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IS THERE A TIMING FOR SENSITIVITY TO ACUTE CEREBRAL ISCHEMIA IN MIGRAINE PATIENTS?

Isabelle Francillard ^{1#}, Lou Grangeon^{1#}, Agathe Cornillot ², Estelle Houivet ³, Ozlem Ozkul,-
Wermester ¹, Aude Triquenot-Bagan¹, Benjamin Hebant¹, David Maltete ¹, Emmanuel
Gerardin ², Evelyne Guegan-Massardier ¹

Co-first authors

Affiliations:

¹ *Department of Neurology, Rouen University Hospital, 76031, Rouen, France*

² *Department of Radiology, Rouen University Hospital, 76031, Rouen, France*

³ *Department of Biostatistics and Clinical Research, INSERM U 1219, Rouen University
Hospital, University of Rouen, Rouen, France*

Corresponding author: Lou Grangeon, M.D.

Department of Neurology

Rouen University Hospital.

76031 Rouen Cedex, France

Tel.: +(33) 2 32 88 82 94; Fax: + (33) 2 32 88 87 41

E-Mail: lou.grangeon@gmail.com

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Table 1: Demographic, clinical, and radiologic characteristics according to migraine status

Figure 1: Flow chart

Figure 2: Frequency histogram of mismatch values for migraine patients and control group

Disclosures: LG, IF, AC, EH, OO, AT, DM, BH, EG and EGM have no disclosures

ABSTRACT:

Background: Migraine may be a factor of increased cerebral sensitivity to ischemia. Previous studies were conducted within 6 to 72 after stroke onset. We aimed to determine if an accelerated infarct growth exists in migraine patients within the first 4.5 hours.

Method: A retrospective case-control study was conducted where all patients admitted for acute stroke started less than 4.5 hours before and who underwent perfusion CT were assessed. The hypoperfusion and necrosis volumes on initial CT perfusion were analyzed, as well as the final infarct volume on MRI performed within 72 hours after admission. A no-mismatch pattern was defined as a ratio necrosis / hypoperfusion volume > 83%.

Results: 24 patients with personal history of migraine were identified, 8 of them with aura. The control cohort included 51 patients. No difference was found between groups in terms of demographics, initial severity or outcome or presumed cause of stroke. Mean time to CT scan was 125 minutes in migraine patients and 127 minutes in the control group. A no-mismatch pattern was equally found in migraine patients and controls, even after adjustment for age, sex and presence of proximal occlusion ($p = 0.22$). The final infarct volume was also similar in both groups.

Conclusions: Migraine patients did not display more no-mismatch pattern than controls within the 4.5 hours of stroke onset. This deviates from previous studies and may be due to our earlier time from stroke onset to CT scan. A history of migraine may lead to malignant progression of ischemia but occurring only after several hours.

KEYWORDS:

Migraine, cerebral ischemia, CT perfusion, infarct growth, mismatch pattern, cortical spreading depression, reperfusion

INTRODUCTION

During acute cerebral ischemia, the penumbra is shown as a rim of tissue surrounding the severely ischemic core (or infarct core) and remains viable for several hours. Reperfusion interventions aim to salvage this moderately ischemic tissue.

Recent data in literature suggest that migraine aura may be a factor of increased cerebral sensitivity to ischemia [1]. Indeed, studies based on animal models for migraine such as the FMH1 (familial hemiplegic migraine type 1) mutant mice showed an accelerated infarct growth compared to wild type [1,2]. This growth was correlated to the cortical spreading depression, which is implicated in migraine aura pathogenesis [3].

To date, few clinical studies were performed to address this issue and further supported this hypothesis. First, Mawet et al. [4] published a retrospective study based on MRI performed in patients with acute ischemic stroke within 72 hours following onset of symptoms. More recently, Pezzini et al. [5] analyzed CT perfusion in migraine patients who underwent reperfusion therapy within 6 hours after onset of symptoms. In both studies, migraine patients were more likely to have a no-mismatch pattern, defined as more than 83% of necrosis compared to the non-migraine patients (respectively 22% versus 4% [4] and 27.9% versus 11.5% [5]).

