Contribution of the apparent diffusion coefficient in perilesional edema for the assessment of brain tumors

Apport du coefficient de diffusion apparent de l’œdème périlésionnel pour l’étude des tumeurs cérébrales

R. Guzman\textsuperscript{a,b}, S. Altrichter\textsuperscript{c}, M. El-Koussy\textsuperscript{d}, J. Gralla\textsuperscript{d}, J. Weis\textsuperscript{e,f}, A. Barth\textsuperscript{a}, R.W. Seiler\textsuperscript{a}, G. Schroth\textsuperscript{c}, K.O. Lövblad\textsuperscript{c,*}

\textsuperscript{a} Department of Neurosurgery, Inselspital, University of Berne, Berne, Switzerland
\textsuperscript{b} Department of Neurosurgery, Stanford University, Palo Alto, USA
\textsuperscript{c} Department of radiology, Neuroradiology Section, Geneva University Hospital, Geneva, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
\textsuperscript{d} Department of Neuroradiology, Inselspital, University of Berne, Bern, Switzerland
\textsuperscript{e} Department of Neuropathology, University of Berne, Berne, Switzerland
\textsuperscript{f} RWTH Aachen University Hospital, Aachen, Germany

Available online 16 April 2008

KEYWORDS
Diffusion;
Brain tumors;
Gliomas;
MRI-ADC

Summary
Objectives. — Diffusion-weighted MRI is sensitive to molecular motion and has been applied to the diagnosis of stroke. Our intention was to investigate its usefulness in patients with brain tumor and, in particular, in the perilesional edema.

Methods. — We performed MRI of the brain, including diffusion-weighted imaging and mapping of the apparent diffusion coefficient (ADC), in 16 patients with brain tumors (glioblastomas, low-grade gliomas and metastases). ADC values were determined by the use of regions of interest positioned in areas of high signal intensities as seen on T2-weighted images and ADC maps. Measurements were taken in the tumor itself, in the area of perilesional edema and in the healthy contralateral brain.

Results. — ADC mapping showed higher values of peritumoral edema in patients with glioblastoma ($1.75 \times 10^{-3} \text{ mm}^2/\text{s}$) and metastatic lesions ($1.61 \times 10^{-3} \text{ mm}^2/\text{s}$) compared with those who had low-grade glioma ($1.40 \times 10^{-3} \text{ mm}^2/\text{s}$). The higher ADC values in the peritumoral zone were associated with lower ADC values in the tumor itself.

* Corresponding author.
E-mail address: karl-olof.Lovblad@hcuge.ch (K.O. Lövblad).

0150-9861/$ – see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.neurad.2008.02.003
Contribution of the apparent diffusion coefficient in perilesional edema

225

Introduction

Diffusion-weighted imaging (DWI) has become a standard routine sequence in most clinical investigations [1,2]. It involves a simple modification of a spin-echo sequence, where two gradient sensitizing pulses are applied before and after the 180 pulse. Diffusion imaging is sensitive to the molecular motion of tissues, allowing it to be used with great success in the setting of stroke [3,4], where it is thought to be able to differentiate between cytotoxic and vasogenic edema. The occurrence of acute ischemia is accompanied by a decrease in the so-called apparent diffusion coefficient (ADC), which allows quantification of the diffusion characteristics of a given tissue. This has been applied to other pathologies such as brain abscess [5] and some tumors, and brain development [6] and aging [7], as well as for monitoring interventions [8]. The possibility of mapping the ADC allows the quantification of water movement. This has already been applied to tumors of the brain, head and neck [9,10]. Previous studies have shown that ADC values reflect both cellularity and edema [11]. The present study aimed to address its capacity to determine the type of intracranial tumor based on the ADC values from the perilesional edema. To do this, we investigated a series of patients who had different types of intracranial tumors.

Materials and methods

Patients

Sixteen consecutive patients (nine men, seven women; ages 35 to 82, mean age 58 years) were prospectively included, having been recruited from the neurosurgical clinic of our hospital over a period of six months (January to July 2001).

All patients had undergone brain MRI because of an intracranial tumor. They were informed of the examination they were about to undergo and had given their consent. The patients all subsequently underwent craniotomy and biopsy/surgery to obtain samples of tumor for histopathological examination.

Imaging studies

Imaging was performed using a commercial 1.5-T clinical system equipped with a head coil (Siemens Vision, Erlangen, Germany) capable of echo-planar imaging, and with a gradient booster and gradient amplitude of 35 mT/m, a rise time of 150 ms and a slew rate of 170 T/m. First, routine axial T1- (TE: 12 ms; TR: 528 ms; matrix 96\times 200; NEX: 2; 5-mm-thick slices) and T2- (TE: 98/16 ms; TR: 3.176 ms; matrix: 180 \times 256; 5-mm-thick slices) weighted imaging was done with postcontrast T1-weighted imaging in three planes after administration of gadolinium (Gd)-DTPA (Magnevist, Schering, Germany) via a cubital-vein cannula, using a power injector (Medrad).

