for factors possibly influencing the occurrence of ICH, patients suffering from hemorrhage were compared with those devoid of any bleeding complication. Thereby, age ($P = 0.681$, Mann–Whitney *U*-test), gender ($P = 0.828$, Fisher's exact test), arterial hypertension ($P = 1.000$, Fisher's exact test), diabetes ($P = 0.065$, Fisher's exact test), hyperlipoproteinemia ($P = 0.082$, Fisher's exact test) and nicotine abuse ($P = 0.164$, Fisher's exact test) were found to do not differ between the groups. Likewise, a history of previous stroke ($P = 0.535$, Fisher's exact test), time from symptom onset to tPA administration ($P = 0.189$, Fisher's exact test), preexisting disability (mRS, $P = 0.524$, Mann–Whitney *U*-test), stroke severity prior to tPA treatment (NIHSS, $P = 0.153$, Mann–Whitney *U*-test), history of drugs influencing the coagulation system ($P = 0.775$, Pearson's chi-squared test), and stroke subtypes ($P = 0.515$, Pearson's chi-squared test) were not related to ICH. These data were mainly confirmed by multivariate regression analysis (*P*-values ranging from 0.064 to 0.980), although diabetes provided a statistical significance ($P = 0.021$) indicating a trend for bleeding complications in concerned patients.

Inter-relation between MRI findings and hemorrhage related to thrombolysis

Representative scans from consecutive MRI and CT scans are shown in Fig. 1. ICH was detected in 20 of 25 patients (80%) exhibiting FLAIR-positive lesions, while tPA administration did not result in any bleeding complication in only five patients (20%) of this group (Fig. 2). Remarkably, hemorrhage was present in only 12 of 72 FLAIR-negative patients (16.7%). Statistical testing using Fisher's exact test confirmed an increased risk of

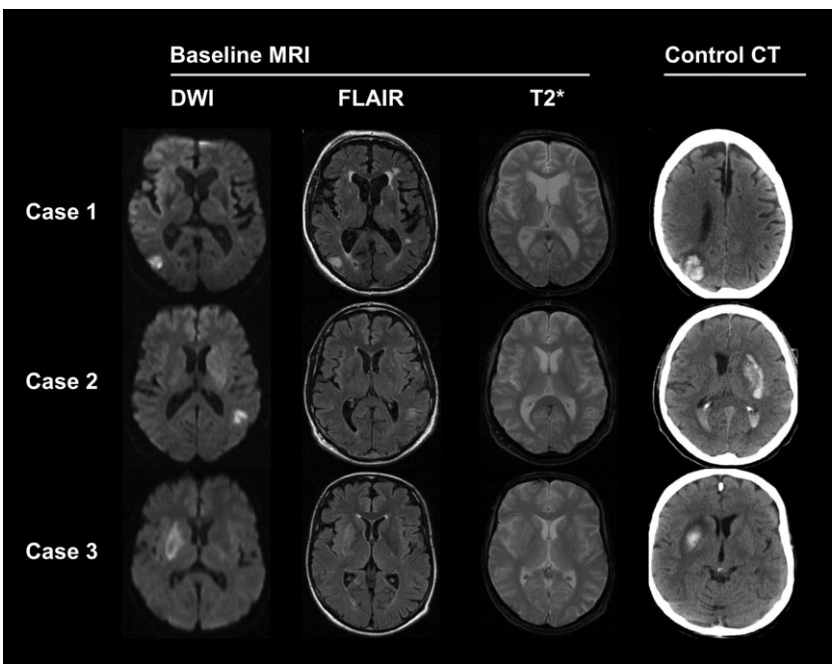

Figure 1. Exemplary scans from 3 ischemic stroke patients using magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) prior to systemic thrombolysis within 3 h after symptom onset. While pre-treatment MRI (T2*) was used to exclude primary hemorrhage, a computed tomography (CT) – performed within 24 after treatment – served to detect bleeding. FLAIR-positive lesions seen prior to systemic thrombolysis were associated with treatmentrelated intracerebral hemorrhage.

