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THÈSE

pour obtenir le grade de

DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement
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par

Marie TISSERAND

le 15 octobre 2010

ISCHEMIES RÉCENTES SILENCIEUSES SUR L'IRM AVANT THROMBOLYSE : PRÉVALENCE ET IMPACT SUR LE RISQUE DE TRANSFORMATION HÉMORRAGIQUE

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À notre Maître et Président de Thèse,

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Vous nous faites l'honneur de présider le jury de cette thèse.

Nous vous remercions de la confiance que vous nous avez accordée.

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En témoignage de notre reconnaissance et de notre profond respect.

À notre Juge

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À notre Maître et Juge

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Je te remercie de l'honneur que tu me fais en acceptant de juger cette thèse.

Travailler avec toi a été une leçon, un honneur et un plaisir.

En témoignage de ma gratitude et de mon profond respect.

Meis et Amicis

SERMENT

"Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité. J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés. J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque".

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INTRODUCTION

Multiple ischemic lesions on diffusion-weighted imaging (DWI) are common in acute stroke patients,¹⁻⁴ reported in about 20% of patients imaged within the first 6 hours.¹ Some multiple lesions occur simultaneously whereas others are discrete events occurring in step wise fashion.^{5,6} MRI provides useful information on the time course of stroke evolution and can serve as a surrogate marker of the age of ischemia.⁷⁻⁹ Using multiparametric MRI, multiple ischemic lesions of varying ages have been reported in 13 to 15% of stroke patients within 24 hours after symptom onset.^{10,11} Most of these lesions are clinically silent^{5,10} and their age can only be estimated using imaging parameters. In patients with multiple lesions, MRI can identify recent silent ischemia (RSI) that occurred before the acute index lesion responsible for symptoms. In candidates for thrombolysis, the frequency of RSI is unknown. Yet this may have practical implications for centers using stroke MRI screening. Indeed, RSI occurring hours or days before the index acute ischemia may increase the risk of hemorrhagic transformation (HT) and contraindicate thrombolysis.^{12,13} The current guidelines cover the case of patients with prior symptomatic ischemic stroke,¹⁴⁻¹⁶ but not that of patients with RSI found on pre-therapeutic MRI. Stroke teams in institutions using MRI as a pretreatment screening modality have to deal with a new potential risk factor of HT, not captured with CT, as was the case when cerebral microbleeds were first described.^{17,18} Given the uncertainties about the frequency and relevance of RSI in thrombolysis candidates, we sought to determine, from a population of consecutive patients treated with thrombolysis, whether MRI-defined RSI are a risk factor for the development of symptomatic or asymptomatic HT.

PATIENTS AND METHODS

Patients. We retrospectively reviewed the medical records of all consecutive stroke patients admitted to our stroke unit who were treated with thrombolysis between January 2006 and November 2009. The study was approved by the Ethics Committee of Ile de France III and was found to conform to generally accepted scientific principles and ethical standards. Inclusion criteria were: (1) an MRI including at least DWI and fluid attenuated inversion recovery (FLAIR) obtained before treatment; (2) an acute ischemic stroke (index ischemia) treated with intravenous (IV) recombinant tissue plasminogen activator (rt-PA); (3) no history of symptomatic stroke within three months before the index ischemia; (4) an imaging follow-up within 3 days after treatment. In order to ensure that the treatment decision had not been influenced by the presence of RSI, we also reviewed the reasons for not giving rt-PA in patients who were eligible for thrombolysis but did not receive this treatment. This analysis was restricted to the period from December 2008. Indeed, although all patients who receive thrombolysis are registered in our database, those eligible for rt-PA but not subsequently treated have only been systematically identified since December 2008.

IV thrombolysis using 0.9 mg/kg body weight rt-PA was done within 3 hours of symptom onset, in accordance with National Institute of Neurological Disorders and Stroke (NINDS) study,¹⁹ until November 2008, and thereafter within 4.5 hours in accordance with European Cooperative Acute Stroke Study (ECASS) III criteria.²⁰ Demographic details (age, gender), risk factors (cigarette smoking, hypertension, diabetes, hyperlipidemia, alcohol, history of prior (> 3 months) symptomatic stroke, myocardial infarction or lower limb claudication), migraine, current use of anticoagulation or antiplatelets, systolic and diastolic blood pressure, glycemia, and platelet count at admission were recorded in a standardized case note. Onset-to-MRI and onset-to-needle times, stroke territory (anterior or posterior circulation), stroke volume on baseline DWI, presence of microbleeds on T2* sequence and old infarction on initial MRI were recorded. Stroke mechanism was assessed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.²¹ Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score before treatment, 24 hours after treatment and in case of neurological deterioration.

