Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

Original research article

The evaluation of the effects of steroid treatment on the tumor and peritumoral edema by DWI and MR spectroscopy in brain tumors

Cahit Kural^a, Gokce Kaan Atac^b, Ozkan Tehli^a, Ilker Solmaz^a,
Caglar Temiz^a, Irgen Hodaj^a, Yusuf Izci^{a,*}

^aDepartment of Neurosurgery, University of Health Sciences, Gulhane Education and Research Hospital, Ankara, Turkey

^bDepartment of Radiology, Ufuk University, Ankara, Turkey

ARTICLE INFO

Article history:

Received 25 December 2017

Accepted 4 March 2018

Available online 13 March 2018

Keywords:

Glioma

Metastasis

Steroid

Diffusion weighted image

Spectroscopy

ABSTRACT

Objective: To investigate the effects of dexamethasone on brain tumor and peritumoral edema by different sequences of magnetic resonance imaging (MRI).

Materials and methods: MRI was performed in 28 patients with brain tumor. Patients were divided into the 3 groups based on the histological diagnosis; Group I: high-grade glial tumor, Group II: low-grade glial tumor, and Group III: brain metastasis. The measurements of peritumoral edema volume and apparent diffusion coefficient (ADC) values were performed while the peak areas of cerebral metabolites were measured by spectroscopy in groups I and II. The changes in edema volumes, ADC values and cholin/creatine peak areas were compared.

Results: The volume of peritumoral edema was decreased in groups I and II, but increased in group III after dexamethasone treatment. These changes were not statistically significant for 3 groups. ADC value was decreased in group I and increased in groups II and III. Changes in ADC values were statistically significant. Cholin/creatine peak areas were decreased after dexamethasone in groups I and II, but these changes were also not significant.

Conclusion: Dexamethasone has no significant effect on the volume of peritumoral edema in glial tumor and metastasis. Moreover, dexamethasone increases the fluid movements in low grade gliomas and metastases, decreases in high grade gliomas. However, more comprehensive clinical studies are needed to show the effects of dexamethasone on brain tumors and peritumoral edema.

© 2018 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

* Corresponding author at: Department of Neurosurgery, University of Health Sciences, Gulhane Education and Research Hospital, 06010 Etlik, Ankara, Turkey.

E-mail address: yusufizci@yahoo.com (Y. Izci).

<https://doi.org/10.1016/j.pjnns.2018.03.002>

0028-3843/© 2018 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

1. Introduction

About 80% of brain tumors are primary, metastatic tumors contribute to the remaining 20%. Brain is the second most common site for metastasis and accounted for 15% of all metastases. Brain tumors may occur at any age, but they are observed more common between the ages of 55 and 65 years. Most common primary brain tumors are gliomas [1-4].

Glial tumors are the widest group of all intracranial tumors (40-45%) [5]. Gliomas may be solitary or multicentric [2]. These tumors are divided into 2 groups such as low-grade glioma and high-grade glioma based on histological examination of the tumor specimen. Subependymal giant cell astrocytoma, pilocytic astrocytoma, ganglioglioma, and diffuse astrocytoma are examples of low-grade glial tumors. Anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma are the examples of high-grade glial tumors. Although the accurate diagnosis of gliomas is made by histological examination of the tumor tissue, many studies attempted to reveal some biomarkers of brain gliomas in blood and in other body fluids [3].

Metastatic tumors of the brain generate about 50% of all supratentorial brain tumors. Breast, lung, malignant melanoma, and gastrointestinal tract malignancies frequently metastasize to the brain [1,5,6].

Brain tumors are usually diagnosed with imaging techniques. Currently, magnetic resonance imaging (MRI) is widely accepted all over the world as the best imaging study for the detection of brain tumors [5]. The characteristics of solitary metastasis and primary gliomas are non-specific in conventional MRI studies and cannot be reliably distinguished by this examination. Contrast agent uptake of tumor cells can be seen both of tumors and varying degrees of peritumoral edema can be observed in MRI of patients. The most important criteria for histological grading of gliomas are vascular proliferation and the degree of cellularity. Contrast-enhanced MRI scans may provide information about the vascularity of tumor. Diffusion-weighted and diffusion-tensor imaging may be useful to provide information about cell density of tumor. Metastases and high grade gliomas cause different types of peritumoral edema in the brain. Infiltrative edema is observed in gliomas, while metastases form pure vasogenic edema. Apparent diffusion coefficient (ADC) measurements are used to separate these two types of edema in the brain [6]. Magnetic resonance spectroscopy (MRS) is a method that distinguishes tissue metabolites using different resonance peaks [7]. High cellularity and cell-cycle secondary choline (Cho) increase are usually seen in gliomas and N-acetyl aspartate (NAA) reduction draw attention when neurons were replaced by mass or normal neurons take damage. Cho signals are higher in high grade gliomas compared to low grade gliomas.