These first results were consistent with an increased vulnerability to cerebral ischemia in migraine sufferers and pave the way for further studies. Given the growing nature of the necrosis, the timing of such increased sensitivity to ischemia remains unknown and can deeply affect the efficacy of reperfusion therapies in migraine patients. Indeed, thrombolysis is most likely to be effective in the penumbra than infarct core (or necrosis) and can only be used within the first 4.5 hours [6, 7].

Thus, we sought to determine if an accelerated infarct growth exists in migraine patients within 4.5 hours following stroke onset.

METHODS

1/ Migraine patients

This retrospective study was conducted in neurological vascular intensive care unit (NVICU) of the Rouen University Hospital between January 2014 and December 2016.

All consecutive patients with prior diagnosis of migraine admitted for symptoms suggestive of acute stroke started less than 4.5 hours before were assessed (Figure 1- Flow chart). Migraine status was recorded in the NVICU standard medical file upon initial examination according to the International Classification of Headache Disorders - third edition (ICHD-3 β) diagnostic criteria [8]. Only patients who underwent the in-house stroke alert protocol including multimodal CT performed upon admission and who showed perfusion abnormality in anterior circulation allowing further mismatch evaluation were included. Definitive diagnosis of acute ischemic stroke should have been confirmed on MRI performed 24 to 72 hours after admission. Consecutive patients with a known non-migraine status admitted to NVICU during the same period, using the same diagnostic assessment were used as a control population.

Exclusion criteria were age under 18 years old, other cerebral lesion diagnosed on initial CT, contrast allergy, history of severe renal failure, pregnancy and non- available imaging (MRI or CT perfusion). The study protocol was approved by the Ethics Committee of Rouen University Hospital. We would be willing to share the de-identified Excel database, which includes all the clinical and radiological data of the participants upon reasonable request

2/ Clinical assessment

Demographic characteristics, individual vascular risk factor, time from symptom onset to admission multimodal CT, modified RANKIN score before admission and baseline National Institute of Health Stroke Scale (NIHSS) at admission and discharge were recorded.

According to the ICHD-3 β diagnostic criteria, patients were classified as migraine with or without aura. For each patient, we evaluated the cause of stroke, including arteriosclerosis, small-vessel disease, cardiac embolism, cervical artery dissection and other or undetermined pathogenesis.

3/ Neuroimaging protocol

All neuroimaging were performed according to the standard local stroke alert protocol. All patients admitted for symptoms suggestive of acute stroke within 6h of onset received multimodal computed tomography (CT), including a non-contrast brain CT, perfusion CT (PCT) and CT angiography of the cervical and intracranial arteries (CTA) with a General Electric Lightspeed 64-slice scanner. A two-phase PCT was then performed after a 47-ml injection of iodinated contrast at 4 ml/s. The PCT-first phase was a 60-second cine series, covering 4 cm centred on the basal ganglia. In the second phase, the same slices were obtained at 30-second intervals for additional 90 seconds. CTA was performed after a 5-min delay from the aortic arch to the vertex with 70 ml of iodinated contrast at 3.5 ml/s.

Brain MRIs were performed within 72hours after admission on either a 1.5 or 3 Tesla scanner to determine final infarct size. DWI, gradient echo T2-weighted, fluid attenuated inversion recovery and three-dimensional time-of-flight sequences were performed.

4/ Imaging analysis

All images (CT and MRI) were analysed by the same neuroradiologist (AC) blinded to the migraine status, using a GE Healthcare workstation (ADW 4.6, GE Healthcare, Waukesha, Wis., USA).

Regarding CTA analysis, we recorded whether there was intracranial arterial occlusion. A proximal occlusion was defined as occlusion within the first 3 segments of the intracranial arterial system.

Regarding perfusion CT, all perfusion maps were processed using OLEA SPHERE® software (Olea Medical®, La Ciotat, France). Cerebral blood volume (CBV), cerebral blood flow (CBF), mean-transit-time (MTT) and Time to maximum (Tmax) maps were generated for each patient using block-circulant Singular Value Decomposition (oSVD) deconvolution method [9] – the concentration-time curves of tissue were deconvoluted by the arterial input function (AIF) to obtain a residue function. To avoid partial volume effect, the AIF curve was rescaled using a venous output function (VOF). Both AIF and VOF were automatically selected. The automatic AIF selection algorithm is based on a clustering method, which classifies curves using their area under curve, their roughness, and their first moment in order to distinguish arterial signals from tissue ones. As for VOF, the algorithm is similar to the AIF one with slight adaptations to pick up vein signals instead of arteries.