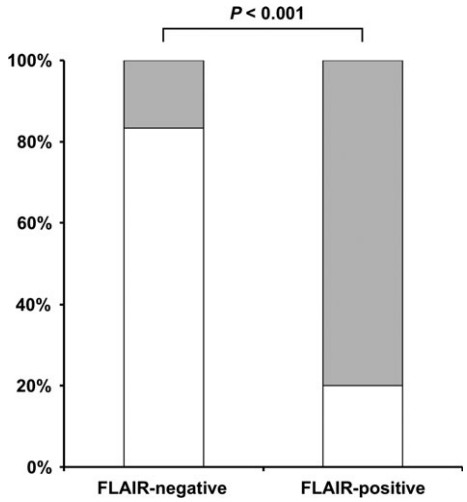

Figure 2. Rate of any intracerebral hemorrhage detected on computed tomography within 24 h after systemic thrombolysis depending on FLAIR status assessed on pre-treatment MRI. Gray bars represent the proportion of patients with intracerebral hemorrhage, while white bars indicate the proportion of patients without signs of bleeding complications. *P* indicates level of statistical significance.

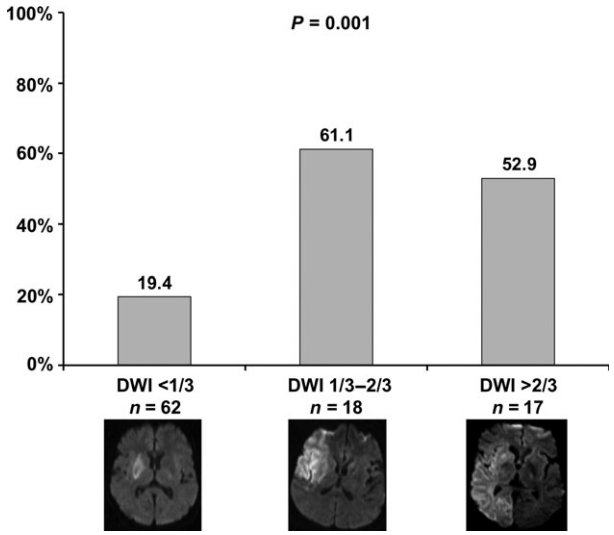

Figure 3. Rate of any intracerebral hemorrhage detected on computed tomography within 24 after systemic thrombolysis depending on initial lesion size as assessed by diffusion-weighted imaging (DWI) in relation to the vascular territory. For practical reasons, patients were allocated to the three groups 'DWI < 1/3', 'DWI 1/3–2/3' and 'DWI > 2/3'. For illustration, a representative DWI sequence taken from the magnetic resonance imaging prior to treatment was added under each category. *P* indicates level of statistical significance.

tPA-related bleeding complications in patients characterized by FLAIR-positive lesions on pre-treatment MRI ($P < 0.001$, specificity 92%, sensitivity 63%). The odds ratio of suffering from treatment-associated hemorrhage in FLAIR-positive patients was 20.0 (95% CI: 6.3–63.8), while the positive predictive value achieved 0.8 and the negative predictive value 0.83. However, in patients with FLAIR-positive lesions intracranial hemorrhage was not more frequently associated with clinical deterioration (six of 20 patients with bleeding complications, 30.0%) when compared with FLAIR-negative patients (five of 12 patients with bleeding complications, 41.6%; $P = 0.703$, Fisher's exact test). The rate of severe bleedings (PH-2) was not higher in patients with FLAIR-positive lesions than in FLAIR-negative patients ($P = 0.144$, Fisher's exact test). As an additional finding, in some cases bleeding occurred at locations outside of the FLAIR-positive region. In all of these cases, however, bleeding was also located within diffusion-restricted areas (see also Fig. 1).

