

SHORT REPORT

Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study

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Objectives: Glucocorticoids (dexamethasone) are thought to reduce peritumoural brain oedema by decreasing the permeability of neoplastic capillaries and/or enhancing the clearance of extracellular water. Diffusion tensor magnetic resonance imaging (DT-MRI) was used to measure the water diffusion parameters of oedematous and normal brain in a group of patients with intracranial tumours before and after steroid treatment.

Methods: Fifteen patients with intracranial tumours (seven with high-grade glioma, four with metastatic carcinoma and four with meningioma) were examined before and 48–72 h after dexamethasone treatment (16 mg/day). The mean diffusivity (<D>) and fractional anisotropy (FA) were measured for oedematous brain and apparently normal contralateral white matter before and after steroid therapy.

Results: In all three patient groups there was a significant decrease in <D> of oedematous brain after steroid treatment ($p < 0.01$). There was no significant change in FA of oedematous brain after treatment in any of the three groups. There was also no significant change in either <D> or FA of apparently normal contralateral white matter after treatment.

Conclusion: These data indicate that dexamethasone produces a localised reduction in the magnitude of extracellular water molecule mobility, and hence water content, in peritumoural oedematous brain. Furthermore, the magnitude of these changes is similar for both intra- and extra-axial tumours.

In patients with malignant cerebral tumours, the signs and symptoms are due to not only the location and mass effect of the tumour, but also the associated peritumoural oedema. Following several studies that documented a decrease in both surgical morbidity and mortality following glucocorticoid (dexamethasone) treatment,^{1,2} steroid therapy is now routinely used in the management of patients with brain tumours and peritumoural oedema. Although their modes of action are poorly understood, steroids are thought to play a major role in decreasing oedema formation by reducing the permeability of neoplastic capillaries and/or enhancing the clearance of extracellular water.³

The effects of glucocorticoids on water abnormalities in peritumoural brain can be assessed non invasively using diffusion tensor magnetic resonance imaging (DT-MRI). This technique permits the spatial mapping of the apparent diffusion tensor of water (**D**) in the brain, from which the mean diffusivity (<D>) and scalar diffusion anisotropy indices, such as the fractional anisotropy (FA), can be determined.^{4,5} The parameter <D>, which is thought to reflect the average microscopic mobility of water molecules in the extravascular extracellular space,⁶ can detect and

characterise brain oedema, while FA provides a scalar measure of the deviation from pure isotropic diffusion of water mobility in vivo.⁵ Recent studies have shown that <D> and FA of peritumoural oedematous brain are respectively increased and reduced compared with normal healthy cerebral tissue.^{7–9} This rise in <D> indicates an increase in the magnitude of water mobility, whereas the decrease in FA suggests a loss of structural organisation within peritumoural brain. These alterations in <D> and FA are thought to arise from a combination of increased water content and tumour infiltration.⁹ If steroids act by producing a normalisation in peritumoural brain water homeostasis, then this action should reduce <D> and increase FA towards the values seen in healthy brain parenchyma. In this paper this hypothesis is investigated by measuring the water diffusion parameters of oedematous and normal brain in a group of patients with intracranial tumours before and 48–72 h after dexamethasone treatment.

METHODS

Subjects

Twenty consecutive patients presenting with a newly diagnosed, supratentorial, solitary, intracranial tumour were enrolled in this prospective study. Each subject had evidence of oedema on the initial CT scan, but without indication of other concurrent neurological disease. At the time of imaging, none of the patients had (i) begun steroid treatment, (ii) had any prior radiotherapy or chemotherapy, or (iii) undergone any prior cranial surgery. They also had no contraindications to MRI. The local ethics committee approved the study and informed consent was obtained from each patient.