Axial isotropic single-shot whole-brain multislice DWI (TR: 4000 ms; TE 36 ms; 18 5-mm-thick slices) was performed, and ADC maps derived from the $b_0$ and $b_{max}$ images ($b$ values of 0 and 1000 s/mm$^2$) by pixel-by-pixel analysis. The images were then transferred to a dedicated workstation. Signal anomalies on DWI and ADC images were determined by two experienced neuroradiologists (KOL, MEK). Regions of interest (ROI) on the ADC maps were also selected in: (i) the areas seen with high signal intensities on T2-weighted images and ADC maps that corresponded to perilesional edema (Figs. 1 and 2); (ii) the tumor itself; and (iii) the contralateral healthy brain. Thus, there were three measurements per patient. Mean ROI size was 1.6 mm$^2$.
Peritumoral signal alteration  ADC measurement

Figure 1 In a patient with a high-grade glioma of the left hemisphere, the peripheral edema can be seen on T2 images and ADC maps.

Figure 1 Patient présentant un gliome de haut grade. L'œdème est visualisé sur les séquences T2 et les cartographies ADC.

Statistical analysis

Student's t test was used to compare the two groups of patients with those who had low-grade glioma.

Results

On histology, eight patients showed high-grade gliomas, four had cerebral metastases and four had low-grade gliomas (Fig. 3).

ADC values in peritumoral edema

The absolute values in the peritumoral edema of the glioblastomas were: median: $1.75 \times 10^{-3} \text{ mm}^2/\text{s}$, SD: 13.76; range: $1.55 - 1.95 \times 10^{-3} \text{ mm}^2/\text{s}$; 25th percentile: 1.65, 75th percentile: 1.88; lower 95% CI of mean: 1.674, upper 95% CI of mean: 1.826 (Fig. 3B).

The absolute values in the metastases were: median: $1.61 \times 10^{-3} \text{ mm}^2/\text{s}$, SD: 19.13; range: $1.21 - 1.93 \times 10^{-3} \text{ mm}^2/\text{s}$; 25th percentile: 1.525, 75th percentile: 1.89; lower 95% CI of mean: 1.454, upper 95% CI of mean: 1.748.

The absolute values in the low-grade gliomas were: median: $1.40 \times 10^{-3} \text{ mm}^2/\text{s}$, SD: 20.42; range: $1.08 - 1.60 \times 10^{-3} \text{ mm}^2/\text{s}$; 25th percentile: 1.10, 75th percentile: 1.55; lower 95% CI of mean: 1.17, upper 95% CI of mean: 1.547.

The difference was significant for the perilesional edema of glioblastomas compared with low-grade gliomas ($P=0.0071$), but not between metastases and low-grade gliomas ($P=0.0811$).

Figure 2 In this patient with a metastasis in the left frontal region, there is a central contrast-enhancing nodule on T1 images. The ADC map shows the ROIs in the lesion, in the edema and in the contralateral brain.

Figure 2 Patient présentant une métastase de la région frontale gauche. Un nodule prenant le contraste en T1 est entouré d'un œdème visible sur les images ADC sur lesquelles sont placées les régions d’intérêt.
Contribution of the apparent diffusion coefficient in perilesional edema

The ratios for the glioblastomas were: median: 2.38, SD: 0.41; range: 1.7–2.9; 25th percentile: 1.8, 75th percentile: 2.6; lower 95% CI of mean: 2.013, upper 95% CI of mean: 2.476 (Fig. 3A).

The ratios for the metastases were: median: 2.143, SD: 0.27; range: 1.66–2.57; 25th percentile: 1.86, 75th percentile: 2.25; lower 95% CI of mean: 1.9, upper 95% CI of mean: 2.3.

The ratios for the low-grade gliomas were: median: 1.57, SD: 0.27; range: 1.24–2.05; 25th percentile: 1.3, 75th percentile: 1.74; lower 95% CI of mean: 1.32, upper 95% CI of mean: 1.83.

**ADC values in the tumors themselves**

The intratumoral values for the glioblastomas were: median: $3.0 \times 10^{-3} \text{mm}^2/\text{s}$, SD: 16.75; range: $1.02–1.53 \times 10^{-3} \text{mm}^2/\text{s}$; 25th percentile: 1.16, 75th percentile: 1.39; lower 95% CI of mean: 1.124, upper 95% CI of mean: 1.433 (Fig. 3C).