Dexamethasone is a main glucocorticoid agent that is used to treat brain edema secondary to tumors. It was begun to use in the early 1960s and it was previously shown that the preoperative dexamethasone administration reduces peritumoral edema and so mortality. Daily dose may range about 4-100 mg/day. It is also reported that the most powerful effect of steroids begins within 24-72 h of treatment [8,9]. Dexamethasone treatment decreases brain edema without distinct

absorption effect. Although there are a lot of articles about dexamethasone's effect on reduction of tumor size in addition to decreasing brain edema, these statements are not widely accepted by scientists [8,10].

The purpose of this study is to investigate the effects of dexamethasone on the intensity of primary tumor and peritumoral edema using advanced MRI techniques. Diffusion-weighted imaging (DWI), T2-weighted-MRI and MRS were used for this purpose.

2. Materials and methods

After receiving approval from our national ethics committee (Approval no: 25.04.2012/i B.10.4.ISM.4.06.68.49), 28 patients were enrolled in this study. All of the patients were over the 18-years old and signed written consent form for this study. Pregnant women and patients who previously underwent brain tumor surgery had been excluded from this study. Seventeen of 28 patients were male and 11 were female. Mean age was 46 years (46.00 ± 18.33) for male patients and 54.45 (54.45 ± 13.32) years for female patients. Based on histological diagnosis, the patients were divided into 3 groups:

- **Group 1:** High-grade tumors ($n = 11$)
- **Group 2:** Low-grade tumors ($n = 10$)
- **Group 3:** Metastatic tumors ($n = 7$)

The diagnosis was high grade glial tumor in 11 patients, low grade glial tumors in 10 patients and metastasis in 7 of 28 patients. One of the high grade tumors was gliosarcoma, while the others were glioblastoma. One of the low grade glial tumors was ganglioglioma, 2 were pleomorphic xanthoastrocytomas, 2 were oligodendrogliomas and 5 were diffuse astrocytomas. One of the metastatic tumors was breast cancer metastasis, the others were lung cancer metastasis. Locations of tumors were frontal, temporal, parietal and occipital lobes respectively in order of frequency.

The main complaints of patients were headache, fatigue, arm or leg weakness, seizure and speech disorder. Complaints were much more in the patients with metastatic tumors and high grade gliomas. Eleven of 28 patients had normal neurological examination; neurological deficit was present in remaining 17 patients at different levels. Patients with neurological deficits were 94.5% of metastasis and high grade glioma patients.

All patients with the diagnosis of brain tumor were screened using 3T magnet (Achieva 3 T, Philips Medical Systems, The Netherlands) preoperatively. Besides with axial T1- and T2-weighted spin-echo imagings, T2-A fluid attenuated inversion recovery (FLAIR), diffusion-weighted axial echo-planar, and post-contrast axial, coronal and sagittal images were also obtained. Spectroscopy sequences were also performed. Magnetic resonance sequences which were used in this study are shown in Table 1. Eight-channel head coil was used during the cranial MRI. Ten milliliters of intravenous gadoterate meglumine (Dotarem®, Guerbet) was administered in contrast-enhanced studies. MRI's were performed pre-treatment and 48 h after the initiation of steroid treatment. A total of 32 mg ($16 \text{ mg/day} \times 2$) dexamethasone was used as a

Table 1 – The parameters and MRI sequences that were used in this study.

Sequence	TR	TE	Slice thickness (mm)	Slice gap (mm)	Flip angle	Resolution
T1	536	14	4.5	6.2	90	512 × 512
T2	2790	80	5	6.5	150	512 × 512
FLAIR	11,000	120	4.5	6.2	90	512 × 512
Diffusion	2690	68	4.0	5.0	90	490 × 539

steroid treatment. MRI cross-sections were prepared for measurement and transferred as DICOM format to a separate computer (MacPowerBook G4, Apple, USA). Evaluations were performed using a program that used open source DICOM processing and visualization (OsiriX 32-bit, Pixmeo, Geneva, Switzerland).