Pretreatment MRI acquisition. MRI studies were performed as the sole and first line diagnostic tool on a 1.5T scanner (Signa EchoSpeed, General Electric Health Care, Milwaukee, WI) with 33 mT/m gradient strength and an eight-channel head coil. A T2-weighted baseline and DWI were acquired with a single-shot echo-planar spin-echo sequence with repetition time (TR)/ echo time (TE) 6400/85.4 ms, 24×24 cm² field of view, 128×128 matrix, 2 NEX, 24 slices, 6-mm slice thickness, no gap. The trace images were calculated from three diffusion-weighted acquisitions with gradients sequentially applied along each of three orthogonal axes ($b=1000$ s/mm²). The acquisition parameters of FLAIR were TR/TE/inversion time (TI) 9802/155.5/2300 ms, 256×192 matrix, 1 NEX, all other parameters being identical. The acquisition parameters of the T2* sequence were TR/TE 460/13, flip angle 25°, 24×18 cm² field of view, 256×224 matrix, 1 NEX, all other parameters being identical. The total acquisition time was less than 7 minutes.

Identification of RSI. Our aim was to identify, on pretreatment MRI, ischemic lesions of varying age, including the acute ischemia for which the patient was subsequently treated with thrombolysis (i.e. index ischemia) coexisting with RSI of older age. Based on previous reports by our group⁹ as well as others,^{7,8} showing that FLAIR/T2 can be used as a surrogate marker of ischemic lesion age, we searched for two types of ischemic lesions: (1) acute index ischemia, corresponding to an area of DWI hyperintensity without well developed FLAIR signal changes; (2) MRI-defined RSI, corresponding to an ischemic area with well developed brain hyperintensity on both DWI and FLAIR (figure 1).⁷⁻⁹ Patients in whom both types of lesion coexisted were assigned to the RSI+ group while those with only acute ischemia were assigned to the RSI- group. Group assignment was done independently by two neuroradiologists (M.T. with 2 years of experience, C.O. with 14 years of experience), blinded to clinical data and follow-up imaging, who reviewed FLAIR and DWI of patients, randomly presented on a dedicated workstation. For each RSI, readers systematically checked that the apparent diffusion coefficient (ADC) was decreased as compared with the contralateral side, in order to rule out chronic vascular changes that produce hyperintensities on FLAIR and T2-shine-through effects on DWI. Discordances between observers were resolved by consensus. Finally, one reader (M.T.) searched for susceptibility effects on baseline T2* sequence within each RSI.

Follow-up. Brain MRI was repeated after treatment. Restless or medically unstable patients were followed up with plain CT scan. HT was assessed on follow-up imaging by consensus of two readers (M.T. and C.O.), blinded to patients' group assignment, clinical information, baseline imaging and clinical outcome, who reviewed images randomly presented on a dedicated workstation, following the established definitions according to ECASS imaging criteria:²² hemorrhagic infarction type 1 (HI-1) was defined as small petechiae along the margins of the infarct; hemorrhagic infarction type 2 (HI-2) as confluent petechiae within the infarcted area but without space-occupying effect; parenchymal hemorrhage type 1 (PH-1) as blood clots not exceeding 30% of the infarcted area with some mild space-occupying effect; and parenchymal hemorrhage type 2 (PH-2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect. For PH-1 and PH-2 patients, we further identified those with PH remote from the index ischemia, according to SITS-MOST imaging criteria.²³ PHs were also classified according to the presence and type of pre-existing lesion on baseline MRI i.e. within index ischemia, at the site of a RSI, a microbleed, within old infarct/leukoaraiosis, or within normal brain. Symptomatic intracranial hemorrhage was defined according to NINDS,¹⁹ ECASS II,²⁴ SITS-MOST,²³ and ECASS III²⁰ criteria and determined by an experienced neurologist (E.T.).

Statistical analysis. The two groups were compared for all recorded variables using unpaired Student's *t* test for continuous variables and the Chi-square test or Fisher's exact test where appropriate for categorical variables. The Wilcoxon test was used for continuous variables that were not normally distributed. The interobserver agreement and its 95% confidence interval (CI) for the identification of patients with or without RSI were computed using the kappa statistic (κ). The two groups were compared for the rates of HT using the Chi-square test or Fisher's exact test where appropriate. For each comparison, odds ratios (OR) with 95% CI were computed. The SPSS software package (version 15.0 for Windows, SPSS Inc., Chicago, Ill) was used for the statistical analysis.

RESULTS

Among 144 consecutive acute stroke patients treated with thrombolysis during the study period, 29 were excluded for the following reasons: intra-arterial procedures (n=16), no MRI screening (n=9, including MRI contraindication in six cases, technical MRI unavailability in two cases and one restless patient), MRI not available in digital imaging and communications in medicine (DICOM) format (n=2), major motion artifacts on FLAIR (n=1) or inclusion in a therapeutic trial (DIAS 3 [Desmoteplase in Acute Ischemic Stroke Trial 3], n=1). These 29 excluded patients did not differ from the 115 patients of the study group regarding age (mean $\pm$ standard deviation [SD], 62.2 $\pm$ 18.2 versus 64.8 $\pm$ 14.6 years, $p=0.41$), sex (% women, 65.5% versus 47%, $p=0.07$), or baseline NIHSS (15.8 $\pm$ 6.9 versus 14.6 $\pm$ 5.9, $p=0.40$). The characteristics of the 115 patients of the study population are detailed in table 1. Eighty-seven patients were treated within 3 hours and 28 beyond 3 hours after stroke onset.

