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Internal borderzone involvement predicts the functional outcome of acute MCA stroke patients

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Additional information

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Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

**Internal border zone injury predicts the functional outcome of
acute MCA stroke patients**

ABREVIATIONS

ASPECTS: Alberta **Stroke** Program Early CT Score

CST: Corticospinal tract

D: Deep

DWI: diffusion-weighted imaging

FLAIR: Fluid-attenuated inversion recovery

IA: Intraarterial

IBZ: Internal Border Zone

ICA: Internal carotid artery

IV: Intravenous

MCA: middle cerebral artery

MNI: Montreal Neurological Institute

MRA: Magnetic resonance angiography

mRS: Modified Rankin Scale

NIHSS: National Institute of Health Stroke **Score**

ROI: Region of Interest

S: Superficial

TOAST: Trial of Org1072 in Acute Stroke Treatment

tPA: Tissue plasminogen activator

ABSTRACT

Background and Purpose

Classification of deep (D), superficial (S) MCA territories and their junctional vascular area (the internal border zone, IBZ) can help to identify patients most likely to benefit from aggressive reperfusion therapy after stroke. We tested the prognostic value of an IBZ injury compared to DWI-ASPECTS and infarct volume.

Materials and Methods

DW lesions of 168 patients with acute (4.2 ± 6.5 h) MCA strokes were retrospectively examined and manually delineated. Patients with haemorrhagic transformation or other neurological diseases were excluded. Clinical data were recorded within 24 h following symptom onset and 48 h for patients who benefited from reperfusion therapy. The occurrence of an IBZ injury was determined using a standardized stereotaxic atlas. Performance to predict a good outcome (mRS<3 at 3 months) was estimated through ROC curves for DWI-ASPECTS ≤ 6 , lesion volume ≥ 100 mL and IBZ injury. Logistic regression models were performed to estimate independent outcomes for infarct volume and IBZ injury.

Results

Infarcts involving the IBZ were larger (94.9 ± 98.8 mL vs. 30.2 ± 31.3 mL), had higher NIHSS (13.8 ± 7.2 vs. 7.2 ± 5.7), more frequent MCA occlusions (64.9% vs. 28.3%), and worse outcomes (mRS 3.0 ± 1.8 vs. 1.9 ± 1.7), and were less responsive to IVtPA ($34\pm 47\%$ vs. $55\pm 48\%$ of NIHSS improvement). The area under the ROC curves was comparable between the occurrence of IBZ injury (0.651), ASPECTS ≤ 6 (0.657) and volume ≥ 100 mL (0.629). Logistic regression analyses showed an independent effect of an IBZ injury, especially for superficial MCA strokes and for patients who benefited from reperfusion therapy.

Conclusion

An IBZ injury is an early and independent marker of stroke severity, functional prognosis and treatment responsiveness.

Introduction

A large lesion on diffusion-weighted imaging MRI (DWI) is a major predictor of death and disability[1], and it influences the response to aggressive revascularization strategies, such as IV thrombolysis (IV tPA) or mechanical thrombectomy[2]. Specifically, a volume of 100 mL has been proposed as a reliable cut-off for poor patient outcome prediction[3]. The Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) - initially introduced on CT - has also been applied with DWI, and DWI-ASPECTS ≤ 6 is the most effective cut-off to identify DWI lesion volumes ≥ 100 mL[4]. However, the ASPECTS is also controversial, as there is an unequal weighing between the different MCA regions, favouring the basal ganglia[5], as well as a wide variation in lesion volumes for each score value and a rather poor correlation with stroke lesion volume in the deep MCA territory[4].

The insula, putamen and operculum, which are commonly involved in ischaemic injuries[9][10][11], may be markers of stroke severity and poor clinical outcome[12]. We believe that these regions are located within the same vascular field: the internal border zone or IBZ[13]. Indeed, the MCA territory is frequently divided into two subdivisions, corresponding to the deep and superficial perforating artery vascular fields. The internal border zone is located in the watershed area between deep and superficial subterritories. Isolated IBZ infarcts represent only 6% of all MCA infarcts[6] and have been described as multiple infarcts in a rosary-like pattern along the lateral ventricle[7]. Because of its distal location with terminal vascularization, the IBZ is considered an area of major haemodynamic susceptibility[7,8]. To our knowledge, no study has specifically examined the clinical, aetiological and prognostic features of infarcts involving the IBZ among MCA infarcts. This approach has some practical advantages because it may be more suitable for urgent decision-making processes than complex and time-consuming volume estimation measures, and it is easier to handle than the ASPECTS.