The following formulas were used to calculate the total volume of peritumoral edema.

1. **Cross-sectional area of the edema of the tumor** = cross-section of tumor × (slice thickness + cross-sectional thickness)
2. **Total volume of edema**: tumor volume of first cross-section + tumor volume of second cross-section + tumor volume of n. section

During the assessment, area of the peritumoral edema was determined manually in T2 axial slices in order to include the tumor. The hyper-intense area that belongs to the edema was drawn manually in circumferential fashion for each cross-section (Fig. 1). Volume of edema (Fig. 2) for each slice was calculated by multiplying the sum of cross-sectional edema area and the cross section slice thickness. The total volume of edema was calculated by addition of each slice volume (Fig. 3). The area was calculated digitally. The data was transferred to a database (Excel 2007, Windows 2007, Seattle, USA). Total volume of edema and total tumor volume before and after steroid treatment were determined by these calculations.

ADC maps were created from diffusion weighted images by ADC Map application on the same computer. A group of diffusion weighted cross-section of twenty image with the values of $b = 0$ and $b = 1000$ processed by the program and

created a map. From the map, about 2 mm² wide area created from tumor, edema area and at other hemisphere symmetrical of tumor but from normal-appearing area. This process was repeated three times and resulted with creating an area of interest (ROI = region of interest) with minimal ADC values were averaged. ADC values and ratios of average were created with Excel program as described previously. The ratio of tumor-edema area, tumor-normal appearing area and normal-edema area was calculated separately.

Cho, Cr and NAA values generated from tumor and peritumoral areas in MRS that were created with multi-voxel spectroscopic images written separately and were calculated using the same data base (Excel 2007) before and after steroid treatment. SPSS 15.0 program (Standard version, SPSS Inc., USA) was used for statistical evaluation. The changes in peritumoral edema volume before and after steroid treatment and numerical changes in diffusion images related to the treatment were assessed using Wilcoxon and Friedman test. Neurological examination findings before and after dexamethasone treatment were compared using Chi-square test. p -Value less than 0.05 was considered significant.

3. Results

The mean volume of peritumoral edema before and after steroid treatment for all patients is shown in Table 2. The mean volume of peritumoral edema in 28 patients before the treatment with dexamethasone was 1790.8489 mm³ (41.73–4945.34). Mean volume of peritumoral edema after the treatment was 1733.8743 mm³ (35.83–4890). Despite there was a decrease in the volume of edema after treatment, it was not statistically significant ($p = 0.56$).

The mean peritumoral edema volume of 11 patients with high grade glial tumors (Group 1) was 3014.6173 mm³ (ranged between 1771.73 and 4945.34) before the treatment, 2959.5561 mm³ (ranged between 1896.32 and 4890.52) after the treatment. The change in peritumoral edema volume was not statistically significant ($p = 0.76$) (Fig. 4). The mean peritumoral edema volume of 10 cases with low grade gliomas (Group 2) was 635.554 mm³ (ranged between 41.73 and 2014.08) in pre-treatment period, 503.277 mm³ (ranged between 35.83 and 1678.7) after the treatment. The change in peritumoral edema volume was not statistically significant ($p = 0.73$) in Group 2. The mean peritumoral edema volume in 7 patients with metastases was 1518.2057 mm³ (ranged between 174.87 and 3006.93) before the treatment and 1565.7943 mm³ (ranged between 156.72 and 3062.02) after the treatment. The change in peritumoral edema volume was not statistically significant ($p = 0.7$) in metastasis group (Table 3 and Fig. 5). The mean volume of peritumoral edema in Group 2 was less than the

Fig. 1 – Hand-drawn image for the tumor edema single cross section area and the representative image of cross-sectional thickness.

Fig. 2 – T2-weighted cross sections of each patient's tumor (A). Slice thickness multiplied by sum of cross-sectional thickness of the space and so volume of edema can be calculated (volume of the slice = $a \times h$) (B).

other groups. In this group, 2 patients with ganglioglioma and pleomorphic xanthoastrocytoma did not have significant peritumoral edema. Based on our data, dexamethasone treatment does not modify significantly the volume of peritumoral edema in glial tumors and metastatic tumors.

