Journal of Neuroradiology (2011) 38, 105—112

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ORIGINAL ARTICLE

Early ADC changes in motor structures predict outcome of acute stroke better than lesion volume

Prédiction du handicap par les valeurs d'ADC dans les structures motrices à la phase hyper-aiguë de l'AVC ischémique : étude comparative avec le volume en diffusion

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Available online 21 August 2010

KEYWORDS
Stroke;
DWI;
ADC;
Outcome

Summary
Objectives. — The lesion volume assessed from diffusion-weighted imaging (DWI) within the first six hours to first week following stroke onset has been proposed as a predictor of functional outcome in clinical studies. However, the prediction accuracy decreases when the DWI lesion volume is measured during the earliest stages of patient evaluation. In this study, our hypothesis was that the combination of lesion location (motor-related regions) and diffusivity measures (such as Apparent Diffusion Coefficient [ADC]) at the acute stage of stroke predict clinical outcome.
Patients and methods. — Seventy-nine consecutive acute carotid territory stroke patients (median age: 62 years) were included in the study and outcome at three months was assessed using the modified Rankin scale (good outcome: mRS 0—2; poor outcome: mRS 3—5). DWI was acquired within the first six hours of stroke onset (H2) and the following day (D1). Apparent Diffusion Coefficient (ADC) values were measured in the corticospinal tract (CST), the primary motor cortex (M1), the supplementary motor area (SMA), the putamen in the affected hemisphere, and in the contralateral cerebellum to predict stroke outcome.

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0150-9861/$ - see front matter
doi:10.1016/j.neurad.2010.05.001

Results. — Prediction of poor *vs*. good outcome at the individual level at H2 (D1, respectively) was achieved with 74% accuracy, 95%CI: 53—89% (75%, 95% CI: 61—89%, respectively) when patients were classified from ADC values measured in the putamen and CST. Prediction accuracy from DWI volumes reached only 62% (95%CI: 42—79%) at H2 and 69% (95%CI: 50—85%) at D1.
Conclusion. — We therefore show that measures of ADC at the acute stage in deeper motor structures (putamen and CST) are better predictors of stroke outcome than DWI lesion volume.

Introduction

Improving prediction of stroke outcome at the acute stage is critical to assist clinicians in guiding therapies [1], improving patient selection and protocol design in randomized trials [2], in better informing patients or relatives and adapting rehabilitation programs [3]. Magnetic resonance imaging (MRI) — with diffusion-weighted imaging (DWI) in particular — is of considerable interest to the clinical evaluation of acute stroke patients [4,5]. The volume of the regions emphasized by strong brightness (hypersignal) in DWI images has been proposed as a surrogate marker of stroke outcome [6,7] within the first 6 hours [8,9] to 7 days following stroke onset [10—15].

Yet, the location of the lesion has been suggested to represent a better predictor than the DWI lesion volume [16,17]. At the subacute or chronic phases, previous studies have shown that damages to the pyramidal tract [18—28] and lesions to the primary sensorimotor cortex [16] correlated with poor motor outcome. In [25] for instance, no significant early difference in fractional anisotropy or mean diffusivity in the damaged CST was detected within the first week but only from the second week poststroke. Since diffusivity measures from tensor imaging are not enough sensitive in the hyperacute acute stage (within the first 24 hours from stroke onset), regional changes in apparent diffusion coefficient (ADC) were suggested as early quantitative indices of regional irreversible ischemic damage [29,30,31]. Of practical interest, ADC changes can be routinely assessed in hyperacute stroke patients from routine diagnosis DWI acquisitions.

Here, our specific aim was to assess the value of regional ADC changes in predicting stroke outcome at the hyperacute and acute stages. Our working hypothesis was that ADC changes in regions of the motor system — cortical motor and supplementary motor areas, subcortical regions (putamen and cerebellum), and the main outflow tract (corticospinal tract) — would define better predictors of stroke outcome than the DWI lesion volume.

