Distinct peak at 3.8 ppm observed by 3T MR spectroscopy in meningiomas, while nearly absent in high-grade gliomas and cerebral metastases

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Abstract. The purpose of the present study was to evaluate distinct metabolic features of meningiomas to distinguish them from other brain lesions using proton magnetic resonance spectroscopy. The study was performed on 17 meningiomas, 24 high-grade gliomas and 9 metastases. Elevated signal intensity at 3.8 ppm observed in low TE spectra adequately differentiated meningioma from other brain tumors while alanine was not indicative of meningioma occurrence; the presence of lipids and lactate did not provide a strong index for meningioma malignancy.

Introduction

The majority of meningiomas can be well differentiated from other brain lesions using conventional magnetic resonance imaging (MRI) techniques, as they demonstrate unique imaging characteristics that reveal their extracranial location, dura matter conjunction and sinus involvement (1). However, 15% of meningiomas exhibit atypical MRI features such as cystic and necrotic areas, ring-like enhancement and parenchymal invasion, resembling malignant brain lesions such as gliomas or metastatic brain tumors leading to false radiological reports and misinterpreted treatment decisions (2,3).

According to the World Health Organization's (WHO) histopathologic criteria, meningiomas are separated into three grades: typical or benign meningioma (WHO grade I), atypical meningioma (WHO grade II) and malignant (anaplastic) meningioma (WHO grade III). Their occurrence rates are 90.5, 7.2 and 2.4%, respectively (4).

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Thus, distinction between malignant and benign brain tumors may determine the aggressiveness of surgical resection, and decide whether combined radiation therapy is necessary.

Several MRI modalities have been used for meningioma differentiation from other intracranial brain tumors and their characterization according to the various meningioma grades. Diffusion-weighted MRI (DWI), perfusion-weighted MRI (PWI) and proton magnetic resonance spectroscopy (^{1}H-MRS) provide additional structural and metabolic information (5-7). ^{1}H-MRS alone can reach up to 82.5% accuracy (58.7-82.1% CI), 100% sensitivity and 91.1% specificity on predicting tumor type (8). With the advent of 3T MR scanners into clinical practice there has been growing interest in analyzing brain tumor spectra, as signal to noise ratio and spatial, temporal and spectral resolution have remarkably been improved compared to that of lower magnetic fields. To the best of our knowledge, to date the metabolic characteristics of meningioma on 1.5T MR scanners have been well discussed in the literature but not on 3T.

^{1}H-MRS studies of meningiomas have repeatedly revealed an increase in alanine (Ala), choline (Cho) and glutamate-glutamine complex (Glx), and decreased N-acetylaspartate (NAA) and creatine (Cr) (9). However, Ala and Glx concentrations are not always easy to evaluate during clinical practice (10). The aforementioned results of accuracy, sensitivity and specificity should be expected to improve when using quantitative MRS methods allowing for the determination of metabolite concentrations rather than using the rather specific Cho/Cr and Cho/NAA ratios as a measure of tumor activity (11). Lactate (Lac) and lipids (Lip) are usually taken as proof of nonbenign tumors, indicating intratumoral hypoxia and micronecrosis, respectively. Lipids have been positively correlated with the grade of malignancy of gliomas and metastatic brain tumors; nevertheless the question is whether they indicate malignancy in meningiomas as well. Qi *et al* (1) have suggested lipids as a useful marker for evaluating the histopathologic grade of intracranial meningiomas. However, those findings are still controversial and only a few studies have elaborately investigated the lipid peak in the diagnosis of meningioma.

Summing up, controversy still remains, since there are several case studies reported in the literature pointing out the

problem of differential diagnosis between meningiomas and metastatic tumors, especially when metastatic tumors have radiological features that strongly suggest a primary tumor.

In this study, localized ¹H-MRS was performed on untreated tumors diagnosed as meningiomas, cerebral metastasis and high-grade gliomas. Spectral characteristics of those tumor types were investigated according to the histological subtypes, retrospectively. We aimed to evaluate the metabolic features of meningiomas and especially a distinct peak at 3.8 ppm, for their early differentiation from other brain lesions in clinical practice and primarily verify the ability or inability of lipids and lactate to constitute an accurate index of meningioma malignancy.

Materials and methods

Patients. A total of 50 patients aged 16-78 years with untreated brain tumors were enrolled in the study at our institution, after providing written informed consent. Patients were examined by conventional MRI including contrast enhanced imaging and ¹H-MRS before contrast administration. Seventeen intracranial meningiomas were studied and 33 of the most frequent intracranial tumors; high-grade glioma (n=24) and metastases (n=9), were included in the examined brain tumors for comparison purposes. Histologic types of all tumor lesions were confirmed by intraoperative biopsy after obtaining ¹H-MR spectra.

