PROTON MAGNETIC RESONANCE SPECTROSCOPY IN DIFFERENTIAL DIAGNOSIS OF BRAIN TUMORS

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The aim of the investigation was to assess the informativity of proton magnetic resonance spectroscopy (PMRS) data in differentiation of brain tumors and nonneoplastic diseases with similar signal characteristics on standard MRI scans, as well as glioma grade determination.

Materials and Methods. We examined 45 patients aged from 25 to 56 years with suspected expansive process of brain using proton magnetic resonance spectroscopy. The study was performed on MRI scanner "Magnetom Symphony 1.5 T" (Siemens, Germany) using software package Spectroscopy Evaluation. The examination included routine brain investigations (MRI), as well as diffusion weighted images with diffusion factors of b=0, b=500, b=1000 with the following ADC-mapping. To receive graphic spectra and parametrical maps, there was used SE impulse sequence. To assess the grade of gliomas and metabolic changes in peritumoral area we studied peak height of choline, creatine, N-acetyl aspartate and their ratio.

Results. According to histologically confirmed PMRS, 18 from 30 patients with cerebral gliomas were found to have low-grade gliomas (grade II), 12 patients — high-grade gliomas (grade III–IV). The results of the examination indicated high informative value of proton MR spectrometry as an important diagnostic technique in neuro-oncology. The modality is the most valuable and informative in the differentiation of cerebral gliomas, metastatic lesions, lymphomas, as well as in tumor grade determination of gliomas.

Key words: proton magnetic resonance spectroscopy; brain tumors; tumor grade of gliomas.

Magnetic resonance imaging (MRI) is commonly used to diagnose expansive processes of brain, however the nature of neoplasm cannot always be determined according to the data of standard T1-and T2-weighted images [1]. Gliomas, metastatic lesions, brain lymphoma, as well as tumors and non-neoplastic lesions are the most difficult to distinguish. Proton magnetic resonance spectroscopy (PMRS) is a functional technique, which on the basis of evaluation of the content of the received spectra of major metabolites allows us to determine the nature of the pathological process in cases when signal and morphological characteristics of the identified focus are non-specific [2].

The aim of the investigation was to assess the informativity of proton magnetic resonance spectroscopy data in differentiation of brain tumors and nonneoplastic diseases with similar signal characteristics on standard MRI scans, as well as glioma grade determination.

Materials and Methods. We examined 45 patients aged from 25 to 56 years with suspected expansive process of brain. The study was performed on MRI scanner Magnetom Symphony 1.5 T (Siemens, Germany) using head coil. At first stage patients underwent standard brain research with creation of axial, sagittal and coronal T2- and T1-weighted images, axial T2 Flair images, as well as diffusion weighted images with diffusion factors of b=0, b=500, b=1000 with the following ADC-mapping. The received images revealed area of interest for multi-voxel 2D spectroscopy. A square coil 8x8 cm was set on axial parameter image. After preliminary adjustment of the imager, such as shimming and signal suppression from protons of water molecules, protocol csi_se 30 was launched using software Spectroscopy Evaluation. In the course of post-processing treatment spectra graphics, parameter mapping of metabolites distribution and their ratios were obtained. Spectra graphics in each voxel of area of interest and distribution maps of the following metabolites were recorded: choline (Cho), N-acetylaspartate (NAA), lactate (Lac), creatine (Cr), glutamine-glutamate (Glx), myo-inositol (Ins) and maps of metabolite ratios: Cho/Cr, Cho/NAA and Lac/Cr. Tumor grade of gliomas was determined using Cho/Cr and Cho/NAA index. Their application is appropriate due to significant difference in the Cho levels in the spectra of gliomas of high and low degree of anplasia [1]. The NAA/Cr ratio was not used in the determination of glioma grade due to low information content [3], this index was useful in differential diagnosis of tumors with demyelinating processes [4]. The Cho level in the spectra as the most important parameter for evaluation of the anaplasia degree of gliomas [5], and

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the Lac level, which rises simultaneously with glioma grade, were evaluated on a mandatory basis [2, 6]. The NAA peak was used as a neuronal marker in determining the extent of damage to the brain tissue during neoplastic and non-neoplastic processes [7–9]. Metabolism in peritumoral area was also evaluated according to Cho, NAA peaks and Cho/Cr index for the differential diagnosis of gliomas and metastases [9].

