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ORIGINAL ARTICLE

The Value of Magnetic Resonance in Differentiation between Brain Glioma and Treatment Induced Injury

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Summary
Introduction. The further therapeutic management decisions in glioma patients after the radiation/chemotherapy may be difficult because the treatment induced brain injury can mimic tumor recurrence clinically and on neuroimaging.
Aim of the Study was to assess the usefulness of magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) in differentiation between glial tumor recurrence and radiation/chemotherapy-induced changes in the brain.
Material and methods. 73 patients with primary brain gliomas and 77 gliomas patients after combined therapy with possibly treatment induced changes underwent MRS and DTI. Fractional anisotropy (FA) and metabolite ratios were measured in the tumor and pathological signal intensity area adjacent to post-surgical cavity.
Results. Mean choline/creatine (Cho/Cr), myoinositol/creatine (MI/Cr), lactate-lipid/creatine (LL/Cr) ratios of brain gliomas was statistically significant higher and FA values lower than those in the pathological signal intensity area adjacent to post-surgical cavity. No differences were found in mean N-acetyl aspartate/creatine (NAA/Cr) ratios among two groups.
Conclusions. Our study suggests that Cho/Cr, MI/Cr, LL/Cr and FA measures should be recommended as additional highly informative tool to conventional structural magnetic resonance imaging (MRI) when monitoring gliomas patients after combined therapy.
Key words: brain glioma, treatment induced injury, fractional anisotropy, magnetic resonance spectroscopy.

INTRODUCTION

Currently, the worldwide recognized treatment method of choice for brain glioma is surgical resection followed by radiotherapy with concurrent chemotherapy (Hygino et al., 2011). The further therapeutic management decisions in glioma patients after the radiation/chemotherapy may be difficult because the treatment induced brain injury can mimic tumor recurrence clinically and on neuroimaging. With the standard magnetic resonance imaging (MRI) sequences differential diagnostic difficulties arise in both contrast enhancing and non-enhancing lesions (Hygino et al., 2011; Brandsma et al., 2008; Nelson, 2011; Sundgren, 2009; Yaman et al., 2011; Weybright et al., 2005). In such cases, new, advanced imaging techniques could be important, which provide physiological and metabolic characteristics of the tumor and surrounding brain tissue (Nelson, 2011). Diffusion tensor imaging (DTI) with fractional anisotropy (FA) quantitative characteristics is non-invasive approach for brain white matter study and particularly in patients with glial cerebral tumors while values of FA reflect the integrity state of white matter tracts (Goebell et al., 2006). Magnetic resonance spectroscopy (MRS) is a technique for non-invasive in vivo assessment of brain metabolites concentration (Bonicelli et al., 2009; Sundgren et al., 2009; Costanzo et al., 2008). It is believed that the MRS may serve as an accurate imaging method for assessment of radiation therapy toxic effects (Weybright et al., 2005; Sundgren et al., 2009). A proposal has been made that combination of DTI and MRS can improve the differentiation of recurrent glioma and post-treatment injury (Nelson, 2011). Metabolites that are observed and well tested in the brain include choline (Cho), creatine (Cr), N-acetylaspartate (NAA), myoinositol (MI), lactate and lipids (LL). NAA is regarded as a marker for neuronal function (Nelson, 2011; Oshiro et al., 2007). Cr is a marker of cellular energy metabolism. Cr is considered the most stable brain metabolite (Sundgren et al., 2009). Cho is a marker of cell membrane (Nelson, 2011; Sundgren, 2009). MI is a marker of glial cells (Kallenberg et al., 2009). Lipids are brain destruction products. Lactate is product of anaerobic glycolysis (Nelson, 2011).

AIM OF THE STUDY

The aim of this study was to assess the usefulness of MRS and DTI in differentiation between glial tumor recurrence and radiation/chemotherapy-induced changes in the brain.

MATERIAL AND METHODS

Patients. 73 patients (40 women and 33 men, mean age 48 years, range, 14-78 years) with brain gliomas and 77 patients (50 women and 27 men, mean age 48 years, range, 19-72 years) with possible treatment induced injury were studied retrospectively. The tumor diagnosis was determined based on morphological confirmation. Histological type was classified according to the WHO brain tumor classification (Louis et al., 2007) and consisted of 44 glioblastomas, 9 anaplastic oligoastrocytomas, 12 anaplastic astrocytomas, 3 oligoastrocytomas, 3 astrocytomas, 1 anaplastic oligodendroglioma and 1 oligodendroglioma. Treatment

induced injury was diagnosed, based on structural MRI findings in control examination using the following criteria: long-term stability of the structural MRI or spontaneous regression of lesion (Weybright et al., 2005; Huang et al., 2011). The approvals of local Institutional Review Board of the Riga East Clinical University Hospital and the Ethics Committee of Riga Stradins University before study initiation were obtained.

