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Reliability of the ECASS Radiological Classification of Postthrombolysis Brain Haemorrhage: A Comparison of CT and Three MRI Sequences

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Key Words
Stroke · Thrombolysis · Haemorrhagic transformation · Reproducibility · ECASS classification

Abstract
Background: Postthrombolysis brain haemorrhagic transformations (HT) are often categorized with the CT-based classification of the European Cooperative Acute Stroke Study (ECASS). However, little is known about the reliability of this classification and its extension to MRI. Our objective was to compare the inter- and intraobserver reliability of this classification on CT and 3 MRI sequences. ***Methods:*** Forty-three patients with postthrombolysis HT on CT or at least 1 of the 3 MRI sequences: fluid-attenuation inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and T2* gradient recalled echo (T2*GRE) were selected. Twelve control patients without any bleeding were added to avoid a bias based on a pure HT-positive cohort. Each series of images were independently classified with the ECASS method by 6 blinded observers. Inter- and intraobserver reproducibility was categorized from poor to excellent depending on κ values. ***Results:*** The inter- and intraobserver overall concordance of the classification was good for T2*GRE, DWI and CT ($\kappa > 0.6$) and moderate for FLAIR ($\kappa < 0.6$). The interobserver concordance for parenchymal haematomas was excellent for T2*GRE ($\kappa > 0.8$) and moderate for CT, FLAIR and DWI. ***Conclusion:*** The T2*GRE sequence is the most reproducible method to categorize postthrombolysis HT and has an excellent reliability for the severe parenchymal haematoma category, suggesting that this sequence should be used to assess HT in thrombolytic therapy trials.

Introduction

Severe haemorrhagic transformation (HT) of acute cerebral infarction is one of the main safety endpoints used in thrombolytic therapy trials, and identification of risk factors for HT is an issue often brought up in the literature [1, 2]. However, HT are not systematically correlated to worse prognosis. Indeed, the spectrum of HT is broad and spans from trivial haemorrhagic petechiae to voluminous parenchymal haematomas with a space-occupying effect. Thus, it would be of major interest to identify which type of HT really influences the functional prognosis of patients.

Various definitions of severe HT are used across studies, based on different clinical and/or radiological find-

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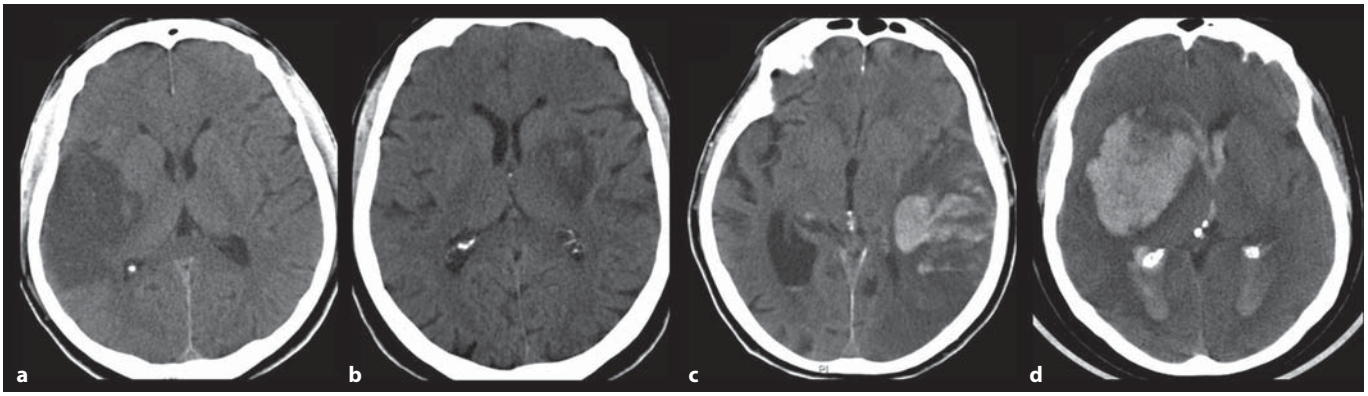