MRI and ¹H-MRS protocol of brain tumors. The study was performed on a 3-Tesla MRI unit (GE, Healthcare, Signa® HDx) applying a standardized MRI and MRS examination patient protocol and using a birdcage and an 8-channel phased-array head coil. Before ¹H-MRS was performed, sagittal and axial T1-weighted fast spin-echo (FSE) (TR/TE/700/9.3 m/sec) and T1-weighted fluid attenuation inversion recovery (FLAIR) images (TR/TE/3.000/9.2 m/sec), axial T2-weighted FSE (TR/TE/2.640/102 m/sec) and coronal T2-weighted FSE (TR/TE/2.920/102 m/sec), T2-weighted FLAIR (TR/TE/8.500/130 m/sec), and multiple echo recombined gradient echo (MERGE) (TR=460 m/sec) images were obtained for each patient using a slice thickness of 5 mm with a 1-mm gap. Diffusion-weighted MRI was performed via a single shot, spin echo, echo planar sequence with b-value of 1.000 sec/mm².

Subsequently, ¹H-MRS studies were performed using both proton brain exam (PROBE) single voxel (SV) and two dimensional-multivoxel (2D-Chemical Shift Imaging) spectroscopy packages before contrast administration to avoid signal disturbance. Data were acquired using point-resolved spectroscopy (PRESS) pulse sequence with phase encoding gradients in two directions, automatic and manual shimming and Gaussian water suppression. Measurement parameters used in single voxel technique were 1.500/35 m/sec (TR/TE), voxel size was not less than 3.375 cm³ always carefully adjusted inside the tumor and 128 signal acquisitions (Nacq), whereas, measurement parameters used in 2D-CSI were 1.000/144 m/sec (TR/TE), 16x16 phase encoding steps, 10-mm section thickness and the field of view size was adjusted to each patient's brain anatomy. Spectra scans for both techniques were accomplished approximately within 4-5 min each, including the shimming procedure.

Measured spectra for each patient consisted of healthy and pathologic brain regions. Inside the region of tumor tissue,
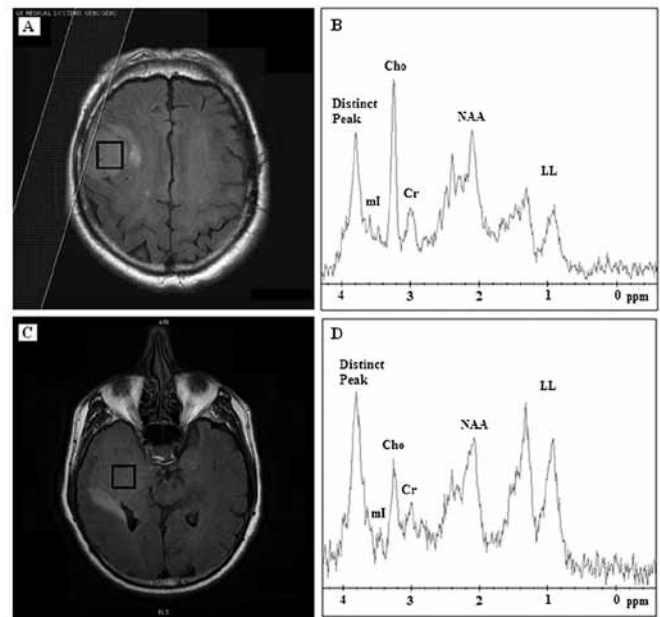

Figure 1. FLAIR (A and B) T2 images of two of the typical meningiomas with their corresponding spectra (B and D) at short TE (35 m/sec). Elevated Cho and lipid resonances at 3.2 and 1.3 ppm, respectively. Also a distinct chemical compound was detected in all cases of meningiomas, resonating at 3.8 ppm.

obvious necrosis, cyst, hemorrhage, edema, calcification and normal appearing brain tissue were excluded from the voxel whenever possible, in order to avoid false lesion estimation.

For voxel positioning, T1-weighted FSE, T2-weighted FLAIR and T2-weighted imaging sequences in sagittal, axial and coronal planes retrospectively, were preceded.

When ¹H-MRS examination was completed, contrast enhanced, T1-weighted FSE in axial plane and 3D FSPGR sequences were performed for every patient enrolled in the study.

Post processing of the raw spectral data included baseline correction, frequency inversion and phase shift.

