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Original Artitle

Alterations of contralateral white matter in glioma and meningioma patients: a numerical diffusion-weighted imaging approach

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Abstract: Few studies have examined apparent diffusion coefficient (ADC) values of white matter (WM) in the opposite hemisphere of the cranial tumor. Therefore, this study aimed to assess the utility of ADC obtained from quantification of diffusion weighted (DW) magnetic resonance imaging (MRI) for differentiation between healthy and pathological contralateral normal-appearing white matter (CNAWM) in patients diagnosed with glioma or meningioma. A total number of 1,306 subjects (979 regular individuals, 250 diagnosed with glioma, and 77 having meningioma) underwent DWI examinations, considering factors such as age, gender, hemisphere, and histopathological findings. Bilateral ADC values were calculated in healthy WM participants and unilateral measurements were evaluated on the remote opposite NAWM from the tumor containing hemisphere. ADC ranges in CNAWM of high-grade gliomas ($0.823 \pm 0.016 \times 10^{-3}$ mm^2/s) differed significantly from ADC spectrum of low-grade gliomas ($0.797 \pm 0.018 \times 10^{-3}$ mm^2/s) and meningiomas ($0.778 \pm 0.008 \times 10^{-3}$ mm^2/s). Compared to ADC values of healthy individuals ($0.752 \pm 0.017 \times 10^{-3}$ mm^2/s), these results suggest that quantification of DWI encompasses high sensitivity in early detection and specificity in differentiating abnormalities in macroscopically unsuspicious WM structures. In conclusion, an increase of apparent diffusion coefficient was found in the normal appearing white matter from the opposite area to the lesion (both benign and malign), statistically correlating to the grading of the tumor.

Keywords: Apparent diffusion coefficient, contralateral hemisphere, white matter, glioma, meningioma

Introduction

According to the World Health Organization (WHO), brain tumors are categorized into two categories, benign (noncancerous) and malignant (cancerous). Furthermore, each category is divided into different types of tumors depending on the nature of cells involved [1-4].

Meningiomas usually belong to the benign division, with only 8% of these lesions being atypical and potentially harmful [4]. Diagnos-tics are generally established with routine MRIs, using combined information from different sequences, appearance of the tissues, and location in the brain [5-7].

In contrast, concerning the malignant category, gliomas are the most common form of ce-rebral neoplasia. WHO provides a classification of gliomas into 4 grades, with worse prognosis for more advanced grades [2, 3, 8]. Although the classification clearly differentiates between grades, in practical medicine, reality often proves that there are mixed gliomas with elevated levels of malignancy intra lesion and lower levels at the periphery [1, 9-11]. Accordingly, this research will consider low-grade gliomas labeled as grade I, I/II, and II and high-grade gliomas will encompass the following levels: II/III, III, III/IV, and IV. Concerning the benign category, this study will consider only WHO grade I meningioma. The WHO grading criteria for each lesion was obtained from histopathological laboratory analysis.

The nature and grading of a brain mass is, preferably, established through a histopathological method. However, there are cases when biopsy and/or surgery are not preferable options. On that premise, noninvasive investigations are considered [12-20]. One of these is magnetic

resonance spectroscopy (MRS), which has proven its feasibility due to accurate values of metabolic changes that occur in tumors, appearing tissues [21, 22]. The main disadvantages of MRS are the limited area of evaluation, long scanning times, and elaborate post-processing of image data. Consequently, the present study aimed to discover if DWI might potentially be a shortened alternative to noninvasively assess extensive regions of the brain [23-25], such as the contralateral white matter side in the cerebral neoplasia.

Anterior studies of DWI applied in characterization of white matter were conducted solely to determine the tissue in or around the tumor [26-34]. Few studies have examined apparent diffusion coefficient values of white matter in the opposite hemisphere of cranial tumors [9, 35-37]. The added value of studying this part of the brain, compared to lesions directly, consists of displaying the extension of alteration processes concerning the normal appearing white matter. In consideration of establishing the pathological values for CNAWM, measurements of normal white matter of healthy participants were established. Although current literature computes various normal ranges of ADC [38], there are previous studies demonstrating that ADC values alter due to post processing methods [39], configuration of MRI equipment [40, 41], laterality, age, and gender [42-44]. Therefore, it was mandatory to begin this research by first evaluating the quantification data of DWI in normal patients, grouped by factors such as age, sex, and brain hemisphere.