Overall, 21 (18.3%) patients were assigned to the RSI+ group (figures 1-3). Interobserver agreement for the identification of RSI was almost perfect ($\kappa=0.97$; 95%CI=0.38-1.56) with a discrepancy in only one patient. The mean DWI volume of RSI was 6.5 $\pm$ 12 mL (range, 0.2-54.0, interquartile range 0.6-9) and RSI were multiple in 12 patients. The mean ADC ratio were 0.67 $\pm$ 0.15, (range=0.4-0.9). At least one RSI was located in a different arterial territory than that of the index ischemia in eight patients (figures 1,3). In two cases, the RSI and index ischemia were contiguous (figure 2). RSI showed no signs of hemorrhage on baseline T2* sequence. Demographic parameters, risk factors, concomitant medical conditions and baseline characteristics were similar between groups (table 1).

During the year 2009, 42 ischemic stroke patients did not receive IV thrombolysis among the 147 patients referred for thrombolysis within 4.5 hours with a baseline MRI. Of these 42 patients, RSI were observed in six (14.3%) patients, with a median volume of 0.3 mL (range 0.2-12.4). All six patients were excluded from thrombolysis for other reasons than the presence of RSI. Clear signs of HT at the site of a RSI on baseline MRI might, however, have influenced the treatment decision in an 88-year-old patient.

After IV rt-PA, 100 of the 115 patients of the study population were followed up with MRI and 15 with plain CT scan with a mean (SD) delay from treatment to follow-up imaging of 22.8 (9.7) hours. Symptomatic HT occurred in 11 (10%) patients according to NINDS, in six (5%) patients according to ECASS II, and in three (3%) patients according to SIST-MOST and ECASS III classifications. The OR for symptomatic HT according to NINDS in RSI+ versus RSI- patients was 0.42 (95% CI, 0.05-3.47). On imaging, HI-1 or HI-2 were found in

32 (28%) patients, PH-1 in six (5%) and PH-2 in six (5%). The OR for PH-1 or PH-2 in RSI+ versus RSI- patients was 0.88 (95% CI, 0.18-4.37). There was no significant difference in frequency of any type of HT between the two groups (table 2). Remote PH-2 or symptomatic remote PH-1 did not occur. Asymptomatic remote PH-1 occurred in four cases, including one in the 21 (5%) RSI+ patients and three in the 94 (3%) RSI- patients ($P=0.56$, OR = 1.52 (IC95% 0.15-15.3)). Of the 12 PH observed in the whole study group, eight (66%) occurred within the index ischemia, one (8%) at the site of a preexisting RSI (figure 3), one (8%) at the site of a pre-existing microbleed, and two (16%) within normal brain. None occurred within old infarct or leukoaraiosis.

DISCUSSION

The identification and exclusion of stroke patients with increased risk of secondary HT are major challenges for diagnostic imaging before thrombolysis. Potential risk factors, extracted from pretherapeutic stroke MRI, include leukoaraiosis due to cerebral microangiopathy, lesion size on DWI, perfusion measurements²⁵ and cerebral microbleeds. To date, both severe cerebral microangiopathy^{26,27} and large lesion size on DWI²⁸ are established risk factors for symptomatic ICH following thrombolysis, while the risk estimate of hemorrhage in the presence of microbleeds is unlikely to exceed the benefit of thrombolysis in MRI-selected patients.¹⁷ Prior stroke is another risk factor for HT. This comes from large studies of patients with acute myocardial infarction showing that history of stroke was an independent risk factor for intracranial hemorrhage after thrombolysis.^{12,13} To limit the risk of intracranial hemorrhagic complication, prior stroke has been incorporated in the exclusion criteria of all major thrombolytic trials in acute stroke. Yet, guidelines concern symptomatic prior stroke, while they do not cover the situation of patients with RSI seen on pretherapeutic MRI.

We found MRI-defined RSI in 18% of the 115 acute stroke patients treated by IV rt-PA in a stroke unit, in line with the previously reported rate of 15% of patients who had multiple strokes of varying ages on baseline DWI obtained within 24 hours after stroke onset.¹⁰ Our results expand these findings to the acute phase of stroke by showing that MRI-defined RSI is not a rare finding. More importantly, we found that the presence of RSI was not associated with an increase in the risk of symptomatic or asymptomatic HT following thrombolysis, supporting the view that patients should not be withheld from thrombolytic therapy solely because RSI is incidentally seen on pretreatment MRI.