Impact of DWI lesion size on intracerebral hemorrhage after tPA treatment

To explore the impact of DWI lesion size on treatment-associated hemorrhage, patients were stratified to the following groups depending on the proportion of DWI-restricted area with reference to the whole supplying territory of the affected cerebral artery: <1/3 ($n = 62$), 1/3–2/3 ($n = 18$) and >2/3 ($n = 17$). As shown in Fig. 3, the occurrence of ICH was found to be clearly associated with the size of DWI lesion while patients exhibiting of at least 1/3 of the respective territory are characterized with an increased bleeding rate ($P = 0.001$, Pearson's chi-squared test). Overall, the provided categories for DWI lesion size significantly predicted ICH with an odds ratio of 5.6 (95% CI: 2.2–13.9).

Inter-relation between bleeding complications and FLAIR/DWI proportion

To test the hypothesis that an increasing size of FLAIR-positive lesions with respect to the area of restricted diffusion in DWI might be associated with an increased risk of ICH due to tPA treatment, the occurrence of any bleeding was investigated depending on the proportion of FLAIR-positive over to the DWI-positive lesion. Out of the 25 patients showing FLAIR-positive lesions, a FLAIR/DWI proportion could be derived in 24 patients, who were stratified into the following three groups: proportion <1/3 ($n = 14$), 1/3–2/3 ($n = 3$) and >2/3 ($n = 7$). Remarkably, occurrence of bleedings (ranging from 66.7% to 85.7%) was not associated with the FLAIR/DWI proportion ($P = 0.788$, Pearson's chi-squared test).

Discussion

The present study examined whether specific MRI sequences obtained prior to systemic thrombolysis in acute ischemic stroke patients might be useful to predict secondary hemorrhage after systemic treatment with tPA initiated within 3 h after symptom onset. In our study population, the CT-based rate of any intracerebral bleeding after thrombolysis was 33%, which is in good agreement with previous reports (ECASS II, 43.0% (1); ECASS III, 27.0% (2)).

The incidence of 25.8% for FLAIR-positive lesions in pretreatment MRI of acute stroke patients treated within <3 h after symptom onset agrees with earlier studies that have reported FLAIR-positive rates between 15% (15) and about 50% (6, 16), including quite different timeframes. However, as the incidence of FLAIR hyperintensities is known to increase over time (6, 8, 15), the rate of about one-fourth observed in the present study might represent an adequate proportion for the first 3 h.

We found that FLAIR-positive lesions within diffusion-restricted areas detected on MRI prior to intravenous treatment with tPA was significantly and strongly associated with an increased risk for ICH (odds ratio 20.0). A previous report from Cho et al. (17) found an odds ratio of 13.64 of symptomatic ICH in FLAIR-positive patients compared with FLAIR-negative patients treated with intravenous and/or intra-arterial thrombolysis up to 6 h after symptom onset. However, Campbell et al. (18) failed to link the existence of FLAIR hyperintensities with ICH in patients ranging from 3 to 6 h after symptom onset, leading to the suggestion that time-of FLAIR positivity may be associated with development of ICH only when detected in the very early period (i.e., within 3 h) after symptom onset. The apparently different impact of FLAIR positivity in the early period (0–3 h) and the late period (3–6 h) might be attributed to the rate of recanalization, which has been found to decrease over time (19), and the maintenance of blood supply via collaterals.

The sensitivity of our study was enhanced by considering any type of ICH, irrespective of clinical manifestations. This approach was based on a previous report indicating that delayed neurological deterioration may occur even after small bleedings by virtue of delayed hematoma growth (20), and further, on the observation that the presence of small and clinically asymptomatic hemorrhages represents a negative predictor for clinical outcome independent of hematoma growth (20). On the other hand, mild hemorrhagic transformation – irrespective of FLAIR status – has also been discussed to represent a marker of early recanalization, associated with an improved clinical outcome (21, 22).