The purpose of this study consisted of establishing normal white matter ADC values on a large cohort, analyzing results concerning age and gender, calculating the spectrum of variability for ADC alterations in CNAWM from patients with gliomas (low and high grade), as well as meningiomas, and determining the extent of modification that could lead to early detection of progressive/invasive malignant status.

Materials and methods

Patient recruitment

This study was approved by the appropriate Institutional Review Board and all enrolled subjects provided written informed consent to safely undergo the MRI examination and have their data stored and used for research purposes.

During a period of 35 months, 1,306 subjects were scanned using the MRI procedure. Of these, 979 participants were from a healthy population, 250 patients received a glioma radiological and histopathological result (low and high grade), and 77 individuals were diagnosed with typical benign meningioma.

General exclusion criteria for all participants, regardless of the inclusion group (normal or pathological) were as follows: inability to express informed consent, claustrophobic patients, comatose/under anesthesia patients, pediatric patients, insufficient compliance, cognitive status impairment, language impediments, motion/metallic/susceptibility artifacts, allergic reactions to gadolinium based contrast agents, chemotherapy or radiotherapy in history, evidence of neoplasm across the body, history of any neurologic or systemic disease that might have affected the brain (for example, diabetes, chronic obstructive pulmonary disease, hypertension, metabolic disorders, dementia), and none were taking medication regularly (except for topical drugs).

Concerning the normal group of participants, apart from the general restrictions metioned above, volunteers had to receive a normal radiological result, described no brain lesions whatsoever (minor white matter changes in the older subjects, named leukoaraiosis, were considered as normal), and absence of a family history of psychiatric disorders, dementia, or multiple sclerosis.

Other than the nature of the tumor, the following exclusion criteria were applied in the process of participant selection for the tumoral group: status of post brain surgery in history, recidival tumor, and evidence of abnormal changes on MRI images that revealed unexpected cerebral lesions in the CNWM. Another important issue was the presence of histopathological proof of the stated form of lesion, meaning that the MRI examination was preceded or followed by resection of the tumor and laboratory analysis.

The normal group consisted of 979 participants, with 364 males (37.2%) and 615 females (62.8%). Ages ranged from 18 to 84 years

old (mean age was 36 years old). The meningioma category had 77 subjects: 17 men (22.1%) and 60 women (77.9%), aged between 29 and 84 years old (average 60 years old). Concerning patients with gliomas, this study divided the participants into a low-grade category, encompassing 73 subjects (almost equally distributed to 36 female participants and 37 male participants, aged between 18-75, mean 40 years old) and hi-gh-grade category with 183 subjects (105 males, 54.3% and 72 females 40.7%, aged between 22-86, mean 48 years old).

Imaging techniques

All studies were performed with a Magnetom Avanto Imager (Siemens Medical Systems, Erlanger, Germany) operating at 1.5 Tesla, using a standard head coil. In addition to axial DW images, the scanning protocol included conventional T2-weighted (sagittal and axial), fluid-at-tenuated inversion recovery (3D), and T1-weigh-ted (axial and coronary, both before and after administration of contrast agent) to exclude gross brain disease for normal brains and to characterize neoplastic lesions for the tumor category. All imaging procedures were completed without any adverse effects or complications.

Diffusion-weighted imaging derives its contrast from differences in the motion of water molecules in biologic tissues, which can become restricted due to interactions with cell membranes and macromolecules. The severity of restriction of water diffusion is proportional to cellular tissue density, meaning that any presence of other types of cells (for example, tumor cells) interfere with the normal free movement of water molecules, appearing as restriction. The precision to detect abnormalities in water motion can be raised by increasing the amplitude, duration, and temporal spacing of two gradients. Gradient properties determine the parameter known as the "b-factor". For a brain examination, at least two b-values ranging betw-een 0-1000 mm^2/s (in this study, DWI parameters included three values: 0, 500, 1000 $mm^2/-s$) are necessary to obtain DW images in three orthogonal directions that will be combined into isotopic DW images and apparent diffusion coefficient maps calculated on a pixel-by-pixel basis [19, 45, 46].