Fig. 1. Examples of different subtypes of HT according to the ECASS classification [9]. **a** HI1: small petechiae along the periphery of the infarct. **b** HI2: confluent petechiae within the infarcted area, without space-occupying effect. **c** PH1: bleeding ≤30% of the infarcted area with some mild space-occupying effect. **d** PH2: bleeding >30% of the infarcted area with significant space-occupying effect.

ings [3–8], but a standardized and reproducible method to define HT is necessary to assess the safety of thrombolysis, particularly in therapeutic trials. Recent observations suggest that the functional outcome may vary with the type and extent of HT, indicating a relevant part of imaging for the evaluation of severe haemorrhages [9–14]. Thus, the European Cooperative Acute Stroke Study (ECASS) radiological classification could be an appropriated and objective tool to characterize HT. This classification, established for CT, evaluates both the extent of bleeding and the space-occupying effect due to this bleeding, using the distinction between haemorrhagic infarcts without space-occupying effect (HI1 and HI2) and parenchymal haematomas with space-occupying effect (PH1 and PH2) (fig. 1). Moreover, this classification seems to be clinically relevant as several studies demonstrated that PH2 [9, 12], but also PH1 [13, 15], significantly increased the risk of a poor clinical outcome.

Although this radiological classification is attractive, its reproducibility has not been evaluated yet. Furthermore, given the increasing availability and efficacy of MRI for rtPA patient selection [16], the extension of this CT-based classification to MRI should be evaluated. The main objective of the present study was to evaluate the inter- and intraobserver reliability of 4 imaging modalities: noncontrast CT, MRI fluid-attenuation inversion recovery (FLAIR), MRI diffusion-weighted imaging (DWI) and MRI T2* gradient recalled echo (GRE) in detecting and categorizing postthrombolysis HT.

Methods

Patients

The patients were retrospectively extracted from the prospective stroke thrombolysis database of our institution. They had all received intravenous thrombolysis within 5 h after the onset of symptoms between March 2001 and June 2006. All imaging and clinical data were generated during routine clinical work-up of the patients in our stroke centre. The regulation concerning electronic filing was respected, and both the patients and their relatives were informed that the patient data might be used in retrospective clinical studies. Inclusion criteria were the following: (1) noncontrast CT and MRI performed 24–72 h after intravenous thrombolysis for acute ischaemic stroke in the middle cerebral artery territory and a time period between CT and MRI <24 h; (2) postthrombolysis MRI including the following 3 sequences: DWI, FLAIR and T2* GRE imaging, and (3) postthrombolysis brain haemorrhage identified after a consensual reading by 4 experienced stroke neurologists (S.D., S.C., Y.S. and P.R.) on CT or at least 1 of the 3 MRI sequences.

In order to avoid a bias based on a pure HT-positive cohort, additional patients without any HT were extracted from the same thrombolysis database. Inclusion criteria were the following: (1) and (2) the same as above, and (3) no postthrombolysis brain haemorrhage identified by the 4 readers on CT or any MRI sequences.

Imaging Protocol

MR imaging was performed on a 1.5-tesla whole-body MR General Electric Signa Horizon Echospeed unit with enhanced gradient hardware for echoplanar imaging. MR imaging included 3 sequences: DWI, FLAIR and T2*GRE. The acquisition parameters for the 3 analyzed sequences were as follows: (1) FLAIR [slice thickness = 5 mm; interslice gap = 1.5 mm; matrix = 256 × 256; field of view = 240 × 240 mm; repetition time (TR) = 8,800 ms; echo time (TE) = 140 ms; inversion time = 2,200 ms]; (2) axial isotropic DWI spin echo EPI (24 slices, slice thickness =

Table 1. Interobserver concordances with each imaging modality and with the combined reading of FLAIR/DWI/T2* GRE for: bleeding detection, overall concordance, bleeding categorization and distinction HI versus PH