Statistical analysis. The main metabolites identified by ¹H-MRS were NAA at 2.0 ppm, Cr at 3.0 ppm, Cho-containing compounds at 3.2 ppm, myo-inositol (mI), lactate as a doublet at 1.33 ppm and methylene groups of lipids resonating between 0.8 and 1.4 ppm (7-10). Patients were grouped according to tumor type (meningioma, high-grade glioma and metastasis). Data analysis was performed using the SPSS (v13) statistical software package. Metabolite ratios were expressed as mean ± SD. Bivariate correlation using 1-tailed Pearson's correlation coefficient, was employed to explore the relationship among meningioma and the other solid brain lesions (meningioma vs. high-grade gliomas and meningioma vs. metastasis). A P-value <0.05 was considered to be statistically significant.

Results

After MRI and ¹H-MRS examination, before tumor resection, 17 patients were diagnosed as having meningioma, 24 as high-grade glioma (grade III and IV) and 9 as cerebral metastases. All lesions were verified by post operative pathologic examination and particularly for meningiomas; 1 was diagnosed as atypical meningioma and 16 as typical meningiomas.

Table I. Mean values and standard deviation of the tumor metabolite ratios as well as the 3.8 ppm peak, LL and Ala findings at short TE (TE=35 m/sec) and Pearson's correlation results with the corresponding level of significance.

Metabolite ratios (TE=35 m/sec)	Meningiomas (17 cases) mean ± SD	High-grade gliomas (24 cases) mean ± SD	Solitary metastasis (9 cases) mean ± SD	Meningioma vs. high-grade glioma (R)	Meningioma vs. metastasis (R)
NAA/Cr	1.34±0.11	1.11±0.48	1.44±0.5	9.7% (0.19)[a]	2.25% (0.36)[a]
Cho/Cr	1.19±0.73	1.76±0.48	1.46±0.58	14.5% (0.03)[b]	4.4% (0.256)[a]
mI/Cr	0.51±0.39	0.87±0.26	0.77±0.27	16% (0.05)[b]	15% (0.15)[a]
Distinct peak at 3.8 ppm	Present 10/17	Absent 0/24	Absent 0/9	100% (0.000)[b]	100% (0.000)[b]
LL (+)	13/17	12/24	2/9		
LL (++)	5/13	12/24	7/9		
LL (-)	4/17	-	-		
Ala (+)	4/17	-	-		

[a]Accounts for non-statistically significant result and [b]statistically significant result. +, Present; -, absent; ++, elevated. NAA, N-acetylaspartate; Cho, choline-containing compounds; Cr, creatine and phosphocreatine; LL, lipids+lactate; Ala, alanine.
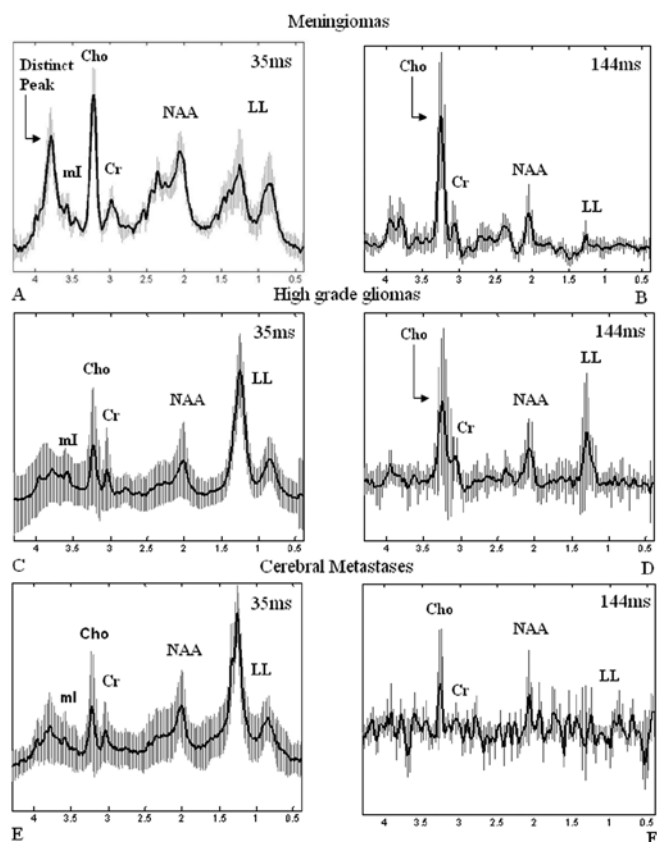

Figure 2. *In vivo* short (A, C and E) and (B, D and F) mean spectra and standard deviation (vertical lines) of the 3 tumor groups. Obvious elevation of Cho and lipid resonances at 3.2 and 1.3 ppm, respectively, for all tumors. Also a distinct chemical compound (black arrow) at 35 m/sec detected in all cases of meningiomas, resonating at 3.8 ppm but not for high-grade gliomas and metastases.

