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Magnetisation transfer parameters and stroke outcome

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ABSTRACT

Our aim was to evaluate the association between magnetisation transfer imaging (MTI) parameters measured 30 to 45 days after a cerebrovascular insult and post-stroke functional outcome at the same time. MTI offers the opportunity to depict subtle microstructural changes in infarcted areas. The clinical significance of the heterogeneity of brain damage within ischaemic stroke lesions is unknown. We prospectively included 58 patients with acute middle cerebral artery stroke. Diffusion-weighted imaging was performed within 12 hours after onset and the final infarct was documented by MRI with fluid-attenuated inversion recovery (FLAIR) and MTI at 30 to 45 days follow-up. We evaluated the association between MTI histogram parameters and the clinical outcome assessed by dichotomised (threshold >2) modified rankin scale (mRS) using multivariable logistic regression models adjusted on baseline characteristics. In multivariable analyses, stroke outcome was mostly driven by initial National Institutes of Health Stroke Scale (odds ratio [OR] = 1.23; 95% confidence interval [CI] = 1.07–1.41; $p < 0.01$) while after adjustment of initial stroke severity magnetisation transfer ratio peak position was the only MRI parameter associated with functional status at 30 to 45 days post-stroke (OR = 0.86; 95% CI = 0.75–0.98; $p = 0.02$); lower peak position values associated with higher mRS. Conversely, stroke volume measured on FLAIR sequence was not associated with stroke prognosis ($p = 0.87$). The intensity of microstructural changes within the infarct core measured at 30 to 45 days follow-up is independently associated with the functional status evaluated at the same time. MTI and related parameters could be used as surrogate markers of treatment response in stroke clinical trials.

1. Introduction

Stroke is the leading cause of acquired physical disability in adults in industrialised countries and the second most common cause of cognitive impairment after Alzheimer's disease [1]. Currently, admission to a stroke unit and early thrombolysis with tissue plasminogen activator are the only effective strategies for ischaemic stroke patients. Because of the narrow therapeutic window of less than 4.5 hours and safety concerns, fewer than 5% of stroke patients receive thrombolytic therapy in most acute stroke units [2]. Besides recanalisation, neuroprotection could represent an important alternative to reduce the lesion burden following an ischaemic insult [3]. Several studies have been performed to evaluate neuroprotective therapies but to date none of them have demonstrated significant clinical efficacy of these treatments [4]. These failures have raised concerns about the validity of the methodology used to evaluate the potential benefit of new therapeutic strategies in the field of cerebrovascular disease. Important efforts have been made to establish Stroke Therapy Academic Industry Roundtable criteria that are now used to improve the evaluation of new drugs in the preclinical setting [5]. For that purpose, research clinicians have tried to develop new strategies and methodologies of evaluation that could be less sensitive to inter-observer variability and could improve the detection of a potential benefit of such drugs. Besides clinical evaluation, MRI techniques have created new tools to explore the extent of brain lesions and pathophysiology *in vivo* [6]. Following ischaemic stroke, the spectrum of brain lesions is very large encompassing severe macrostructural changes in the central core of the infarction and more subtle microstuctural damage markers that may occur in the so-called penumbral area [7].

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T2 or fluid-attenuated inversion recovery (FLAIR) imaging is the sequence most commonly used in the evaluation of chronic ischaemic lesions. However, weak correlation has been reported between the final infarct volume measured on T2/FLAIR and the patient's clinical outcome defined by the modified Rankin score (mRS). That result could in part be explained by the fact that the severity of neuronal loss within FLAIR lesion is heterogeneous and does not perfectly reflect ischaemic damage. But this size-approach is strongly confounded by the strategic importance of the site of the lesion on neurological and functional consequences and on clinical outcome. Until now it has remained difficult to sort out the respective contributions of site and size. Magnetisation transfer imaging (MTI) has proven superior to conventional MRI in the detection and quantitation of subtle brain tissue changes [7,8]. Contrast on MTI is based on the interactions between protons in a relatively free environment and in an environment in which motion is restricted [8]. In the brain, these two states correspond to the protons in tissue water and in the macromolecules of myelin and other cell membranes. Off-resonance irradiation, which saturates the magnetisation of the less mobile protons, is applied but this is transferred to the mobile protons therefore reducing the signal intensity from the observable magnetisation. The degree of signal loss depends on the density and nature of the macromolecules in a given tissue. Reduced magnetisation transfer ratio (MTR) has been previously demonstrated in the infarct core as well as in the penumbra area [9,10]. However, the clinical significance of MTR reduction has been scarcely investigated. The aim of the present study was to evaluate the relationship between MTR parameters and post-stroke functional outcome measured 30 to 45 days after stroke.