	Interobserver Fleiss' κ								
	CT		T2*GRE		DWI		FLAIR		FLAIR DWI T2*GRE
	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1
Bleeding detection	0.66 (0.43–0.82)	0.59 (0.39–0.77)	0.80 (0.61–0.94)	0.75 (0.57–0.90)	0.50 (0.30–0.66)	0.58 (0.39–0.74)	0.51 (0.32–0.67)	0.19 (0.02–0.37)	0.87 (0.72–0.97)
Overall concordance									
Simple κ	0.54 (0.42–0.64)	0.48 (0.34–0.59)	0.63 (0.50–0.76)	0.58 (0.45–0.69)	0.39 (0.26–0.52)	0.47 (0.36–0.58)	0.35 (0.22–0.47)	0.22 (0.10–0.33)	0.53 (0.41–0.63)
Weighted κ	0.70 (0.63–0.77)	0.68 (0.61–0.75)	0.74 (0.66–0.82)	0.75 (0.69–0.82)	0.54 (0.45–0.62)	0.66 (0.59–0.73)	0.55 (0.47–0.64)	0.42 (0.33–0.51)	0.74 (0.68–0.80)
Bleeding categorization									
HI1	0.60 (0.40–0.77)	0.42 (0.20–0.60)	0.34 (0.21–0.45)	0.42 (0.19–0.62)	0.25 (0.08–0.40)	0.34 (0.17–0.50)	–0.11 (–0.17 to 0.06)	0.03 (–0.10 to 0.15)	0.29 (0.02–0.52)
HI2	0.50 (0.31–0.68)	0.44 (0.24–0.61)	0.56 (0.38–0.73)	0.47 (0.22–0.66)	0.31 (0.12–0.49)	0.38 (0.18–0.57)	0.32 (0.14–0.49)	0.31 (0.12–0.48)	0.33 (0.17–0.49)
PH1	0.43 (0.23–0.62)	0.34 (0.10–0.54)	0.61 (0.21–0.86)	0.54 (0.30–0.73)	0.43 (0.08–0.67)	0.52 (0.25–0.75)	0.34 (0.08–0.57)	0.10 (–0.11 to 0.33)	0.49 (0.26–0.69)
PH2	0.41 (–0.03 to 0.78)	0.87 (0.49–1.00)	0.82 (0.38–1.00)	0.77 (0.54–0.94)	0.85 (–0.01 to 1.00)	0.58 (0.18–0.87)	0.55 (–0.02 to 0.86)	0.64 (0.23–0.89)	0.66 (0.33–0.88)
Distinction PH/HI	0.66 (0.46–0.83)	0.51 (0.26–0.71)	0.83 (0.62–0.96)	0.78 (0.65–0.91)	0.53 (0.26–0.73)	0.75 (0.57–0.89)	0.55 (0.34–0.74)	0.34 (0.11–0.55)	0.78 (0.63–0.92)

Figures in parentheses are 95% CI.

5 mm; interslice gap = 0.5 mm; FOV = 280 × 210 mm; matrix = 96 × 64; TE = 98.9 ms; TR = 2825 ms), and (3) T2*GRE (slice thickness = 6 mm; interslice gap = 0.6 mm, matrix = 256 × 192; TR = 500 ms; TE = 15 ms).

Noncontrast CT examinations were performed with a Somatom Sensation 16 CT scanner (Siemens): 120 kV, 370 mA, H45 filter and a slice thickness of 5 mm without interslice gap.

Image Analysis

After the study population had been selected, each MRI sequence (FLAIR, T2*GRE and DWI) and the CT images were archived separately. The sets of images were anonymized and randomly numbered.

To assess the interobserver reliability of the classification, 2 groups of 3 readers, not informed of the number of patients with or without HT and blinded to the clinical data, individually analyzed the CT and MR examinations. The first group consisted of 2 neurologists with at least 10 years of experience in neurovascular medicine (F.R., I.S.) and 1 neuroradiologist with 4 years of experience in neuroimaging (T.T.). The second group included 2 neuroradiologists with 10 and 4 years of experience in neuroimaging (D.G., A.D.) and 1 neurologist with 6 years of experience in neurovascular medicine (C.R.). The 6 readers rated each CT and MR sequence as negative or positive for cerebral bleeding. If haemorrhage was present, they had to score the image according to the ECASS radiological classification: haemorrhagic infarct type 1 (HI1): small petechiae along the periphery of the infarct; haemorrhagic infarct type 2 (HI2): confluent petechiae within the infarcted area without a space-occupying effect; parenchymal haematoma type 1 (PH1): bleeding ≤30% of the infarcted area with a mild space-occupying effect, and parenchymal haematoma type 2 (PH2): bleeding >30% of the infarcted area with a significant space-occupying effect. Each observer was given a model of this classification (fig. 1). They were invited to note comments in cases of difficult bleeding detection or categorization.