DWI was performed in all cases and ADC values in the tumor were calculated before and after dexamethasone treatment (Table 4). The highest ADC increase was detected in metastatic tumors (Group 3). ADC value decreased in high grade glial tumors (Group 1). ADC increase in low grade glial tumors (Group 2) was similar to those of metastatic tumors.

Fig. 3 – Tumor edema volume was measured for each section and calculated for total tumor volume.

ADC values in peritumoral edema before and after dexamethasone treatment are shown in Table 5. ADC values for normal brain parenchyma before and after dexamethasone treatment are given in Table 6. The highest ADC increase was observed in Group 3 (Table 6). ADC values decreased in high grade glial tumors. The increase in ADC values of normal brain parenchyma in Group 2 was also close to ADC level in Group 3.

The effect of dexamethasone treatment on cerebral metabolites in the tumoral and peritumoral area of 21 glioma cases was also investigated in this study. Cho/Cr quantified peak areas are shown in Table 7. In Group 1, the mean Cho/Cr peak area was 170 mm² (8.9–280) before the dexamethasone treatment and 167 mm² (8.7–267) after the treatment. Dexamethasone treatment did not cause a statistically significant change in MRS of high grade glial tumor group ($p = 0.59$). In Group 2, the mean Cho/Cr peak area was 126 mm² (7–146) before the treatment and 125 mm² (7.1–148) after the treatment. Dexamethasone treatment did not cause a statistically significant change in MRS of low grade glial tumors and did not decrease intensity of the tumoral cells at peritumoral region ($p = 0.59$) (Fig. 6).

Some neurological findings such as full or partial extremity weakness, slurred speech and consciousness were detected before dexamethasone treatment in 17 (60.71%) of 28 patients with the diagnosis of brain tumors. Neurological examination was in normal ranges in 11 patients. Neurological improvement was seen in 9 (52.94%) cases after the dexamethasone treatment, but neurological findings remained unchanged in 8 patients. There was no neurological worsening in any patient after the treatment. The effect of dexamethasone treatment on the patient's neurological condition was statistically significant ($p < 0.001$).

4. Discussion

Brain tumor is a significant health problem nowadays and may cause mortality even if treated surgically. The most common primary brain tumor is glial tumor or glioma. Although it can

Table 2 – The changes of mean peritumoral edema volume after dexamethasone treatment in all patients.

	n	Mean peritumoral edema volume (mm ³)	Standard deviation	Minimum	Maximum	p*
Before the dexamethasone treatment	28	1790.8489	1312.48019	41.73	4945.34	0.56
After the dexamethasone treatment	28	1733.8743	1341.95685	35.83	4890.52	

* Friedman test.

Fig. 4 – 72 years-old female patient with high grade glioma (gliosarcoma). (A) T2 axial sections edema was marked. (B) A slightly decrease in the volume of edema was observed two days after steroid treatment. (C) MRS images after the treatment show significant increase in peak NAA. (D) In the post-treatment MRI, T1-axial cross sections showed hypointense edema area and intense contrast enhancement in the tumor.

be detected at any age group, the mean age is 62 years. It is 40% more common in males than females. Most types of glial tumors are malignant and the average life expectancy of patients ranged from 12 to 24 months. Metastases are the most common brain tumors in adults. It has been previously reported that 25–40% of patients with systemic cancer have brain metastasis [7,11].

MRI is the gold standard imaging technique for the diagnosis and follow-up of brain tumors [2,3,12]. MRI was first described in 1946 by Bloch and Purcell. In 1980, Hawkens revealed multiplane (multiplanar) feature of MRI and identi-

fied first brain tumor with this technique. Contrast agent (gadolinium) was used for MRI for the first time in 1984. Advanced MRI techniques, such as DWI, Diffusion Tensor Imaging (DTI), perfusion MRI and MRS provide more information beyond the anatomical knowledge [12]. Diffusion-weighted sequence of MRI is described by Stejskal and Tanner in 1965. Diffusion of H₂O (water) molecules in the tissue contributes less the quality of imaging at conventional MRI. But it is possible to view the movement of water molecules in a very strong magnetic field gradient at diffusion MRI [6]. DTI techniques are used for differentiation and grading of gliomas,

Table 3 – The changes of mean peritumoral edema volume for each group after the dexamethasone treatment.