MRI protocol

All MRI data were obtained using a GE Signa LX 1.5 T (General Electric, Milwaukee, WI, USA) clinical scanner, equipped with a self-shielding gradient set (22 mT/m maximum gradient strength and 120 T/m/s slew rate) and a manufacturer-supplied “birdcage” quadrature head coil. The MRI examination consisted of a standard fast spin-echo (FSE) T₂-weighted sequence, a DT-MRI protocol described previously, and a contrast-enhanced T₁-weighted volume sequence.^{7,8} The duration of the examination was approximately 40 min. This protocol was repeated 48–72 h after dexamethasone treatment (16 mg/day) had begun.

To ensure that the slice locations used in the second examination corresponded as closely as possible to those in the first, the subject's head position and tilt in the first scan were recorded and the patient repositioned in exactly the same manner for the second scan. At least one of the slices

Abbreviations: DT-MRI, diffusion tensor magnetic resonance imaging; DW, diffusion-weighted; EP, echo-planar; FA, fractional anisotropy; FOV, field of view; FSE, fast spin-echo; GBM, glioblastoma multiforme; ROI, region of interest; SD, standard deviation

was taken through a prominent anatomical landmark so as to minimise any deviation in slice location in the second scan. Computational image realignment techniques were then used to warp the images in the second exam to the first, thereby minimising any small remaining positioning errors.

In the DT-MRI experiment diffusion-weighted (DW) images were acquired using a single-shot spin-echo echo-planar (EP) imaging sequence in which two symmetric trapezoidal gradient pulses of duration $\delta = 32.2$ ms, separation $\Delta = 39.1$ ms, and rise time $\eta = 1.2$ ms were inserted around the 180° refocusing pulse in the required gradient channel. Sets of axial DW-EP images ($b = 0$ and 1000 s/mm²) were collected with diffusion gradients applied sequentially along six non collinear directions.¹⁰ Five acquisitions consisting of a baseline T₂-weighted EP image (\mathbf{G}^0) and six DW-EP images (\mathbf{G}^1 to \mathbf{G}^6), a total of 35 images, were collected per slice position. The acquisition parameters for the DW-EP imaging sequence were 15 axial slices of 5 mm thickness and 1.0 mm slice gap, a field of view (FOV) of 240×240 mm, an acquisition matrix of 128×128 (zero filled to 256×256), a TR of 10 s, and a TE of 98.8 ms.

After the DT-MRI protocol, 20 ml of gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ, USA) was administered intravenously. Acquisition parameters for the contrast enhanced T₁-weighted volume sequence were 110 contiguous axial slices of 1.5 mm thickness, an FOV of 240×240 mm, an acquisition matrix of 256×256 , a TR of 7.3 ms, a TE of 3.2 ms, and a TI of 400 ms.

Image analysis

Quantitative co-registered maps of brain water diffusion parameters for the pre- and post-treatment examinations were obtained in the following manner. Bulk patient motion and eddy current induced artefacts were removed from the component EP images using FLIRT (www.fmrib.ox.ac.uk/fsl), a three-dimensional computational image alignment program.¹¹ Firstly, EP images with the same b-matrix were rigidly aligned to remove patient motion. Secondly, affine transformations were used to align the DW-EP images acquired with diffusion gradient directions \mathbf{G}^2 to \mathbf{G}^6 to the first gradient direction \mathbf{G}^1 . Thirdly, all DW-EP images were aligned to the T₂-weighted (\mathbf{G}^0) EP images acquired in the first examination. Next the set of five EP images collected for each gradient direction was averaged to give seven high signal-to-noise ratio images for each slice. From this MRI data \mathbf{D} was calculated in each voxel from the signal intensities in the component EP images.⁴ After diagonalisation of \mathbf{D} to yield the magnitude sorted eigenvalues ($\lambda_{i=1,2,3}$), maps of the T₂-weighted signal intensity, mean diffusivity

$$\langle D \rangle = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}, \quad (1)$$

and the fractional anisotropy⁵

$$FA = \sqrt{\frac{3}{2} \frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}, \quad (2)$$

were generated on a voxel-by-voxel basis and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format. The FA measures the fraction of the total "magnitude" of \mathbf{D} that is anisotropic, and takes a value of 0 for isotropic diffusion ($\lambda_1 = \lambda_2 = \lambda_3$) and 1 for completely anisotropic diffusion ($\lambda_1 > 0; \lambda_2 = \lambda_3 = 0$).

