New observations concerning the interpretation of magnetic resonance spectroscopy of meningioma

Qiang Yue
Tomonori Isobe
Yasushi Shibata
Izumi Anno
Hiraku Kawamura
Youhei Yamamoto
Shingo Takano
Akira Matsumura

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T. Isobe
Department of Medical Technology, School of Allied Health Sciences, Kitasato University, Minato, Japan

I. Anno
Department of Radiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Abstract This study was aimed to clarify some ambiguities in the interpretation of proton magnetic resonance spectroscopy (1H-MRS) of meningiomas. The cases of 31 meningioma patients (27 benign and 4 nonbenign meningiomas) that underwent single-voxel 1H-MRS (PRESS sequence, TR/TE=2,000 ms/68, 136, 272 ms) were retrospectively analyzed. To verify the findings of in-vivo study, phantoms were measured, and pathological sections of 11 patients were reviewed. All meningiomas demonstrated increased choline and decreased creatine, except for a lipomatous meningioma that only displayed a prominent lipid (Lip) peak. Alanine (Ala) and lactate (Lac) coexisted in eight cases, indicating an alternative pathway of energy metabolism in meningiomas. They partially overlapped with each other and demonstrated a triplet-like spectral pattern, which was consistent with phantom study. Glutamine/glutamate (Glx) was helpful for the recognition of meningioma when Ala was absent. N-acetyl compounds (NACs) were observed in nine cases whose voxels were completely limited within the tumors, indicating that meningiomas might have endogenous NACs. Lac was indicative of an aggressive meningioma, although not always a nonbenign one. Lip not only represented micro necrosis in nonbenign meningiomas, but also reflected microcystic changes or fatty degeneration in benign meningiomas. 1H-MRS reflects some distinctive biochemical and pathological changes of meningiomas that might be misinterpreted.

Keywords Meningioma · Proton magnetic resonance spectroscopy · Phantom · Pathology

Introduction

As the most common tumor arising from meninges, meningioma accounts for approximately 25% of all primary intracranial tumors [1]. Proton magnetic resonance spectroscopy (1H-MRS) is considered to be useful for the diagnosis of meningiomas whose radiological appearance is atypical [2, 3] and may also play a role in the evaluation of the malignant potential [4, 5]. Until now the spectral pattern of meningiomas has been well discussed in the literature. However, controversy exists in several aspects: (1) Alanine (Ala) is considered as the maker of meningioma [3, 6–8], but how can the fact that Ala is not detected in some meningiomas be interpreted? And when Ala is absent,
which metabolite may help to recognize a meningioma? (2) A peak around 2.02 ppm is observed in some meningiomas [2, 6]. Does it represent N-acetylaspartic acid (NAA) resulting from the partial volume effect of brain? (3) Lactate (Lac) and lipid (Lip) are usually taken as proof of nonbenign tumors, indicating intratumoral hypoxia and micronecrosis, respectively [9–11]. Do they represent the same pathological changes and thus also indicate malignancy in meningiomas? This study aimed to answer these questions.

Materials and methods

1H-MRS study of meningiomas

Thirty-one consecutive cases were retrospectively reviewed. The gender ratio of men to women was 11:20, with an average age of 59.7 (25–77) years. Patients who underwent embolization or radiotherapy before 1H-MRS were excluded. All patients received surgery, and intracranial tumors were pathologically proven as meningiomas, including 12 meningotheliomatous, 4 fibrous, 7 transitional, 1 microcystic, 1 secretory, 1 angiomatous, 1 lipomatous, 1 atypical, and 3 anaplastic meningiomas. Anaplastic (WHO grade III) and atypical (WHO grade II) meningiomas were classified as nonbenign group (totally 4 cases); other meningiomas of WHO grade I were classified as benign group (totally 27 cases). This study was approved by the Ethical Committee of the University Hospital, and informed consent was obtained for every case.