In the present study, we investigated the use of patterns of distribution of ischaemia in the clinical setting and specifically tested whether (1) infarcts involving the IBZ would be larger than other MCA strokes, (2) patients with an IBZ injury would show lower functional outcome than others and (3) the prognostic value of an IBZ injury would be comparable to those of the ASPECTS ≤ 6 and lesion volume ≥ 100 ml.

Materials and Methods

Patients

The Institutional Review Board approved this retrospective analysis of clinical data (CRM-2003-080, Comité d'éthique de la recherche en imagerie médicale). The study population consisted of consecutive acute MCA stroke patients, although the analyses were retrospective. All patients with isolated acute ischaemic stroke in the MCA territory were included. Exclusion criteria included (1) haemorrhagic transformation, (2) other neurological disease that may have a functional impact on the mRS, or association of lesion in any other vascular territory, (3) time from onset of the symptoms to MRI >48 hours and (4) poor image quality. Clinical data, including history of cardiovascular risk factors, anticoagulant or antiaggregant use, NIHSS score at arrival, time from symptom onset to imaging and time to thrombolysis, were collected. We determined the delay between the onset of symptoms as stated in the patient's medical record and the exact time of the MRI acquisition. Clinical data were recorded within 24 h following symptom onset and one day after treatment for patients who benefited from IV tPA or mechanical thrombectomy. Patients were scheduled for follow-up appointments at least 90 days after the stroke. Stroke severity was then assessed by the modified Rankin scale (mRS)[14]. The mRS score was assessed on the basis of patient consultation reports. If the score was not recorded on the consultation report, it was evaluated according to the description of the patient's clinical condition, with confirmation of the mRS score by the neurologist in charge of the patient. A good clinical outcome was defined as an mRS score <3, and a poor clinical outcome was defined as an mRS score >2.

Imaging

DWI images were obtained using one of the three protocols described in the supplementary methods. MCA vessel status was explored using magnetic resonance angiography (MRA), and MCA stenosis was assumed either with a reduction of more than 50% of the signal column or a signal discontinuity. ICA status (occlusion/stenosis) was determined either from Doppler ultrasound reports or injected MRI centred on the supra-aortic trunks. Arterial stenosis was defined as at least 50% narrowing of the lumen. Recanalization or occlusion after IV tPA was investigated using CT one day after treatment. For each patient, a concomitant visual analysis of DWI and FLAIR sequences was performed to establish the presence of a DWI/FLAIR mismatch. Each DW and FLAIR image was inspected for image quality. A subjective quality score was constructed using a 5-point Likert-scale with 5 corresponding to the best quality. The quality of images with a score below 4 was considered poor, and corresponding patients were excluded from further analyses.

Registration and segmentation

Volumetric analysis of stroke lesions was performed at the acute stage using DWI images. Infarcts were manually delineated using the MRICron (www.mricron.com) software package (version: June 2015). Lesion volumes were calculated at this stage. DWI images were then registered to FLAIR images and normalized to the MNI space using the elderly FLAIR template of the clinical toolbox[15], SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12), and lesion cost function masking[16]. If necessary, images were left-right inverted so that all lesions appeared in the right hemisphere to increase the statistical power of subsequent analyses.

The DWI-ASPECTS (Alberta Stroke Program Early CT score[17]) was estimated in a semiautomated manner. First, ASPECTS regions were manually segmented on the FLAIR template of the clinical toolbox using MRICron and the same slice orientation as in Barber et al.[17], both using the two reference slices of the ASPECTS (2DASPECTS) and the whole brain volume (3DASPECTS). The resulting ASPECTS regions of interest (ROIs) were then registered back to the original orientation of the clinical toolbox template using SPM12. The infarct volumes in each ASPECTS ROI were computed for every patient. One ASPECTS point was considered to indicate whether more than 30% of an ASPECTS region was injured[17]. Each 2DASPECTS and 3DASPECTS was visually verified by an experienced neuroradiologist (either RG or SG).

Patterns of distribution of ischaemia

In a previous study, we built a probabilistic spatial estimate of the IBZ[13], which extended from the anterior part of the internal capsule to the caudate nucleus head and encompassed the external section of the globus pallidum, the rostral part of the corona radiata, the anterior portion of the putamen and the insular cortex. This atlas divides the MCA territory into three regions (S, D and IBZ) that we used to create some patient groups based on lesion topography. The transformations computed during the normalization step were exploited to wrap the atlas of S, D and IBZ to the patient space. The atlases and the infarct delineations were then in the same space and thus comparable. We considered a region as injured if at least 30% of its volume[17] was superimposed on the patient infarct delineation. Six topography groups were then created: internal border zone (IBZ); superficial (S); superficial and IBZ (S+IBZ); deep (D); deep and IBZ (D+IBZ); and territorial (Figure 1). From these 6 groups, we considered lesions involving the IBZ (D+IBZ, S+IBZ, IBZ and territorial) compared to those preserving the IBZ (S and D). Moreover, we compared the sensitivity and

specificity of IBZ involvement, ASPECTS ≤ 6 and DWI volume of infarct ≥ 100 ml to predict poor clinical outcome 90 days after stroke using receiver operating characteristic (ROC) curves.