In this study, DW imaging was performed with a spin-echo echo-planar imaging sequence with a TR/TE of 7000/103, 40 slices, 3 mm thick sections, and a field of view of 230/230 mm^2. Diffusion was measured in three orthogonal directions (x, y, and z) with three b values (0, 500 and 1000 s/mm^2). The total acquisition time for DW images was approximately 4 minutes.

The technique can be performed at a rapid scanning time, without the necessity of contrast agent administration. It is cost effective with reduced sensitivity to motion artifacts, providing both qualitative and quantitative information.

The qualitative part refers to the visual representation of the lesion due to the mobility of water molecules restricted in the tumor tissue (appearing "brighter" on images).

The quantification aspect is less used in conventional MRI evaluations and refers to the sensitivity to water motion arising in DWI sequence. It is represented by the apparent diffusion coefficient.

Data analysis

DW images and automatically generated ADC maps were transferred to a separate workstation for data analysis. Apparent diffusion coefficient values were derived from post-processing the obtained images by manually drawing regions of interest (ROIs) on the ADC map, within the selected tissue. First, ROIs were drawn on the T2-weighted (b=0) images, in which the structures could easily be identified. Next, they were subsequently tr-ansferred to the equivalent ADC maps. For each ROI, the surface area, minimum, maximum, mean, and standard deviation ranges for ADC values were obtained. ROI analysis was performed with imagine analysis software (Syngo Via Plaza version VB10A, Siemens Medical Systems, Erlanger, Germany), allowing ROI positioning as a single point (round shape, minimal size) rather than an area, reducing the risks of encircling surrounding tissue (for example, grey matter).

For the normal group, ROIs were drawn on each hemisphere, symmetrically bilateral, in the white matter tissue (**Figure 1**).

Concerning the glioma and meningioma category, ROIs were drawn only on the opposite si-

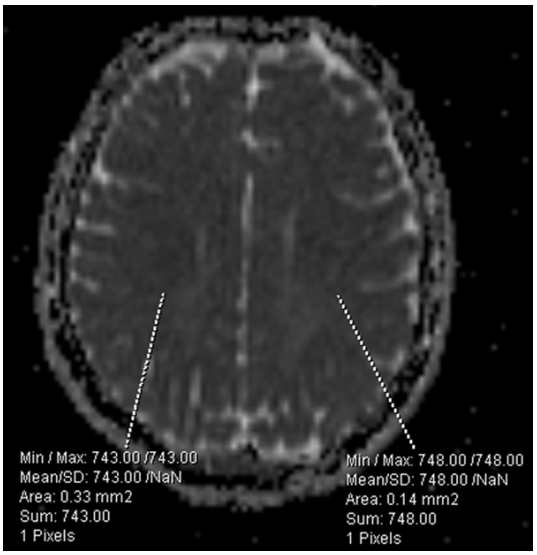

Figure 1. Example of ROI placement in a healthy patient, with emphasis on ADC value.

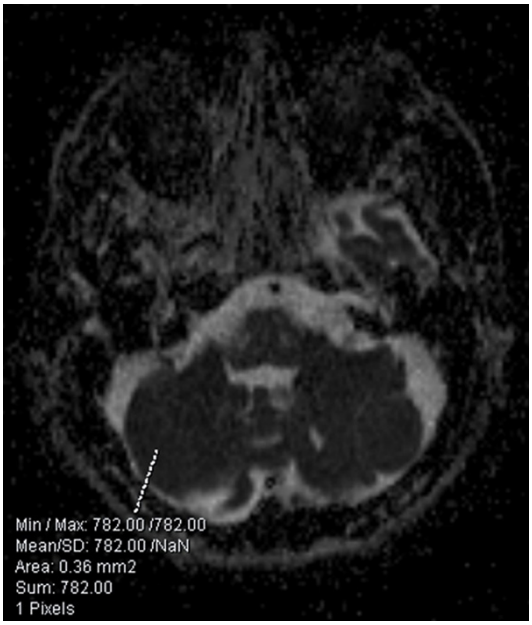

Figure 2. Example of contralateral ROI placement on NAWM, in a patient diagnosed with meningioma, with emphasis on ADC value.

de, symmetrically placed in the white matter structure (**Figures 2**, **3**).