Metabolic findings associated with lesion type. When short TE (35 m/sec) was performed, all 17 meningioma cases were characterized by increased levels of Cho and by a distinct chemical compound resonating at 3.8 ppm (Fig. 1). Of the 17 meningiomas, 10 (59%) revealed Cho contents and the distinct compound as the prominent peaks. mI was absent or reduced to noise level in 10 (59%) meningioma cases. Lipids and lactate (LL) were present in 13 (76%) meningiomas whereas it was the dominant peak in 5 (38%) (Table I), which were classified as atypical meningiomas before biopsy.

The mean spectrum at 35 m/sec from all 17 meningiomas accompanied with the standard deviation is illustrated in Fig. 2A highlighting the variability among meningioma spectra and the presence of the distinct chemical compound at 3.8 ppm.

All 24 cases of high-grade gliomas (grade III and IV) appeared with high lipid and lactate peaks and low or absent NAA (Fig. 3B). Twelve out of twenty-four (50%) high-grade gliomas exhibited a dominant lipid peak, indicative of extensive necrosis, obscuring all the other metabolite peaks, whereas the other half (50%) appeared with high levels of Cho and lactate suggesting tissue hypoxia. mI was observed to be increased for high-grade gliomas.

In 7 (77%) cases of metastasis, dominant lipid and lactate peaks were detected (Fig. 3D), and in 2 cases (22%), high levels of Cho were found, whereas NAA was only present in 2 (22%) cases. The distinct resonant peak at 3.8 ppm observed in meningioma spectra was not revealed in high-grade gliomas or in metastatic cerebral tumors.

When long TE (144 m/sec) was performed, NAA and Cho content were more accurately determined, as both chemicals have long T2 time. Thirteen out of 17 (76%) meningiomas revealed high concentrations of Cho-containing compounds (Fig. 4B); the LL peak was present only in 4 (23%) (Table II). NAA was present in 14 (82%) meningioma cases. Among them only 6 cases had a little brain substance involved in their voxels, including 2 meningiomas that invaded adjacent brain. The other 8 cases had their voxels completely limited within the tumors (Fig. 4A). On the other hand, among the cases that did not demonstrate NAA, 3 cases had their voxels contaminated by a small amount of brain substance. Alanine
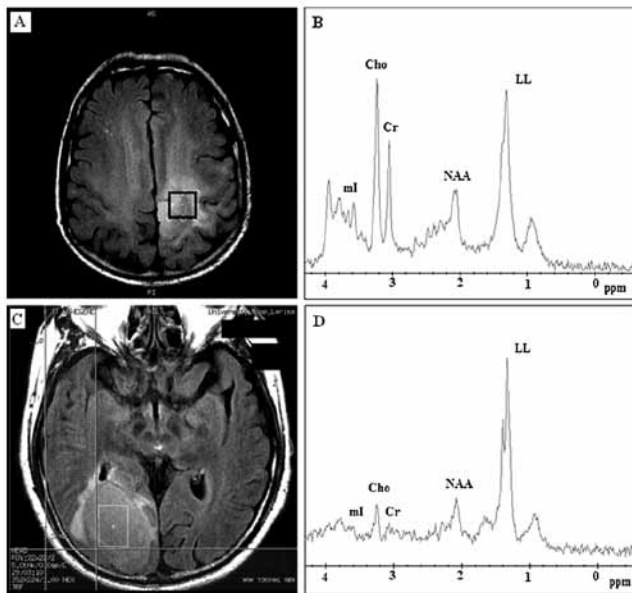
Figure 3. FLAIR (A) and FSE (C) T2 images of high-grade gliomas and metastases respectively with their corresponding spectra (B and D), at short TE (35 m/sec).
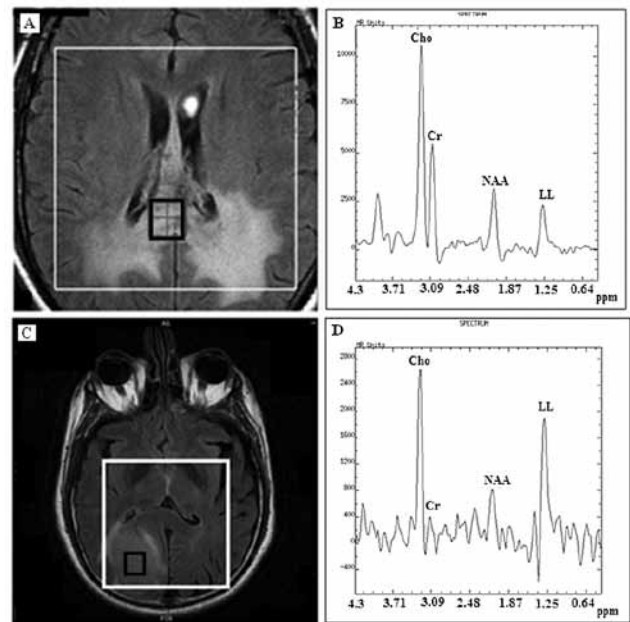