Patients and methods

Subjects

Consecutive patients meeting the following criteria were included to participate in the study: ischemic stroke in carotid territory, initial MRI with DWI performed within the first six hours following stroke onset, and control MRI with DWI performed in the next 3 days. Exclusion criteria were symptomatic hemorrhagic transformation or death during follow-up (90 days). The patients could receive intravenous rtPA within a 5-hour time window according to the routine clinical procedure at our institution. In this procedure, intravenous rtPA is given based on clinical and MRI criteria including baseline National Institute of Health Stroke Scale (NIHSS) > 4 without major improvement, acute cerebral ischemia detected from MRI data, an exclusion of hemorrhage, and evidence of an intracranial occlusion.

The neurological examination was assessed using NIHSS at admission (H2) and at day 1 (D1). The modified Rankin Scale (mRS) was used to assess the outcome at 90 days. A good outcome was defined as independency (mRS 0—2) and a poor outcome as a moderate to severe disability (mRS 3—5).

Intracranial artery occlusion was detected on the initial (H2) magnetic resonance angiography (MRA).

MCA recanalization was evaluated on the follow-up MRA (D1) by at least two observers. MCA complete recanalization was rated as 0, partial as 1 and persistent occlusion as 2. Patients with complete or partial recanalization were further considered as ''recanalized'' patients.

The study was approved by the local Ethics Committee and explicit informed consent was waived since, according to French legislation, all imaging and clinical data were generated during routine clinical workup and were retrospectively extracted for the purpose of this study.

MRI data

MRI acquisition and preprocessing

The MR imaging was performed using a 1.5 Tesla MR unit (General Electric Signa Horizon Echospeed) with enhanced gradient hardware for echoplanar imaging. We performed three sequences: DWI, Fluid Attenuated Inversion Recovery (FLAIR), and an intracranial time-of-flight MRA. Axial DWI spin echo EPI parameters were: 24 slices, 2825 ms repetition time (TR), 98.9 ms echo time (TE), 90° flip angle, field-of-view (FOV) of $280 \times 210\,mm^2$, 96×64 matrix, 5 mm slice thickness, and 0.5 mm interslice gap. A baseline T2 image and three diffusion-weighted images in the *x*, *y*, and *z* directions using a b-value of $1000\,s\,mm^{-2}$ were acquired within 40 s. Axial fast-FLAIR sequence parameters were: 28 slices covering the entire brain, TR = 8800 ms, TE = 140 ms, 2200 ms inversion time (TI), 90° flip angle, $240 \times 240\,mm^2$ FOV, 256×256 matrix, 5 mm slice thickness, 1.5 mm interslice gap, and 2 minutes 40 s acquisition time. MRA parameters were: vascular time-of-flight with a spoiled gradient-recalled acquisition, TR = 2825 ms, effective TE = 92.6 ms,

20° flip angle, 256 × 192 matrix, 240 × 180 mm^2 FOV, 36 locations per slab, 1.4 mm axial slice thickness, and 2 minutes 39 s acquisition time.

The quantitative ADC maps were generated using commercially available software (Functool 2, General Electric, Buc, France). The ADC maps were normalized to the Montreal Neurological Institute (MNI) reference frame with using the T2-weighted template from SPM5 (Statistical Parametric Mapping, Wellcome Department of Neurology, Institute of Neurology, London, UK). To rule out effects due to lateralization and since the side of the infarction is not correlated to outcome in our study (rho = 0.07, $p = 0.52$), the T2-weighted template was made symmetric by averaging the template with its mirrored image. ADC maps with infarct lesions located in the left hemisphere were flipped to the right so that all infarcts in the study would be located in the same hemisphere. ADC maps were thresholded between 150 and 1200 × 10^{-6} mm^2 s^{-1} to remove voxels contaminated by partial volume effects from the cerebrospinal fluid [32].