Group	n	Mean peritumoral edema volume (mm ³)	Standard deviation	Minimum	Maximum	p [*]
High grade glial tumor						
Before the treatment	11	3014.6173	823.36699	1771.73	4945.34	0.76
After the treatment	11	2959.5561	885.86281	1896.32	4890.52	
Low grade glial tumor						
Before the treatment	10	635.554	680.77382	41.73	2014.08	0.73
After the treatment	10	503.277	498.092	35.83	1678.7	
Metastasis						
Before the treatment	7	1518.2057	932.63096	174.87	3006.93	0.7
After the treatment	7	1565.7943	1054.80822	156.72	3062.02	

* Friedman test.

Fig. 5 – 47-Years-old male patient with left parietal metastatic tumor. (A) Peritumoral edema area in T2 axial slice before the steroid treatment. (B) The peritumoral edema area is increased in T2 axial slice after the steroid treatment. (C) The sagittal T2 slice of the patient shows the peritumoral edema after the steroid treatment.

Table 4 – The changes of ADC values in tumoral mass for each group after the dexamethasone treatment.

Group	<i>n</i>	Mean ADC value	Standard deviation	Minimum	Maximum	<i>p</i> [*]
High grade glial tumor						
Before the treatment	11	608.6	259.26492	361	986	0.047
After the treatment	11	564.8	313.07395	104	922	
Low grade glial tumor						
Before the treatment	10	525.33	159.21474	416	708	0.041
After the treatment	10	703	141.55211	711	966	
Metastasis						
Before the treatment	7	321.524	115.86199	146	443	0.025
After the treatment	7	524.2	159.68625	241	628	

* Friedman test.

metastasis, lymphoma and meningiomas. MRS is a method that distinguishes tissue metabolites using different resonance peaks. The first brain spectroscopy results were obtained by Behar and colleagues at Yale University in 1983 [7]. First medical applications are made on the body fluids and secretions. MRS, perfusion MRI and DWI sequences are also in use for this purpose. In this study, we used conventional MRI, DWI and MRS techniques in 28 patients with glioma and metastatic tumors and we compared the results for the effects of dexamethasone treatment on tumor and peritumoral edema.

Metastases cause significant peritumoral edema like high-grade glial tumors [8]. Solitary metastasis and primary characteristics of high-grade glial tumors are nonspecific in conventional MRI and it is not always possible to differentiate these tumors. Both of tumors show variable degrees of contrast enhancement and forms peritumoral edema. T2 flair, DWI, MRS and MRI images were used in our study.

The causes of peritumoral edema are not well understood, but it is assumed that edema is secondary to excess fluid build up in the extravascular space surrounding the tumor. Brain is unable to remove this fluid due to the disrupted blood-brain

Table 5 – The changes of ADC values in peritumoral edema for each group after the dexamethasone treatment.

Group	n	Mean ADC value	Standard deviation	Minimum	Maximum	p [*]
High grade glial tumor						
Before the treatment	11	869.4	409.96073	339	1458	0.047
After the treatment	11	741.7	386.88435	84	1047	
Low grade glial tumor						
Before the treatment	10	370.6667	126.72937	235	486	0.041
After the treatment	10	586	182.78676	456	795	
Metastasis						
Before the treatment	7	386	59.37295	296	441	0.025
After the treatment	7	648.6	121.58248	469	796	

* Friedman test.

Table 6 – The changes of ADC values in normal brain tissue for each group after the dexamethasone treatment.

Group	n	Mean ADC value	Standard deviation	Minimum	Maximum	p [*]
High grade glial tumor						
Before the treatment	11	443.2	197.83756	174	688	0.047
After the treatment	11	380.8	178.2602	70	519	
Low grade glial tumor						
Before the treatment	10	326.3333	92.3598	261	432	0.041
After the treatment	10	528	170.32616	403	722	
Metastasis						
Before the treatment	7	195.6	21.07843	173	222	0.025
After the treatment	7	359.4	45.76899	304	428	

* Friedman test.

Table 7 – The changes in Cho/Cr peak areas for high and low grade glial tumors after the dexamethasone treatment.