To assess the intraobserver reliability of the classification, the first group performed a second analysis with an interval of 1 month. In this second analysis a combined analysis of FLAIR, DWI and T2* GRE was added to evaluate if the reproducibility could be improved by the simultaneous reading of these 3 MRI sequences, as it is performed in clinical practice.

Statistical Analysis

The interobserver agreement of each group for the diagnosis of HT and for categorizing the bleeding according to the ECASS classification was assessed by calculating the Fleiss κ, which must be used when there are >2 raters. κ values <0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80 and 0.81–1.00 were considered to indicate poor, fair, moderate, good and excellent agreement, respectively. We analyzed: (1) the overall concordance of each imaging modality, which corresponds to the weighted average of the κ values of each bleeding category. It was calculated with a simple κ, which treats all disagreements equally, and a weighted κ, which takes into account the different types of disagreement in case of ordered scale such that disagreements of varying gravity are weighted accordingly; (2) the concordance of each bleeding category with the 4

Table 2. Intraobserver concordances with each imaging modality for: bleeding detection, overall concordance, bleeding categorization and distinction HI versus PH

	Intraobserver Cohen's κ			
	CT	T2*GRE	DWI	FLAIR
Bleeding detection	0.60 (0.46–0.75)	0.81 (0.71–0.92)	0.72 (0.60–0.84)	0.65 (0.53–0.77)
Overall concordance				
Simple κ	0.47 (0.38–0.56)	0.59 (0.50–0.68)	0.51 (0.41–0.61)	0.45 (0.36–0.55)
Weighted κ	0.83 (0.78–0.88)	0.85 (0.79–0.91)	0.75 (0.67–0.83)	0.76 (0.68–0.84)
Bleeding categorization				
HI1	0.43 (0.27–0.58)	0.31 (0.08–0.54)	0.40 (0.21–0.58)	0.14 (–0.06 to 0.34)
HI2	0.43 (0.27–0.59)	0.53 (0.40–0.65)	0.41 (0.27–0.56)	0.40 (0.25–0.55)
PH1	0.38 (0.21–0.56)	0.44 (0.26–0.62)	0.42 (0.25–0.59)	0.37 (0.17–0.56)
PH2	0.53 (0.32–0.73)	0.84 (0.70–0.99)	0.74 (0.49–0.98)	0.53 (0.30–0.76)
Distinction PH/HI	0.68 (0.55–0.80)	0.67 (0.54–0.80)	0.58 (0.44–0.72)	0.69 (0.56–0.82)

Figures in parentheses are 95% CI.

imaging modalities; (3) the concordance of the severe PH category (PH1 + PH2), and (4) the concordance of the combined analysis of FLAIR, DWI and T2* performed by the first group.

The intraobserver agreement of the first group was assessed by calculating Cohen's κ. Overall concordances were assessed by the simple κ.

Confidence intervals were calculated by generation of 1,000 bootstrap samples.

Results

Patients

Among the 276 patients entered in the database, the 4 readers identified 113 patients with HT and 163 without HT. Among the 113 patients with HT, 43 fulfilled the inclusion criteria: 57 did not have a T2*GRE sequence and among the 56 remaining patients, 13 did not have MRI and CT with a time period <24 h. Among the 163 patients without HT, 57 fulfilled the inclusion criteria; 12 patients were randomly selected among them, in order to have a cohort of 55 patients, that is 220 sets of images (55 FLAIR, 55 DWI, 55 T2*GRE and 55 CT).

The patients had follow-up MRI and CT either 24–48 h after thrombolysis (n = 51) or 48–72 h after thrombolysis (n = 4).

Reproducibility of the Detection of Haemorrhagic Transformations

Quantitative results demonstrated that the T2*GRE sequence had the best inter- and intraobserver agreement for bleeding detection with excellent κ values (tables 1 and 2).

