NTRACRANIAL meningiomas are frequently occurring tumors that grow slowly and usually are amenable to surgical treatment. Nevertheless, 5 to 20% of meningiomas display atypical features and 1.4 to 11.1% display malignant histological features. These nonbenign meningiomas grow rapidly, invade adjacent brain, tend to recur, and, sometimes, result in a poor outcome despite aggressive treatment. Patients in whom a meningioma is found incidentally on imaging studies sometimes may be followed clinically without surgical intervention. Reliable noninvasive preoperative evaluation of tumor grade is, therefore, a very important goal.

Computerized tomography (CT) and magnetic resonance (MR) imaging are generally excellent studies to facilitate the diagnosis of meningiomas. Although these imaging modalities also contribute to an assessment of malignancy or tumor grade, they have only a limited usefulness for evaluation of tumor growth rate. MR spectroscopy offers a more accurate means of estimating these tumors’ growth rate. An immunohistological method of identifying cell proliferation by using MIB-1 antibody staining has proved very useful for evaluating proliferative and malignant potentials in tumor specimens. In the present study we used an MIB-1 staining index (SI) as a standard for evaluating the usefulness of preoperative MR spectroscopy in determining the proliferative potential of meningiomas. We also used MR spectroscopy to evaluate specific characteristics of atypical meningiomas.

Clinical Material and Methods

Patient Population

Participants in the study were recruited from among 62 patients with meningiomas who were admitted to the Department of Neurosurgery at Shiga University of Medical Science from August 1990 to March 1992 and from September 1993 to December 1998. A total of 32 patients...
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with meningiomas large enough for MR spectroscopy assessment were enrolled in this study. Of the 32 patients, three had postoperative tumor recurrences. One of these three patients was studied twice, once at the time of initial presentation and again at tumor recurrence. The study was approved by the university ethics committee and a written explanation of its objectives and methodology was provided to all patients and their families. Tumors were surgically excised in all patients. To reduce intraoperative bleeding, seven patients underwent preoperative embolization in which 50- to 200-μm polyvinyl alcohol particles were superselectively introduced into the tumor’s feeding vessels via a microcatheter.

Magnetic resonance imaging and MR spectroscopy were performed using a 1.5-tesla whole-body MR imaging device with a conventional birdcage head coil. Patients who had received any previous radiotherapy or chemotherapy were excluded from this study. The imaging protocol included T1-weighted spin-echo images (TR 500 msec, TE 10 msec) with and without intravenous injection of 0.2 ml/kg gadolinium (Gd)-diethylenetriamine pentaacetic acid (DTPA) as well as T2-weighted images (TR 2400 msec, TE 100 msec). To minimize the effects of T2 relaxation in which 50- to 200-μm polyvinyl alcohol particles were used, resulting in excellent water suppression factors.

To invert the doublets with spin–spin coupling at approximately 7.35 Hz. Proton MR spectra of meningiommas usually show a prominent Cho resonance, whereas the Cr signal is small. A short TE is advantageous for detection of Cr and aliphatic signals because the T1 of these compounds is shorter than that of others. At a short TE, a sufficient signal is available and the phase and amplitude errors associated with J modulation of signal intensity are minimized.

Proliferative potentials evident in excised meningiomas were studied using MIB-1 antibody staining against the Ki-67 antigen. Details of how the MIB-1 SI was determined are described elsewhere. Briefly, paraffin sections cut at a 5-μm thickness were deparaffinized and incubated with MIB-1 antibody and developed with diaminobenzidine. The MIB-1 SI was calculated as the percentage of MIB-1–positive cells among all tumor cells in the microscopic fields examined. At least 2000 tumor cells were counted in randomly chosen fields and the percentages of positively staining cells were calculated.

Statistical Analysis

Statistical analyses, including establishment of a regression line, calculation of a correlation coefficient, and determination of significance of regression between the MIB-1 SI and Cho/Cr values, were performed using commercially available computer software.

Sources of Supplies and Equipment

The MIB-1 antibody was purchased from Immunotech (Marseille, France) and the LSAB kit used to immunostain the specimens was obtained from Dako Corp. (Carpinteria, CA). The manufacturer of the MR imaging device was General Electric Medical Systems (Milwaukee, WI). Statistical analysis was performed using StatView IV statistical software available from Abacus Concepts (Berkeley, CA), which was installed on a Macintosh computer manufactured by Apple Computers, Inc. (Cupertino, CA). Data were extracted and processed using Omega software (version 6.0.2), which was provided by General Electric and installed on a Sun Sparc 10/30 workstation manufactured by Sun Microsystems (Mountain View, CA).