Definition of regions of interest

Region volumes

The initial (V1) and final (V2) infarct volumes were defined as the areas of abnormal bright signal on the initial and follow-up non-normalized DWI images respectively, and measured by interactive manual outlining. Such approach has been documented as bearing high reliability [33]. Mean ADC values, ADC_{V1} and ADC_{V2}, were then computed from these values in the V1 and V2 DWI lesion volumes, respectively.

Extraction of regions of interest (ROI)

Right and left M1 regions, putamen, SMA, and cerebellum were extracted using the ''Anatomical Automatic Labeling template'' (AAL template, version vbeta1, GYN, UMR6095, CYCERON, Caen, France) from SPM5 (Fig. 1).

A CST template was obtained from histological data available at http://www.fz-juelich.de/inm//spm_anatomy_toolbox [34]. For this analysis, the CST template was resliced and registered to the same origin as SPM5's T2 template.

Statistical analysis

Data analysis. Descriptive statistics of the two populations are presented as median ± InterQuartile Range (IQR). A Chi^2 test was used to compare rates or proportions. Group comparisons were obtained using Mann-Whitney U non-parametric tests, because the empirical probability distributions of the data measures were not normal.

Comparison of ADC values was performed by a Student's *t*-test (ADC values have been reported to follow a normal distribution [35,36]). Statistical significance was set to $P < 0.05$. All the statistical analysis was performed using MedCalc software (version 9.3.2.0, Mariakerke, Belgium).

Individual prediction of stroke outcome. In-house software [37] was used for univariate data analysis, the calculation of accuracy, sensitivity, specificity, negative and positive predictive values, the 95% confidence interval (95%CI) of each parameter and determination of an optimal cut-off value. This classification was based on the nearest-neighbour method and a bootstrap strategy. This procedure allows a robust estimate of the correct classification rate when external validation is not possible when sample size is small [39]. This procedure was used for each variable in the ROI analysis: V1, V2, ADC_{V1} and ADC_{V2}. For ROIs, classification was performed along the supero-inferior *z*-axis and the best *z*-coordinate to predict patient outcome was chosen on the basis of the best classification rate (accuracy).

Multivariate analysis was based on multiple logistic regressions with stepwise variable selection. The dependent variable was mRS. This latter was transformed in a binary variable by splitting the patient sample in two categories: mRS within 0—2 *vs.* mRS within 3—5. The independent variables were the significant predictors revealed by the univariate analysis at H2 and D1.

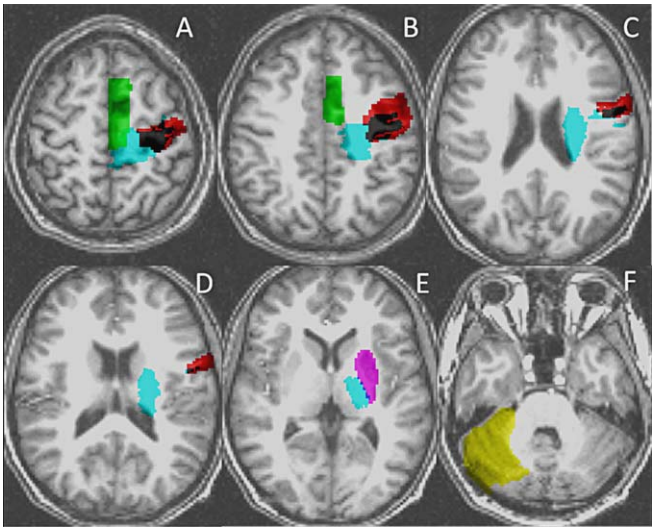

Figure 1 Regions of interest extracted from the AAL template on typical T1-anatomical images normalized in the MNI referential. Images are shown using neurological convention (right on the right). Controlateral supplementary motor (green), primary motor cortex (red), putamen (purple), corticospinal tract (blue) and ipsilateral cerebellum (yellow). (A) $z = 52$ mm, (B) $z = 42$ mm, (C) $z = 24$ mm, (D) $z = 18$ mm, (E) $z = 12$ mm, and (F) at $z = -34$ mm.