Statistical analysis

Data derived from ROI measurements were statistically analyzed using SPSS 16.0 software (SPSS Inc. Chicago, IL, USA). Effects of tumor presence on ADC values were studied using Spearman's analysis since the groups

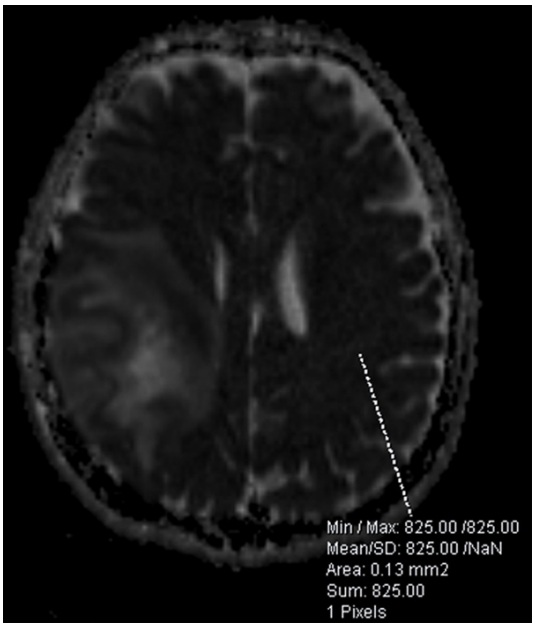

Figure 3. Example of contralateral ROI placement on NAWM, in a participant diagnosed with high grade glioma, with emphasis on ADC value.

were not normally distributed. One-way analysis of variance was applied to study the average values in normal participants for each hemisphere and in tumor category for unilateral evaluation. Groups representing different age cohorts and different sexes were compared with multivariate analysis of variance. Two-tailed *P*-values less than .05 indicate significant differences.

Results

In normal brains, mean ADC values were (0.752071 ± 0.0171) × 10^{-3} mm^2/s (range, 0.710-0.797 × 10^{-3} mm^2/s). Differences in the left hemisphere (mean 0.75229 ± 0.0143 × 10^{-3} mm^2/s) from the right hemisphere (mean 0.75250 ± 0.01474 × 10^{-3} mm^2/s) were insignificant. Also, no statistically significant differences were fo-und between the gender groups (male participants had a mean ADC of 0.753 × 10^{-3} mm^2/s compared to female patients that had 0.7515 × 10^{-3} mm^2/s) or among various age groups (mean of ADC values was constant at about 0.752 × 10^{-3} mm^2/s until ages 40-50 years old when a slight increase was noticeable - a mean of 0.760 × 10^{-3} mm^2/s).

Concerning the meningioma category, average ADC values were (0.778 ± 0.0089) × 10^{-3} mm^2/s (range, 0.775-0.806 × 10^{-3} mm^2/s).

Table 1. Minimum, maximum, mean, and standard deviation (SD) values of ADC in each of the four categories studied

ROI placement	Minim	Maxim	Mean ± SD
Normal brain	0.710	0.797	0.752071 ± 0.0171
Contralateral meningioma	0.775	0.806	0.778 ± 0.0089
Contralateral low-grade glioma	0.774	0.857	0.797 ± 0.0183
Contralateral high-grade glioma	0.783	0.875	0.823 ± 0.016

Table 2. Spearman's correlation in SPSS stating significant positive correlation between grading of the tumor and ADC values (where "ADC contralateral" encompass ADC values for both meningiomas and gliomas)