MR image acquisition. MR imaging was performed on a 1.5-T General Electric Signa EXCITE MR unit with 8-channel head coil. Standard conventional brain MRI protocol (T2-weighted, FLAIR, diffusion weighted images, unenhanced and gadolinium-enhanced T1-weighted images) was supplemented with MRS ((8ch) PROBE-2DSI PRESS 144TE) and DTI (TENSOR 25 directions 1000b). MRS was performed with multivoxel technique prior to contrast administration. The volume of interest for MRS was determined by using T2-weighted or FLAIR images in axial plane and it was defined including the pathological signal intensity area as well as normal appearing brain tissue. The row data of DTI were obtained using the axial commissural plane.

MRI data post-processing and image analysis. Post-processing of MRS and DTI images was performed on a MR GELS (General Electric) workstation. The axial T2 or FLAIR images were used to place defined regions of interest (ROI) in spectroscopic matrix in the tumor as shown in Fig. 1.C, and pathological signal intensity area in the white matter adjacent to post-surgical cavity. We calculated metabolite ratios using the Cr signal as a reference (NAA/Cr, Cho/Cr, LL/Cr and MI/Cr). Round-shaped, uniform sized (30 pixels) ROI for FA measuring was placed in the identical areas (Fig. 2.B).

Statistical analysis. Statistical analyses were performed with the Statistical Package for Social Sciences software (SPSS) version 20. We used descriptive statistics to calculate means and standard deviations of measurements. Related sample Wilcoxon signed rank test was used to compare mean metabolite ratios and FA between patients with typical brain glioma and treatment induced injury. P values less than 0.05 were considered statistically significant.

RESULTS

Results of DTI and MRS were analyzed separately for each group of patients. On the basis of morphological results from biopsy or surgical resection, the lesions of 73 patients were categorized as a glial tumor. On the basis of the clinical and imaging follow-up data the lesions of 77 patients were categorized as radiation injury. The follow-up time of the patients after the initial MRI was a mean of 9.41 months (range, 3–24 months) in patients whose lesions were classified as radiation injury.

Using a nonparametric related sample Wilcoxon signed rank test were compared metabolites and FA values of the tumor and post-treatment injury zone. The mean values (and standard deviations) of the Cho/Cr, MI/Cr, LL/Cr, NAA/Cr ratios and FA in respective lesions are summarized in Table 1. Cho/Cr, MI/Cr, LL/Cr values of glial brain tumors were statistically significant higher and FA values lower than those in the post-treatment zone. No differences were found in NAA/Cr ratios among two groups. Examples of metabolic spectra and FA measurements obtained in areas consistent with glial tumor and treatment induced injury are given in Fig. 1 and Fig. 2.

Table 1. The comparison of metabolites ratios and FA measurements (mean and standard deviation in parentheses) in the glial tumor and treatment induced injury zone

Ratio and FA	Brain glioma (73 patients)	Treatment induced injury (77 patients)	p value
Cho/Cr	2.305(±1.543)	1.355(±0.606)	p<0.001
NAA/Cr	1.031(±0.517)	1.153(±0.507)	p=0.147
MI/Cr	0.814(±0.509)	0.607(±0.362)	p=0.010
LL/Cr	3.933(±1.547)	2.304(±1.213)	p<0.001
FA	0.122(±0.049)	0.185(±0.065)	p<0.001

Abbreviations in the table: Cho, choline; Cr, creatine; NAA, N-acetyl aspartate; MI, myoinositol; LL, lactate and lipid

