Proton magnetic resonance spectroscopy and apparent diffusion coefficient in evaluation of solid brain lesions

Protonska magnetnorezonantna spektroskopija i prividni difuzioni koeficijent u proceni solidnih lezija mozga

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Abstract

Background/Aim. Advanced magnetic resonance techniques can provide insight in physiological changes within pathological canges and contribute to better distinguishing between different tumor types and their discrimination from non-neoplastic lesions. The aim of this study was to evaluate the role of proton magnetic resonance spectroscopy (1H-MRS) and apparent diffusion coefficients (ADC) in distinguishing intracranial glial tumors from tumor like non-neoplastic lesions, as well as for differentiating high- from low-grade gliomas.

Methods. This retrospective study included 47 patients with solid brain lesions (25 non-neoplastic, 14 low-grade and 8 anaplastic glial tumors). In all patients 1H-MRS (at a TE of 135 ms and 30 ms) and diffusion-weighted imaging (DWI) were performed. The choline to creatine (Cho/Cr), choline to N-acetyl aspartate (Cho/NAA), N-acetyl aspartate to creatine (NAA/Cr) and myoinositol to creatine (mIn/Cr) ratios and the apparent diffusion coefficient (ADC) were determined.

Results. The Cho/Cr ratio was significantly higher in glial tumors grade II than in non-neoplastic lesions (p = 0.008) and in glial tumors grade III than in non-neoplastic lesions (p = 0.001). The Cho/NAA ratio was significantly higher in glial tumors grade II than in non-neoplastic lesions (p = 0.037). ΔADC/ADC between glial tumors grade II and glial tumors grade III showed a statistical significance (p = 0.023).

Conclusion. Our study showed that 1H-MRS and apparent diffusion coefficients can help in evaluation and differentiation of solid brain lesions.

Key words: brain neoplasms; glioma; brain ischemia; diagnosis; diagnostic techniques and procedures; magnetic resonance imaging; magnetic resonance spectroscopy.

Apstrakt

Uvod/Cilj. Savremene tehnike magnetne rezonance mogu pružiti uvid u fiziološke promene unutar patoloških i doprijeti boljem razlikovanju različitih tipova tumora, kao i njihov odvajanje od bolesti koje nisu maligne. Glij ovog istraživanja bio je da se utvrdi uloga magnetnorezonante spektroskopije i prividnog difuzionog koeficijenta u razlikovanju intrakranijalnih glijalnih tumora od netumorskih oboljenja, kao i u razlikovanju visokogradusnih od niskogradusnih glijalnih tumora.

Metode. Ovom retrospektivnom studijom obuhvaćeno je 47 bolesnika sa solidnim lezijama mozga (25 netumorskih, 14 niskogradusnih i 8 anaplastičnih glijalnih tumora). Kod svih bolesnika rađena je protonска magnetnorezonantna spektroskopija (sa vremenom eha 135 ms i 30 ms) i difuziono snimanje. Određeni su odnosi holin/kreatin (Cho/Cr), holin/N-acetil aspartat (Cho/NAA), N-acetil aspartat/kreatin (NAA/Cr), mioinozitol/kreatin (mIn/Cr), kao i prividni difuzioni koeficijent (ADC).

Rezultati. Nađena je statistički značajna razlika između indeksa Cho/Cr za glijalne tumore gradusa II i netumorske promene (p = 0,008) kao i za glijalne tumore gradusa III i netumorske promene (p = 0,001). Odnos Cho/NAA bio je statistički značajno viši kod glijalnih tumora gradusa II u odnosu na netumorske promene (p = 0.037). Odnos standardne devijacije ΔADC/ADC između glijalnih tumora gradusa II i glijalnih tumora gradusa III pokazao je statistički značajnu razliku (p = 0.023).

Zaključak. Naše istraživanje pokazalo je da protonска magnetnorezonantna spektroskopija i prividni difuzioni koeficijent mogu biti korisni u evaluaciji i diferencijaciji solidnih lezija mozga.