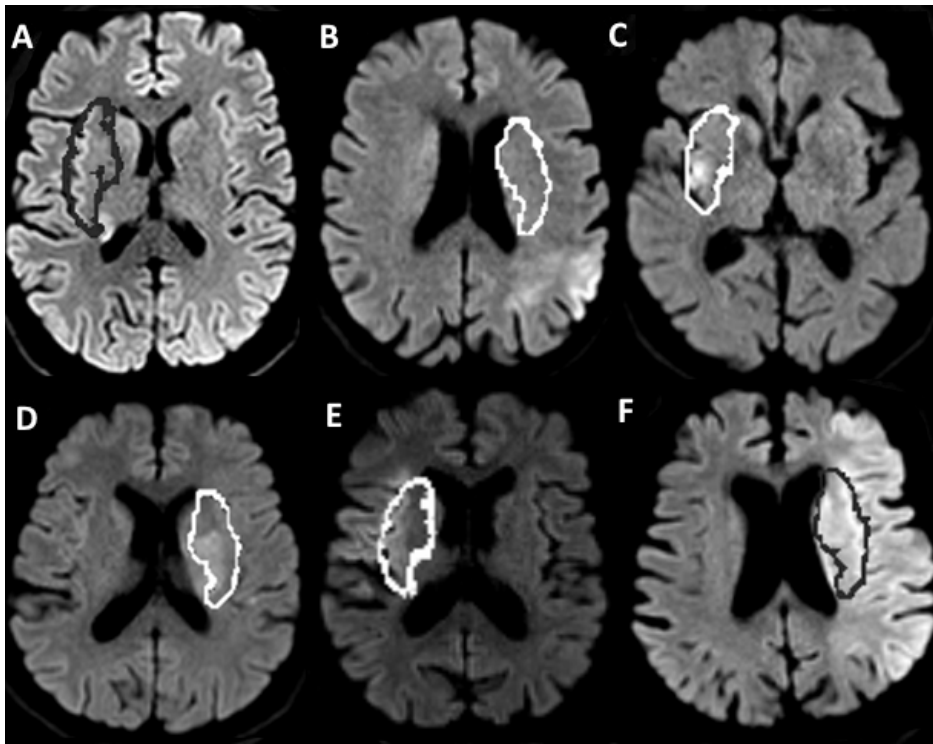


Figure 1

The following topography groups are shown by axial DWI images of six patients: deep (A); superficial (B); IBZ (C); deep and IBZ (D); superficial and IBZ (E); and territorial (F). Outer contours of the IBZ (in the native patient space) are displayed either in black (A and F) or in white (B, C, D and E).

Statistical analyses

Statistical analyses were performed using SPSS software (IBM, version 20). We reported continuous variables as the mean with standard deviation and compared them using Student's t test. Categorical variables were compared using chi-square or Fisher exact tests. Logistic regression models were also performed with the patient outcome as the dependent variable and the predictors being IBZ involvement in ischaemia and the lesion volume (to independently estimate both effects). The results are expressed as follows: Predicted logit of (Poor Outcome) = constant + β_1 x IBZ + β_2 x DWI Volume. Models were built using either the whole sample, lesion groups, or patients who received thrombolysis or not. Analyses were similarly performed using an ASPECTS ≤ 6 and a volume ≥ 100 ml instead of IBZ involvement.