Figure 5. FLAIR (A and C) T2 images of high-grade gliomas (A) and metastases (C) respectively, with their corresponding spectra (B and D) at long TE (144 m/sec).
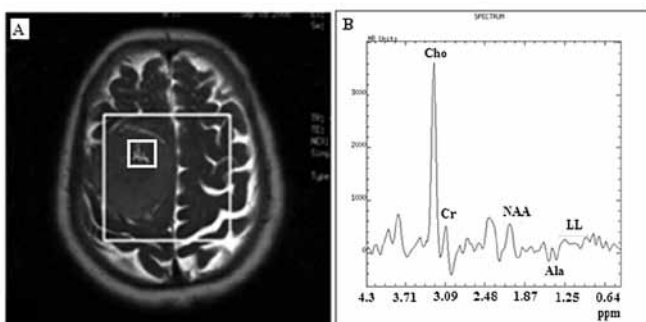

Figure 4. FSE (A) T2 image of a typical meningiomas with its corresponding spectra (B). Elevated Cho in 3.2 ppm and absence of N-Acetyl-aspartate in 2.02 ppm at long TE (144 m/sec). Ala doublet inversion at 1.47 ppm suggestive of meningioma.

was observed in 4 (23%) cases of the 17 meningiomas on both short and long TE (Tables I and II), but it was better identified at long TE as an inverted douplet peak (Fig. 4B), however, its detection rate was low either for short or long TE.

Increased Cho was found in 19 (79%) out of 24 cases of high-grade gliomas (Fig. 5B) and in 5 (55%) out of 9 cases of metastatic tumors (Fig. 5D).

Fig. 2 represents all mean spectra with their corresponding deviations from the mean for meningiomas, high-grade gliomas and metastases verifying the overall metabolic findings according to tumor group and highlighting the presence of the distinct chemical compound at 3.8 ppm for meningiomas (Fig. 2A), and the lack of that peak at the short TE spectra in the other tumors (Fig. 2C and E).

Metabolite ratio for the differentiation of meningioma from other brain tumors. Additionally, Tables I and II exhibit metabolite ratios (mean ± SD) and the determination coefficients (R)-derived from 1-tailed Pearson's correlation coefficient to

investigate their ability to differentiate meningiomas from other solid brain tumors. ^{1}H-MRS in short TE (TE=35 m/sec) revealed a high mean NAA/Cr ratio (1.34±0.11) for meningiomas, due to voxel contamination with brain neurons. High-grade gliomas indicated the highest mean Cho/Cr (1.76±0.48) and mean mI/Cr (0.87±0.26) ratios, among meningiomas and metastases, whereas, meningiomas revealed the lowest mI/Cr ratio (0.51±0.39) among high-grade gliomas and metastases.

When long TE (TE=144 m/sec) was performed, mean Cho/Cr (4.64±2) and mean Cho/NAA (4.46±2.2) ratios were higher for meningiomas, whereas metastatic brain tumors revealed the highest mean NAA/Cr (2.7±1.26) ratio among the other tumor types.

It was concluded that when short TE (TE=35 m/sec) was implemented, the variability in Cho/Cr accounted for 14.5% (P<0.03) in differentiating between meningiomas and high-grade gliomas, whereas, NAA/Cr did not allow their significant differentiation. Moreover, the mI/Cr ratio accounted for 16% (0.05) in discriminating meningiomas from high-grade gliomas, while the presence of the distinct peak at 3.8 ppm appeared to have the highest and most statistically significant correlation in differentiation of meningiomas from all studied brain tumors (Table I). None of the metabolite ratios allowed the significant differentiation between meningiomas and cerebral metastases. However, when long TE (TE=144 m/sec) was performed, it was observed that NAA/Cr accounted for 34% (P<0.037) of the differentiation among meningiomas and metastases, while Cho/Cr and Cho/NAA accounted for 39% (P<0.001) and 21.5% (P<0.004) respectively, for differentiating meningiomas from high-grade gliomas while Cho/NAA accounted for 50% (P<0.005) for differentiating meningiomas from metastases (Table II).

Lipids and lactate as an index of meningioma malignancy, after tumor resection. Dominant lipid and lactate peaks were

Table II. Mean values and standard deviation of tumor metabolite ratios as well as the 3.8 ppm peak, LL and Ala findings at long TE (TE=144 m/sec) and Pearson's correlation results with the corresponding level of significance.