CBV was derived from the area under the convoluted concentration-time curve, CBF from the height of the impulse of the residue function, MTT from the weighted average of the area under the residue function curve, and Tmax from the delay between the beginning of the acquisition and the impulse time of the residue function.

The total hypoperfusion was then defined as the area with Tmax >6s and the infarct core (necrosis) was defined by the hypoperfused area with a relative CBF <40% of the contralateral-side mean value and Tmax > 2s. [10].

We finally calculated the penumbra volume and absolute mismatch value, defined as the ratio necrosis / hypoperfusion volume. We used a ratio > 83% to define a no-mismatch pattern as previously reported [4].

Based on the MRI DWI sequences, infarct volume (in millilitres) was calculated by manual delineation of the lesion on each slice multiplied by slice thickness.

5/ Statistical analyses

We performed univariate analysis to compare clinical and imaging data between the two groups. Fisher's exact test and Chi square were used for categorical data, and the Mann-Whitney U test was used for continuous data. In order to assess the association between migraine status and the infarct growth, we used a stepwise logistic regression. All variables assumed to be relevant or potentially implying confusion bias were fed into a multivariable regression model. All statistical analyses were performed using SPSS 16.0. The threshold for statistical significance was set at $p \leq 0.05$.

RESULTS

We identified 24 patients, with personal history of migraine, who fulfilled the inclusion criteria (Figure1, flow chart). Among them, 8 patients were diagnosed with migraine with aura. The control cohort included 51 patients with no migraine history. The clinical and radiological characteristics of the migraine patients and control group are described in Table 1. The mean age at inclusion in migraine patients was 63 +/- 13.7 years old. No difference in terms of age was found between both groups ($p= 0.09$). Migraine group included more female patients (58% vs 33%, $p= 0.04$), in keeping with the female predominance of migraine.

No difference was found in terms of initial severity (NIHSS at admission 5.5 +/- 6.9 vs 10 +/- 7.5, $p = 0.26$), outcome at discharge (NIHSS 0 +/- 3.6 vs 1 +/- 5.3, $p = 0.1$), or assumed cause of stroke between the two groups. Among migraine patients, nine stroke were considered of

cardio-embolic origin (37.5%), one carotid dissection (4.1%), eight of atherosclerosis origin (33.3%) and 6 (25%) of undetermined or other origin.

Mean time to CT scan was 125 minutes in migraine patients and 127 minutes in the control group, similar in both groups ($p=0.97$).

Regarding the radiological findings, proximal occlusion was found within the first segment of the middle cerebral artery in 5 migraine patients and 9 controls, within the second segment in 5 migraine patients and 14 controls and within the cervical carotid artery in 2 migraine patients and 7 controls. All but one carotid occlusion were associated with occlusion within middle cerebral artery.

We did not find any difference of absolute mismatch value between the two groups (6.9% Vs 13%, $p=0.46$). A no-mismatch pattern was equally found in migraine patients and controls (0% vs 3.8%, $p=1$). The frequency histogram of mismatch values displayed a single cluster of patients in low ratios, with no difference between control and migraine patients (Figure 2).

The final infarct volume measured on MRI was not significantly different between migraine and control groups (30.3 ml Vs 51.3 ml, $p=0.38$).

These radiological findings remained unchanged when restricting to the 8 patients with aura migraine only: the absolute mismatch value was also 6.9%. No statistical analysis was performed considering the small number of patients.

The rate of reperfusion treatment was 79% in migraine patients: 19 underwent thrombolysis and three thrombectomy. This rate was equivalent, of 71%, in the control group: 36 patients underwent thrombolysis and 9 thrombectomy. Hemorrhagic transformation occurred in three (14%) migraine patients and in 15 (29%) control patients, 7 of which were significant (PH1 and PH2 scores according to the ECASS scale). This rate was similar between the two groups ($p=0.23$). On the control MRI, the revascularization rate was 7/12 (58.3%) in migraine patients and 27/31 (87%) in controls with proximal occlusion ($p=0.09$).

Multivariate analysis confirmed the absence of difference between groups in terms of mismatch after adjustment on age, sex and presence of proximal occlusion on initial CT scan ($p = 0.22$).