Group	n	Mean Ch/Cr peak area (mm ²)	Standard deviation	Minimum	Maximum	p [*]
High grade glial tumor						
Before the treatment	11	170	21.439	8.9	280	0.59
After the treatment		167	19.97	8.7	267	
Low grade glial tumor						
Before the treatment	10	126	19.26	7	146	0.62
After the treatment		125	18.22	7.1	148	

* Wilcoxon test.

barrier [9]. Dexamethasone is widely used for the medical treatment of peritumoral edema in the brain tumors for many years [13,14]. According to the current knowledge, dexamethasone treatment reduces peritumoral edema and improves neurological findings. Many studies have been performed on this issue, and similar results were reported [15,16]. However, none of these studies focused on peritumoral edema volume and none of them used spectroscopic examinations to investigate the correlation between the dexamethasone treatment and clinical condition of the patients. In 1982, Hatam et al. [17] followed three cases with serial head CT scans. Fan et al. showed that dexamethasone inhibits glioma cell growth. In addition, it has neuroprotective effects in brain and reduces tumor-induced angiogenesis [18]. Andersen et al. [19], in a series of 23 cases, investigated the effect of dexamethasone on peritumoral edema in 1994. Andersen

got MRI on the first, 3rd, and 7th days of dexamethasone treatment and found that peritumoral edema decreased 4.6% at 1st day and 13.5% at 7th days of treatment [19]. Gaspar et al. [15] published an article in 2000 and claimed that the usage of dexamethasone 4–8 mg/day reduce peritumoral edema of metastases radiologically and bring about a significant improvement in patient's clinical condition. In 2006, Soffietti et al. [20] revealed that dexamethasone treatment reduces cerebral edema significantly and cause clinical improvement in 75% of patients within 24–72 h. The common point of these studies is the use of dexamethasone reduces peritumoral edema and intracranial pressure temporarily and improves the patient's clinical condition [19,20]. In our study, we examined 28 cases of glioma and metastatic tumor and compared the volume of peritumoral edema using MRI. Although there is a slight reduction in the volume of the

Fig. 6 – 39-Years-old female patient with low grade glioma (grade 2 astrocytoma). (A) Pre-treatment MRS examination did not show significant difference between NAA, choline and creatine peaks for before and after treatment. (B) The same patient's post-treatment MRS images.

post-treatment peritumoral edema, this reduction is not statistically significant. Dexamethasone does not significantly reduce the overall volume of peritumoral edema. So, our results are different from those of the literature.

Each of 3 groups was examined separately in order to evaluate how dexamethasone effect groups individually. The change of peritumoral edema volume in all of 3 groups after the dexamethasone treatment was not statistically significant ($p > 0.05$ for all groups). Based on the data of 28 cases, we can suggest that the dexamethasone treatment does not modify the peritumoral edema significantly.

Although the use of dexamethasone does not reduce the volume of peritumoral edema, interestingly dexamethasone treatment caused neurological improvements in 9 (52.9%) of 17 patients with neurological findings. Although our study varies from current literature in terms of dexamethasone's effect on peritumoral edema, its positive impact on clinical situation is similar to those. This significant improvement in clinical condition may not be secondary to decrease at peritumoral edema. Our study is one of the largest studies on this issue as a radiological study, but more comprehensive studies with larger series are needed.

DWI was first used in the diagnosis of cerebral ischemia, but it may be used for the diagnosis of traumatic brain injury, demyelinating diseases, and determination of the tumoral cellularity [6]. ADC values may be used for differential diagnosis of intracranial tumors and differentiation of peritumoral edema from tumor area [4]. There are very few clinical studies on the use of DWI for the evaluation of dexamethasone treatment in brain tumors. Sinha et al. [10] published a paper on the changes of ADC value of peritumoral edema after dexamethasone treatment in 15 patients with brain tumor. In this study, 7 patients had glioblastoma, 4 patients had metastasis and 4 patients had meningioma. They revealed significant reductions in ADC values of all patients with dexamethasone treatment after 48–72 h. They emphasized that dexamethasone reduces the extracellular water movements of peritumoral brain edema and strengthens the density of water [10]. Lu et al. [21] compared ADC changes after dexamethasone treatment in 12 patients with glioma and 12