Results

Subjects

Seventy-nine stroke patients (median age: 62 years, IQR: 52—72) fulfilled the inclusion criteria. Seven patients were excluded from the study due to head movements during initial ($N = 3$) or follow-up ($N = 7$) DWI acquisitions. Median NIHSS was 15 (IQR: 10—20) at baseline and 11 (IQR: 4—17), 24 hours later. Sixty-six patients (84%) received intravenous rtPA. The initial MRI (H2) was performed with a median delay of 2.5 hours (IQR: 1.8—3.4 hours). All of the patients suffered from intracranial artery occlusion as detected from initial MRA. The follow-up MRI (D1) was performed within a median interval of 1.2 days (IQR: 1—1.8 days) and revealed that stroke was located either in the territory of the middle cerebral artery (MCA) ($N = 70$, 88.6% of all patients), the middle and the anterior cerebral artery ($N = 5$, 6.3%), the

Table 1 Characteristics of the patients involved in the study.

	Good outcome group ($n = 41$)	Poor outcome group $n = 38$)	p value
Baseline NIHSS	11 (7—14)	19 (16—22)	< 0.001
Age	59 (48—69)	65 (59—74)	0.009
Time to initial MRI (min)	129 (108—171)	164.5 (110—208)	0.2
V1 (cm^3)	16.5 (10.8—31.4)	27.6 (12.5—55.3)	0.2
V2 (cm^3)	32.1 (17.5—66)	76.3 (37.2—119.1)	0.002
Infarct growth V2—V1 (cm^3)	13.5 (4.0—33.4)	34.9 (14.5—63.3)	0.002
NIHSS at day 1	5 (2—9)	17 (14—21)	< 0.001
NIHSS at day 7	2 (0—3)	16 (11—19)	< 0.0001
MCA* Recanalisation (n)	93% (38)	53% (20)	< 0.001

Numbers are given as the median and the interquartile range. MCA: middle cerebral artery; V1: admission DWI volume; V2: follow-up DWI volume.

middle and the anterior choroidal artery ($N = 3$, 3.8%), and the middle and the posterior cerebral artery ($N = 1$, 1.3%). MCA infarct lesions were located in deeper territories in nine patients (11%), in superficial territories in 21 patients (27%) and in both in 49 patients (62%). Median V1 was 22.8 cm^3 (IQR: 11.3—46.1 cm^3), and median V2 was 50.9 cm^3 (IQR: 24.9—98.6 cm^3).

Forty-one patients (52%) were independent at 90 days (mRS 0—2), and 38 patients (48%) were severely disabled (mRS 3—5). Table 1 shows the respective characteristics of the poor and good outcome groups.

Prediction of stroke outcome

Univariate analysis

ADC values in the damaged CST and putamen were found to be the only significant early predictors of patient outcome at H2 (Table 2), with best accuracy for the ADC measures in the putamen (74%, $p < 0.001$). The prediction by the DWI volume (V1) did not reach a significant p-value.

ADC values in all the motor ROIs, together with V2 and ADC_{V2} were significant predictors of patient outcome at D1 (Table 3), with best classification accuracy from the damaged CST and putamen ROIs (75 and 74% respectively). The affected SMA and the controlateral cerebellum were inversely predictive of patient outcome, with higher ADC values found in the poor patient outcome group. Fig. 1 shows the axial slices with the z-coordinates that allowed for best prediction of stroke outcome at D1. Fig. 2 shows two examples of patients well predicted by ADC values in deep motor-related structures and not by DWI volume.

Multivariate analysis

At H2, the multivariate analysis revealed that only the ADC value in the damaged putamen remained a significant predictor of patient outcome (regression coefficient = 0.008, $p = 0.0003$). At D1, the multivariate model included two factors: the CST with lower ADC values in the poor outcome group (regression coefficient = 0.01, $p < 0.0001$), and the SMA with higher ADC values in the poor outcome group (regression coefficient = —0.02, $p = 0.01$). This latter model reached 80% accuracy to classify patients between the two groups. Note however that this model did not perform significantly better ($p = 0.97$) than a logistic regression model including the CST alone, which reached 78% accuracy .