Table 1: Demographic and clinical characteristics of the study population

	IBZ injured	IBZ preserved	Total
Number of patients (%)	77 (45.8%)	91 (54.2%)	168
Age (y)	70.6±14.4	68.9±14.4	69.5±15.2
Male (%)	38 (49.4)	47 (51.6)	85 (50.6)
Cardiovascular risk factors			
Diabetes n (%)	6 (7.8)	19 (20.9)	25 (14.9)
Hypertension n (%)	47 (61.0)	62 (68.1)	109 (64.9)
Smoke n (%)	15 (19.5)	18 (19.8)	33 (19.6)
Coronary artery disease n (%)	13 (16.9)	9 (9.9)	22 (13.1)
Hyperlipidaemia n (%)	28 (36.4)	30 (33.0)	58 (35.1)
Obesity (BMI>30 kg/m ²) n (%)	4 (5.2)	6 (6.6)	10 (5.9)
Atrial fibrillation n (%)	25 (32.5)	30 (33.0)	55 (32.7)
Anticoagulation n (%)	5 (6.5)	12 (13.2)	17 (10.1)
Antiaggregant n (%)	14 (18.2)	15 (16.5)	29 (17.3)
History of stroke n (%)	4 (5.2)	9 (9.9)	13 (7.7)
Right laterality of infarct n (%)	34 (44.2)	37 (40.7)	71 (42.3)
Delay between stroke and MRI (h)	3.1±3.9	4.2±4.8	4.2±6.5
DWI lesion volume (cc)	94.9±98.8	30.2±31.3 *	59.4±76.6
Admission NIHSS score	14[8;20]	6[3;20] *	8[5;16]
3-mo clinical outcome (mRS)	3.0±1.8	1.9±1.7 *	2[1,4]
[0,2] n (%)	32 (41.6)	66 (72.5) *	98 (58.3)
[3,6] n (%)	45 (58.4)	25 (27.5) *	70 (41.7)
Deaths at 3 months n (%)	6(7.8)	6(6.6)	12(7.1)
ASPECTS 3D	7[6;8]	10[8;10] *	9[7;10]
ASPECTS 2D	7[6;9]	9[8;10] *	8[7;10]
DWI/FLAIR mismatch	59 (76.6)	57 (62.6)	116 (69.0)
IV tPA administration n (%)	50 (64.9)	33 (36.3)	83 (49.4)
Time to thrombolysis (h)	3.0±0.7	3.2±0.8	3.1±0.7
Repermeabilisation after IVtPA n (%)	31/50 (62.0)	23/28 (82.1)	54/78 (69.2)
IA mechanical n (%)	13 (16.9)	4 (4.4)	17 (10.0)
Decrease of NIHSS at Day 1 after IVtPA administration	5.1±7.9	4.2±4.6	4.7±6.8
Evolution NIHSS at Day 1 after IVtPA administration (%)	33.6±63.2	55.0±48.4	42.1±42.5
TOAST-I. LAA n (%)	16 (20.8)	21 (22.8)	37 (22.0)
TOAST-II. CE% n (%)	41 (53.2)	49 (53.3)	90 (53.6)
TOAST-III. SVO n (%)	2 (2.6)	1 (1.1)	3 (1.8)
TOAST-IV. OT n (%)	6 (7.8)	6 (6.5)	12 (7.1)
TOAST-V. UD n (%)	12 (15.8)	15 (16.3)	27 (16.1)
Vascular status			
Cervical ICA occlusion n (%)	10 (13.0)	7 (7.7)	17 (10.1)
Cervical ICA stenosis n (%)	4 (5.2)	9 (9.9)	13 (7.7)
MCA occlusion n (%)	50 (64.9)	26 (28.3)*	76 (45.2)
MCA stenosis n (%)	7 (9.1)	8 (8.8)	15 (8.9)

Average values ± standard deviation or number (percentage) are reported. * P<0.05
The median (interquartile range) is displayed for NIHSS, mRS, ASPECTS 2D and ASPECTS 3D.

Results

Of the 656 patients meeting the inclusion criteria, 447 lesions occurred in the MCA territory. The following lesions failed to meet the inclusion criteria: 184 lesions were excluded because of an MRI acquisition >48 h after the onset of the symptoms; 42 lesions were excluded due to haemorrhagic

transformation on MRI images; and 53 lesions were excluded due to poor-quality images. Overall, 168 patients with acute ischaemic stroke of the MCA territory were included (Table 1) as follows: 164 patients (97.6%) had an MRI acquisition within 24 hours (overall range 1-34 h); 98 patients (58.3%) had a good functional outcome three months after stroke onset; 85 patients (50.6%) were males; 71 patients (42.3%) had a stroke involving the right hemisphere; 83 patients (49.4%) received IV thrombolysis; and 17 patients (10.1%) underwent IA mechanical thrombectomy. Forty-five percent had MCA occlusion, 8.9% had stenosis of the MCA (8.9%), 7.7% had stenosis of the internal carotid artery, and 10.1% had ICA occlusion. In 5/83 patients, reperfusion after IV tPA could not be evaluated (CT images could not be retrieved), and reperfusion was observed in 54/83 patients (64.3%).