Results and Discussion. According to MRI findings, 30 examined patients were found to have cerebral gliomas, 3 patients — brain metastases, 1 patient — lymphoma, 1 patient — neurotoxoplasmosis, 1 patient — neurosyphilis, 5 patients — multiple sclerosis and 4 patients — ischemic brain damage. According to histologically confirmed PMRS, 18 from 30 patients were found to have low-grade glioma (grade II), namely fibrillar-protoplasmic astrocytoma, 12 patients — high-grade tumors, of which 3 anaplastic astrocytomas (grade III), 2 malignant ependymomas (grade III), 3 anaplastic oligodendrogliomas (grade III) and 4 glioblastomas (grade IV).

According to PMRS data, spectra of gliomas of low-grade anaplasia are characterized by an increase in the Cho peak, a moderate decrease in the NAA peak and a moderate increase in the Lac peak [10]. According to our data, 14 from 18 cases of low-grade gliomas showed a significant increase in the Cr peak. In most cases, the Cr and Cho peaks were approximately at the same level, so the Cho/Cr ratio was within 1.0 (Fig. 1). In 13 cases NAA integral values exceeded integral Cho values and in 5 cases Cho values were higher than NAA values. A moderate increase in the Cho/NAA values was registered (See the Table). The Lac peak and the Lac/Cr ratio rose slightly. The area of development of metabolic changes beyond the

hyperintensity on T2-weighted images in the form of a slight relative increase in the Cho peak and Cho/Cr index in grade II gliomas was revealed in 14 from 18 cases (77%).

Grade III gliomas are characterized by a more significant increase in the Cho peak, than in case of low-grade gliomas (Fig. 2). The Cr peak in all cases decreased and Cho/Cr index had a much higher value than in the spectra of low-grade gliomas. The NAA peak and its integral values were significantly lower than the Cho peak, while Cho/NAA index had higher values (See the Table). The Lac peak and Lac/Cr index in the spectra of grade III gliomas were rather high. The area of development of metabolic changes beyond the hyperintensity on T2-weighted images in the form of a moderate increase in the peak of Cho and Cho/Cr index, Cho/NAA in grade III gliomas was revealed in all cases.

Glioblastomas are characterized by an increase in the Cho peak, moreover, in one case significantly higher values of this metabolite were detected, and in three cases there was a slight increase in the Cho value or even its decrease, especially in the areas of necrosis. The creatine peak in all cases sharply declined, that is why the Cho/Cr ratio was still very high. The NAA peak in all cases was significantly reduced, especially in areas of necrosis, so the Cho/NAA index was not very high. The examined patients with glioblastomas were found to have the highest Lac peak and Lac/Cr index in the spectra (see table). The high Lac peak value was recorded in the areas of necrosis in the presence of marked reduction of other metabolites (Fig. 3). It shall be noted that the area of development of metabolic changes beyond hyperintensity on T2-weighted images in the form of increased Cho peak and Cho/Cr, Cho/NAA index in glioblastomas was observed in all cases of our study.
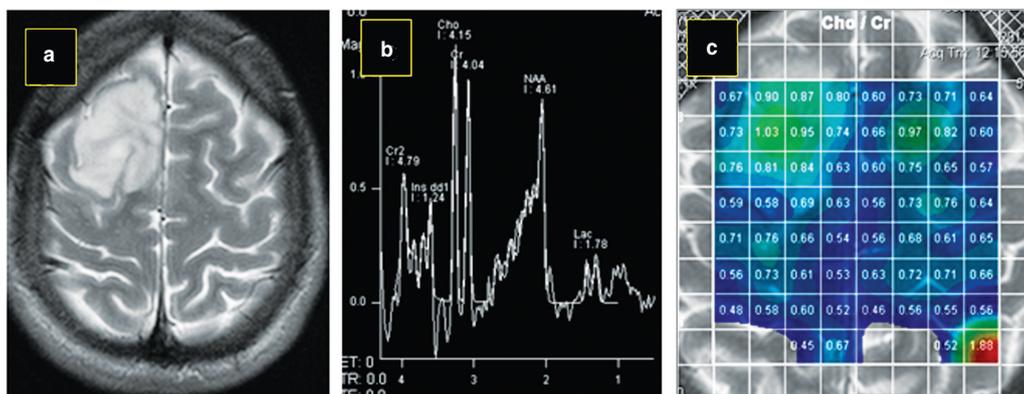