DISCUSSION

In this study in CT perfusion within the 4.5 hours of stroke onset, migraine patients did not display more no-mismatch pattern than controls.

This deviates from the conclusion of previous studies and may be due to our earlier time from stroke onset to CT scan. Indeed, our study showed a similar pattern in CT perfusion between migraine and control patients, possibly representing an early picture of the infarct growth during acute ischemia. In this study, the median time to CT scan was 2 hours, compared to 3 hours in Pezzini's study [5] and 7 hours in Mawet's study [4]. Herein, due to this earlier timing, all patients in both groups were clustered in the low ratio of mismatch value. Previous studies with delayed perfusion CT showed a more flat distribution in both groups with an upsurge in the high ratio for the migraine patients. No details regarding patients who received MRI or CT perfusion within the first 4.5 hours were available in those two studies [4], [5]. Apart from timing, no other relevant difference in our study compared with the previous ones in terms of age, gender, cause of stroke or site of occlusion can explain the diverging results. Similarly to animal studies, this would imply an accelerated growth of infarct and not a constant and steady sensitivity to ischemia [1]. Despite the absence of a prominent no-mismatch pattern in the early hours of stroke, migraine may lead to accelerated loss of viable tissue at risk for infarction but measurable from a certain time only. It has been suggested that higher number of cortical spreading depression (CSD) accelerates the growth of the necrosis core and that area of hypoperfusion directly correlates with CSD frequency [11, 12]. Migraine status could influence the rate of progression to infarction through enhanced susceptibility to developing CSD during stroke [13,14]. Indeed, previous study showed even a stronger association between no-mismatch pattern and migraine with aura, in which the role of CSD is clearly established [4, 3, 15].

In animal models, accelerated infarct growth would be explained by faster anoxic depolarization and more frequent peri-infarct CSD. Observational studies showed a frequency of zero to ten CSD in an hour [11]. The number of CSD developed in human brain during ischemia remains unknown. Since time is necessary to the propagation of CSD and the accumulation of their negative effects, measurable difference in perfusion CT in migraine patients may appear after a few hours [16]. Further studies addressed to analyse the necrosis growth over time with repeated perfusion CT or MRI for each patient are needed.

One intriguing point is the similar final infarct volume between migraine patients and controls, in our study as in previous one [5]. This deviates from previous animal studies, where *FMHI* mutant mice developed larger infarct after occlusion of the middle cerebral artery [2]. Increased compensatory mechanisms to brain ischemia, possibly through ischemic preconditioning may explain the absence of larger infarct in human migraineurs despite an accelerated growth of necrosis [5]. Ischemic preconditioning involves that cerebral tissue with previous ischemic events shows better tolerance to subsequent events [17]. Indeed, several studies have demonstrated that CSD could induce ischemic preconditioning in animal models, although the exact pathway is still debated [18,19]. After experiencing many CSD over the years, migraine patients may partially compensate the growth of infarct, even if accelerated.

Another possible explanation could be that the perfusion abnormalities displayed in migraine patients have been falsely increased by repeated CSD without indicating a perfect match with the growth of necrosis. Moreover, given the retrospective nature of this study, we were not able to accurately record whether a migraine attack had occurred during CT perfusion in our patients. This would probably have also had an impact on CT perfusion abnormalities. Indeed, reversible cerebral blood flow associated with elevated mean transient time has already been reported during migraine aura [20] but this needs to be confirmed by larger studies.

Some limitations in this study should be considered. The small number of patients and the retrospective character do not allow us to establish definitive conclusions. The small proportion of migraine with aura might also have prevented significant differences to be detected. Nevertheless, reliable assumptions can be made teaming up our findings and previous studies given that the only difference between those studies is the delay from symptoms onset to perfusion imaging. Another important point to discuss is the choice of no-mismatch with the cut-off of 83% as primary endpoint. Given our early timing of CT scans, almost no patient has reached this no-mismatch level. Nevertheless, no difference was found in terms of necrosis and penumbra volumes, nor of their ratio in absolute value. As post-hoc analysis, we used a different ratio, with the cut-off of 38%. This cut-off has been described in literature as providing the highest sensitivity and specificity for identifying patients in whom reperfusion was associated with a favorable response [21]. No migraine patient and only one control showed a ratio necrosis/ ischemia higher than 38%.