In the present study, RSI corresponded to well developed focal FLAIR hyperintensities, which were distant or occasionally contiguous to the index ischemia. Another group used a similar FLAIR-based approach to search for risk factors associated with HT on baseline stroke MRI.²⁹ Unlike us, that group focused on focal FLAIR hyperintensity located within the acute lesion and found that it may be associated with an increased risk of symptomatic HT after thrombolysis. In their study, FLAIR hyperintensity was located within the ischemic core, which leaves open the possibility that signal changes were related to a difference in collateral compensation or in tissue vulnerability rather than to recurrent ischemic events in the same arterial territory. Both hypotheses may also be proposed for the two patients in our study with RSI contiguous to the index acute lesion.

Overall, 5% of our patients presented symptomatic HT according to ECASS II criteria, and 5% presented PH-2, in line with other reports.^{30,31} On follow-up images, HT, including HI and PH, was detected in up to 38% of patients. This high rate of HT is most likely explained by the use of T2* sequences in the vast majority of patients. The high sensitivity of T2* sequences for the detection of blood products likely increased the detection of petechial HT.^{18,32} This also explains the relatively high rate of symptomatic hemorrhage defined, according to the NINDS study, as any type of hemorrhage coexisting with any decline in neurological status. In the NINDS study, up to 20% of thrombolysis-related hemorrhages occurred elsewhere in the brain remote from the infarct area.³³ Two postulated mechanisms for this were hemorrhage at the site of a preexisting microbleed or hemorrhage into an area of silent ischemia. Each of these mechanisms was observed once in our series, in two different patients. However, remote hemorrhage remained unexplained in two other patients suggesting that other mechanisms may be at play.³⁴

The potential impact of RSI on the risk of HT in patients treated with thrombolysis has never been assessed. The risk of spontaneous HT of ischemic lesion is high during the first two weeks and maximal during the first 48 hours.³⁵ It is well established that the risk of HT is increased by antithrombotic or fibrinolytic drugs. However, it is unclear whether the risk of HT after treatment increases with the age of ischemia. Prior stroke is listed as a contraindication for thrombolytic therapy in all current guidelines,¹²⁻¹⁶ although data are scarce regarding the risk of HT associated with prior stroke after thrombolysis. In rt-PA trials, although the benefit of treatment decreases with time from stroke onset, there is no clear relationship between the risk of serious HT and time to treatment.³⁶ In line with this, we found that RSI do not promote subsequent HT while they most likely correspond to lesions that are beyond the therapeutic window for rt-PA.

We acknowledge that our study has several limitations. First, our study population may not be representative of the whole RSI spectrum. Given that our database did not allow a systematic analysis over the entire study period of all patients eligible for thrombolysis, whether treated or not, we cannot exclude the possibility that the treatment decision might have been influenced by the MRI findings. We did, however, verify that during the last year of the study period, RSI was not more frequent or larger in patients excluded from thrombolysis than in treated patients and that in no case was thrombolysis withheld solely because of RSI. In addition, in our series, 25% of the RSI corresponded to lesions larger than 9 mL, suggesting that large size RSI was not systematically considered as an exclusion criterion for thrombolysis. Second, our results cannot be extrapolated to patients with prior symptomatic

recent stroke given that this was an exclusion criteria. We cannot, however, rule out the possibility that some RSI were associated with a subtle deficit in physical and cognitive function that might have gone unnoticed in the emergency setting of thrombolysis. Third, it may be argued that the MRI-based definition of RSI is subjective. Lastly, given the low rate of HT and the unique observation of an asymptomatic HT at the site of a preexisting RSI, our findings need to be confirmed in other studies. The crude analysis between exposure (RSI prevalence) and outcome might have been confounded by other risk factors of HT. Although we did not adjust for these potential confounders in a multivariate analysis, we checked that the RSI+ and RSI- groups did not differ for any of the known risk factors for HT. If confirmed, our findings will fill in the existing gap in rt-PA guidelines concerning patients with RSI found on pretreatment MRI.