Discussion

In this study, we have demonstrated that ADC values in deeper regions such as the putamen at H2 and the CST at D1 classified patients better than DWI lesion volumes and even than cortical regions according to their stroke outcome.

Multiple studies reported that a good outcome in motor stroke is conditioned to preserved integrity of motor regions and of their main efferent tract, the CST [19,38—40]. The crucial role of CST integrity in motor outcome was previously reported in subacute [18—20,23,25—27,41] and chronic stroke patients [21,22,24,38,42]. Our study extends these results at the acute stage (D1) and suggests assessing early CST damages using ADC measures. This finding was recently supported by another study [43] which have underlined that ADC decrease in the ipsilateral cerebral peduncle was a biomarker of Wallerian degeneration at the hyperacute phase. Indeed, we have shown the ADC decrease in the CST was the best predictor of functional outcome (with 75% accuracy), with better performances than measures of ADC decrease in the primary motor cortex, ADC_{V2} and V2 itself. Damage to primary motor regions was found being also a predictor of motor outcome at the acute stage

Table 2 Early (H2) predictions of good outcome with 95% CI.

	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off Value	z-coordinate (mm, MNI space)	p-value
V1 (cm^3)	62 42—79	82 60—100	41 11—67	60 47—77	66 50—86	< 35	NA	0.19
ADC_{V1}	51 30—75	47 20—70	54 20—90	51 27—75	51 29—73	> 629	NA	0.70
Damaged CST	67 47—84	67 44—100	67 40—90	69 50—100	64 47—100	> 670	18	**0.001**
Damaged M1	53 37—74	65 30—100	39 11—67	54 38—73	51 25—83	> 777	18	0.45
Damaged putamen	74 53—89	76 44—100	72 50—100	77 60—100	70 55—100	> 701	−4	< **0.001**
Damaged SMA	54 26—84	58 20—90	50 11—89	56 25—100	52 20—100	< 887	44	0.36
Controlateral cerebellum	54 26—84	51 20—90	56 22—100	56 30—100	51 20—86	> 863	30	0.30

CST: corticospinal tract; M1: primary motor cortex; SMA: supplementary motor area; NPV: negative predictive value; PPV: positive predictive value; V1: initial DWI volume and ADC_{V1}: mean ADC value in V1. The ADC cut-off values are given in units of $\times 10^{-6}\,mm^2.s^{-1}$.

(note however than the best z-level for outcome prediction was not found in upper limb cortical regions), with a lesser contribution than the CST's however. The preeminence of CST integrity in patient outcome with respect to primary motor cortical regions was relatively expected because of DTI studies results [18—27]. Nevertheless, previous functional imaging studies have shown that recovery was essentially associated with the reorganization of the preserved cortical motor network involving peri-infarcted areas, secondary motor-related areas in the affected hemisphere [39] and homologous areas in the intact hemisphere [44]. Although these findings demonstrate the critical role of plastic properties of cortical motor areas in the patient recovery process, our results strengthen the greater impact of the CST over cortical lesions. Indeed, we may hypothesize that when the main motor outflow tract is interrupted, motor commands cannot be conveyed to the spinal cord and therefore reorganization at the cortical level remains insufficient to the patient recovery.

This hypothesis is also supported by a study from Seitz et al. [15], in which periventricular white matter damages were associated with a poor patient outcome. Additionally, a number of previous studies using either standard MRI or CT-scans [24,38] or measures of other diffusion variables [18—20,23,41] at the subacute or chronic stages have shown how CST lesions relate to motor outcome. At the same stages, decreases in fractional anisotropy located in the brainstem [45] or the posterior limb of the internal capsule [41] were also found to correlate with motor deficit. Studies using DTI-tractography have further shown that interruption

Table 3 Day-one predictions of good outcome with 95% CI.