Nevertheless, the emerging evidence from our and previous studies suggest the perspective that FLAIR-positive lesions detected in the pretreatment MRI with 3 h after symptom onset might represent a useful marker to predict tPA-associated bleeding complications potentially leading to poor clinical outcome. However, as an earlier report demonstrated that the FLAIR status in an extended timeframe of up to 4.5 h after symptom onset was not predictive of either worse neurological outcome at day 1 or growth of the ischemic lesion (16), it may be premature to exclude FLAIR-positive patients from systemic thrombolysis. On the other hand, as clinical deterioration may occur at later stages, FLAIR positivity within 3 h from symptom onset may raise clinical alertness to developing treatment complications.

We also found a significant association of DWI lesion size and risk of ICH. When the DWI lesion comprised at least 1/3 of the vascular territory, the rate of bleeding complications due to tPA was remarkably increased. Although recent evidence has criticized the earlier concept of a distinct relationship between DWI and definitely infarcted brain tissue (23), increased risk of tPA-induced ICH in patients with extended DWI lesions appears to support a link between restricted diffusion and tissue infarction.

In our population with symptom onset strictly limited to the first 3 h, we found substantial variability of ratios of FLAIR/DWI across patients. As a separate finding, our data provide circumstantial evidence to suggest that the time of stroke onset cannot be easily and confidently inferred from a combination of FLAIR-negative and DWI-positive stroke lesion, a finding at variance from previous claims (5–7, 9, 15). Further, the present data do not support the hypothesis that the extension of FLAIR-positive lesions in relation to the diffusion-restricted area influences the risk of ICH, at least when FLAIR/DWI proportion was stratified into three categories (<1/3, 1/3–2/3 and >2/3). In CT-based studies, bleeding risk after tPA was increased in patients exhibiting signs of infarction in at least 33% of the middle cerebral artery territory on pretreatment CT (11, 24). In a study utilizing MR stroke imaging the number of FLAIR-positive lesions, but not their volume, was found to correlate with DWI lesion size 1 day after ischemia onset in a subset of stroke patients not undergoing thrombolysis (25), indicating a complex relationship between FLAIR-positive areas, diffusion restriction and infarction. Because in the

present study, the proportion of FLAIR-positive lesions was calculated based on the area of restricted diffusion, but not on vascular territory it remains a possibility that a significant association would have emerged from a traditional analysis based on vascular territory.

The present study has some limitations: First, the retrospective design only allowed processing of imaging data from a standardized time-saving scanning protocol. Future studies might therefore focus on the relationship between FLAIR-positive lesions and parameters more closely capturing functional aspects as for instance the cerebral blood flow. However, such increase on data acquisition prior to treatment is generally hampered by the fact that treatment should not be delayed by extensive diagnostics. Second, bleeding complications were assessed by CT as an established technique for screening of ICH. As MR imaging has recently been discussed to be more sensitive for the detection of hemorrhagic transformation (26), future studies might use a homogenous setup in cerebral imaging with MRI at both time points (pre- and post-treatment).

Summary

Based on a large data set, this study has revealed a dramatically increased risk for development of any ICH when FLAIR-positive lesions within DWI-restricted areas are present on pretreatment MRI in stroke patients undergoing systemic thrombolysis within 3 h after symptom onset. An increase rate of intracerebral bleeding was also noted in patients characterized by a DWI lesions size of at least 1/3 of the vascular territory. Our findings might be helpful to raise clinical alertness and to guide treatment decisions in patients with FLAIR-positive lesions.