FIGURES AND TABLES

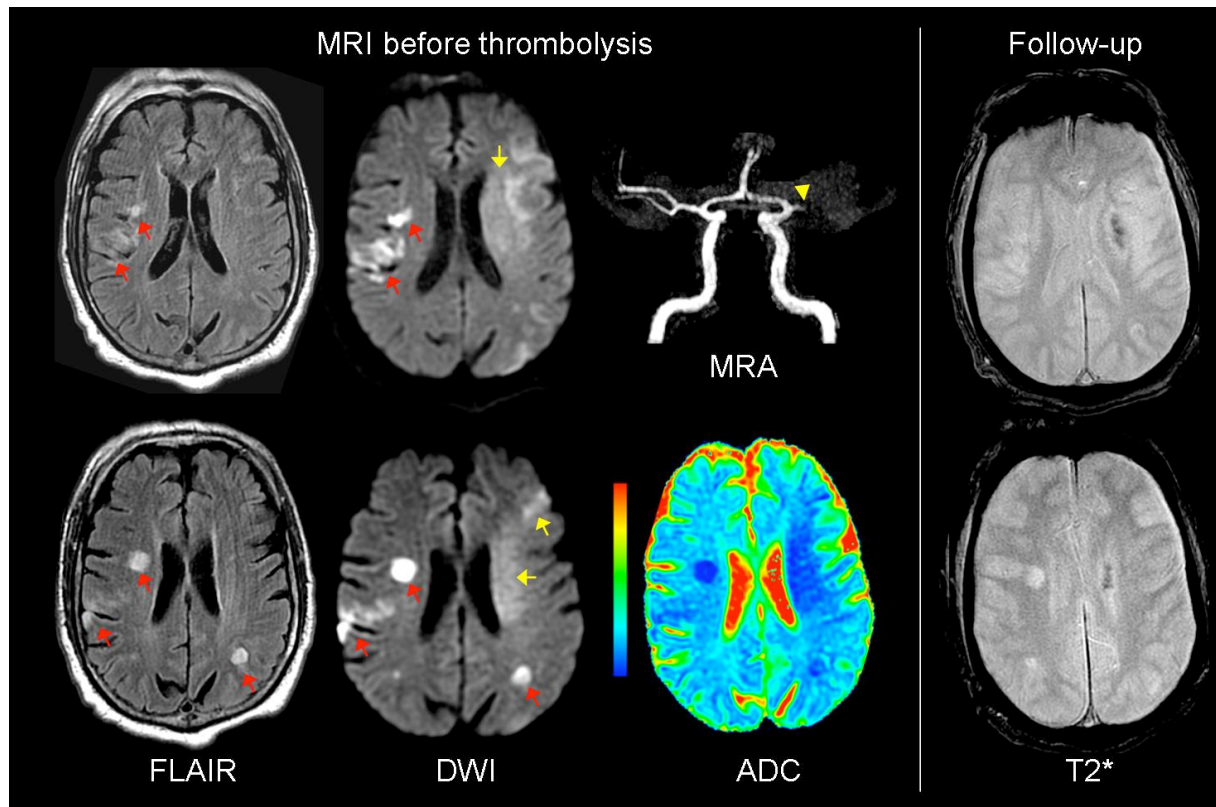


Figure 1. Recent silent ischemia (RSI) coexisting with an acute symptomatic ischemic stroke

Baseline MRI, acquired 90 minutes after the onset of right sensory-motor deficit and lateral homonymous hemianopsia (NIHSS = 23) in a 58-year-old man, revealed two types of ischemic lesions: index acute ischemia in the left middle cerebral artery (MCA) territory corresponding to an area of DWI hyperintensity without well developed FLAIR signal changes (yellow arrows) and multiple RSI corresponding to areas with well developed brain hyperintensities on both DWI and FLAIR (red arrows). Proximal occlusion of the left MCA (yellow arrow head). After thrombolysis, the follow-up T2* sequence revealed petechial hemorrhage, classed as HI-2, within the index ischemia, whereas no signs of HT were seen within the RSI areas.