Qualitative analysis of the observers' comments revealed redundant difficulties for bleeding detection, particularly with CT, FLAIR and DWI sequences, such as the interpretation of a hypodensity/hyposignal in the lenticular nuclei (fig. 2a–d) and the interpretation of a isodensity/isosignal within the ischaemic area (fig. 2e–h).

Reproducibility of the Categorization of Haemorrhagic Transformations

Considering the interobserver reliability (table 1), quantitative analysis revealed that the overall concordance of the ECASS classification for bleeding categorization was moderate for the CT, T2*GRE and DWI sequences, and fair for the FLAIR sequence with simple κ. When the more appropriated weighted κ was used, the overall concordance of each imaging modality was equally improved and became good for CT and T2*GRE, good or moderate for DWI according to the group and moderate for FLAIR. Among all the modalities, T2*GRE had the best interobserver overall agreement. Regarding parenchymal haematomas, the interobserver agreement for the PH/HI distinction and PH2 categorization was excellent for T2*GRE, good for DWI, fair to moderate for CT and fair for FLAIR. For the HI1, HI2 and PH1 categories, the reliability of the classification was poor to moderate whichever modality was used. The combined analysis of FLAIR, DWI and T2* GRE performed by the first group did not improve the in-

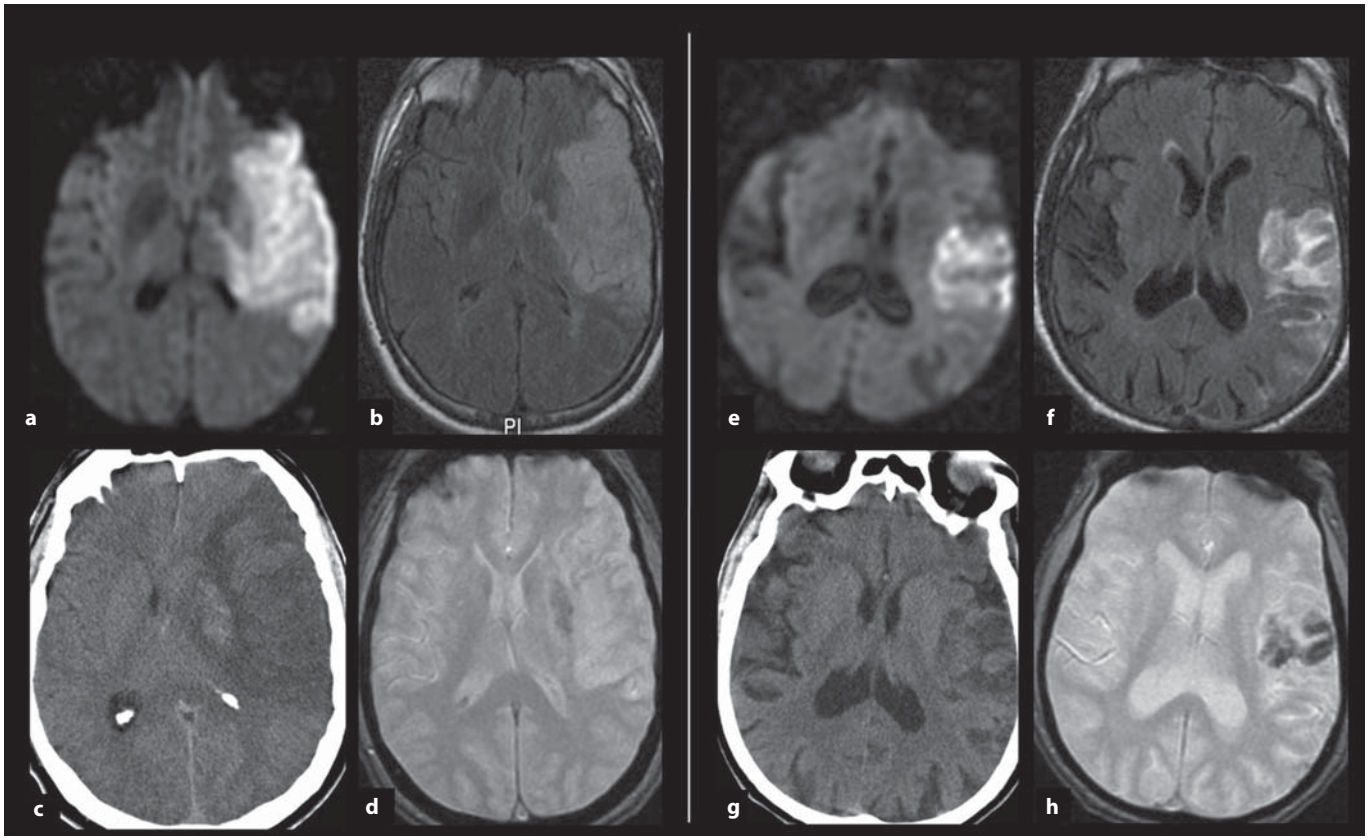

Fig. 2. Two ambiguous examples of bleeding detection (patient 1: **a–d**, patient 2: **e–h**). Hyposignal within lenticular nuclei on DWI (**a**) and FLAIR (**b**) sequences that can be interpreted either as bleeding or as susceptibility effect of the physiologic iron accumulation. In this case, noninjected CT (**c**) shows