patients with brain metastases but they did not find statistically significant results on the effect of dexamethasone. Bastin et al. [22] performed the same study but they showed significant decrease in ADC values of just only one case of glioblastoma patient. In our study, we measured ADC values before and 48 h after dexamethasone treatment of 11 patients with high grade glioma, 10 patients with low grade glioma and 7 patients with brain metastases. ADC values of tumoral mass, peritumoral edema, and normal cerebral tissue before and after dexamethasone treatment were evaluated separately. Statistically significant changes in mean ADC values of tumoral mass were detected in 3 groups after dexamethasone treatment ($p < 0.05$ for each group). These changes in peritumoral edema were also statistically significant in 3 groups after dexamethasone treatment ($p < 0.05$ for each group). The changes in normal brain tissue were also statistically significant after the treatment ($p < 0.05$ for each group). Based on our results, ADC values in high grade glial tumors decrease with dexamethasone treatment. This may be due to rise of internal water movements of low grade glial tumors and brain metastases with dexamethasone treatment. Clinical improvement in patients probably may be secondary to the movement of water. This study is still the most comprehensive and detailed assessment and contains discrepancies with earlier publications. There are a lot of different results in the current literature review. DWI studies and ADC measurements of brain tumors after dexamethasone treatment are still a mysterious subject and we believe that there is a need for investigation and evaluation in a larger tumor groups.

There was a decrease in NAA peak at MRS, significant increase in Cho levels and a moderate decrease of Cr levels (sometimes not change) in glial tumors. NAA decrease and Cho increase are more evident in high grade glial tumors than low grade glial tumors [23]. In 1994, Kamada et al. [23] and in 1996 Preul et al. [24] analyzed the values of NAA, Cho, Cr, etc. metabolites and published their results. They found a significant Cho peak, NAA and Cr reduction at glial tumors in two studies [23,24]. In 1997, Chumas et al. [9] gave 12 mg/day dexamethasone to 9 patients with brain tumors for their study

and they analyzed pre-treatment exchange value of cerebral metabolites like NAA, Cho and Cr. They observed no significant increases or decreases of cerebral metabolites depending on dexamethasone treatment [9]. In our study, we examined changes in MRS findings related to the treatment with dexamethasone in 21 patients with glioma. Patients with brain metastases were not included in the assessment with MRS. We examined the Cho and Cr values in tumor mass and peritumoral area and their relative proportions with multi-voxel two-dimensional imaging before and 48 h after dexamethasone treatment. The mean Cho/Cr peak area was decreased after dexamethasone treatment in high grade glioma group but this is not statistically significant. There was also decrease in mean Cho/Cr peak area after dexamethasone treatment in low grade glioma group and this is also not statistically significant. Our results with MRS are similar with those of the previous studies.

There are 2 limitations of this study. First is the low number of patient for a precise outcome for the effect of steroids on brain tumors. Second is the limited number of tumor types was included in this study. Only glial tumors and metastases were analyzed for the effects of steroids. Because these tumors are mostly treated in neurosurgery clinic, we selected these types of tumors and performed MRI with different sequences in order to reach a most accurate outcome.

5. Conclusion

Steroid treatment improves clinical signs of glial tumors and brain metastases. But this effect is not secondary to the reduction of swelling around the tumor or changes in cerebral metabolites. It is probably due to water movements in tumoral mass, peritumoral edema or normal brain parenchyma. However, more detailed studies with larger series should be done for more accurate knowledge on this topic.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