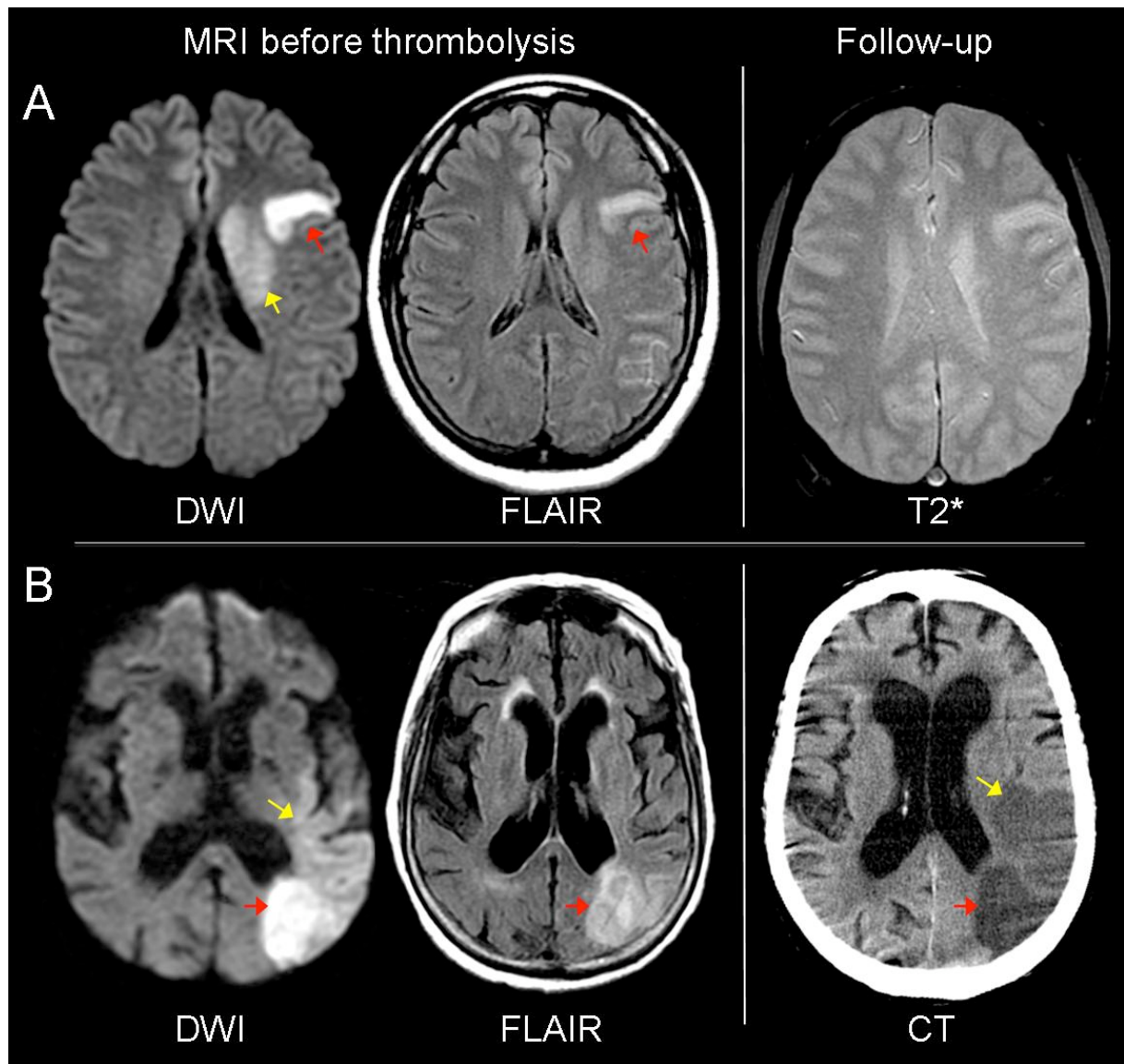


Figure 2. Illustration of two patients with recent silent ischemia (RSI+)

- A. Pretreatment and follow-up MRI from a 37-year-old woman with right motor deficit and aphasia (NIHSS = 17). Baseline MRI, acquired 90 minutes from the onset of symptoms, showed a acute index ischemia in the left deep MCA territory (yellow arrow) and RSI in the left superficial MCA territory (red arrow). After thrombolysis, there was no sign of HT on the follow-up T2* sequence.
- B. Pretreatment and follow-up MRI from a 73-year-old woman with right hemiparesia, aphasia and right lateral homonymous hemianopsia (NIHSS = 14). Baseline MRI, acquired 130 minutes from symptom onset, showed an acute index ischemia (yellow arrow) and a large contiguous RSI (red arrow) in the left MCA territory, without HT on follow-up CT scan after thrombolysis.