Results

No definite signal peak could be identified in three of
the 32 cases evaluated by MR spectroscopy. Data obtained in these three patients were excluded from further consideration. One patient who had a tumor recurrence approximately 1 year after the first operation underwent MR spectroscopy twice, at the time of initial symptoms and at the time of tumor recurrence. Thus, we evaluated 30 MR spectroscopy studies in 29 patients. Meningioma was diagnosed in all patients on the basis of surgically excised tissue specimens. The 29 patients (10 men and 19 women) ranged in age from 22 to 81 years (mean \( \pm \) standard deviation [SD], 57.6 \( \pm \) 14.1 years).

**Histopathological Diagnosis**

We used the histopathological classification of meningioma subtypes that was established by the World Health Organization in 1993. Specimens obtained before 1993 were reclassified in accordance with 1993 criteria. The numbers of patients with each subtype were as follows: meningothelial, 13; fibrous, three; transitional, four; angiomatous, four; chordoid, one; atypical, four; and papillary, one. Atypical (Grade II) and papillary (Grade III) meningiomas comprised the nonbenign group, whereas the other subtypes comprised the benign group. The recurrent tumor studied by MR spectroscopy twice was atypical. Necrosis was demonstrated histologically in four of the five meningiomas classified as either atypical or papillary. No meningiomas in the benign group, with the exception of those cases in which preoperative embolization was performed, showed any necrosis on histopathological examination. The subtypes of the three recurrent meningiomas did not change.

**Results of MR Spectroscopy**

A Cr signal at 3 ppm and a Cho signal at 3.2 ppm were present in all 30 MR spectroscopy studies. In 26 of the 29 patients, an overlapping glutamate/glutamine multiplet was present at 2.3 to 2.5 ppm. An alanine signal was observed in 12 cases and a lactate signal in five. An undefined signal at 1.9 ppm was thought to represent acetate.

The mean Cho/Cr ratio was 7.85 \( \pm \) 3.23 in nonbenign meningiomas and 2.56 \( \pm \) 1.26 in benign meningiomas. Statistical analysis confirmed a significantly higher Cho/Cr ratio in the nonbenign meningiomas (p = 0.0002, Mann–Whitney U-test).

In five tumors, a signal at 1.3 ppm represented a singlet from methylene (CH\(_2\)). Four of these five tumors were atypical meningiomas and necrotic foci were found during histopathological examination. The remaining tumor was angiomatous. Because preoperative embolization had been performed in the latter case, determination of whether the necrosis had been present before embolization was not possible. A doublet signal of lactate was present in five tumors: two of these were meningothelial, whereas the other three were nonbenign.

**Fig. 1.** Scatterplot showing the regression line for the Cho/Cr ratio and MIB-1 SI. Open and closed circles represent benign and nonbenign meningiomas, respectively. Meningiomas demonstrating a methylene signal are marked by an asterisk. The hatched lines represent the 95% confidence interval. The MIB-1 SI values are percentages.

**Fig. 2.** Representative series of spectra in a meningioma before embolization and 1, 5, and 8 days after embolization. The lactate signal increased immediately after embolization of feeding vessels and gave place to a methylene signal several days later. Choline-containing compounds and Cr signals decreased immediately after embolization, although the glutamine/glutamate and methyl signals did not. These spectra were obtained with a TE of 19 msec and were averaged from 128 acquisitions.
Comparisons Between the MIB-1 SI and MR Spectroscopy Findings

Because the MIB-1 SI is affected by tissue changes following embolization, seven cases in which preoperative embolization had been performed were excluded from the MIB-1 SI data analysis. The remaining 23 meningiomas, representing 22 cases, were evaluated with respect to the MIB-1 SIs. The MIB-1 SIs of histopathologically benign meningiomas ranged from 0.15 to 4.58% (mean ± SD 1.34 ± 1.32%). The MIB-1 SIs of the atypical and papillary meningiomas ranged from 2.43 to 4.63% (mean ± SD 3.46 ± 0.95%). In the nonbenign group the MIB-1 SI was significantly higher than that in the benign group (p = 0.0041, Mann–Whitney U-test).