Metabolite ratios (TE=144 m/sec)	Meningiomas (17 cases) mean ± SD	High-grade gliomas (24 cases) mean ± SD	Solitary metastasis (9 cases) mean ± SD	Meningioma vs. high-grade glioma (R)	Meningioma vs. metastasis (R)
NAA/Cr	1.21±0.86	1.06±0.38	2.7±1.26	1.6% (0.25)[a]	34% (0.037)[b]
Cho/Cr	4.64±2	2.52±0.75	2.37±0.62	39% (0.000)[b]	22% (0.086)[a]
Cho/NAA	4.46±2.2	2.6±1.31	0.81±0.23	21.5% (0.004)[b]	50% (0.005)[b]
Distinct peak at 3.8 ppm (-)	Absent 0/17	Absent 0/24			
LL (+)	4/17	11/24			
LL (-)	13/17	13/24			
Ala (+)	4/17	-			

[a]Accounts for non-statistically significant result and [b]statistically significant result. +, Present; -, absent; ++, elevated. NAA, N-acetylaspartate; Cho, choline-containing compounds; Cr, creatine and phosphocreatine; LL, lipids+lactate; Ala, alanine.

Table III. Histological results of the meningiomas classified as atypical before biopsy and 1-tailed Pearson's correlation endpoint of lipid occurrence and meningioma malignancy, with the corresponding level of significance.

Lipid presence in meningiomas (TE=35 m/sec)	Histopathologic (WHO)	Histologic subtype	Lipid and lactate finding occurrence vs. meningioma malignancy (R)
Case 1/65/M	Typical (WHO grade I)	Meningothelial	
Case 2/78/M	Typical (WHO grade I)	Fibroblastic	
Case 3/67/M	Atypical (WHO grade III)	Papillary	12.7% (0.357)[a]
Case 4/86/F	Typical (WHO grade I)	Meningothelial (microcystic)	
Case 5/54/M	Typical (WHO grade I)	Fibroblastic	

[a]Accounts for non-statistically significant result.

observed in 5 meningiomas (38%) which were diagnosed as atypical, before tumor resection. All the appropriate measures were taken to avoid voxel contamination by subcutaneous fat. More specifically, in cases where the lesions were close to the skull; i) the voxel grid was designed and applied on axial images that accommodated the positioning as far as possible from the scull and ii) signal saturation bands were carefully adjusted to annihilate voxel signal contamination from the adjoined subcutaneous fat (Fig. 1A), due to the chemical shift effect and the non-square nature of the voxel-selected pulses used in the PRESS sequence. Among the aforementioned meningiomas, only one proved to be anaplastic with observed micronecrosis. Lipids and lactate did not reveal a statistically significant index to differentiate typical from atypical meningiomas. Their occurrence accounted only for 12.7% for differentiating typical from atypical meningiomas with low level of significance. Histopathological findings and the corresponding correlation coefficient are depicted in Table III.

Discussion

Meningiomas are common intracranial tumors and are generally diagnosed by their characteristic radiological imaging appearance of solid mushroom imaging pattern, extracranial location, dura matter conjunction and sinus involvement. They constitute 20% of all intracranial tumors and they are classified as typical, atypical and malignant histological variants according to the presence of increased mitotic activity, high cellularity and necrosis. However, 15% of meningiomas exhibit rim-like enhancement, a prominent cystic component, hemorrhage, or even metaplasia (2,3), posing an atypical radiological pattern. These meningioma types mimic gliomas or cerebral metastatic tumors with cystic or necrotic alterations. Furthermore, the dural sign is not a specific finding for extra-axial tumors only because it may also be observed in metastases and glial tumors (2,10,12). Thus, using conventional MRI techniques, some high-grade glial tumors and metastases may pose difficulties in differentiation from meningiomas when they are located close to leptomeninges or remote from the intra-axial region together with the presence of dural invasion, or have cystic or/and necrotic components, leading to false radiological reports and treatment decision.

Several studies are dedicated to the differentiation of meningiomas among other solid brain lesions using various MRI techniques such as conventional MRI, DWI, PWI and MRS (2-7).

^{1}H MRS is a non-invasive techniqie of showing the biochemical content of living tissue, which provides additional information regarding the metabolism of cerebral tumors which can be useful in diagnosis, tumor extent prior to surgery or post treatment progress evaluation.

Previously reported MRS findings of brain tumors overall include a decrease in NAA, a marker of neuronal integrity; an increase in Cho involved in increased cell membrane and myelin turn over and a decrease in Cr, which provides inorganic phosphates for adenosine triphosphate production involved in cellular energetics and osmotic balance (7). The presence of lactate and lipid peaks are usually consistent with the aggressive tumors, reflecting increased anaerobic metabolism and cellular necrosis, respectively. Elevated alanine resonances, although characteristic of meningiomas, are not found in all meningiomas and seem to correlate inversely with necrosis within these tumors (13).