	Accuracy	Sensitivity	Specificity	PPV	NPV	Cut-off value	z-coordinate (mm, MNI space)	P-value
V2 (cm^3)	69% 50—85%	78% 50—100%	59% 30—80%	68% 50—86%	71% 50—100%	< 68.9	NA	< 0.001
ADC_{V2}	70% 53—89%	66% 40—90%	74% 44—100%	74% 57—100%	66% 50—90%	> 631	NA	< 0.001
Damaged CST	75% 61—89%	83% 60—100%	66% 38—100%	75% 62—91%	76% 57—100%	> 622	24	< 0.001
Damaged M1	67% 44—83%	80% 50—100%	51% 25—88%	67% 43—100%	67% 54—86%	> 731	18	0.02
Damaged putamen	74% 56—94%	76% 50—100%	72% 38—100%	77% 63—100%	70% 54—100%	> 618	12	< 0.001
Damaged SMA	68% 50—89%	73% 50—100%	62% 25—88%	71% 56—90%	65% 47—100%	< 875	52	0.02
Controlateral cerebellum	63% 44—83%	65% 40—90%	61% 25—88%	67% 50—91%	58% 38—86%	< 844	−34	0.01

Numbers are given as the median and the interquartile range. V2: follow-up DWI volume; ADC_{V2}: mean ADC value in V2.