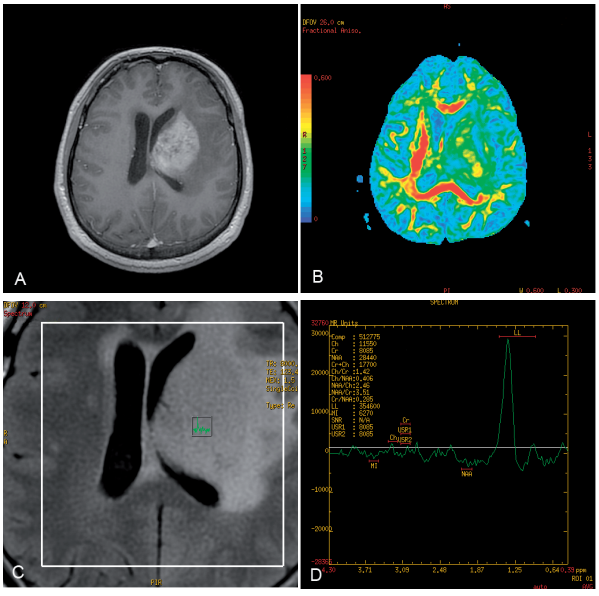

Fig. 1. MRI in a 45-year-old man with morphologically confirmed recurrent anaplastic oligoastrocytoma. Axial T1 post-contrast MRI shows a heterogeneously enhancing mass in the left frontal lobe. Surrounding hipointensity represents edema and/or tumor cells (A). Axial FA map shows reduced FA in left internal capsule (B). Region of interest for metabolites measurements is placed in the spectroscopic matrix on axial FLAIR image in the tumor (C). Proton MRI spectra from selected region of interest shows high LL peak and reduced NAA peak (D).

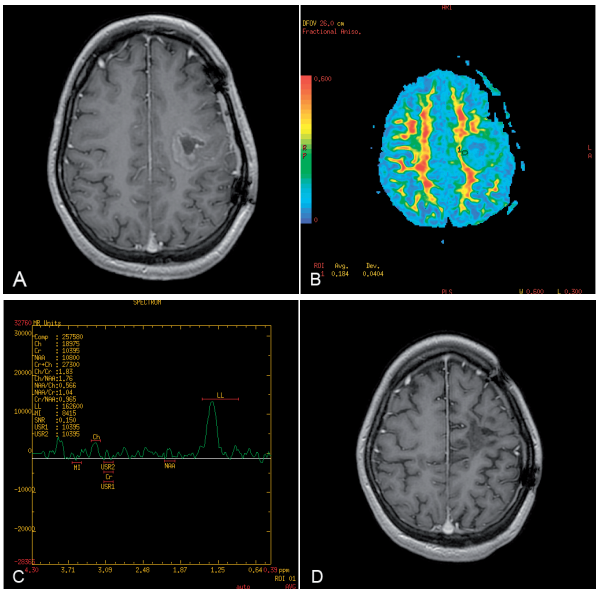

Fig. 2. 44 year old female with treatment induced injury related to radiation therapy for left parietal anaplastic astrocytoma. Axial post-contrast T1 MRI shows an enhancing lesion around postoperative cavity during radiotherapy 2 months after operation (A). Axial FA map shows reduced FA in left parietal lobe around the resected tumor bed. Region of interest for FA measurement is placed in the pathological signal intensity area (B). Proton MRI spectra from identical selected region of interest shows high LL peak and reduced NAA peak. Compared to the tumor (Fig. 1.D) post-treatment injury shows lower LL peak (C). Axial post-contrast T1 MRI 7 months later shows regression of lesion around post-surgical cavity. No enhancement is seen, typical of late delayed radiation-induced injury (D).

DISCUSSION

Routinely, conventional MRI plays an important role in the diagnosis and therapeutic monitoring of malignant brain gliomas. However, interpretation of conventional MRI may be challenging, especially in cases of new contrast enhancing lesion seen adjacent the resected tumor bed (Sundgren, 2009; Yaman et al., 2010; Weybright et al., 2005; Chaskis et al., 2009), because in the post-therapy period the structural MRI is often non-specific – both recurrent and inflammatory and/or necrotic changes due to radiotherapy/chemotherapy typically accumulate contrast (Sundgren, 2009; Principi et al., 2009). Non-enhancing tumors can be difficult to differentiate from other underlying reasons that cause hyperintense changes in T2 and FLAIR images, for example, radiation-induced gliosis (Pope et al., 2011). Temozolamide can promote early radiation damage (Chaskis et al., 2009) that reminds tumor progression (Yaman et al., 2010). Differentiation between radiation necrosis and tumor recurrence is critical for the correct therapeutic management (Nakajima et al., 2009).

This study aimed to evaluate the usefulness of MRS and DTI in differentiating gliomas from therapy induced changes in the brain. We obtained metabolite ratios and FA of brain from 73 patients with brain glioma and 77 patients in clinical and radiological remission with possible treatment induced changes adjacent to previous tumor location.