Instead of the aforementioned metabolite quantitation, many studies use metabolite peak area ratios to describe changes in the metabolic profile. An advantage of ratios is that the effects of a general reduction in the measured metabolite concentrations due to variations in cellular density (cause by necrosis for example) will cancel out.

In the present study, all studied 50 untreated solid brain lesions exhibited high concentrations of Cho and lactate, and decreased or absent amounts of NAA (Fig. 2). Lipids were present in high-grade gliomas, metastases and meningiomas due to extensive necrosis or fatty degeneration, in agreement with previous research (14). We sought to detect distinct features of meningioma spectra that accurately separate them from high-grade gliomas and solitary metastases.

NAA is the major contributor of the peak at 2.02 ppm in normal brain as it is present within neurons and it is usually taken as a marker of neurons.

It is generally considered that in meningiomas, by definition NAA is not observed, since this lesion is extra-axial and NAA is a neuron-specific marker (13). This is consistent with previous *in vitro* analysis of meningioma extracts for which NAA was not detected (15). However, in our short TE spectra, meningiomas revealed a quite high mean NAA/Cr ratio, which can be ascribed to the partial volume effect of the brain. This may account for some of our cases whose voxels enclosed adjacent healthy brain parenchyma. However, this result cannot explain other cases whose voxels were completely located within the tumor. On the other hand, although in certain cases, voxels were indeed contaminated by normal brain parenchyma, NAA peaks were not evident at all. This probably indicates that partial volume effect may not be the only source of sufficient NAA signals. This observation is in good agreement with Yue *et al* (14) who mention that a peak of NAA at 2.02 ppm of meningioma spectra collected, may also represent other endogenous NAA compounds such as N-acetylaspartylglutamate, N-acetylneuraminic acid and N-acetylgalactosamine of meningiomas.

Studying the metabolic profile of different cerebral tumors, Howe *et al* found that low levels of mI were characteristic of meningiomas (10). In the present study, meningiomas also revealed the lowest mI/Cr ratio in comparison with the other brain lesions.

Furthermore, from our spectroscopic data analysis it is evident that all meningiomas revealed a distinct signal at 3.8 ppm (Fig. 2), which can be considered characteristic in differentiating them from other cerebral lesions, obviously, due to the underlying metabolic differences. Hence this distinct metabolic characteristic can establish a rather specific marker in differential diagnosis of meningiomas during clinical routines.

This chemical substance observed at 3.8 ppm in short TE, might correspond to Glx-a peak or Glx together with glutathione (12,14,16), Majos *et al* graphically demonstrated an elevation of Glx-a in meningiomas compared to other brain masses (16). Theoretically, if the 3.8 peak corresponded to Glx, then there should be a correlation between the 2.35 multiplet signal and that at 3.8 ppm, an observation which was not verified in our study. Tugnoli *et al* (17) elaborately identified the *in vitro* metabolic patterns of 6 meningioma subjects by implementing high resolution magic angle spinning (HR-MAS) MRS and compared them with *in vivo* ^{1}H-MRS results at 3T. They revealed that it is possible to differentiate among different meningioma subtyptes (fibrous, oncocytic and meningothelial) as they exhibit different metabolic characteristics. Both *in vivo* and *in vitro* studies showed the absence of NAA in accordance with the extracerebral origin of meningiomas. Only oncocytic and meningothelial exhibited a distinct peak at 3.8 ppm which according to their *ex vivo* study receives contribution from phosphoethanolamine (PE) and amino acids, such as leukine, alanine, glutamate, glutamine, glutathione, lysine, arginine and serine. Moreover, Tugnoli *et al* (17) reported that the resonances of CH_2OH in glycine are also found at 3.8 ppm, and these data suggest the presence of oligosaccharides, probably maltotriose and maltotetraose, which are small sugars detected very rarely by MRS in human meningiomas. Our results in short TE MRS verify this finding.

When long TE was performed, meningiomas revealed the highest mean Cho/Cr ratio among all intracranial tumors and the highest Cho/NAA due to both Cho increment and NAA reduction. Howe *et al* (10) also observed the highest Cho/Cr ratio for meningiomas (n=8), when compared with grade II astrocytomas (n=5), AAs (n=7), GBMs (n=13) and metastases (n=9). On the other hand, in our study, Ala was only present in 4/17 meningiomas, confirming the findings of other studies, that it is not always detectable (4). It has been suggested that the presence of Ala indicates that the metabolism of meningiomas involves partial oxidation of glutamine rather than glycolysis. Thus, the varying metabolic profiles of meningiomas, high-grade gliomas and metastases, indicate differences in cell type and metabolism (10). As observed in Fig. 4, a long TE allows Ala identification, because its doublet is inverted due to the J-coupling phase modulation, making it easier to differentiate this resonance from lipids and other macromolecules (5).