IBZ injury

In total, 77 patients (46%) showed lesions involving the IBZ, and the IBZ was preserved in 91 patients (54%). There were no significant differences between these two groups in terms of cardiovascular risk factors (diabetes, active smoking, high cholesterol and hypertension), anticoagulant and antiaggregant therapy, TOAST scores or laterality of stroke (Table 1). The patients with an infarct involving the IBZ showed a larger lesion volume ($94.9 \pm 98.8 \text{ cm}^3$ vs. $30.2 \pm 31.3 \text{ cm}^3$, $p < .0001$; the 90th percentile was composed of IBZ lesions at 86.7%), had a lower ASPECTS (2DASPECTS 6.9 ± 2.3 vs. 8.8 ± 1.4 , 3DASPECTS 6.7 ± 2.5 vs. 9.1 ± 1.3 , $p < .0001$), were clinically more severe (NIHSS: 13.8 ± 7.2 vs. 7.2 ± 5.7 , $p < .001$) and were associated with poorer outcome at follow-up (mRS at 3 months: 3.0 ± 1.8 vs. 1.9 ± 1.7 , $p < .05$). Poor outcomes were observed among 45/77 patients (58.5%) with infarcts that included the IBZ, whereas 25/91 patients (27.5%) had infarcts that included other regions. We further investigated the ability of the occurrence of an IBZ injury to identify a patient worsening in comparison to the following two clinical biomarkers: an ASPECTS ≤ 6 and a diffusion volume ≥ 100 ml. To predict poor functional outcome, the area under the ROC curve of IBZ involvement (average 0.651 and 95% confidence interval: [0.566; 0.736]) was comparable to that of an ASPECTS ≤ 6 (3DASPECTS: 0.657 [0.570; 0.744], 2DASPECTS: 0.662 [0.575; 0.749]) and a diffusion volume ≥ 100 ml (0.629, [0.540; 0.717]).

Moreover, the NIHSS reduction after IV thrombolysis was lower for the patients with an infarct including the IBZ ($33.6\% \pm 63.2\%$) compared to patients with a preserved IBZ ($55.0\% \pm 48.4\%$, $p < .01$). These patients were significantly more frequently treated with IV thrombolysis (64.9% vs. 36.3% , $p < .05$) or IA mechanical thrombectomy (16.9% vs. 4.4% , sample size too small to be tested). Moreover, MCA occlusions were detected most frequently in patients with an IBZ injury (64.9% vs.

28.3%, $p < .0001$, Table 1; OR=4.8 [2.5–9.4]). Among the 76 patients with MCA occlusion, 50 patients (66%) showed an IBZ injury and had larger infarct volumes than the 26 patients with no IBZ injury ($92.8 \pm 91.5 \text{ cm}^3$ versus $41.4 \pm 31.9 \text{ cm}^3$, $p < .001$). No significant difference between the two patient groups was found in terms of MCA stenosis, ICA stenosis or ICA occlusion.

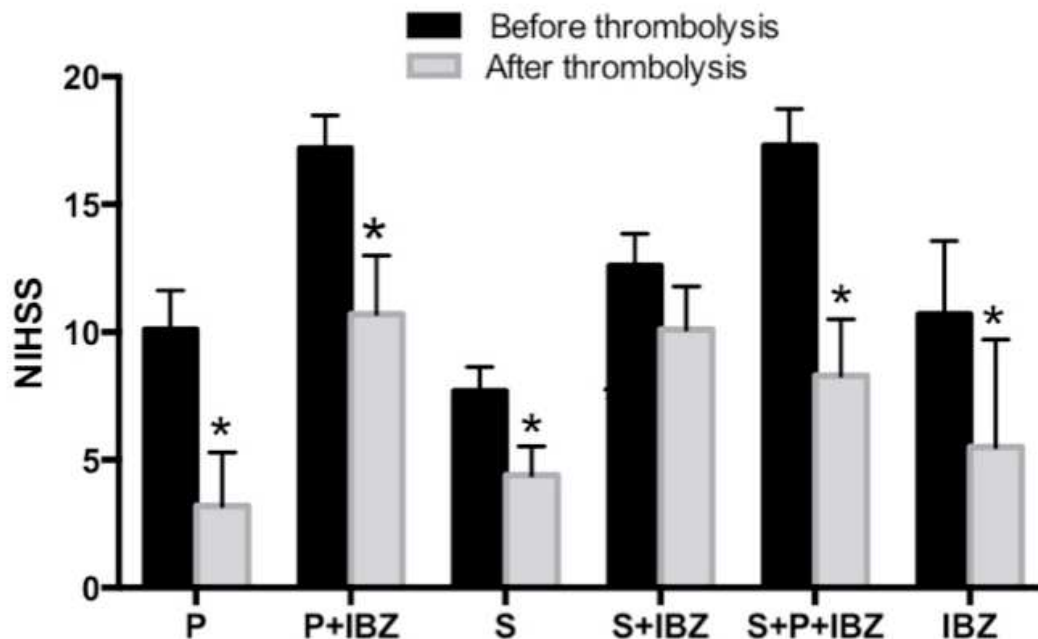


Figure 2

The effect of IV thrombolysis (in terms of NIHSS reduction) was significant for each patient group, except S+IBZ. * $p < .05$.