Ključne reči: mozak, neoplasme; gliom; mozak, ischemija; dijagnoza; dijagnostičke tehnike i procedure; magnetna rezonanca, snimanje; magnetna rezonanca, spektroskopija.
Introduction

Conventional magnetic resonance (MR) imaging has become the gold standard for detection and morphological assessment of solid brain lesions. However, MR imaging-based differentiation of neoplastic from non-neoplastic brain masses and the establishment of tumor grade are often difficult. Further evaluation and follow-up are often necessary, including histopathological examination of biopsy specimens. When lesions cannot be treated surgically or when they are located at areas of high risk for biopsy, greater accuracy of non-invasive imaging evaluation is desirable. Assessment of MR images obtained after administration of a paramagnetic contrast agent must be done with caution, because any pathology associated with disruption of blood-brain barrier (BBB) results in post-contrast enhancement. Advanced MR techniques, like MR spectroscopy and diffusion-weighted imaging, can provide insight in physiological changes within pathology and contribute to more successful distinguishing between tumor types and their separation from tumor mimicking lesions.

The radiological differential diagnosis of solid brain masses varies from tumors (gliomas WHO grades I–III), benign pseudotumoral lesions to demyelinating or ischemic lesions. Therefore, establishment of correct diagnosis is crucial for choosing appropriate therapeutic procedure and patient outcome. Gliomas are the most common primary neoplasms of brain, typically heterogeneous, varying histologically from low grade to high grade. Although golden standard in diagnosis of brain glioma, histological evaluation can be misleading, because sampling regions may or may not correspond to increased cellularity and/or neoangiogenesis. Therefore, more accurate information about tumor physiology, such as metabolism, cellularity and microstructure are important in determining tumor grade and cannot be collected only based on conventional MR imaging.

Tracing of brain metabolites concentrations using proton MR spectroscopy (1H-MRS) and diffusion-weighted MR imaging (DWI) can provide insight in those features and hence increase accuracy of prediction of tumor histological grade. Tracing of brain metabolites concentrations using 1H-MRS can provide information about cell proliferation, degradation, energetic metabolism and appearance of ischemia or necrosis. DWI and apparent diffusion coefficient (ADC) values obtained from DWI, provide complementary information about cellular density and tissue microstructure.

The aim of this study was to assess the role of proton MR spectroscopy and DWI in discrimination of gliomas from non-neoplastic mimics, as well as for differentiation of grade II from grade III of glial neoplasms.

Methods

Patients

This study was conducted in the Center for Radiology and Magnetic Resonance Imaging, Clinical Center of Serbia, Belgrade between November 2006 and August 2010. Retrospective study included 47 patients (22 women and 25 men, age range: 12–72 years, mean age 43 years) with solid brain lesions that were with 22 histopathologically (WHO classification) proven gliomas (14 grade II and 8 anaplastic tumors grade III) and 25 with non-neoplastic lesions (5 hamartomas, 11 demyelinating lesions, 9 ischemic lesions) whose diagnosis were established by clinical examination or MR imaging. All the glioma patients underwent MR imaging examination followed by surgery and histological evaluation of the lesion. Fourteen of them were assigned to be grade II (5 diffuse astrocytomas, 4 oligoastrocytomas and 5 oligodendrogliomas) and 8 as anaplastic astrocytomas grade III (Table 1).

<table>
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<th>Pathologies</th>
<th>Total number</th>
<th>M</th>
<th>F</th>
<th>Median of age (years)</th>
<th>SVS*</th>
<th>CSI*</th>
<th>SVS†</th>
<th>CSI†</th>
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<td>45.9</td>
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<td>43</td>
<td>9</td>
<td>13</td>
<td>16</td>
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TE-echo time; *TE 30 ms; †TE 135 ms; SVS – single voxel spectroscopy; CSI – chemical shift imaging
5 mm, no gap, matrix 256 × 224, NEX 2, FOV 24 cm) sequences. After administration of contrast agent (gadopentetate dimeglumine, 0.1 mmol/kg body weight; Magnevist, Schering, Germany), 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was performed.

1H-MRS

Proton MR single voxel spectroscopy (SVS) or chemical shift imaging (CSI) with a TE of 30 ms and TE of 135 ms, was performed immediately after completion of conventional MR imaging. SVS was used for well-circumscribed lesions and CSI for diffuse infiltrative lesions. Post contrast T1-weighted MPRAGE images were used for positioning of the volume of interest (VOI). Typical VOIs sizes were 100 × 80 mm². VOIs for SVS were placed at image regions to show post-contrast enhancement. For CSI, voxels which showed the greatest departure of Cho/Cr from the values for normal appearing white matter were selected. To suppress the water signal, chemical shift selective saturation was applied. The acquisition time was approximately 7 min for CSI and 4 min for SVS. Spectroscopic data were processed with the Syngo v14 software implemented on MR imaging console. The processing algorithm included the application of a Hanning filter, baseline and phase correction. Metabolite peak areas were fitted. 