Fig. 1. Fibrillar-protoplasmic astrocytoma (grade II): *a* — T2-weighted image; *b* — magnetic resonance spectroscopy of the tumor area shows a moderate increase in the Cho peak, a moderate decrease in the NAA peak and a slight increase in the Lac peak; the creatine peak is increased; *c* — color-coded parametric map for the Cho/Cr ratio

Average values and standard deviations of metabolite ratios in the spectra of cerebral gliomas

Metabolite ratios	Low-grade gliomas (grade II)	Anaplastic gliomas (grade III)	Glioblastoma (grade IV)
Cho/Cr	1.28± 0.31	1.63± 0.21	2.34±0.22
Cho/NAA	1.16± 0.21	1.76± 0.19	1.51±0.17
Lac/Cr	1.03± 0.51	6.18± 0.64	9.82±2.42

Among 3 patients with metastatic brain lesions, the first patient was found to have a solitary metastasis with undiagnosed primary focus, the second — multiple lesions with high-grade adenocarcinoma of the lung and the third — a single metastasis of epithelioid skin melanoma. A single large metastatic node with an undiagnosed primary focus on standard MRI images did not differ from glioblastoma. Magnetic resonance spectroscopy of metastases showed a significant increase in choline peak, a decrease in creatine peak and absence of N-acetylaspartate peak (Fig. 4). Metastases in contrast to glioblastoma had no significant increase in the Cho/Cr index in the peritumoral area, however the tissue of the tumor node had very high values (4.5±0.65) due to a significant increase in the Cho peak and a marked depression of the NAA peak (0.28 [0.20, 0.36]). In case of tumor node, the size of which was much less than the voxel size, the metastasis spectra had the NAA peak (due to summation of signals from parenchyma of the tumor node and the intact brain).

MRI spectrum of metastatic epithelioid skin melanoma showed a moderate increase in the Cho peak, absence of the NAA peak and a high lactate peak caused probably by the impact of hemorrhagic sites and necrosis areas.

According to the MRI data, cerebral lymphoma looked like an expansive lesion of rather homogeneous structure, sometimes with areas of decay, having moderate hyperintense or isointense signal on T2-weighted images, hypointense signal on T1-weighted images with clear irregular contours, moderate perifocal edema. Diffusion-weighted images with diffusion factor of b=1000 showed high MRI signal from lymphoma, while the ADC-map demonstrated its heterogeneity with apparent diffusion coefficient values in the range of (0.86–1.19)·0.001 mm^2/s. A rather uniform amplification of the signal intensity of the tumor parenchyma was observed. MR spectroscopy of lymphoma showed a significant increase in the Cho peak and even higher Lac peak, as in malignant gliomas, however lymphoma spectra unlike them had a slight decrease in the NAA peak (Fig. 5). Therefore, the Cho/NAA ratio was low, preferably in the range of 1.0. On the contrary, Cho/Cr and Lac/Cr indices were rather high. One could also observe an increase in the glutamate peak and a decrease in myo-inositol peak.