Acknowledgements

The authors would like to thank Ms. Daniela Urban and Ms. Rita Lachmund (Department of Neurology, University of Leipzig) for assistance in completing and fostering the underlying database. Further thanks goes to Ms. Elfi Boxhammer (Department of Neuroradiology, University of Leipzig) for assistance in imaging analyses.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Hacke W, Kaste M, Fieschi C et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;**17**:1245–51.
2. Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;**359**:1317–29.
3. Singer OC, Hamann GF, Misselwitz B, Steinmetz H, Foerch C. Arbeitsgruppe Schlaganfall Hessen: time trends in systemic thrombolysis in a large hospital-based stroke registry. Cerebrovasc Dis 2012;**33**:316–21.
4. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;**371**:1612–23.
5. 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**:724–32.
6. 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**:978–86.
7. Emeriau S, Serre I, Toubas O, Pombourcq F, Oppenheim C, Pierot L. Can diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch (positive diffusion-weighted imaging/negative fluid-attenuated inversion recovery) at 3 tesla identify patients with stroke at 3 Tesla identify patients with stroke at <4.5 hours? Stroke 2013;**44**:1647–51.
8. 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**:782–92.
9. 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**:435–41.
10. Cho AH, Sohn SI, Han MK et al. Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. A preliminary report. Cerebrovasc Dis 2008;**25**:572–9.
11. Schellinger PD, Fiebach JB, Hacke W. Imaging-based decision making in thrombolytic therapy for ischemic stroke: present status. Stroke 2003;**34**:575–83.
12. Kucinski T, Vaterlein O, Glauche V et al. Correlation of apparent diffusion coefficient and computed tomography density in acute ischemic stroke. Stroke 2002;**33**:1786–91.
13. Singer OC, Humpich MC, Fiehler J et al. Risk for symptomatic intracerebral hemorrhage after thrombolysis assessed by diffusion-weighted magnetic resonance imaging. Ann Neurol 2008;**63**:52–60.
14. Adams HP, Bendixen BH, Kapelle LJ et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;**24**:35–41.
15. 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**:39–44.
16. Ebinger M, Ostwaldt AC, Galinovic I et al. Clinical and radiological courses do not differ between fluid-attenuated inversion recovery-positive and negative patients with stroke after thrombolysis. Stroke 2010;**41**:1823–5.
17. Cho AH, Kim JS, Kim SJ et al. Focal fluid-attenuated inversion recovery hyperintensity within acute diffusion-weighted imaging lesions is associated with symptomatic intracerebral hemorrhage after thrombolysis. Stroke 2008;**39**:3424–6.
18. Campbell BC, Costello C, Christensen S et al. Fluid-attenuated inversion recovery hyperintensity in acute

ischemic stroke may not predict hemorrhagic transformation. Cerebrovasc Dis 2011;**32**:401–5.
19. Dorado L, Millán M, Pérez de la Ossa N et al. Time to recanalization and risk of symptomatic intracerebral haemorrhage in patients treated with intravenous thrombolysis. Eur J Neurol 2012;**19**:1251–5.
20. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Terasawa Y. Hemorrhagic transformation of ischemic brain tissue after t-PA thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. J Neurol Sci 2008;**272**:136–42.
21. Molina CA, Alvarez-Sabín J, Montaner J et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. Stroke 2002;**33**:1551–6.
22. Thomalla G, Schwark C, Sobesky J et al. Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials. Stroke 2006;**37**:852–8.
23. Campbell BC, Purushotham A, Christensen S et al. The infarct core is well represented by the acute diffusion lesion: sustained reversal is infrequent. J Cereb Blood Flow Metab 2012;**32**:50–6.
24. von Kummer R, Allen KL, Holle R. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology 1997;**205**:327–33.
25. Hohenhaus M, Schmidt WU, Brunecker P. FLAIR vascular hyperintensities in acute ICA and MCA infarction: a marker for mismatch and stroke severity? Cerebrovasc Dis 2012;**34**:63–9.
26. Nighoghossian N, Hermier M, Berthezène Y et al. Early diagnosis of hemorrhagic transformation: diffusion/perfusion-weighted MRI versus CT scan. Cerebrovasc Dis 2001;**11**:151–6.