hyperdensity and T2*GRE (**d**) shows clear and asymmetrical hyposignal, confirming HT. Hypointensity on DWI (**e**) and FLAIR (**f**) sequences and isodensity on CT (**g**) within the ischaemic area which can be considered either a petechial haemorrhage or tissue spared by the ischaemic process or sulcus. The hyposignal on the T2*GRE (**h**) sequence confirms the HT.

terobserver agreement regardless of the category studied, with similar results for the analysis when isolating the T2*GRE sequence.

The intraobserver reliability demonstrated comparable results to the interobserver reliability (table 2): the T2*GRE sequence had the highest, though moderate, overall concordance and an excellent reliability for the severe PH2 category. For the HI1, HI2 and PH1 categories, the intraobserver reliability was again poor to moderate.

From qualitative analysis of the observers' comments, we noticed iterative difficulties in bleeding categorization: (1) distinction between HI1 and HI2 (fig. 3a); (2) distinction between HI2 and PH1, which was the most frequent difficulty reported (fig. 3b and 3c), and (3) distinction between PH1 and PH2 (fig. 3d).

With the use of T2*GRE, we noticed a low rate of HI1 and a high rate of HI2 in group 1 analyses (compared to CT, FLAIR and DWI), suggesting an upward shift from HI1 to HI2.

Discussion

Our results indicate that the overall inter- and intraobserver reproducibility of the ECASS classification for categorizing postthrombolysis brain HT is good or moderate with all the tested imaging methods. Among all of them, the T2*GRE sequence is the most reproducible option for detecting and categorizing HT.

Noncontrast CT has long been considered as the gold standard for assessing intracerebral haemorrhage. How-