One HIV-positive patient with clinical implications of encephalitis in the cerebellar hemispheres was found to have two foci of heterogeneous hyperintense signal on the T2-weighted images and hypointense signal on the T1-weighted images with signs of perifocal edema. Diffusion-weighted images demonstrated a very high MRI signal of revealed foci while on ADC-map it was nearly isointense with apparent diffusion coefficient being within (0.87–0.124)·0.001 mm^2/s. In this situation it was impossible to exclude lymphoma. The received proton magnetic resonance spectra in the focal zone showed a significant increase in the Lac and Lip peaks in case of marked reduction of other metabolite peaks. A small Cho and Cr content was observed in the spectrum. Most voxels demonstrated absence of NAA
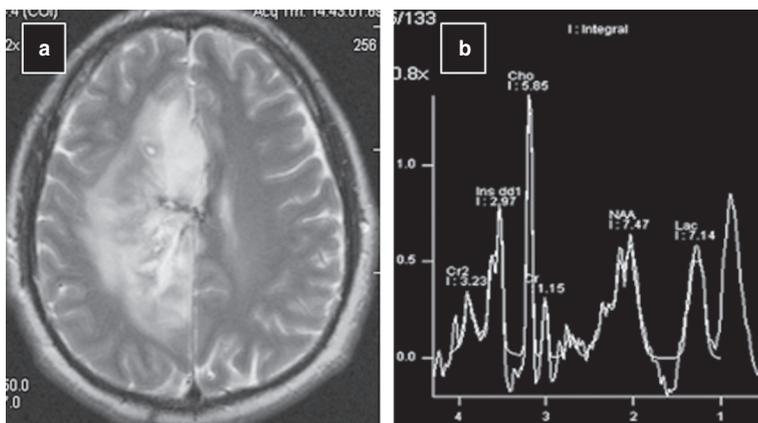

Fig. 2. Anaplastic oligodendroglioma (grade III): *a* — T2-weighted image; *b* — magnetic resonance spectroscopy of the tumor area shows a significant increase in the Cho peak, a significant reduction of the NAA peak and a marked increase in the Lac peak
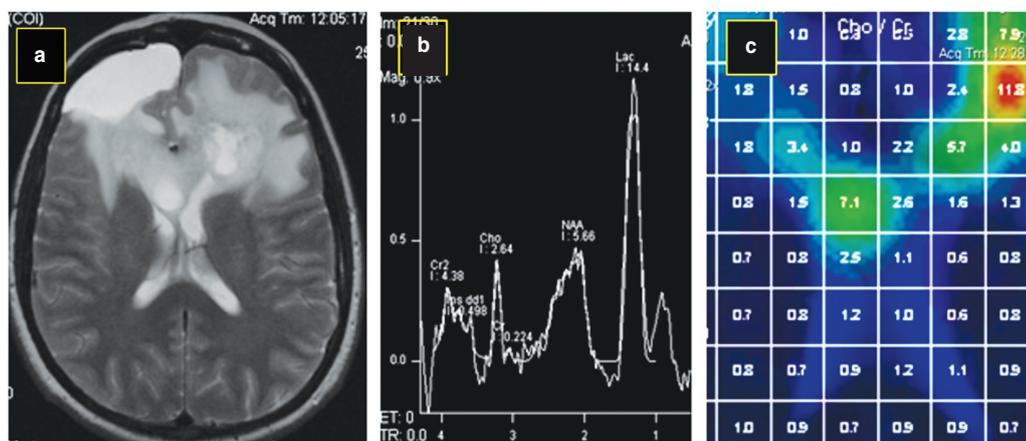

Fig. 3. Glioblastoma (grade IV): *a* — T2-weighted image; *b* — magnetic resonance spectroscopy of the tumor area reveals a small increase in the Cho peak, a marked decrease in the NAA peak, the Lac peak is the highest, double-peaked; the creatine peak is reduced; *c* — color-coded parametric map for the Cho/Cr ratio

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peaks, which was not typical for lymphoma and malignant gliomas. The Cho/Cr ratio was low, much lower than in case of malignant gliomas, but the Lac/Cr index was very high. According to [11], such spectra accounts for neurotoxoplasmosis in 75% of cases. Later neurotoxoplasmosis diagnosis was proved by enzyme-linked immunosorbent assay.