We also had a look at the « extremely small ratio » patients, and arbitrarily used the cut-off of 10% : Seven migraineurs (33%) showed a ratio higher than 10% compared to 13 controls (25%). It was also similar between groups according to Chi-square test ($p=0.49$). This secondary analyses must be interpreted with great caution, but seem to confirm our results with a similar pattern of mismatch between migraine patients and controls during the first few hours of a stroke.

To conclude, a history of migraine may lead to malignant progression of ischemia with penumbra quickly recruited into the infarct core but occurring only after several hours from symptoms onset and not initially. This would make the precocity of reperfusion therapies all the more crucial in migraine patients. Further larger and prospective study to properly address this issue is needed

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AUTHORS CONTRIBUTION:

IF: collection, analysis and interpretation of data, drafting of manuscript

LG: analysis and interpretation of data, drafting and revision of manuscript.

AC: collection and analysis of data

EH: Statistical analysis and interpretation of data

OO: Recruitment of subjects, drafting of manuscript

AT: Recruitment of subjects, drafting of manuscript

BH: Recruitment of subjects , drafting of manuscript

DM: Drafting and revision of manuscript

EG: Interpretation of data and manuscript revision

EGM: study concept, recruitment of subjects, interpretation of data and manuscript revision.

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TABLES AND FIGURE CAPTIONS

Table 1: Demographic and clinical characteristics according to migraine status

	Migraine patients (n=24)	Controls (n=51)	p
Migraine with aura, n (%)	8 (33%)	NA	NA
Age, y, mean +/- SD	63 +/- 13.7	68.7 +/- 12.4	0,09
Female, n (%)	14 (58%)	17 (33%)	0,04
Risk factors, n (%)			
High blood pressure	13 (54%)	27 (53%)	1
Diabetes mellitus	3 (13%)	6 (12%)	1
Smoking history	8 (33%)	24 (47%)	0,32
Hyperlipidemia	9 (38%)	20 (39%)	1
Personnal vascular history	3 (13%)	15 (30%)	0,15
Familial vascular history	2 (8%)	6 (12%)	1
Clinical scores, median +/- SD			
RANKIN at admission	0 +/- 0,3	0 +/- 0,3	0,85
NIHSS at admission	5,5 +/- 6,9	10,0 +/- 7,5	0,26
RANKIN at discharge	0 +/- 1,5	1,0 +/- 1,6	0,23
NIHSS at discharge	0 +/- 3,6	1,0 +/- 5,3	0,1
Stroke etiologic subtype	***	***	0,98
Intravenous thrombolysis ,% (n)	19 (79%)	36 (71%)	0,58
Mechanical thrombectomy, % (n)	3 (13%)	9 (18%)	0,74

(*) significant. (**) Non applicable. (***) Categories non detailed, SD Standard deviation

Table 2: Radiological characteristics according to migraine status

	Migraine patients (n=24)	Controls (n=51)	<i>p</i>
Time from onset in minutes, mean +/- SD			
To CT scan	125 +/- 55	127 +/- 54	0,97
To intravenous thrombolysis	173 +/- 51	154 +/- 50	0,22
To mechanical thrombectomy	235 +/- 18	249 +/- 76	0,61
Occlusion on initial angiogram, n (%)	12 (50%)	31 (60.7%)	0,37
Within 1 st segment of middle cerebral artery	5 (20.8%)	9 (17.6%)	
Within 2nd segment of middle cerebral artery	5 (20.8%)	14 (27.4%)	
Within cervical carotid artery	2 (8%)	7 (13.7%)	
Within anterior cerebral artery	0	0	
Volumes, ml, mean +/- SD			
Necrosis volume on perfusion CT	8,6 +/- 18,5	8,8 +/- 16,2	0,66
Ischemia volume on perfusion CT	69,4 +/- 65,0	71,1 +/- 68,9	0,95
Stroke volume on MRI	30,3 +/- 46,8	52,3 +/- 70,6	0,31
Necrosis volume/Ischemia volume, mean	6,9%	13,1%	0,48
No mismatch pattern, %	0	2 (3,9%)	1

Figure 1: Flow chart**Figure 2: Frequency histogram of mismatch values for migraine patients and control group**

Percentage of population