Data analysis showed that the Cho/Cr ratio was significantly higher in glial tumors grade II compared to non-neoplastic lesions (p = 0.008) and that the Cho/Cr ratio was significantly higher in glial tumors grade III than in non-neoplastic lesions (p = 0.001) (Figure 1). The Cho/NAA ratio was significantly higher in glial tumors grade II than in non-neoplastic lesions (p = 0.37). 

NAA/Cr, and mln/Cr ratios could not differentiate between non-neoplastic lesions, glial tumors grade II and III. Statistically significant difference was also revealed between Cho/Cr ratios of anaplastic astrocytoma and ischemic lesions (p = 0.003), demyelinating lesions (p = 0.002)
and hamartomas ($p = 0.01$) respectively (Figure 2). The NAA/Cr ratio was significantly different between diffuse astrocytomas and hamartomas ($p = 0.046$), oligoastrocytoma and demyelinating lesions ($p = 0.006$) (Figure 3), anaplastic astrocytoma and ischemic lesions ($p = 0.048$) and anaplastic astrocytoma and oligodendroglioma ($p = 0.004$). In two cases of anaplastic astrocytoma ratios NAA/Cr were increased compared to the normal values, which can be assigned to contribution of Glx resonances. Therefore, they were excluded from evaluation of NAA/Cr and Cho/NAA ratios in statistical analysis.

Comparison of ADC, $\Delta$ADC and $\Delta$ADC/ADC values between tumors and non-neoplastic lesions showed a statistical significance of $\Delta$ADC/ADC between glial tumors grade II and glial tumors grade III ($p = 0.023$).

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the same pathologies using proton MR spectroscopy, echo time = 30 ms are shown in Figure 4.

Axial T2 weighted MR images of diffuse astrocytoma, hamartoma, oligoastrocytoma and demyelinating lesion are shown in Figure 5 (a–d, respectively), while the same sessions are examined using MR spectroscopy echo time = 30 ms or echo time = 135 ms (Figure 5 – others).

Discussion

Differentiation of non-neoplastic lesions, which look similar to neoplastic, on conventional MR images presents a particular challenge regarding establishing the correct diagnosis and following treatment. Advanced MR imaging techniques, like MR spectroscopy and DWI, which show physiological status of tissue, may contribute to better characterization of those pathologies. When brain lesion is solid, without necrosis, the main diagnosis include beside glial tumors (grade I-III), pseudotumoral demyelinating disease and some ischemic lesions with atypical presentation.

Our research showed that the Cho/Cr ratio is higher in glial tumor grade III than in demyelinating lesions and NAA/Cr ratio is lower in oligoastrocytoma (grade II) than in demyelinating lesions (Figure 5c, d, g, h). These results can be explained by the higher loss of functional neuronal cells and the larger membrane turnover in gliomas compared to demyelinating lesions. Cho is a component of the phospholipid metabolism of cell membranes and its increase is related to cell membrane turnover and higher cell density from tumor proliferation. NAA is a neuronal marker and a decrease of NAA levels is caused by replacement of healthy brain tissue by tumor cells. Brain tumor 1H-MRS spectroscopy typically shows elevated Cho levels and reduced NAA levels. MR imaging findings of acute demyelinating lesions can mimic glial neoplasias especially tumefactive demyelinating lesions. They present as T1 hypointense and T2 and FLAIR hyperintense lesions similar to tumours and can show enhancement after administration of contrast agent because of inflammatory BBB breakdown. Acute demyelinating lesions are also characterized by the increase of Cho levels and decrease of NAA levels. This is due to inflammation, demyelination and intense reactive astroglisis.

Bitsch et al. found that elevated Cho levels correlate with glial proliferation, since Cho is a component of glial cell membranes and that there is a connection between the Cho level, neuronal dysfunction and patient’s disability. The decrease of NAA is also common finding in acute demyelinating lesions. Also, Bitsch et al. showed that axonal degeneration and decreased axonal density, characteristic for demyelinating process, are associated with decreased NAA.