One patient was found to have multiple focal changes of the brain matter, with moderate hyperintense MRI signal on T2 and T2 Flair images, without clear contours and of irregular shape (in the anamnesis the patient reported having syphilis). Against the background of intravenous contrast enhancement, a solely diffusive increase in signal intensity of the identified foci was observed. Proton magnetic resonance spectra demonstrated a slight increase in the Cho peak and a moderate increase in the Lac peak. Further examination proved neurosyphilis.

All patients with ischemic lesion without signs of secondary hemorrhagic infarction in the acute phase, according to the PMRS data, were found to have an increase in the Lac peak and in the Lac/Cr ratio (1.10±0.46). The NAA peak decreased moderately, in rare cases showed a slight decrease in the Cho and Cr peaks. In the presence of secondary hemorrhagic infarction against the reduction of peaks of other metabolites a very high Lac peak was revealed. All cases of acute ischemia demonstrated a decrease in the Cho peak or its normal integral factors that sufficiently distinguish this type of pathology from neoplastic lesions. Integral factors in areas of ischemic brain for NAA constituted 7.39 [6.22; 8.16], for Cho — 3.06 [2.84; 3.29]. The Lac peak decreased over time and the NAA peak was about to restore.

The area of postischemic cystic glial changes showed a high Lac peak and a decrease in the Cho and NAA peaks. During examination of patients with acute cerebrovascular accident of ischemic type, diffusion-weighted images with the following ADC-mapping were made on a mandatory basis, which in the foci of acute ischemic lesions revealed a very low apparent diffusion coefficient level (0.31–0.63)·0.001 mm^2/s), not specific for tumors.

In case of multifocal lesions, as a rule, it is not difficult to diagnose multiple sclerosis, but in case of single large foci it is necessary to differentiate this pathology from brain tumors. All our patients in the acute phase had on diffusion-weighted images with diffusion factor b=1000 an increase in the MRI signal from the identified foci, while ADC-maps demonstrated a moderately increased MR signal with apparent diffusion coefficient being within (0.98–1.12)·0.001 mm^2/s. Against the background of intravenous contrast
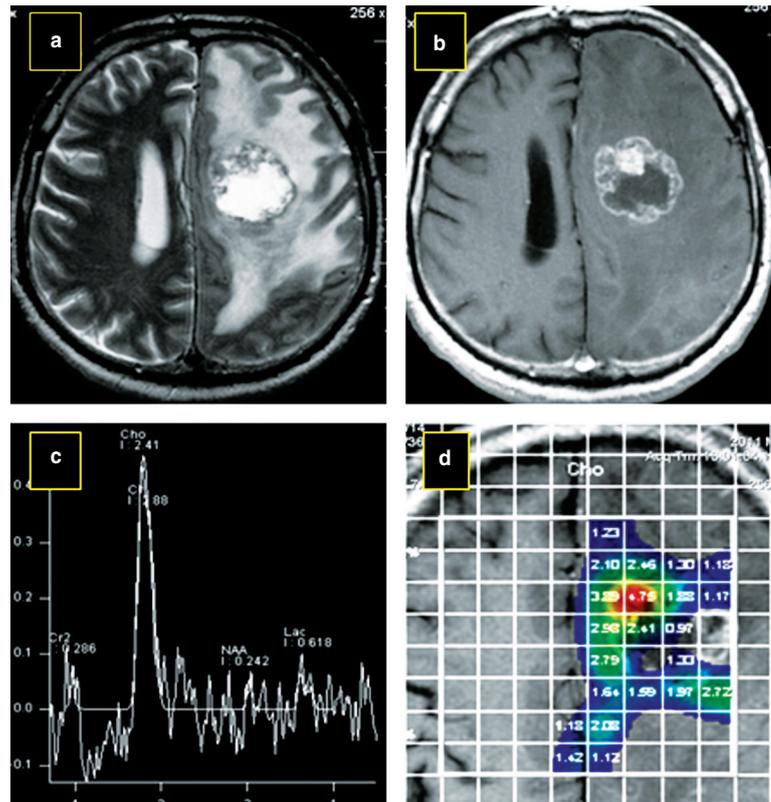