Region-of-interest analysis

The effects of dexamethasone on the brain water diffusion parameters of peritumoural oedematous brain were quantified using a previously described region-of-interest (ROI) analysis.⁷ Blinded as to whether the imaging data came from the pre- or post-treatment examination, the observer (SS) identified for each slice the largest region of signal hyperintensity on the T₂-weighted EP images which extended beyond the enhancing tumour margin present in the co-registered contrast-enhanced T₁-weighted volume images. This oedematous brain region was overlaid on the $\langle D \rangle$ and FA parametric maps obtained from both examinations. For each appropriate slice, values of $\langle D \rangle$ and FA for the entire oedematous brain region and apparently normal contralateral white matter in the centrum semiovale were measured. Overall mean $\langle D \rangle$ and FA values were then calculated from these data to give volume measures for the two tissue types in each patient. The volume measurements of $\langle D \rangle$ and FA were typically obtained from several thousand voxels in five to 12 slices for oedematous brain, and hundreds of voxels in a single slice for apparently normal contralateral white matter in the centrum semiovale.

Statistical analysis

All data are reported as a mean with one standard deviation (SD) in parentheses. For each patient the percentage change in $\langle D \rangle$ and FA for oedematous and normal brain following steroid treatment was determined as follows

$$\epsilon(X) = 100 \frac{X_{\text{post}} - X_{\text{pre}}}{X_{\text{pre}}}, \text{ where } X = \langle D \rangle \text{ or FA.} \quad (3)$$

The percentage change (ϵ) in $\langle D \rangle$ and FA for both tissue types was calculated for each patient, and a mean value ($\langle \epsilon \rangle$) obtained for each of the three disease groups. To assess whether changes in these water diffusion parameters were significant, the mean pre- and post-treatment values of $\langle D \rangle$ and FA for each patient were compared using a paired-samples Student's *t* test (SPSS 10.0, SPSS, Chicago, IL, USA), with $p < 0.05$ being considered statistically significant.

RESULTS

Of the 20 patients initial enrolled in the study, seven men and eight women (mean (SD) age 58.6 (9.7) years) tolerated both examinations and had an enhancing lesion on the T₁-weighted volume scan. Of these 15 patients, seven had glioblastoma multiforme (GBM), four had metastatic carcinoma, and four had meningioma. In all patients the tumour type was confirmed histologically, with all surgical procedures performed after the second MRI examination. There was a significant improvement in limb function in one of the seven patients with GBM following steroid therapy, while in the remaining subjects improvement was more limited and subjective, with the typical benefit being relief from headache.

Pre- and post-treatment values of $\langle D \rangle$ and FA for oedematous and normal brain in these patients are shown in table 1, along with their demographic information. Fig 1 shows maps of T₂-weighted signal intensity, $\langle D \rangle$, and FA before and after steroid treatment for a representative slice acquired from a 55 year old female patient with GBM (patient 1). These maps show the marked difference in the water diffusion parameters between oedematous and normal brain, with the former characterised by high values of $\langle D \rangle$ and low values of FA. This figure also shows that although the water diffusion abnormalities of oedematous brain are not completely resolved by steroid treatment after 72 h, there is a widespread reduction in the T₂-weighted signal intensity