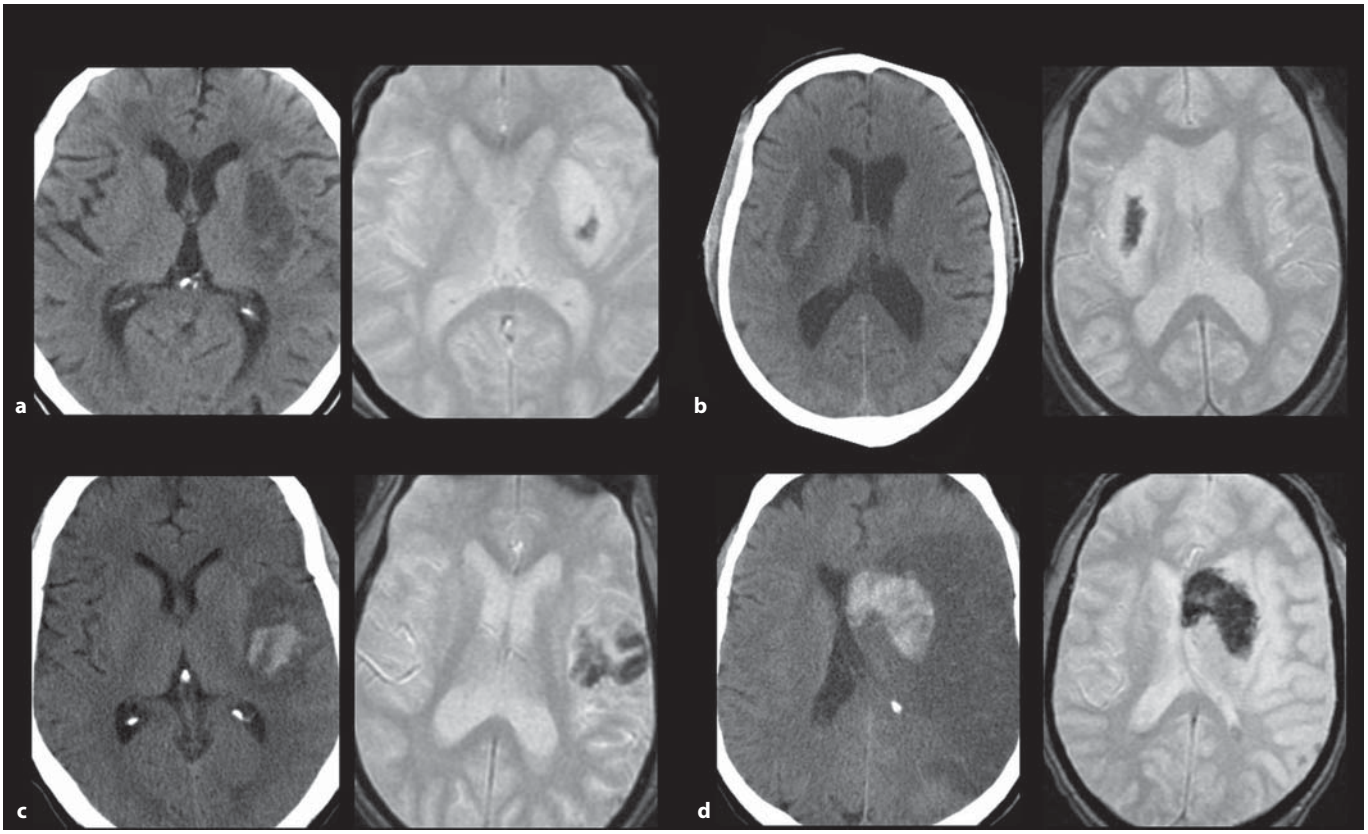

Fig. 3. Ambiguous examples of bleeding categorization (CT image on the left, T2*GRE sequence on the right). **a** Distinction HI1/HI2: bleeding interpreted as HI1 on CT image and HI2 on T2*GRE sequence. **b** Distinction HI2/PH1: confluent petechiae interpreted as an HI2 but with space-occupying effect as a PH1. **c** Distinction HI2/PH1/PH2: parenchymal haematoma ~30% of the infarcted area as a PH1 or a PH2 but without any space-occupying effect like an HI2. **d** Distinction PH1/PH2: bleeding <30% of the infarcted area as a PH1 but with significant space-occupying effect like a PH2.

ever, in our study, its reliability was poor to moderate for bleeding detection, whereas the reproducibility of T2*GRE was excellent. Similar results had previously been reported by Arnould et al. [17], who found higher sensitivity and reproducibility for the T2*GRE sequence than CT in HT detection. These results are concordant with recent studies which demonstrated that MRI is at least as accurate as CT for bleeding detection [18, 19]. The high sensitivity of MRI, particularly the T2*GRE sequence, for HT detection was previously suggested by Kidwell et al. [19], who reported 4 cases of HT on T2*GRE that were not apparent on the corresponding CT. This accuracy is due to the high sensitivity of T2*GRE to the paramagnetic effect of deoxyhaemoglobin and methaemoglobin, which allows blood detection as a hypointensity within the ischaemic field.

Our data demonstrate an excellent interobserver agreement with the T2 GRE sequence for the severe PH (PH1 and PH2) category. It is interesting to note that among the 55 patients studied, 4 had a symptomatic intracerebral haemorrhage (i.e. clinical deterioration by at least 4 points on the NIHSS temporally related to an HT). They were all categorized as PH (PH1 for 2 patients and PH2 for the other 2) on T2*GRE by the 6 readers. Secondary analysis of the stroke trials demonstrated that PH2 [9, 12] and also PH1 [13, 15], but not HI, were associated with a poor outcome at 3 months. Thus, these results suggest that the T2*GRE sequence could be a clinically relevant and reliable tool to evaluate severe postthrombolysis haemorrhages that impact prognosis.