Fig. 4. Metastasis: *a* — T2-weighted image; *b* — T1-weighted image on the background of intravenous contrast enhancement; *c* — magnetic resonance spectroscopy of the tumor area reveals an increase in the Cho peak on the background of a sharp decline in the peaks of other metabolites; the NAA peak is nearly absent; *d* — color-coded parametric map for choline (Cho); areas of the increased choline almost coincide with the area of contrast enhancement on T1-weighted image
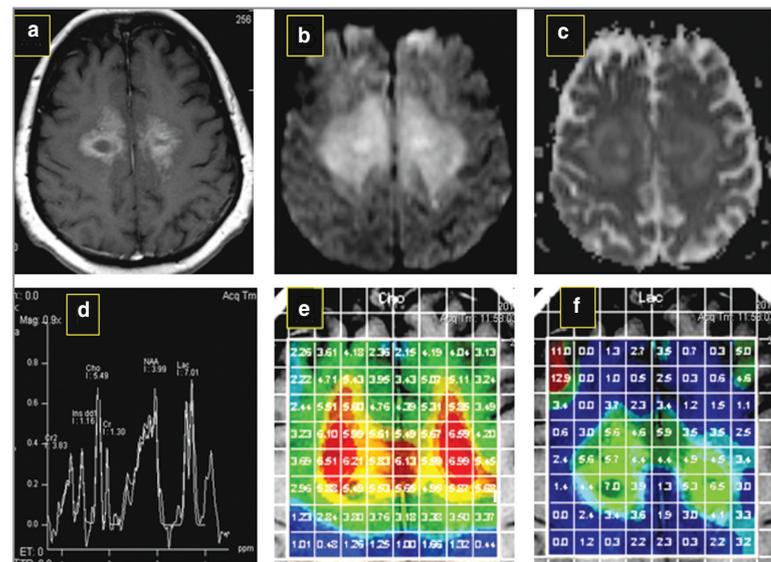

Fig. 5. Lymphoma: *a* — T1-weighted image on the background of intravenous contrast enhancement; *b* — diffusion-weighted image (b=1000), high magnetic resonance signal; *c* — ADC-map, apparent diffusion coefficient in the tumor area (0.86–1.19)·0.001 mm^2/s; *d* — magnetic resonance spectroscopy of the tumor area shows an increase in the Cho peak, a slight decrease in the NAA peak and a marked increase in the Lac peak; *e* — color-coded parametric map for choline (Cho); *f* — color-coded parametric map for lactate (Lac)

enhancement, one could see an increase in signal intensity of focal lesions of ring or half ring type. Proton magnetic resonance spectra demonstrated a moderate increase in the Cho peak (3.63 [3.58; 3.68]), an increase in the Lac peak and a slight decrease in the NAA peak (5.95 [5.77; 6.12]). One could observe a decrease in the NAA/Cr index (1.31±0.16). There is evidence that the NAA/Cr index in the central parts of pathological processes during demyelinating processes is higher than in the intact brain, and in case of gliomas — on the contrary [4]. Examination of patients after conducted treatment revealed a further increase in the Cho peak (in three cases), or its decrease down to normal levels (in two cases).

Thus, the results of our studies indicate high informative value of PMRS in the differential diagnosis of neoplastic and nonneoplastic brain lesions that have similar signal characteristics.

Conclusion. Proton magnetic resonance spectroscopy is high-performance method of differentiation of pathological processes, such as solitary metastasis without identified primary focus and glioblastoma. The analysis of metabolite peaks and their ratios in MR spectra provides useful additional information for identification of CNS lymphoma, demyelinating processes, ischemic and inflammatory brain diseases. Color-coded parametric maps provide a more clear assessment of the nature of metabolic changes in the area of interest.

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