Value-Added of Combined Proton MR Spectroscopic Imaging and Diffusion-Weighted MRI to Assess the Heterogeneity of Tissue Injury during Acute Ischemic Stroke. A Human Study

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Introduction
Recent studies demonstrate that brain MR diffusion-weighted imaging (DWI) performed during acute ischemic stroke (AIS) detects but does not differentiate irreversible and reversible ischemic regions while this discrimination is crucial to optimize the selection of patients for thrombolytic therapy. Using proton MR spectroscopic imaging (SI), we describe, for the first time, the relationship between DWI data and brain metabolic abnormalities in human stroke and demonstrate a gradient of ischemia-related metabolic consequences within the abnormal area delineated by DWI during AIS. Several authors have suggested that DWI can identify and quantitate the extent of irreversible tissue injury during AIS. Such a characterization is of great importance since a large extent of tissue necrosis would predict a lesser benefit of thrombolysis with a higher risk of brain hemorrhage. However, recent data from animal and human studies (1,2) demonstrate that the ischemic area defined by DWI during the first hours of stroke (area of decreased apparent diffusion coefficient (ADC) values) includes also a significant part of the so-called ischemic penumbra which represents potentially salvageable tissue if reperfusion is reinstated by thrombolysis. At the moment, a large abnormal area of ischemia-related decreased ADC is not systematically considered as contraindication to this treatment. In order to confirm the hypothesis that a heterogeneity of ischemia-related brain metabolic abnormalities might exist within the abnormal area delineated by DWI, we have explored, in this preliminary study, two AIS patients using a multimodality MR protocol.

Patient Reports and Methods
The first patient, a 48 year-old right-handed man, was explored 6 hours after a sudden left hemiplegia with anosognosia. DWI revealed a large area of decreased ADC involving the superficial territory of the right middle cerebral artery. The other patient, a 64 year-old right-handed woman, was explored 20 hours after a sudden right hemiplegia with aphasia. DWI revealed a large area of decreased ADC involving the deep territory of the right middle cerebral artery. No brain hemorrhage was detected on T2*-weighted MRI nor on CT performed just before MR examination in these two patients. Brain MR angiography showed a proximal occlusion of the middle cerebral artery in patient 1 and was normal in patient 2. MR examinations were performed on a 1.5 T Vision Plus system (Siemens Erlangen, Germany) at day 0 and day 2. Isotropic ADC maps were reconstructed using images acquired with EPI sequence (b=0, 500, 1000 s/mm² sensitized in the x, y and z directions). Three consecutive slices were averaged in order to match the regions explored by SI. 2-Dimensional spin-echo SI was recorded with acquisition weighted 2D CSI (TE / TR = 135 ms / 1600 ms, 524 acquisitions, matrix size = 25x25, slice thickness = 15 mm) and outer volume suppression to minimize fat scalp contamination. Correlations between ADC mean values and metabolic ratios were studied at 36 volume suppression to minimize fat scalp contamination. Correlations between ADC mean values and metabolic ratios were studied at 36 hours of stroke (area of decreased apparent diffusion coefficient (ADC) values) includes also a significant part of the so-called ischemic penumbra which represents potentially salvageable tissue if reperfusion is reinstated by thrombolysis. At the moment, a large abnormal area of ischemia-related decreased ADC is not systematically considered as contraindication to this treatment. In order to confirm the hypothesis that a heterogeneity of ischemia-related brain metabolic abnormalities might exist within the abnormal area delineated by DWI, we have explored, in this preliminary study, two AIS patients using a multimodality MR protocol.

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Discussion
The value added of SI over DWI is clearly illustrated by the informational content of the Lac/NAA ratio. Also, recent experimental data (4) suggest that measurement of brain lactate concentration might help to predict tissue recovery after thrombolysis. Consequently, we recommend the use of a 135 ms TE for SI evaluation of AIS owing to the higher sensitivity of this method to detect lactate compared to 270 ms TE SI or to shorter TE SI often contaminated with lipids. Moreover, our data suggest that fast proton 3D SI using an echoplanar sequence (5) may have a great clinical interest for the assessment of AIS. We are now planning to correlate SI data with combined diffusion and perfusion MRI and clinical outcome in order to evaluate the clinical utility of SI in the hyperacute phase of stroke.

References

Y axis : Lac/ NAA
X axis : ADC (x10^9 m^2/s)

Correlation between Lac/NAA ratio and mean ADC values at day 0 (polynomial regression analysis)

The Lac/NAA ratio is significantly correlated with ADC mean values as shown in figure 1 (r² = 0.85, p<0.0001). Moreover, in the core of the area of decreased ADC values, a 25% decrease of ADC mean values (0.6 to 0.45 x10^-9 m²/s) corresponds to a 90% increase of Lac/NAA ratio. These data demonstrate the higher sensitivity of SI to evaluate in these patients early consequences of acute ischemia on brain cells and the existence of a gradient of cellular injury within the area of decreased ADC values. At day 2, the ADC decrease and the decreased NAA/S ratio are still correlated (r² = 0.84; p<0.0001). The Lac/NAA ratio and ADC are less correlated (r²=0.581) in relation with a wider dispersion of metabolic values in the narrow range of ADC values corresponding to the infarcted area. This loss of correlation might be due to the greater tissue heterogeneity of the ischemic area which cannot be evaluated using DWI only since it probably contains, at this sub-acute phase of stroke, a mixture of dead cells, suffering neuronal and glial cells and infiltrating macrophages from the blood.