2. Methods

2.1. Patients

The patients prospectively included in this study were initially admitted to the emergency neurological ward of the University Hospital Pellegrin, Bordeaux, for a suspected cerebral infarct. Primary inclusion criteria were men and women, older than 18 years, with a clinical diagnosis of mild to severe cerebral infarct (National Institutes of Health Stroke Scale [NIHSS] 4–20) in the left or right middle cerebral artery territory less than 12 hours from onset. Exclusion criteria were coma, transient ischaemic attacks or lacunar syndrome, pregnant or breast-feeding women or women without a negative pregnancy test and contraindications to MRI. Written informed consent was obtained from all participants. The study was part of an approved national Research and Clinical Hospital Project called Valeur prédictive des paramètres IRM à la phase aiguë de l'accident vasculaire cérébral: application à la gestion des essais thérapeutiques (VIRAGE) approved by the local research ethics committee.

2.2. MRI protocol

Using VIRAGE data, two MRI studies were analysed. The first was performed within 12 hours after the occurrence of stroke symptoms (MRI.1) and the second was performed between days 30 and 45 after the first (MRI.2). The NIHSS was assessed before MRI.1 and the Barthel Index and mRS before MRI.2. All data were reported on a standardised case report form.

MRI studies were performed on a 1.5-T magnet (Philips Gyroscan; Philips Healthcare, Andover, MA, USA). MRI.1 protocol included diffusion-weighted images (DWI). MRI.2 included a FLAIR and magnetisation transfer (MT) sequences. A 3D T1 was performed in both MRI studies to allow coregistration. All images were acquired in the anterior commissure-posterior commissure plane.

DWI was performed with a single-shot spin echo planar imaging sequence using the following parameters: 24 slices of slice thickness 5 mm, repetition time (TR)/echo time (TE) 6000 ms/114 ms, matrix 128 × 128, field of view 240 mm. Gradients with two different b-values (0 and 1000 s/mm^2) in the x, y, and z axes were used.

For FLAIR sequences we used 24 slices of 5 mm thickness, TR/TE/inversion time (TI) 10,000 ms/110 ms/2380 ms, matrix 256 × 256 and field of view 240 mm.

MT sequences were obtained with a gradient echo imaging sequence with (Ms) and without (M0) a saturating pulse (bandwidth of 250 Hz): 24 slices of 5 mm thickness, TR/TE/flip angle 35 ms/2.3 ms/8°, matrix 256 × 256 and field of view 240 mm. Sinc-shaped radio frequency pulse of 15 ms duration with a flip angle of 520° and an off- resonance frequency of 1500 Hz were used to get the MT effect. The time for the complete MT acquisition was 5 minutes and 30 seconds.

The 3D T1 parameters were 80 slices of thickness 3.4 mm with a slice gap of −1.7 mm, TR/TE/flip angle 20 ms/3 ms/30°, matrix 256 × 256 and field of view 240 mm.

2.3. Data processing

2.3.1. Maps

MTR maps were calculated on a pixel-by-pixel basis using the following equation [11]:

$$\mathrm{MTR} = (\mathrm{M0} - \mathrm{Ms})/\mathrm{M0} \times 100$$

Where M0 and Ms represent the signal intensity with the saturation prepulse off and on, respectively. MTR represents the percentage of signal loss after the saturation pulse and is proportional to the bound proton pools [6].

2.3.2. Coregistration

MRI sequences were spatially registered using a fully automated 3D registration algorithm (BioClinica, San Diego, CA, USA). This uses mutual information as a similarity measure to assess the goodness of match between the reference volume and the source volume. A rigid 3D registration was used. According to mutual information and mutual information derivative values, a gradient descent technique was used to iteratively modify the transformation parameters (rotations and translations) to maximise the mutual information.

A multiresolution, coarse-to-fine strategy was adopted. This means registration started at low resolution and once the convergence is reached a new iteration was initialised based on the result of the previous step. Such a strategy increased the robustness of the registration algorithm. Results were quality controlled for each and every processed MRI sequence to detect potential misregistration that may occur for echo planar imaging-based sequences for which geometric distortion may disturb the registration process. In a few cases, the sequence was manually registered to ensure good spatial correspondence.

2.3.3. Stroke volume measurement and regions of interest (ROI)

All images were read at the coordinating centre by investigators blinded to the clinical information. Images were sent to a workstation using customised software developed by BioClinica. The ROI was the infarct core observed on DWI-MRI.1. This ROI was predetected using an automatic unsupervised 3D segmentation algorithm (BioClinica) followed by a manual validation by the reader by using interactive drawing tools. The infarct core volume was calculated as the sum of the area of the ROI on each slice multiplied by the slice thickness plus the interslice gap. This volume was