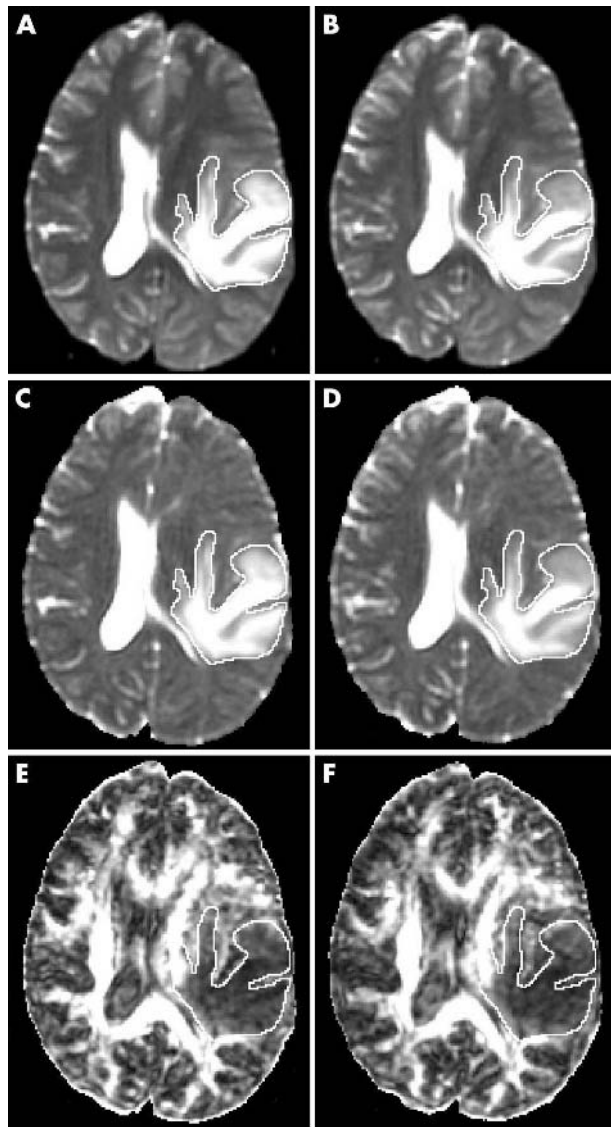


Figure 1 Maps of T₂-weighted signal intensity (A, B), <D> (C, D), and FA (E, F) obtained at the level of the body of the lateral ventricles from a 55 year old female patient with GBM (patient 1) before (first column) and 72 h after steroid treatment. Note the widespread reduction in the T₂-weighted signal intensity and <D> of peritumoural oedematous brain after steroid treatment. No enhancing lesion is visible at this level in the brain in the contrast-enhanced T₁-weighted volume scan (not shown).

and <D> of oedematous brain. There is, however, no apparent change in FA of oedematous brain after steroid treatment.

Table 1 shows that <D> of oedematous brain is significantly higher than that of normal brain both before and after steroid treatment in all three patient groups ($p < 0.001$). Conversely, FA of oedematous brain is significantly reduced compared with normal brain before and after treatment ($p < 0.001$). In all three patient groups, there was a significant decrease in <D> of oedematous brain after steroid treatment ($p < 0.01$). The mean percentage change ($\langle \epsilon \rangle$) in <D> was -7.63 (1.17) % for high-grade glioma, -5.73 (1.04) % for metastatic carcinoma and -5.54 (0.70) % for meningioma. The FA of oedematous brain was not, however, significantly altered by steroid treatment in any of the three disease groups. In addition, there was no significant change in either <D> or FA of apparently normal contralateral white matter after treatment.