REFERENCES

- [1] Stevenson KL. Pediatric brain tumors. *J Neurosci* 2004;1: 10–20.
- [2] Izci Y, Gurkanlar D, Timurkaynak E. Multicentric gliomas: still remains a controversial issue. *Turk Neurosurg* 2005;15 (2):71–5.
- [3] Izci Y. Biomarkers for brain gliomas. In: Barh D, Carpi A, Verma M, Gunduz M, editors. *Cancer biomarkers: minimal and noninvasive early diagnosis and prognosis*. Boca Raton, USA: CRC Press, Taylor & Francis Group; 2014. p. 199–226.
- [4] Ignjatović J, Stojanov D, Zivković V, Ljubisavljević S, Stojanović N, Stefanović I, et al. Apparent diffusion coefficient in the evaluation of cerebral gliomas malignancy. *Vojnosanit Pregl* 2015;72(10):870–5.
- [5] Sugahara T, Korogi Y, Kochi M, Ushio Y, Takahashi M. Perfusion-sensitive MR imaging of gliomas: comparison between gradient-echo and spin-echo echo-planar imaging techniques. *AJNR Am J Neuroradiol* 2001;22:1306–15.
- [6] Gelal F, Calli C, Kitis Ö, Yünter N. Diffusion-weighted magnetic resonance imaging. *J Neurol Sci* 2001;18(2):25.
- [7] Barker PB, Breiter SN, Soher BJ, Chatham JC, Forder JR, Samphilipo MA, et al. Quantitative proton spectroscopy of canine brain: in vivo and in vitro correlations. *Magn Reson Med* 1994;32:157–63.
- [8] Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Support Care Cancer* 2002;10:322–8.
- [9] Chumas P, Condon B, Oluoch-Olunya D, Griffiths S, Hadley D, Teasdale G. Early changes in peritumorous oedema and contralateral white matter after dexamethasone: a study using proton magnetic resonance spectroscopy. *J Neurol Neurosurg Psychiatry* 1997;62:590–5.
- [10] Sinha S, Bastin ME, Wardlaw JM, Armitage PA, Whittle IR. Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. *J Neurol Neurosurg Psychiatry* 2004;75:1632–5.
- [11] Greenberg MS. *Handbook of neurosurgery*. 5th ed. New York: Thieme; 2001. p. 463–9.
- [12] Butowski NA, Chang SM. Glial tumors: the current state of scientific knowledge. *Clinical neurosurgery*. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 106–13.
- [13] Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, et al. Corticosteroids compromise survival in glioblastoma. *Brain* 2016;139(Pt 5):1458–71.
- [14] Izci Y, Akay KM, Gurkanlar D, Deveci MS. Radiation-induced glioblastoma multiforme following surgery for medulloblastoma in a child with neurofibromatosis-1: case report. *Turk Neurosurg* 2005;15(1):36–9.
- [15] Gaspar LE, Gutin PH, Rogers L, Schneider JF, Larson D, Bloomer WD, et al. Pre-irradiation evaluation and management of brain metastases. *American College of Radiology. ACR appropriateness criteria. Radiology* 2000;215 (Suppl.):1105–10.
- [16] Wolfson AH, Snodgrass SM, Schwade JG, Markoe AM, Landy H, Feun LG, et al. The role of steroids in the management of metastatic carcinoma to the brain. A pilot prospective trial. *Am J Clin Oncol* 1994;17:234–8.
- [17] Hatam A, Yu ZY, Bergstrom M, Bergren BM, Greitz T. Effect of dexamethasone treatment on peritumoral brain edema: evaluation by computed tomography. *J Comput Assist Tomogr* 1982;6:586–92.
- [18] Fan Z, Sehm T, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan NE. Dexamethasone alleviates tumor-associated brain damage and angiogenesis. *PLOS ONE* 2014;9(4):e93264.
- [19] Andersen C, Astrup J, Gyldensted C. Quantitation of peritumoural oedema and the effect of steroids using NM relaxation time imaging and blood-brain barrier analysis. *Acta Neurochir Suppl (Wein)* 1994;60:413–5.
- [20] Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, et al. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. *Eur J Neurol* 2006;13:674–81.
- [21] Lu S, Ahn D, Johnson G, Cha S. Peritumoral diffusion tensor imaging of high grade gliomas and metastatic brain tumors. *AJNR Am J Neuroradiol* 2003;24:937–41.
- [22] Bastin ME, Delgado M, Whittle IR, Cannon J, Wardlaw JM. The use of diffusion tensor imaging in quantifying the

- effect of dexamethasone on brain tumours. *Neuroreport* 1999;10:1385–91.
- [23] Kamada K, Houkin K, Iwasaki Y, Abe H, Kashiwaba T. In-vivo proton magnetic resonance spectroscopy for metabolic changes of human brain edema. *Neurol Med Chir (Tokyo)* 1994;34:676–81.
- [24] Preul MC, Caramanos Z, Collins DL, Villemure J-G, Leblanc R, Olivier A, et al. Accurate, noninvasive diagnosis of human brain tumors by using proton magnetic resonance spectroscopy. *Nat Med* 1996;2:323–5.