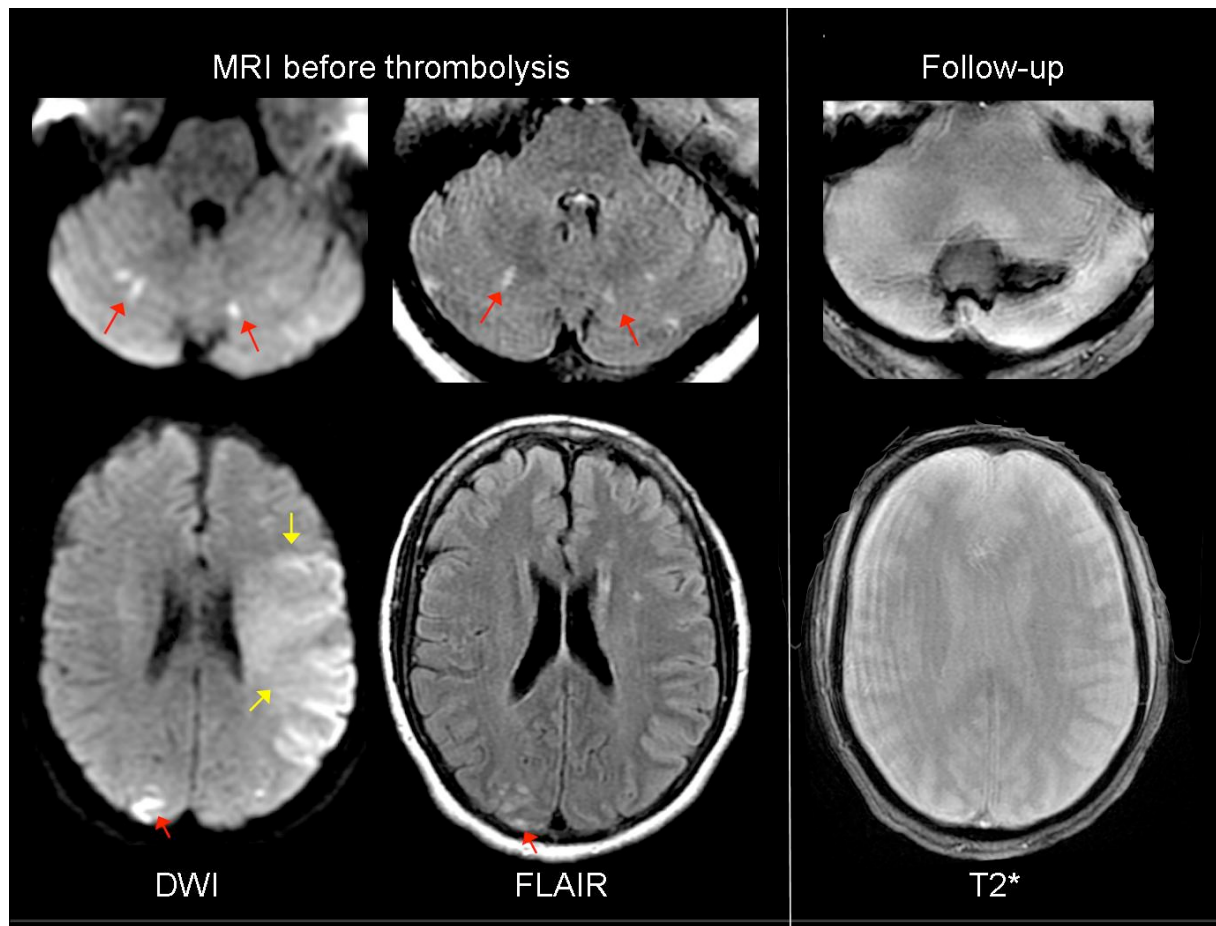


Figure 3. Hemorrhagic transformation at the site of a preexisting RSI

Baseline MRI, acquired 150 minutes after the onset of right hemiplegia and aphasia (NIHSS = 24) in a 63-year-old woman, showed a large acute index ischemia (yellow arrows) in the left MCA territory coexisting with multiple small RSI in the contralateral hemisphere and in the cerebellum bilaterally (red arrows). Follow-up T2* sequence after thrombolysis showed PH-1 at the site of the preexisting RSI, whereas it did not show any HT at the site of the acute index ischemic stroke.

Table 1. Comparison of clinical and imaging findings between patients with and without recent silent ischemia (RSI)

	Overall n = 115	RSI- n = 94	RSI+ n = 21	<i>p</i> value
Age (years)	64.8 ± 14.6	64.8 ± 14.6	64.9 ± 14.9	0.96
Gender M/F (<i>n</i>)	61/54	50/44	11/10	0.95
NIHSS score	15 ± 6	15 ± 6	14 ± 6	0.46
Hypertension, <i>n</i> (%)	64 (56)	51 (54)	13 (62)	0.52
Cigarette smoking, <i>n</i> (%)	48 (42)	38 (40)	10 (48)	0.55
Diabetes, <i>n</i> (%)	10 (9)	8 (9)	2 (10)	1.00
Hyperlipidemia, <i>n</i> (%)	38 (33)	34 (36)	4 (19)	0.13
Alcohol*, <i>n</i> (%)	12 (10)	12 (13)	0 (0)	0.12
Previous TIA or stroke, <i>n</i> (%)	11 (10)	8 (9)	3 (14)	0.42
Coronary artery disease, <i>n</i> (%)	11 (10)	8 (9)	3 (14)	0.42
Lower limb claudication, <i>n</i> (%)	4 (4)	3 (3)	1 (5)	0.56
Migraine, <i>n</i> (%)	9 (8)	5 (5)	4 (19)	0.06
Atrial fibrillation, <i>n</i> (%)	34 (30)	30 (32)	4 (19)	0.24
Anticoagulation or antiplatelets, <i>n</i> (%)	30 (26)	22 (23)	8 (38)	0.17
Systolic blood pressure†‡ mm Hg	149 ± 22	150 ± 23	147 ± 20	0.65
Diastolic blood pressure†‡ mm Hg	80 ± 16	81 ± 16	76 ± 15	0.15
Glycemia† mmol/L	6.8 ± 1.9	6.7 ± 1.6	7.3 ± 2.9	0.20
Platelet count† 10 ³ /mL	235 ± 70	232 ± 67	250 ± 86	0.31
Cardioembolism, <i>n</i> (%)	38 (33)	34 (36)	4 (19)	0.13
Large artery atherosclerosis, <i>n</i> (%)	23 (20)	17 (18)	6 (29)	0.36
Onset-to-MRI, minutes	123 ± 42	122 ± 41	129 ± 45	0.47
Onset-to-needle, minutes	157 ± 45	155 ± 43	165 ± 53	0.39
Ant/post circulation stroke	107/8	89/5	18/3	0.16
DWI volume (mL) #	52 ± 60	53 ± 57	48 ± 70	0.08
Microbleeds, <i>n</i> (%) §	25 (22)	20 (22)	5 (24)	0.78
Old infarction on MRI†, <i>n</i> (%)	15 (13)	10 (11)	5 (24)	0.15

Note. Unless otherwise indicated, data are expressed as mean ± standard deviation. *n* = number; M = male; F = female; NIHSS = National Institutes of Health Stroke Scale; Ant = anterior territory; Post = posterior territory; DWI = diffusion-weighted imaging.