Majos et al. found that elevated Cho levels and reduced NAA levels are more pronounced in brain tumors than in pseudotumoral demyelinating disease. Therefore, analysis of these metabolites values can help in differentiation between glial neoplasms and acute demyelinating lesions. Our findings are in correlation with former published data.

In our research, we found that Cho/Cr ratio is higher in glial tumor grade III than in ischemic lesions. This is because of more intense cell destruction and glial proliferation in glial tumors grade III than in ischemic lesions. Based only on MR imaging examination, ischemic lesions can less frequently be a diagnostic problem for differentiation from glial neoplasms. On 1H-MRS spectroscopy, infarcts typically display with the reduction of NAA level and the elevation of lactate level and a slight increase in choline. In this research we did not observe lactate peaks. Loss of neuronal cells leads to decrease of NAA and increase of Cho level is due to reactive gliosis. The intensity of these metabolite changes reflects the severity of an ischemic process and it is related to the prognosis. Moller-Hartmann et al. found that Cho is a metabolite which can be used for differentiation between ischemic lesions and glial tumors since Cho level observed in glial neoplasm is significantly higher than in an ischemic process. Our findings are in accordance with the previously reported.

By analyzing the spectra obtained in our study we found higher Cho/Cr ratios in anaplastic astrocytomas than in hamartomas and lower NAA/Cr ratio in diffuse astrocytomas than in hamartomas. A lower NAA/Cr ratio in diffuse astrocytomas than in hamartomas could be due to neuronal loss that is more pronounced in glial tumors and higher Cho/Cr ratios in anaplastic astrocytomas than in hamartomas could be explained by intense tumor glial proliferation in high grade gliomas compared to a glial component within the hamartomas as benign lesions. Hamartomas, on MR imaging, appear as isointense to gray matter on T1 and T2-weighted images, but in more recent studies they have been described as T2 hyperintense lesions. On 1H-MRS, hamartomas present with decrease in NAA/Cr and increase in Cho/Cr and mIn/Cr ratios. Since, NAA is a neuronal marker, its decrease is connected with neuronal loss. Reflecting gliosis is related to the increase in mIn. Most commonly, elevated Cho is associated with high – grade gliomas, but this also can be found in benign cerebral pathologies like hamartomas. Cho level increase could be due to increasing glial component within the tumor. Majos et al. and Moller-Hartmann et al. found that addition of spectroscopy to routine MR imaging exam helps in characterization of focal intracranial disease and improves decision making in cases suggestive of brain tumors. Our results are in accordance with data in the literature and suggest that 1H-MRS is useful in evaluation of solid brain masses.

Our research showed a significant difference in ADC/ADC ratio between glial tumors grade II and glial tumors grade III. These findings can be due to the fact that high-grade tumors are characterised by the increased cellularity, microvascular proliferation and/or necrosis, that diffusivity of glial tumors is inversely related to the cellularity and that ADC is inversely proportional to the cellular density. Diffusion of a free water molecule in high grade tumors is reduced because of reduction in extracellular space by increased cellularity. The areas with the lowest ADC value suggest the areas with the highest cellular density and the highest tumor malignant potential. Previous studies showed that DWI can be useful in differentiating benign and malignant tumors from normal parenchyma and in grading gliomas. The results of our research correspond with previous findings from the literature.

This study is limited by the small sample size (47 patients). Different tumor types in a group of glial tumors grade II (diffuse astrocytoma, oligoastrocytoma, oligodendroglioma) is another limitation of this research. Pure astrocytic tumor differs from oligoastrocytoma and oligodendroglioma in its therapeutic response to chemotherapy, so their distinction is of great importance.
Conclusion

Our study showed the potential use of 1H-MRS and DWI in evaluation of solid brain masses. These noninvasive diagnostic techniques have the advantage over histopathologic assessment of focal brain lesions since they allow in vivo examination. ∆ADC/ADC, Cho/Cr and NAA/Cr ratio provided additional valuable information on lesion metabolic structure that can help distinguishing brain tumors from non-neoplastic lesions and tumor grading.

Conflict of interest statement

The authors declare no conflict of interest.

REFERENCES


Received on February 23, 2011.
Accepted on April 8, 2011.