DISCUSSION

There have been several recent studies using DT-MRI to characterise the water diffusion properties of intracranial tumours. Sinha *et al*⁷ investigated whether water diffusion parameters could differentiate tumour margin from oedematous brain in nine patients with GBM. They found that while <D> of tumour margin was significantly different from that of oedematous brain, FA was not. Lu *et al*⁹ measured <D> and FA values in peritumoural brain in 12 patients with high-grade glioma and 12 with metastatic lesions and found that only <D> was significantly different in these two pathologies. Price *et al*¹² found evidence for tumour infiltration in high-grade gliomas, when comparing DT-MRI and T₂-weighted imaging data from 20 patients with gliomas and metastases. By analysing MRI and biopsy data in 31 patients with astrocytic tumours, Beppu *et al*¹³ found evidence that the FA values of glioblastoma and anaplastic, diffuse, and pilocytic astrocytoma are largely affected by cellularity and/or vascularity. Changes in the water diffusion parameters of oedematous brain following dexamethasone treatment have previously only been described by Bastin *et al*.¹⁴ In their small pilot study of six patients with a wide range of tumours, they found evidence for a reduction in <D> of oedematous brain following dexamethasone treatment in one patient with GBM.

The results of the current study show that <D> of oedematous brain associated with high-grade glioma, metastatic carcinoma, and meningioma is significantly reduced 48–72 h after dexamethasone treatment, and that this reduction is of a similar magnitude in all three tumour types. Previous studies have shown that oedematous brain associated with intra- and extra-axial tumours has a much higher proton longitudinal relaxation time (T₁) than normal brain, and that dexamethasone reduces these elevated T₁ values.^{8, 15–17} Since T₁ reflects brain tissue water content, and DT-MRI predominantly measures the mobility of water molecules in the extracellular space,⁶ these data suggest that dexamethasone acts by reducing the extracellular water fraction. This reduction then produces the marked decline in <D> of oedematous brain observed above. Interestingly, however, this effect is not sufficient, at least after 48–72 h, to increase axonal organisation, as measured by FA, towards more normal values. Furthermore, since significant differences in <D> and FA were not seen in normal brain, it is concluded that dexamethasone has only a localised effect on brain water content.

The current study has both strengths and weaknesses. Firstly, none of the patients had undergone previous treatment or had recurrent and/or residual tumours. Since the effect of surgery or adjunct therapy on oedematous brain <D> and FA values is not known, excluding such patients makes quantifying the changes in water diffusion parameters after steroid treatment more straightforward. Secondly, by measuring the water diffusion parameters over the entire oedematous brain volume one avoids any subjective bias that may occur when small ROIs are placed in regions of abnormal signal intensity.⁷ The main limitation of the paper is the small number of patients imaged. However, even with this number of subjects the effects of dexamethasone on the water diffusion parameters of peritumoural oedematous brain are clear.

CONCLUSION

In this study the effects of dexamethasone on the water diffusion parameters of oedema associated with intracranial tumours and apparently normal contralateral white matter have been quantified using DT-MRI. In all three patient groups, <D> of peritumoural oedematous brain was significantly reduced 48–72 h following steroid treatment,

Table 1 Values of the mean diffusivity (<D>) and fractional anisotropy (FA) for peritumoural oedematous brain and apparently normal contralateral white matter (centrum semiovale) pre- and post-steroid treatment for the 15 patients imaged in this study