* more than 10 g alcohol/day.

† before treatment.

‡ data available in 114 patients.

Wilcoxon test.

§ At least one microbleed (assessable in 122 patients).

Table 2. Comparison of hemorrhagic transformation (HT) between patients with and without recent silent ischemia (RSI)

	Overall n = 115	RSI- n = 94	RSI+ n = 21	<i>p</i> value	OR (IC 95%)
HI-1	18 (16)	17 (18)	1 (5)	0.19	0.23 (0.03-1.81)
HI-2	14 (12)	12 (13)	2 (10)	1.00	0.72 (0.15-3.49)
PH-1	6 (5)	5 (5)	1 (5)	1.00	0.89 (0.10-8.04)
PH-2	6 (5)	5 (5)	1 (5)	1.00	0.89 (0.10-8.04)
HI-1 or HI-2	32 (28)	29 (31)	3 (14)	0.13	0.37 (0.10-1.37)
PH-1 or PH-2	12 (10)	10 (11)	2 (10)	1.00	0.88 (0.18-4.37)
HT Total	44 (38)	39 (42)	5 (24)	0.13	0.44 (0.15-1.30)
Symptomatic HT					
NINDS	11 (10)	10 (11)	1 (5)	0.69	0.42 (0.05-3.47)
ECASS II	6 (5)	6 (6)	0 (0)	0.59	—
SITS-MOST	3 (3)	3 (3)	0 (0)	1.00	—
ECASS III	3 (3)	3 (3)	0 (0)	1.00	—

Note.—Unless otherwise indicated, data are n (%), HI = hemorrhagic infarction; PH = parenchymal hemorrhage; HT = hemorrhagic transformation

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VU

NANCY, le 7 septembre 2010
Le Président de Thèse

NANCY, le 1^{er} octobre 2010
Le Doyen de la Faculté de Médecine
Par délégation,

Mme le Professeur K. ANGIOI

Professeur S. BRACARD

AUTORISE À SOUTENIR ET À IMPRIMER LA THÈSE

NANCY, le 5 octobre 2010

LE PRÉSIDENT DE L'UNIVERSITÉ DE NANCY 1
Par délégation

Madame C. CAPDEVILLE-ATKINSON

Objectif. Un antécédent d'accident vasculaire cérébral inférieur à trois mois est une contre-indication à la fibrinolyse. L'IRM avant fibrinolyse retrouve chez certains patients des ischémies récentes silencieuses (IRS). Nos objectifs étaient de déterminer la fréquence de ces IRS et d'évaluer si elles étaient associées à un sur risque hémorragique après fibrinolyse.

Matériel et méthode. Nous avons analysé rétrospectivement les séquences FLAIR et diffusion de l'IRM avant traitement chez 115 patients consécutifs traités par fibrinolyse intraveineuse, à la recherche d'IRS. Nous avons comparé le risque de transformation hémorragique symptomatique et asymptomatique à 36 heures chez les patients sans et avec IRS.

Résultats. Nous avons observé des IRS chez 21 patients (18,3%). Les groupes IRS + et IRS- étaient comparables pour l'âge, le sexe, le NIHSS avant traitement et le délai AVC-fibrinolyse. Il n'y avait pas de différence significative de transformation hémorragique entre les groupes. Une hémorragie parenchymateuse de type 1 (PH-1) ou 2 (PH-2) selon les critères ECASS a été observée chez 10 (11%) patients IRS- et chez 2 (10%) patients IRS+ (OR=0,88, IC 95%=0,18-4,37). Une transformation hémorragique symptomatique définie selon NINDS a été observée chez 10 (11%) patients IRS- et chez un (5%) patient IRS+ (OR=0,42, IC 95%=0,05-3,47).

Conclusions. 18,3% des patients présentaient des ischémies récentes silencieuses sur l'IRM avant fibrinolyse intra-veineuse.

Leur présence n'était pas associée à un risque accru de transformation hémorragique après fibrinolyse.

TITRE EN ANGLAIS

MRI-defined recent silent ischemia before thrombolysis: prevalence and impact on bleeding risk

THÈSE: MÉDECINE SPÉCIALISÉE – ANNÉE 2010

MOTS CLEFS : accident vasculaire cérébral, fibrinolyse, IRM, diffusion

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