Spatial lesion patterns

In our patient sample, an IBZ injury impacted the patient condition differently depending on the spatial lesion arrangement. With IBZ injury (S+IBZ and D+IBZ), lesion volumes were higher (Supplementary Table 1) than with isolated S and D injuries (109.8 ± 75.3 and $28.2 \pm 10.6 \text{ cm}^3$ vs. 35.5 ± 33.5 and $12.8 \pm 10.8 \text{ cm}^3$, $p < .05$). In the S+IBZ group, the NIHSS score increased compared to that in the S group (12.7 ± 5.8 and 14.9 ± 6.8 vs. 6.7 ± 5.8 and 8.6 ± 10.1 , $p < .05$), and the mRS score at follow-up was significantly higher than that in the S group (3.3 ± 1.8 versus 1.7 ± 1.7 , $p < .01$). Furthermore, the NIHSS score decreased significantly at Day 1 after thrombolysis for all topography subgroups, except for S+IBZ lesions (12.6 ± 4.9 at admission and 10.1 ± 1.8 at Day 1, $\Delta = 2.4 \pm 8.4$, $p > .05$) (Figure 2), despite a high rate of early reperfusion (13/21; 61.9%) (Supplementary Table 1). Thus, these data indicated that the implication of the IBZ in superficial infarcts leads to larger lesions, worse acute clinical status,

poorer functional outcome and weaker response to thrombolysis. Moreover, we specifically investigated the sensitivity and specificity of IBZ injury to determine a poor functional outcome through ROC curves. The area under the curve was higher when IBZ was involved (0.687 for superficial lesions and 0.566 for deep infarcts). The 95% confidence intervals were [0.570; 0.803] and [0.379; 0.753], respectively, compared to a diffusion volume ≥ 100 ml (0.615 [0.493; 0.737] for superficial lesions and 0.500 [0.311; 0.689] for deep infarcts) and ASPECTS ≤ 6 (3DASPECTS: 0.531 [0.409; 0.652] for superficial lesions and 0.506 [0.317; 0.694] for deep infarcts; 2DASPECTS: 0.531 [0.409; 0.652] for superficial lesions and 0.532 [0.344; 0.721] for deep infarcts). Thus, an IBZ injury has at least the same level of sensitivity and specificity as an ASPECTS ≤ 6 or a lesion volume ≥ 100 ml. Although we verified that IBZ injury had an impact on the patient state and prognosis, it was challenging to differentiate its effect from that of the lesion volume. To clarify this effect, a two-predictor logistic model was fitted to the data to test the relationship between the likelihood of a poor patient outcome and IBZ involvement in the stroke lesion and the infarct volume. The results showed that the log of the odds of a poor outcome was positively correlated with DWI volume ($\beta = 0.014$, $p < 0.001$, Supplementary Table 2) and tended to be positively correlated with IBZ involvement ($\beta = 0.695$, $p = 0.058$). Larger volumes were more likely to cause poor patient outcomes. Given the same volume, patients with IBZ involvement had an increased risk of a worse outcome (Figure 3B), as the odds for an IBZ injury were approximately 2-fold greater. This effect was mainly driven by the patient sample with superficial MCA lesions, as the logistic regression analyses led to a stronger correlation with the existence of an IBZ injury ($\beta = 1.174$, $p = 0.039$) in this patient group. The odds then reached 3.2, and the correlation with stroke volume was weaker ($\beta = 0.010$, $p = 0.055$). Figure 3A shows a dissociation between the volume and IBZ injury on the likelihood of a poor patient outcome in the superficial territory group. This effect was not observed in the deep lesion group, where only the infarct volume was correlated with the probability of a poor outcome ($\beta = 0.081$, $p < 0.001$). Moreover, the dissociation between the infarct volume and IBZ injury was the strongest for the patients who received thrombolysis (Figure 3C and Figure 3D, Supplementary Table 3), particularly for superficial lesions. In this case, the lesion volume did not reach significance ($\beta = 0.009$, $p = 0.222$), and patients with an IBZ injury had 3-4 times more chances of a poor outcome for the same lesion volume ($\beta = 2.331$, $p < 0.004$). We interpreted these results as a weaker effect of IV thrombolysis in patients with IBZ injury.

We performed the same logistic regression analyses using an ASPECTS ≤ 6 instead of the occurrence of an IBZ injury (Supplementary Figure 1 and Supplementary Table 2). Then, we did not find any

relationship between the ASPECTS predictor and the patient outcome, as most of the variance was explained by the lesion volume.