			Grading	ADC contralateral
Spearman's rho	Grading	Correlation Coefficient	1.000	.746**
		Sig. (2-tailed)	.	.000
		N	1306	1306
	ADC contralateral	Correlation Coefficient	.746**	1.000
		Sig. (2-tailed)	.000	.
		N	1306	1306

**. Correlation is significant at the 0.01 level (2-tailed).

The low-grade group showed mean ADC values of (0.797 ± 0.0183) × 10^{-3} mm^2/s (range, 0.774-0.857 × 10^{-3} mm^2/s) and high-grade category calculations for contralateral ADC were (0.823 ± 0.016) × 10^{-3} mm^2/s (range, 0.783-0.875 × 10^{-3} mm^2/s).

Collected values are listed in **Table 1**, considering the measurement units for ADC values (× 10^{-3} mm^2/s).

Comparing the results of pathological participants to normal brains, a potential connection between the severity of tumor grading and the elevated spectrum of ADC in the contralateral NAWM was observed. To conclude the veridicity of this statement, Spearman's statistical analysis was applied. Results, as shown in **Table 2**, clearly demonstrate a strong positive correlation between tumor grading and the value of contralateral ADC.

Discussion

The present study reported ADC values in normal brains, as well as in the contralateral NAWM, for both benign and malign tumors in a large representative adult population involving pat-ients of both sexes with a wide age range.

To the best of our knowledge, only a few studies have addressed the issue of evaluating the presence of abnormalities in macroscopically unsuspicious parenchyma. None have compared normal healthy WM with NAWM of meningiomas, low, and high-grade gliomas.

Although present results prove a definite correlation between levels of malignancy and values of ADC in the contralateral NAWM (rising from 0.752 × 10^{-3} mm^2/s in normal brains to 0.778 × 10^{-3} mm^2/s in meningiomas, then to 0.797 × 10^{-3} mm^2/s in low grade gliomas, and finally to 0.823 × 10^{-3} mm^2/s in high grade glioma), the causal factors remain unclear.

Typically, on MR images, the contrast-enhancing core of malignant gliomas is located within a much larger area of tissue that is often described as edema. It can be not only reactive brain tissue but also a reflection of tissue infiltrated by tumor cells. This peritumoral tissue has been thought to appear within 3 cm around the tumor, but more recent findings have yielded the probability of a more extended zone of infiltration. In this situation, with malignant cells migrating from a high grade-glioma, the presence of malignant cells at the opposite hemisphere might be considered low, as with the aspect of low-grade gliomas (sometimes indistinguishable from normal brain parenchyma). This explanation might clarify the increased values of ADC in the brain parenchyma of the hemisphere contralateral to the tumor localization in the absence of visible MRI abnormalities.

Also, considering that increased ADC values were revealed in the meningioma group, it can be concluded that DWI is highly sensitive to any interference with cell mobility by different strategies (whether benign or malign), resulting in elevated values directly dependent to the level of malignancy. Modifications could occur due to compression, ischemia, or tumor vascularity

since ADC with monoexponential fitting can also be affected by intra voxel perfusion. However, ADC values were clearly shown to correlate with tumor grades (both in benign and malign cases) on a large cohort, implying that other factors, such as inflammatory process or tumor infiltration of the WM, can affect these results.

The present study assumed that DWI represents an important role in early detection of tissue abnormalities and that tumor infiltration is not the only reason for raised ADC values in the contralateral NAWM. Other factors involved include mass effects, tumor volume, and global vasogenic edema.

Future studies should encompass different types of benign tumors (cysts or lipomas), as meningioma is an extra-axial tumor. Measurements should be calculated at the most distant point from the tumor and histopathological analysis should be conducted on the exact ROI placement to assess the exact extent of DWI sensitivity.

In conclusion, an increase of apparent diffusion coefficient was found in the normal appearing white matter from the opposite area to the lesion (both benign and malign), statistically correlating to tumor grading. In the absence of visible MRI abnormalities, this may be an early indicator of microstructural changes of the NAWM attributed to malignant brain tumors and could have a critical role in therapeutic conduct.

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Disclosure of conflict of interest

None.

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