Nevertheless a factor that may explain the variance of Ala is the voxel size (12). The *in vitro* study of Christiansen *et al* (18) demonstrated that metabolite signal on ^{1}H-MRS significantly correlated (r=0.99) with concentration and selected voxel size (r=1). However, it is not always easy to select a fairly big voxel as shimming worsens. Therefore, when voxel size is limited because a meningioma is small or heterogeneous, it is not surprising that Ala may not be detected.

The diagnostic accuracy of NAA/Cr and Cho/Cr ratios in differentiating meningiomas from all other solid brain lesions was limited when short TE was used. However, the NAA/Cr

ratio did significantly distinguish meningiomas from cerebral metastases and the Cho/Cr ratio distinguished meningiomas from high when long TE was performed. Overall, the Cho/NAA ratio in long TE was the most significant MRS ratio in the differentiation of meningiomas from metastases mainly due to both Cho intense increase and NAA intense decrease in the meningioma cases. Fountas *et al* (19) mentioned that the differentiation of metastases and meningiomas is very difficult using MRS alone, because of spectral similarities referring to the absence of NAA and low concentrations of Cr. However, in the present study the NAA/Cr ratio in long TE accounted for 34% (0.037) in differentiating meningiomas from metastases.

The distinct peak of the chemical substance resonating at 3.8 ppm accounts for 100% in discriminating meningiomas from high-grade gliomas and metastases (Table I) in short TE. Thus, as Ala is rarely distinguished or ambiguously determined, this peak at 3.8 ppm may play a determinant role for the recognition of meningiomas.

Previous studies have correlated the amount of lipids and the presence of micronecrosis and concluded that micronecrosis was highly indicative of nonbenign meningiomas (1,4). In the current study, however, lipids and lactate as the dominant peaks were observed in 5 meningioma cases but micronecrosis was only present in 1 malignant meningioma after tumor histopathological examination. Using 1-tailed Pearson's correlation test, lipids and lactate did not correlated well with meningioma malignancy (Table III). Micronecrosis was not observed in any of the 4/5 meningiomas which demonstrated lipid resonances. Thereby, it is suggested that there is a great possibility that lipid resonances do not correlate with meningioma malignancy as observed in this particular study. Other studies also have detected that lipids were not uncommon among benign meningiomas (17), whereas micronecrosis was rare. Thus, there may be other pathological changes responsible for lipids in benign meningiomas and that probably is microcystic changes or fatty degeneration (14). Lipid accumulation has been observed in microcystic meningiomas that exhibit predominant microcystic changes (14). On the other hand, lipids detected in the lipomatous meningiomas should be attributed to fatty degeneration because of intratumoral adipocyte-like cells (14). It will be valuable though, to investigate whether Cho levels can predict meningioma malignancy together with lipid presence.

There are some limitations in the present study. Firstly, in order to show intense differences in meningioma spectra which are immediately visible during clinical routine, we focused on a qualitative spectral evaluation and not on a quantitative analysis. Thereby, evaluation of lipids and NAA/Cr ratio may have contributions from signals of alanine and Glx, respectively, and also of several macromolecules. Cr concentration levels used as reference for ratio calculation were derived from the pathological region. Cr levels are supposed to be stable among lesions; however, several studies have shown that the Cr concentration tends to decrease with tumor malignancy (1,4). As a result, the calculated ratios of the study that highlighted NAA decrease or Cho increment might have been overestimated. Finally, another factor that needs to be taken into account is that newly diagnosed meningiomas were not separated from recurrent ones, so no metabolic differences between them were taken into account. A study of Shimizu

et al (20), reported that new meningiomas had higher Cho/Cr ratios than did recurrent ones.

The present results indicate the usefulness of ^{1}H-MRS in the differentiation of meningiomas from other solid brain tumors in terms of distinct metabolic features and moreover, whether lipids constitute a useful index to predict meningioma malignancy. Our results can be concluded as follows: i) the presence of a high peak at 3.8 pmm on short TE spectra may provide a distinct metabolic feature for the differentiation of meningiomas among other cerebral lesions. Ala also represents a distinct feature of the metabolic pattern of meningioma, but it only appeared in 30-40% of cases and seems to be dependent on voxel size and positioning. ii) Cho/Cr and Cho/NAA ratios can also be a possible index for meningioma differentiation when long TE is performed. Thus, acquiring both short and long TE spectra would increase metabolic information for differential diagnosis. iii) Lipids and lactate do not always represent an index of micronecrosis, and therefore it cannot be taken as a proof of meningioma malignancy. Especially when voxels are located very close to the skull and mastoid, the spectra may be unavoidably contaminated by lipids due to the chemical shift and the non-square nature of the voxel-select pulses used in the PRESS sequence.

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