All patients underwent MR examination on the Philips Gyroscan NT Intera 1.5-T whole-body MR system (Philips Medical System, The Netherlands) with uniform examination protocol, which is the routine MRS procedure in the University Hospital. MRI plain scan was first carried out in three orthogonal planes to define the volume of interest (VOI). Then single-voxel 1H-MRS was performed using the point-resolved spectroscopy (PRESS) sequence. The voxel size ranged from 10 mm×10 mm×10 mm to 30 mm×30 mm×30 mm (in two cases the voxel size was 10 mm×10 mm×10 mm; in one case the voxel size was 30 mm×30 mm×30 mm. Others were between 1,000–27,000 mm³; the average voxel size was 4,752 mm³) according to tumor size. The parameters of PRESS were as follows: TR/TE = 2,000 ms/68, 136, 272 ms; spectral width = 1,000 Hz; data points = 512; number of signals averaged = 32–128 in metabolites and 16 in tissue water.

Using the standard Philips software, raw spectral data were post-processed, including: zero filling to 1,024 points, Gaussian filtering of 3 Hz and exponential filtering of -1 Hz, Fourier transformation, and manual phase and chemical shift correction with water peak set as the reference. Then metabolite peaks were assigned according to their chemical shifts: choline (Cho) at 3.22 ppm, creatine (Cr) at 3.03 ppm, N-acetyl compounds (NACs) at 2.02 ppm, Ala at 1.47 ppm, Lac at 1.33 ppm, Lip at 0.9/1.3 ppm, α-proton group of glutamine/glutamate (Glx-α) at 3.75 ppm, and β and γ-proton group of glutamine/glutamate (Glx-β and γ) at 2.1–2.5 ppm [12, 13]. Spectral patterns were also used for the assignment: short-TE metabolites such as Lip and Glx were recognized when they appeared on the series of the shortest TE (68 ms) and decreased rapidly on the series of longer TEs (136/272 ms); long-TE metabolites such as Cho and NACs were confirmed through all three series. Ala and Lac were recognized as doublet peaks that demonstrated phase reversal when TE was 136 ms.

Histopathological examination

With a research microscope (Olympus BX51, Olympus Corporation, Japan), histopathological examination was performed on the hematoxylin-eosin (HE) sections of cases that demonstrated Lip on 1H-MRS. These sections were made and preserved from the time of operation. Special attention was paid to find out if there was micronecrosis. Representative parts of the resection were photographed by a microphotographic system (Olympus Corporation, Japan) and reviewed by an experienced pathologist.

1H-MRS study of phantom

To examine the interaction between Ala and Lac observed in meningioma spectra, three kinds of phantoms were prepared and measured: (1) Ala (20 mmol/l) and Cr (10 mmol/l); (2) Lac (20 mmol/l) and Cr (10 mmol/l); (3) Ala (20 mmol/l), Lac (20 mmol/l), and Cr (10 mmol/l). Chemicals used for the preparation of solution were L-alanine, creatine monohydrate and DL-lactic acid (Wako Chemicals Corporation, Japan). Mixed solution was infused into a small glass bottle, and then the small bottle was fixed at the center of a bigger glass bottle infused with physiological saline to produce homogeneous background (Fig. 1a). The measurement equipment and methods were the same as for in-vivo study.

Results

1H-MRS of meningiomas

The lipomatous meningioma demonstrated prominent Lip without any other metabolites. The majority of tumor was hyper-intense on T1-weighted imaging, and the signal intensity was reduced after fat suppression (Fig. 2). Except for the lipomatous meningioma, all meningiomas were characteristic of increased Cho and decreased Cr. Cho was detected in all three series, while Cr was absent or reduced to noise level in 12 cases even when the shortest TE (68 ms) was used.
In eight (one atypical and seven benign) cases, three continuous peaks located from 1.3 ppm to 1.5 ppm were observed. The split points among them were 1.33 ppm and 1.47 ppm, respectively. They appeared as positive peaks when TE was 68 ms or 272 ms, and demonstrated phase reversal when TE was 136 ms. They were assigned to partially overlapped Ala and Lac (Fig. 3).

Ala peaks were observed in 10 cases (32%). Two were isolated peaks, and eight were partially overlapped with Lac. In addition, cases displaying Ala had a significantly bigger voxel size (8.52±7.13 cm³) than cases displaying no Ala (3.91±5.70 cm³) (Mann-Whitney U Test, P < 0.01). In one case Ala and Lac were clearly visible when voxel size was 30 mm×30 mm×30 mm, whereas they were reduced to noise level and could hardly be recognized when the voxel size became 15 mm×15 mm×15 mm (Fig. 3).