Figure 3

Predicted probability of a poor patient outcome versus infarct volume measured on DW images. An independent effect of IBZ involvement was found in the subsample of patients with superficial MCA lesions (A) and all patients (B) but not in the deep MCA lesion group. This effect was stronger in patients who received thrombolysis (C and D).

Discussion

The present study demonstrated that acute stroke patients with IBZ injuries had larger infarcts, more frequent MCA occlusions, poorer outcomes and lower thrombolysis responsiveness than patients with a preserved IBZ. The patient outcome was both (and independently) related to the infarct volume observed on DW images and the occurrence of an internal border zone injury. In particular, the additional impairment of the IBZ was related to a worse patient outcome for patients with superficial MCA lesions.

Our results agreed with studies reporting that the insular cortex is regularly associated with large MCA strokes. In a cohort of 861 patients with acute ischaemic stroke, Kodumuri et al.[11] demonstrated that strokes involving the insula are associated with large-volume lesions and MCA occlusions. Furthermore, Fink et al.[18] showed that the insula is injured in more than half of patients and is associated with proximal occlusion and stroke severity. Regions around the insular cortex are located within the same vascular field, which lies within the IBZ. Thus, we hypothesize that the particular sensitivity to ischaemia of the IBZ may explain the high injury frequency of both the insular cortex and the lenticulostriate territory during MCA stroke.

Although the lesion volume was associated with the clinical patient outcome, it may not be the only factor to consider. The injury of one or several specific brain areas of a complex functional network can lead to its complete breakdown, although the other network components may still be operative. In addition, the infarct volume was not associated with the clinical outcome. For instance, the corona radiata, a region of the corticospinal tract, has a negative impact on the functional outcome[19] as measured by mRS. Of note, the mRS assesses the level of disability and dependence in daily life, which strongly depends on intact motor functions and gait[20]. In the same vein, using a probabilistic approach derived from diffusion tensor images, Zhu et al.[19] showed that the degree of functional motor deficit after a stroke is highly dependent on the overlap of the lesion with the corticospinal tract but not on the lesion size. Using the voxel-based lesion symptom mapping approach, Cheng et al.[10] demonstrated in 101 patients with moderate to severe stroke that damage to the corona radiata and to the insula has a negative impact on the 3-month mRS. With the same method, Reynolds et al.[21] reported a negative relationship of corona radiata, insula and caudate nucleus injuries with lower gait speed in 16 patients with unilateral hemiplegia after chronic stroke. More recently, Laredo et al.[22] showed that a lesion of the insula contributes to a poor functional outcome independent of the lesion volume. Thus, the association between poor functional outcome and IBZ involvement may not only be secondary to the lesion volume but also related to the injury of one or several anatomical structures, such as the insula or the corona radiata, which independently triggers a poor functional outcome. In the present study, we reported that patients with an IBZ injury had a 2- to 3-fold greater risk of a poor outcome, and this effect was independent of the lesion size (Figure 3), particularly for superficial MCA infarcts.

The present study did not identify any clinical risk factor or aetiology associated with IBZ injuries even in the injured IBZ group, which is a subject of longstanding debate. Some studies have reported a relationship between hypoperfusion and isolated IBZ infarcts due to either MCA stenosis[23] or

severe ICA stenosis[7], and other studies have suggested that both hypoperfusion and embolism often coexist and result in isolated IBZ infarcts[24]. The absence of MCA or ICA stenosis in our IBZ group was not in favour of the haemodynamic hypothesis. Moreover, isolated IBZ infarcts were not associated with poor functional outcome (mRS at 3 months: 1.7 ± 0.5) or early neurological deterioration (as in Young et al.[25]). The discrepancies between our results and those of previous studies may be related to the low number of patients with this pattern of stroke in our sample but also to differences in the IBZ definition. Previous IBZ definitions have been mostly restricted to the corona radiata and the semioval centre, whereas we also included other structures[13], such as the insula.

A strength of our study lies in the spatial approach, which is simple to use in clinical practice. All of the anatomical structures constituting the IBZ (such as the putamen, corona radiata, insula, caudate nucleus and internal capsule) are clearly identifiable even in the context of the emergency setup, whereas the exact determination of the infarct volume is more complex and time-consuming. Additionally, the ASPECTS, which is now frequently used with DWI, has drawn some controversies in recent years[4,5]. Moreover, it may be difficult to determine the extent of injury in an ASPECTS region. Topographic analysis of DWI images at the acute phase of stroke, combined with clinical prognostic factors (NIHSS and age), is promising to provide relevant predictions of the patient functional outcome in current practice. In the present study, we showed that the ability of our spatial approach, based on the existence of an IBZ injury, to determine poor functional prognosis was comparable to validated methods, such as an ASPECTS ≤ 6 or a lesion volume ≥ 100 ml[4].