According to required data, the mean Cho/Cr ratio of glial brain tumors was statistically significantly higher compared with post-treatment injury areas. Achieved results of current study are consistent with the previous report that considers Cho as a marker of tumor cell proliferation (Oshiro et al., 2007). Cho/Cr in recurrent tumor is higher than in the radiation damage (Weybright et al., 2005; Smith et al., 2009). It was observed that Cho/Cr ratio decreases in irradiated brain (Sundgren, 2009; Sundgren et al., 2009).

NAA is a marker of normal brain tissue; it is believed that this indicates the presence of actively functioning neurons (Nelson, 2011). We found no statistically significant difference in mean NAA/Cr ratios between glial tumors and post-treatment injury. The possible morphologic explanation of this fact may be decreased number or loss of neurons in investigated areas. As it is described previously, the neuronal loss and dysfunction (decreased NAA) could be observed in both types of lesions (Hygino et al., 2011). Studies with animal models and human brain autopsy material analysis indicate that the post-treatment injury in the brain include inflammatory changes, demyelination, blood-brain barrier damage and neurotoxic effects (Sundgren, 2009; Sundgren et al., 2009). Some reports have shown that NAA/Cr in recurrent tumor areas is lower than in the radiation damage zones (Weybright et al., 2005; Pope et al., 2011; Smith et al., 2009). Our results, in contrary to above mentioned, agree with opinion that NAA reductions are most probably non-specific indicator, because it occurs at various pathologies (Dincer et al., 2008). NAA/Cr ratio likely reflects the heterogeneity of recurrent glioma with volume averaging of tumor and treatment induced injury or combination of both (Weybright et al., 2005). However, it must be taken into account also that an increase of Cr could also cause a decrease in NAA/Cr (Sundgren et al., 2009).

FA, similar to the NAA, reflects anatomical features of white matter (Goebell et al., 2006). We observed a statistically significantly lower mean FA values in the tumor comparative to altered pericavital zone in patients with clinical remission. These data agree with Sundgren (2009) study, which shows statistically significant higher FA values in normal signal intensity area around the radiation injury compared to normal signal intensity area around the recurrent glioma (Sundgren, 2009).

We observed elevated LL peaks in both groups but the mean LL/Cr ratio in glial tumors was statistically significantly higher compared to those of potential post-treatment injury zones. It is found that lipids increase in apoptosis and necrotic areas that typically observed

in the glial tumor center (Nelson, 2011). Morphologic changes induced by radiation and chemotherapy are also characterized by cell necrosis (Gerstner et al., 1977). Our results suggest that brain destruction is more pronounced in the tumor than in treatment induced injury.

The mean MI/Cr ratio in glial brain tumors in our study was statistically significantly higher compared with those in post-treatment injury zones. To our knowledge, there is no conclusive report on the MI/Cr role in differentiation between glial tumor and treatment induced injury in the literature. Kallenberg and co-authors showed that MI could be increased in a variety of pathologic conditions that involve astrocytic proliferation (Kallenberg et al., 2009).

Several limitations to our study have to be mentioned: First, lack of morphological verification for approval of radiation damage (Huang et al., 2011). Due to the fact that it is an invasive method, it was not performed for patients in remission. Data from the surgical resection and biopsy histological examinations indicate that the radiation damage characteristics of white matter edema, demyelination, fibrinoid changes in blood vessels, coagulative necrosis and cysts (Wang et al., 2010); Second, although regarded as stable metabolite, abnormal Cr levels have been demonstrated also in other different pathologies such as stroke, tumor, and trauma (Sundgren, 2009). In literature there are indications that a reduced level of Cr can be seen in tumors, but the level of Cr may vary in different areas of a tumor (Yerli et al., 2007).

The results of our study show that Cho/Cr, MI/Cr, LL/Cr ratios and FA are different in patients with brain glioma and areas of possible treatment induced injury. According to our data, NAA/Cr ratios do not differ significantly among two investigated groups of patients. We completely agree that MRS results should always be interpreted together with the structural MRI findings, before the final diagnosis (Schillaci et al., 2008).

CONCLUSIONS

Our study suggests that Cho/Cr, MI/Cr, LL/Cr and FA measures should be recommended as additional highly informative tool to conventional structural MRI when monitoring glial tumor patients after combined therapy.

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Conflict of interest: None

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