Lac peaks were observed in ten cases (32%). Two were isolated peaks, and eight were partially overlapped with Ala. Among these cases were 7 (7/27) benign and 3 (3/4) nonbenign meningiomas. All the seven benign cases demonstrating Lac on 1H-MRS also demonstrated one or more ‘aggressive’ features on MRI, such as mushroom appearance, indistinct margin, and extensive peri-tumoral edema [14, 15] (Fig. 4). These features were rarely observed in benign meningiomas demonstrating no Lac.

Glx was observed in 14 cases (45%). It was confirmed by Glx-α, which appeared as a narrow peak around 3.75 ppm, and its signal intensity decreased rapidly with the prolongation of TE. Glx-β and γ were difficult to recognize because they always demonstrated a broad and flat spectral pattern like baseline distortion (Fig. 5).

NACs were observed in 13 cases (42%). Among them only four cases had a little brain substance involved in their voxels, including two malignant meningiomas that invaded adjacent brain. The other nine cases had their voxels completely limited within the tumors (Fig. 3). On the other hand, among the other 18 cases that did not demonstrate NACs, 4 cases had their voxels contaminated by a little brain substance.

Lip was observed in 11 cases (35%), including 8 benign meningiomas (Fig. 5) and 3 nonbenign meningiomas (Fig. 6). None of their voxels was contaminated by subcutaneous fat. In three cases, Lip overlapped with Lac on short-TE series, while they were separated when TE was 136 ms due to the phase reversal of Lac.

Histopathological results

Among the 11 cases that demonstrated Lip on 1H-MRS, micronecrosis was observed only in two anaplastic meningiomas (Fig. 6). Micronecrosis was not observed in any benign meningiomas. Instead, other pathological changes that might account for Lip were observed, including microcystic changes and fatty degeneration. Microcystic changes were observed in four benign meningiomas as intracellular vacuoles. One of them was microcystic meningioma that exhibited microcystic changes throughout the section (Fig. 5). The other three, although not diagnosed as microcystic meningiomas, exhibited scattered microcystic changes within the tumors. Fatty degeneration was confirmed in the lipomatous meningioma, which exhibited lots of adipocyte-like cells besides meningotheliomatous cells (Fig. 2).

1H-MRS of phantom

Both Ala-Cr phantom and Lac-Cr phantom demonstrated doublet peaks from 1.3 ppm to 1.5 ppm. They were positive peaks when TE was 68 ms or 272 ms, and demonstrated phase reversal when TE was 136 ms. The doublet peaks of Ala were located at 1.53 ppm and...
Fig. 2 Lipomatous meningioma. A 76-year-old female with a parasellar mass: MRI (a T1WI; b T2WI with fat suppression; c gadolinium-enhanced axial T1WI; d enhanced coronal T1WI; e enhanced coronal T1WI with fat suppression) demonstrates the peripheral part of tumor is hyperintense on T1WI and the signal intensity is reduced after fat suppression (arrow in b, e). It demonstrates prominent Lip signal on 1H-MRS (TE=136 ms) without any other metabolites visualized (f). The HE section (g, magnification, ×100) exhibits lots of adipocyte-like cells (arrows) besides meningotheliomatous cells.
1.34 ppm, respectively. The split point between them was at 1.47 ppm (Fig. 1b). The doublet peaks of Lac were located at 1.44 ppm and 1.34 ppm, respectively. The split point between them was at 1.38 ppm (Fig. 1c). Therefore, the right peak of Ala doublet and the left peak of Lac doublet shared an interval of chemical shift.

Ala-Lac-Cr phantom demonstrated three continuous peaks like a triplet located at 1.53 ppm, 1.44 ppm, and 1.34 ppm, respectively. The split points between them were at 1.50 ppm and 1.38 ppm, respectively (Fig. 1d). There were also positive peaks when TE was 68 ms or 272 ms, and these were inverted to negative peaks when TE was 68 ms or 272 ms.
136 ms. Therefore, they were recognized as the result of partial overlapping between Ala and Lac. This spectral pattern was quite similar to that of in-vivo study.