Age/sex	Mean diffusivity, <D> ($\times 10^{-6}$ mm ² /s)				Fractional anisotropy			
	Oedematous brain		Contralateral white matter		Oedematous brain		Contralateral white matter	
	Pre-steroids	Post-steroids	Pre-steroids	Post-steroids	Pre-steroids	Post-steroids	Pre-steroids	Post-steroids
Glioblastoma								
1/55/F	1674 (253)	1561 (318)	750 (18)	740 (24)	0.15 (0.06)	0.16 (0.07)	0.47 (0.10)	0.47 (0.10)
2/50/M	1575 (215)	1430 (256)	758 (24)	766 (22)	0.15 (0.05)	0.17 (0.07)	0.49 (0.05)	0.48 (0.04)
3/61/F	1139 (152)	1046 (144)	719 (25)	716 (22)	0.21 (0.08)	0.21 (0.09)	0.43 (0.05)	0.42 (0.04)
4/65/M	1494 (211)	1377 (228)	717 (46)	711 (54)	0.14 (0.05)	0.15 (0.06)	0.45 (0.13)	0.46 (0.14)
5/71/M	1477 (280)	1347 (289)	775 (63)	733 (24)	0.18 (0.09)	0.19 (0.10)	0.52 (0.07)	0.50 (0.10)
6/42/M	1140 (336)	1068 (288)	690 (25)	704 (22)	0.22 (0.10)	0.20 (0.09)	0.42 (0.08)	0.41 (0.07)
7/75/M	1288 (189)	1206 (189)	775 (75)	767 (61)	0.20 (0.07)	0.19 (0.07)	0.42 (0.13)	0.41 (0.10)
Mean	1398 (212)	1291 (191)	741 (33)	734 (26)	0.18 (0.03)	0.18 (0.02)	0.46 (0.04)	0.45 (0.04)
<ε>, %; p	-7.63 (1.17); <0.01		-0.85 (2.35); 0.36		3.12 (8.48); 0.55		-1.50 (2.11); 0.11	
Metastases								
8/54/F*	1356 (231)	1264 (216)	676 (24)	696 (31)	0.18 (0.07)	0.19 (0.08)	0.41 (0.09)	0.44 (0.09)
9/59/F†	1554 (244)	1460 (224)	721 (52)	733 (55)	0.14 (0.06)	0.13 (0.06)	0.42 (0.12)	0.39 (0.12)
10/61/M‡	1560 (268)	1470 (274)	734 (42)	728 (33)	0.13 (0.06)	0.13 (0.07)	0.48 (0.10)	0.49 (0.08)
11/53/F*	1556 (236)	1489 (216)	764 (22)	724 (24)	0.15 (0.07)	0.14 (0.07)	0.49 (0.07)	0.48 (0.11)
Mean	1507 (100)	1421 (105)	724 (37)	720 (17)	0.15 (0.02)	0.15 (0.03)	0.45 (0.04)	0.45 (0.05)
<ε>, %; p	-5.73 (1.04); <0.01		-0.36 (3.60); 0.81		-2.36 (4.13); 0.37		-0.20 (5.36); 0.94	
Meningioma								
12/60/F	1442 (224)	1371 (219)	742 (14)	732 (12)	0.16 (0.06)	0.16 (0.07)	0.46 (0.06)	0.45 (0.07)
13/52/F	1215 (183)	1155 (166)	720 (14)	723 (20)	0.24 (0.08)	0.23 (0.07)	0.44 (0.08)	0.44 (0.08)
14/74/M	1077 (140)	1011 (141)	741 (45)	778 (43)	0.31 (0.10)	0.28 (0.10)	0.45 (0.09)	0.44 (0.08)
15/47/F	1539 (249)	1444 (241)	723 (37)	722 (35)	0.13 (0.06)	0.14 (0.06)	0.38 (0.13)	0.38 (0.12)
Mean	1318 (210)	1245 (199)	732 (12)	739 (27)	0.21 (0.08)	0.20 (0.07)	0.43 (0.04)	0.43 (0.04)
<ε>, %; p	-5.54 (0.70); <0.01		0.98 (2.77); 0.53		-2.90 (5.09); 0.34		-0.49 (2.12); 0.63	

*Metastasis of malignant melanoma. †Metastasis of lung carcinoma. ‡Metastasis of renal carcinoma. All values are reported as mean (SD). Bold type indicates a statistically significant change in a parameter following steroid treatment.

while FA was approximately unchanged. The water diffusion parameters of normal tissue were also unchanged. These data indicate that dexamethasone produces a localised reduction in the magnitude of extracellular water molecule mobility, and hence water content, in peritumoural oedematous brain. Furthermore, the magnitude of these changes is similar for both intra- and extra-axial tumours. These results also indicate that DT-MRI may provide a sensitive non invasive tool for evaluating the treatment response of peritumoural oedema not only to dexamethasone, but potentially also to other chemotherapeutic agents.

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