Although the T2*GRE sequence seems to be attractive, the qualitative analysis of observers' comments re-

vealed redundant difficulties in classifying numerous 'borderline' haemorrhages. Indeed, the ECASS classification includes 3 characteristics of HT: (1) the type of bleeding (petechiae/haematoma); (2) the extent of bleeding (more or less than a third of the infarct), and (3) the space-occupying effect. The classification imposes that only PH is associated with a space-occupying effect. However, many HT do not fit all these criteria: some petechial haemorrhages are associated with a mass effect, although it is difficult to know if this one is attributable to the haemorrhage or to the vasogenic oedema due to ischemia. On the contrary, some haematomas, particularly PH1, do not seem to induce a mass effect, especially when the HT is situated far from the ventricles, where the space-occupying effect is usually less visible. This difficulty in appreciating a mass effect was reported both by the stroke neurologists and the trained neuroradiologists. Thus, the ECASS classification could be too restrictive and additional bleeding categories such as HI2 with space-occupying effect and PH1 without space-occupying effect could be necessary in order to avoid borderline HT. This could improve the reliability of the classification. Moreover, these additional categories might modify the functional prognosis of the HI2 and PH1 categories and maybe resolve the discordant results with these 2 categories among several studies [9, 11, 12, 20]. Further analyses are needed to test these hypotheses.

Our study has several limitations. (1) Because of a high sensitivity for a susceptibility effect, the T2*GRE sequence is known to overestimate the haematoma volume in comparison with the volume assessed with CT [21, 22], which exposes to the risk of an upward shift to severer bleeding categories. In our study, we noticed an upward shift with the T2*GRE sequence from HI1 to HI2 due to an overestimation of small petechiae converted to confluent petechiae. However, we did not observe any shift from HI2 to PH1 or from PH1 to PH2. Therefore, the CT-based conclusions about the clinical relevance of HT did not differ from MRI, since only PH1 and PH2 are known to be associated with a poor outcome. (2) One might have thought that PH1 and PH2 categorizations would have been difficult with the T2*GRE sequence because the extent of the infarct is not clearly seen on this sequence. However, the combined analysis of FLAIR, DWI and T2*GRE did not improve the interobserver agreement for PH1 and PH2 compared to T2*GRE alone. This result suggests that the T2*GRE sequence alone is sufficient to categorize PH1 and PH2, probably because the T2 shine-through effect is sufficient to approximately evaluate the infarct size. (3) There was a time period of several hours (<24 h) between the CT and the MRI realizations; MRI was often performed before CT (n = 48). Bleeding could have occurred or increased during this elapsed time. However, as we did not evaluate the intersequence agreement (MRI versus CT) but the interobserver agreement, this delay could not introduce a bias. (4) The low prevalence of the PH2 category (2–5 PH2 according to the observer and the imaging modality) could have induced a bias because the κ coefficient is influenced by the prevalence of the event. However, it has been demonstrated that a low prevalence level results in a reduction in κ values [23]. Thus, we can suppose that κ values obtained for the PH2 category are underestimated and that the reproducibility of each imaging modality for the PH2 category is in fact better. Either way, this bias does not modify the result that the T2*GRE sequence is the most reproducible sequence for PH2 categorization.

In conclusion, this study suggests that the T2*GRE sequence is the most reproducible method to detect and categorize postthrombolysis HT. Moreover, this sequence has an excellent inter- and intraobserver agreement for the classification of PH, which are associated with a poor outcome. Thus, the T2*GRE sequence could be a reliable tool that may be used in thrombolytic therapy trials to evaluate severe postthrombolysis haemorrhages that impact prognosis. Finally, to determine if the T2*GRE sequence in place of CT in clinical practice could represent an improvement, we think that the next step would be to prospectively determine if the T2*GRE sequence, using the ECASS classification with additional bleeding categories, gives a better prediction of the impact of HT on clinical outcome than CT.

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