The values for the metastases were: median: $1.44 \times 10^{-3} \text{mm}^2/\text{s}$, SD: 21.73; range: $110–165 \times 10^{-3} \text{mm}^2/\text{s}$; 25th percentile: 119, 75th percentile: 163; lower 95% CI of mean: 119.2, upper 95% CI of mean: 164.8.

Values for the low-grade gliomas were: median: $1.95 \times 10^{-3} \text{mm}^2/\text{s}$, SD: 10.78; range: $1.82–2.08 \times 10^{-3} \text{mm}^2/\text{s}$; 25th percentile: 1.83, 75th percentile: 2.035; lower 95% CI of mean: 1.802, upper 95% CI of mean: 2.07.

The differences were significant for glioblastomas compared with low-grade gliomas ($P=0.0001$) as well as for metastases compared with low-grade gliomas ($P=0.0011$).

The ratios for brain tumors compared with the contralateral healthy brain were: 0.95 for glioblastomas; 1.06 for metastases; and 1.43 for low-grade gliomas.

**Discussion**

This study showed that both high-grade gliomas and metastatic brain tumors have higher ADC values in the perilesional edema than do low-grade gliomas, indicating a higher water content and greater tissue displacement due to vasogenic edema, and probably secondary to a more aggressive histological reaction. Also, there is a tendency for the more malignant lesions to have lower ADC values within the tumor itself, probably due to necrosis. Therefore, DWI-derived ADC maps can be helpful in differentiating tumor malignancy, and provide information not just concerning the tumor, but also about tumor edema extent. Regarding high-grade brain tumors, the study by Castillo et al. [12] found that such tumors have specific values that, however, could not be differentiated from those in the peripheral edema. Other, earlier studies have postulated that diffusion imaging could differentiate the tumor itself from edema [13].

As regards perilesional edema, similar results have been reported in the literature: Lu et al. [14] reported that ADC measurements can differentiate cytotoxic from vasogenic edema, and also between metastases and gliomas: they found increased diffusibility within the vasogenic edema surrounding both high-grade gliomas and metastatic tumors, reflecting increased extracellular water. However, the authors also found that peritumoral fractional anisotropy (FA) demonstrated no statistically significant differences. The FA changes observed around gliomas, therefore, can be attributed not only to increased water content, but also to tumor infiltration [15].

There have also been studies regarding tumor cellularity and diffusibility: increased cellularity is associated with a lower ADC, and lower ADC values appear to be associated with higher-grade tumors [16]. In a study of ADC values and T2 values, Oh et al. [17] found that ADCs for gliomas were similar to those for meningiomas and metastases in all regions. However, tumor T2 values for gliomas were significantly higher than those for meningiomas and metastases. Localized-edema T2 values for meningiomas and metastases were significantly higher than those for gliomas. Peripheral-edema T2 values for gliomas were similar to those for meningiomas and metastases. In addition, they found that using a combination of ADC and T2 values resulted in improved tissue characterization of these lesions. They also found significant correlations between ADC and T2 values. As with this study and that of Baehring et al. [18], we found a decrease in the central ADC of glioblastomas.
Diffusion imaging has been used in the appraisal of tumors and may even have the potential to differentiate between tumor subtypes. However, on reviewing the literature, it is clear that there is overlap between values [19]. Thus, a certain degree of care should be taken before relying on this parameter too strictly [20]. Nevertheless, its findings can certainly be used when carrying out multimodality imaging [21].

Toh et al. [22] did a study of the ADC in the peritumoral edema of metastases and meningiomas, and found that all values were significantly different between the two types of tumors. Provenzale et al. [23] examined the FA and mean ADC values in peritumoral hyperintense regions, and found that mean FA values were significantly higher for meningiomas than for gliomas, while mean ADCs in peritumoral normal-looking white matter were not significantly different.

Overall, this means that ADC mapping is a further means for obtaining improved tissue characterization. This, in addition to the information provided by other techniques such as spectroscopy [24], perfusion [25,26] and diffusion tensor imaging [23], should improve the initial diagnosis and work-up. Indeed, because of the often nonhomogeneous nature of tumors such as glioblastomas, a single measurement in a single area will not necessarily be helpful; it is the use of many parameters that will aid in improving our understanding of the nature of any lesion.

Conclusion

ADC mapping of brain tumors and assessment of the ADC in the peritumoral lesion appears to be promising in the differentiation of tumors and in the assessment of local invasiveness. Glioblastomas, while having a low central ADC, have a high ADC in the periphery, reflecting a central high cellularity and peripheral vasogenic edema.

References