**Discussion**

Ala was suggested by various studies to be the maker of meningioma because it was common in meningioma, but rarely found in other intracranial tumors [3, 6–8]. However, reported occurrence of Ala varied greatly according to different studies, from 0/6 [16] to 21/23 [2]. Our study demonstrated that the variance may arise from two aspects: the overlapping between Ala and Lac, and the voxel size.

As shown by our study, both Ala and Lac spectra were affected by the J-coupling effect, and on a 1.5-T MR scanner, their resonance peaks split as doublets, which were located so closely that the right peak of the Ala doublet and the left peak of the Lac doublet shared an interval of chemical shift. They partially overlapped with each other and formed three continuous peaks like a triplet when they existed together. Similar changes were observed by other in-vivo studies on meningiomas [2, 17–20] and abscesses [20, 21]. However, none of these studies had verified their interpretation by phantom study. Our study demonstrated that Lac and Ala interacted in the same way in phantom as in meningiomas; therefore, such interpretation was reasonable. Overlapping between Ala and Lac should be ascribed to limited magnetic field intensity instead of measurement methods, because different measurement methods yielded similar results [17–21], whereas Ala and Lac were completely separated when the magnetic field intensity was increased [20]. This phenomenon is meaningful for 1H-MRS. On one hand, when the resonance signal of either metabolite is weak, it may be overshadowed by its stronger rival and thus may be underestimated. On the other hand, quantitative measurement of one metabolite should carefully exclude the contribution from the other; otherwise, the metabolite concentration may be overestimated.

Another factor that may explain the variance of Ala is the voxel size. The in-vitro study by Christiansen [22] demonstrated that metabolite signal on 1H-MRS correlated significantly with concentration (correlation coefficient = 0.99) and selected voxel size (correlation coefficient = 1). Although Ala increases in meningiomas, its concentration...
still remains fairly low when compared with other metabolites like Cho [7]. Thus, voxel size will have significant influence on the detection of Ala. We assumed that a larger voxel would produce stronger metabolite signal and consequently yield better signal-to-noise ratio (SNR) and more sensitive detection of Ala. This was consistent with our findings: Ala-positive cases had a significantly bigger voxel size than Ala-negative cases; in one case the Ala peak changed from a visible to invisible level when voxel size was reduced. Therefore, when voxel size is limited because a meningioma is small or heterogeneous, it is not surprising that Ala can not be detected.

The resonance peaks of Glx are contributed from its α, β, and γ proton groups, respectively. Glx-α peak is easier
to define because it usually appears as a narrow peak around 3.75 ppm. In contrast, Glx-β and γ peaks usually demonstrate a broad and flat appearance like baseline distortion [17]. Glx was recognized in 14 (45%) cases in this study. Other studies also revealed a higher occurrence of Glx in meningiomas than in other intracranial tumors [3]. Quantitative 1H-MRS studies also revealed increased Glx concentration in meningiomas as compared with other
intracranial tumors [6, 23]. Therefore, although Glx is not a unique metabolite of meningiomas, it may play a supplementary role for the recognition of meningiomas when Ala is absent or ambiguous. NAA is the major contributor of the peak at 2.02 ppm in normal brain. It is present within neurons and usually taken as the maker of neurons [12, 24]. Theoretically, tumors arising outside the central nervous system contain no NAA [10, 25]. This is consistent with previous in-vitro analysis of meningioma extracts that did not detect NAA [7, 26, 27]. However, in-vivo 1H-MRS did demonstrate a small peak around 2.02 ppm in some meningiomas according to this study and others [2, 6, 28]. It was usually assigned to NAA and ascribed to the partial volume effect of brain. This may account for some of our cases whose voxels enclosed a little brain substance. However, this is not able to explain other cases whose voxels were completely located within the tumor. On the other hand, although some cases had their voxels contaminated by brain substance, they did not demonstrate NAA peaks. This indicated that partial volume effect was too weak to produce sufficient NAA signals. Therefore, there should be some other metabolites that contributed to the peak around 2.02 ppm. They should not be short-TE metabolites because the small peak still remained at long-TE series. They should also be NACs. Possible candidates include N-acetylaspartylglutamate, N-acetylnorleucaminic acid, N-acetylgalactosaminic acid, and some other unknown NACs that contribute to the peak around 2.02 ppm on in-vivo spectra, but decrease to an undetectable level on in-vitro spectra [29–31]. In sum, a peak around 2.02 ppm on meningioma spectra collected using long TE not only represents NAA produced by the partial volume effect of brain, but also represents other endogenous NACs of meningioma.