Conclusion

We reported that IBZ injury visible on acute stroke DWI is an early marker of large-volume infarction, poor functional prognosis and IV thrombolysis resistance. The detection of IBZ damage is simple, suitable for the emergency clinical context and is useful for identifying patients who will most likely benefit from aggressive reperfusion therapies.

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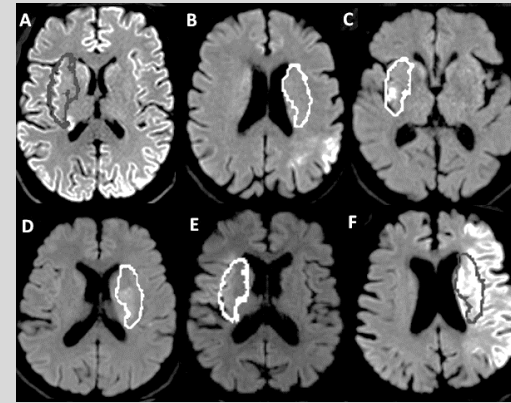
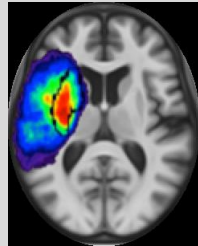
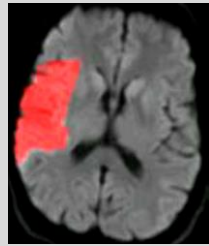
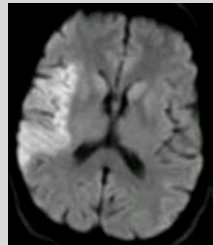
Author Contributions

Conception and study design: CB, FS, RG and SG. Acquisition of data: CB, DM, FS, JV, NL, PG, RG and SG. Analysis and/or interpretation of data: CB, FS, NL and RG. Drafting of the manuscript: FS and RG. Revising the manuscript critically for important intellectual content: SG, FS and CB. Approval of the version of the submitted manuscript: CB, DM, FS, JV, NL, PG, RG and SG.

Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Internal border zone injury predicts the functional outcome of acute MCA stroke patients



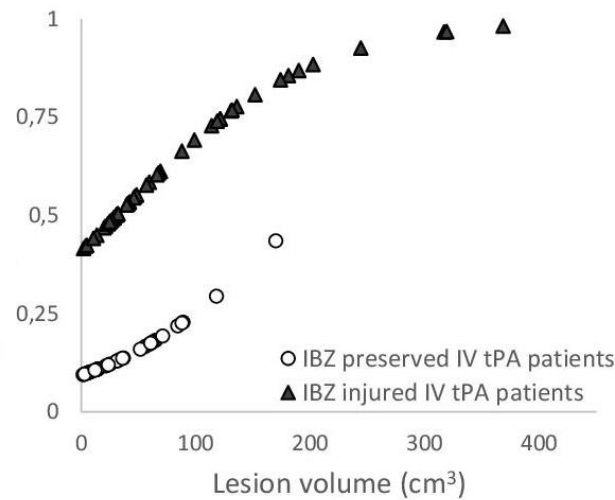
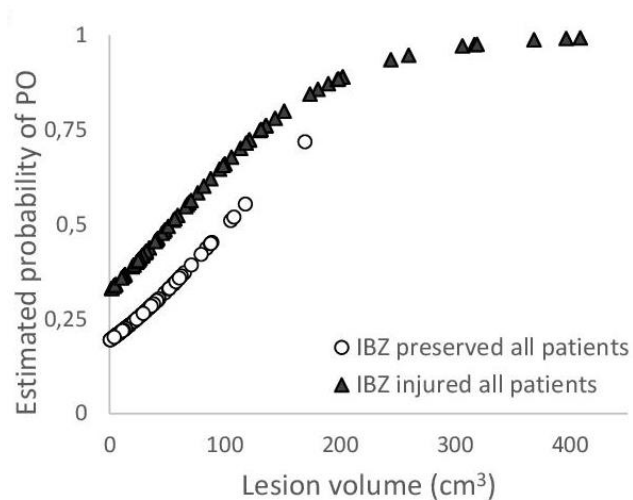
Spatial groups

- Deep
- Superficial
- Internal Borderzone (IBZ)
- Deep + IBZ
- Superficial + IBZ
- Territorial

DWI images (N=168)
acute MCA stroke

Manual
segmentation

Comparison with
territory atlas



IBZ injury is associated with:

- Larger stroke volume
- Worse neurological status (NIHSS)
- Poor functional outcome (PO, mRS)
- IV thrombolysis resistance

CONCLUSION:

IBZ injury is an early marker of stroke severity, functional prognosis and treatment responsiveness.