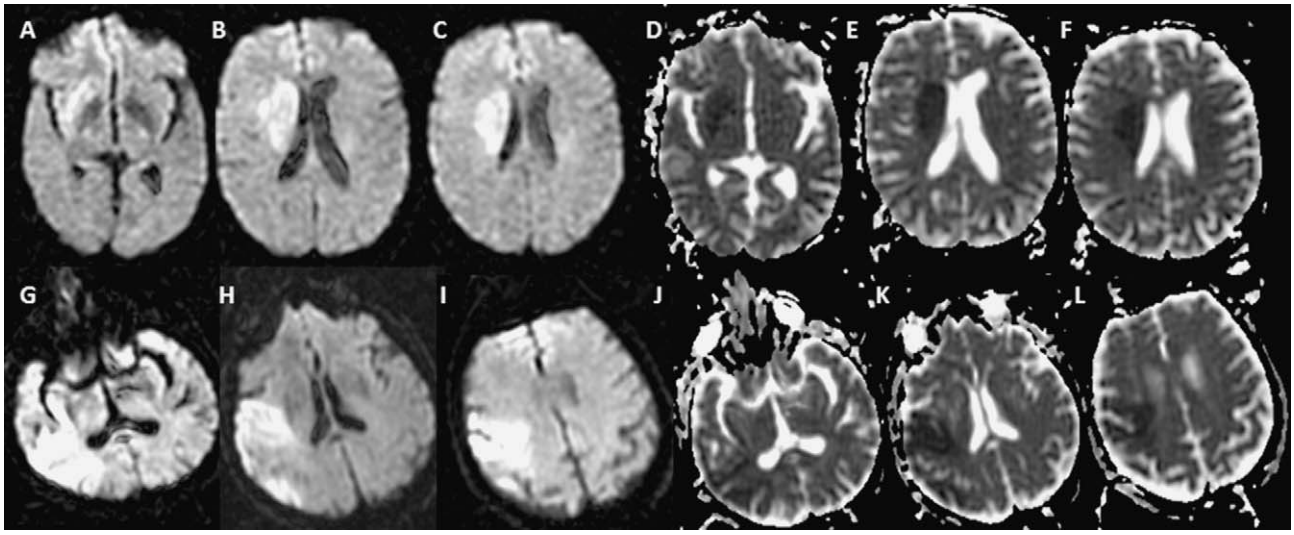

Figure 2 Two patients well predicted by ADC values in the ipsilesionnal putamen at H2, and not by DWI lesion volume. The first row concerns a 74-year-old woman with a right deep MCA territory stroke. DWI (A, B, C) lesion volume at H2 was 28.5 cm^3, and predicted a good outcome. Indeed, ADC values (D, E, F) in the putamen and the CST were low (572 and 677 $\times 10^{-6}$ mm^2/s). This patient had a 3-month mRS of 5. The second row concerns a 67-years old patient with a right MCA superficial territory stroke involving M1. DWI (G, H, I) lesion volume was 86.4 cm^3 and predicted a poor outcome. Nevertheless, ADC values (J, K, L) in the putamen and the CST were normal (889 and 793 $\times 10^{-6}$ mm^2/s). This patient had a 3-month mRS of 2.

of the CST had predictive value for motor outcome in pontine infarct [19] and in infarcts of the lenticulostriate territory [41].

An additional finding of our study is that poor outcome is independently associated with increased ADC values in the ipsilateral SMA. We hypothesize that diffusion changes in the SMA might be a MRI indicator of known remote metabolic effects of stroke [46], which needs to be confirmed by a specific study. Nevertheless, this marker is probably only secondary as its inclusion in a multivariate predictive model did not improve prediction scores with respect to a model based on the measure of ADC decrease in the CST alone.

Lower ADC values in the putamen were the strongest predictor of stroke outcome with a 74% accuracy within the first hours following stroke onset. The initial DWI lesion volume (V1) from DWI did not reach a significant classification rate. This result was somewhat unexpected as although pure putaminal lesions may cause subtle neuropsychological deficits [47,48], they are not known to result in severe motor disability [49]. We hypothesize that the dynamics of early infarct growth may be accounted for this finding. Indeed, the putamen is often located at the core of the initial ischemic damage, especially in the case of proximal MCA occlusion. In addition, ADC decreases at the core of the ischemic focus (i.e., the putamen) have been shown to be more severe in situations where infarct growth is ongoing and therefore likely to reach the CST eventually, than when infarct is stabilized [32]. A recent study [15] has shown that basal ganglia, internal capsule and insular cortex damages in MCA stem occlusions were associated with failed recanalisation and poor outcome.

However, we shall also discuss possible limits in our study. First, the motor-related ROIs were not patient specific. The masks of motor structures were obtained from the AAL template, and the CST had to be estimated from a normalized histological tract template, as no DTI data is acquired in our acute stroke patients. Therefore, even though we carefully checked the normalized images for possible registration errors, more subtle, non-specific registration errors due to geometrical normalization cannot be ruled out.

A second limitation is in the moderate sample size. The bootstrap techniques allowed computing unbiased estimates of classification accuracy, since, at each step, the validation set was not used to train the classifier. This was rather performed using a large number of groups resampled from the original data only. The resulting accuracy may be considered as representative of the generalization ability of the models obtained to new data.

Finally, the ADC cut-off proposed in our study must be confirmed. ADC values are physical measures that are theoretically independent of the MRI system on which they were acquired [50]. But, recent studies have suggested that there is a variability depending on vendors [51], magnetic field strength [51,52] and type of coils [51]. Nevertheless, this variability is small (up to 8%) regarding to inter- or intravariability in DWI measurements [33,53].

Conclusion

This study is the first to demonstrate that the combination of location and pathophysiological information through ADC values at the *very acute* stage has the potential to predict stroke outcome at three months. The results also underline the key role of acute ischemic injury to deeper brain structures (putamen and CST) in the residual disability. Insult to these regions was found to be more critical to cortical motor areas, or the volume of the lesion itself. Considering the general failure of infarct-volume based approach in the design and evaluation of neuroprotective drugs, we emphasize that this finding (i.e., subcortical site vs. size of the lesion) may

be of importance for suggesting improved techniques in that respect.

Disclosure

None.

Acknowledgments

This work was partially supported by the ''Programme Hospitalier de Recherche Clinique EVAL-USINV'' (no. AOM 03 008). We thank Rémi Cuingnet for its helpful suggestions in the statistical analysis.

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