Evaluation of tumor malignancy by 1H-MRS usually involves the analysis of Lac and Lip. Lac is the product of anaerobic glycolysis, and Lip indicates intra-tumoral necrosis. Both metabolites were reported to correlate with tumor grade [9–11, 32]. Our study demonstrated that this method is sometimes, but not always, applicable for meningioma. In our study Lac was more frequently visualized in nonbenign meningiomas (3 of 4 cases) than in benign meningiomas (7 of 27 cases), and benign cases demonstrating Lac behaved more ‘aggressively’ than benign cases demonstrating no Lac. These findings indicate that Lac is indicative of an aggressive meningioma, but not always a nonbenign one. This is consistent with Shino’s study [4], but disputes Demir’s [2]. The controversy may arise from the interpretation of the production of Lac. Based on our finding that Lac was always accompanied by Ala in benign meningiomas, we hypothesize that transamination between Ala and α-ketoglutarate, instead of glycolysis, may account for Lac in benign meningiomas. This pathway produces pyruvate and glutamate. Pyruvate is converted to Lac by Lac dehydrogenase, and glutamate may act as an alternative energy source in meningioma by partial oxidation [3, 33–35]. This alternative pathway may meet the mildly increased energy demands in benign, but somewhat ‘aggressive’ meningiomas. After malignant transformation, however, Ala may be quickly exhausted, and glycolysis may play a major role for vast energy supply. Recent study provided proof that there was genetic and metabolic difference between clinically aggressive grade I meningiomas and clinically benign grade I meningiomas; in particular, Ala was decreased in aggressive meningiomas [36]. These findings are in favor of our hypothesis.

Previous study demonstrated the correlation between Lip and micronecrosis and concluded that micronecrosis was highly indicative of nonbenign meningiomas [4]. In our study, however, Lip represented micronecrosis only in nonbenign meningiomas. Micronecrosis was not observed in any benign meningioma demonstrating Lip. Consistently, other studies also found that Lip was not uncommon among benign meningiomas, whereas micronecrosis was very rare [3, 37]. So there should be some other pathological changes responsible for Lip in benign meningiomas. Our study demonstrated that they might be microcystic changes or fatty degeneration. Lipid accumulation has been observed in microcystic meningiomas that exhibit predominant microcystic changes [38]. Although microcystic meningioma is a rare subtype, scattered microcystic changes are not uncommon in meningiomas [3]. Therefore, Lip detected in these cases should be ascribed to microcystic changes instead of micronecrosis. On the other hand, Lip detected in the lipomatous meningioma should be attributed to fatty degeneration. It is called ‘fatty degeneration’ because intratumoral adipocyte-like cells are not real adipocytes, but ‘lipidized’ meningioma cells [39]. To our knowledge, it is the first 1H-MRS report of a lipomatous meningioma. In sum, Lip does not only represent micronecrosis, and therefore it cannot always be taken as proof of a nonbenign meningioma.

There are several limitations to our study. First, from a technical perspective, the TEs we used were not short enough for the detection of short-TE metabolites, such as Glx and Lip, and the strong filtration we used might affect the identification of Ala doublet, so these metabolites might be underestimated. A prospective study using shorter TE (e.g., 30 ms) and different filtration should be carried out to evaluate their influence. Secondly, we did not quantify metabolites because overlapping between Ala and Lac at 1.3–1.5 ppm, or between Glx and other metabolites (gamma-aminobutyric acid, N-acetylaspartylglutamate, glutathione, etc.) at 2.1–2.5 ppm, could not be avoided at 1.5 T. So we focused on the qualitative analysis of meningioma spectra. We expect a study at higher field could provide better resolution and thus more reliable quantification of these metabolites. In addition, we were not able to prove the existence of Lip in meningiomas by special stain, because Lip was mostly decomposed in paraffin-embedded specimen. We expect a prospective
References

18. Manton DJ, Lowry M, Blackband SJ et al (1994) Quantitative proton MRS of brain tumors reveals increased choline/NAA, and therefore may produce a resonance peak around 2.02 ppm even when the spectral voxel is not contaminated by brain.

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