Figure 1 depicts the regression line for the Cho/Cr ratio in meningiomas compared with the MIB-1 SI; the correlation coefficient was 0.74 (p < 0.001), indicating a significant linear correlation. In the patient with a recurrent atypical meningioma, the MIB-1 SI and the Cho/Cr ratio at initial presentation were 2.43% and 7.2, respectively; at the time of recurrence they were 4.63% and 13.9, respectively. Both the MIB-1 SI and the Cho/Cr ratio were approximately 1.9 times higher at the time of recurrence than at initial presentation.

Figure 2 shows the time course of spectrum evolution after embolization in a representative case. Immediately after embolization, a lactate signal appeared and Cho and Cr signals decreased. On Days 5 to 8 an MR spectroscopy–detectable aliphatic signal indicating mobile lipid was seen. Histopathological examination revealed intratumor necrosis caused by embolization.

Discussion

Preoperative prediction of meningioma grade is clinically important. Jääskeläinen and colleagues have reported 5-year recurrence rates for benign, atypical, and malignant meningiomas of 3%, 38%, and 78%, respectively, following complete surgical excision. Other authors have reported similar high rates of recurrence for
high-grade meningiomas. Therefore, if preoperative examinations suggest a high grade, surgical planning and procedures should address a suspected malignant lesion, including wider resection margins and adequate intraoperative biopsy of the margins. Conversely, if the tumor appears to have a very low proliferative potential, partial excision may sometimes achieve a satisfactory postoperative course, especially in elderly patients.

The antibody MIB-1 “recognizes” nuclear antigens appearing in cell cycle phases other than G0. The MIB-1 positivity rate is thought to be nearly equal to the fraction of the tumor that is actively growing. The statistically significant correlation between the Cho/Cr ratio measured by MR spectroscopy and the MIB-1 SI demonstrated in this study suggests that MR spectroscopy is a useful noninvasive method for predicting the proliferative potential of meningiomas. Reports to date concerning CT and MR imaging indicate that absence of calcification, heterogeneity, neous enhancement, intratumoral necrosis, irregular margins, and a mushrooming pattern are frequent findings, suggesting a nonbenign meningioma. However, these neuroimaging patterns, even together with findings from angiography, are not sufficient in themselves to predict the malignancy of meningiomas. Magnetic resonance spectroscopy provides additional information useful to diagnosis by virtue of its biochemical ability to predict the proliferative potential of tumors. As shown by the case represented in Fig. 3, a meningioma that appears to be benign according to MR imaging may nonetheless prove to be atypical. In such cases, MR spectroscopy offers a more accurate means of predicting the tumor’s proliferative potential.

Resonance at 3.2 ppm is a signal that can represent various metabolic products including trimethylamine groups. Reported metabolites include glycerophosphocholine, phosphocholine, free choline, chlordiazepoxide choline, acetylcholine, and, sometimes, phosphatidylcholine. Abundant in cell membranes, phosphatidylcholine is not generally detectable by MR spectroscopy. Free choline, phosphocholine, and glycerophosphocholine are major contributors to the peak at 3.2 ppm observed in vivo proton MR spectroscopy of human brain tumors. These compounds are the metabolites produced during biosynthesis and catabolism of cell membranes. The main pathways of free choline involve synthesis of acetylcholine and phosphocholine, and the latter is used to synthesize phosphatidylcholine via the Kennedy pathway. The concentration of Cho that is visible on proton MR spectroscopy is thought to correlate with increased membrane biosynthesis and/or increased cellularity. In gliomas, several reports have shown a correlation between high concentrations of Cho and malignancy when necrotic areas can be excluded from the VOI. One reason for the positive correlation between the MIB-1 SI and the Cho/Cr ratio in our study is probably an increased pool of Cho involved in membrane turnover.

The major contributor to 3-ppm resonance detectable on MR spectroscopy is Cr. Because neurons and muscle consume adenosine triphosphate at a high rate, phosphocreatine, a temporary storage form of high-energy phosphate, is abundant in these cells. In contrast, the total Cr concentration of meningiomas is only approximately one fifth of that found in normal brain. This results in difficulty in obtaining an adequate Cr signal from meningiomas, but the short TE of 19 msec used in this study elicited a sufficient Cr signal. The Cr peak sometimes is used as an internal standard because it is relatively stable despite various diseases. However, in tumors, total Cr is decreased relative to nonneoplastic tissues. Rat meningioma cells show an increased phosphocholine concentration and decreased Cr concentration in comparison with human meningiomas. Similarly, the Cr concentration in human gliomas is also lower than that in normal brain. In addition, Cr concentration reportedly tends to decrease, correlating with the increasing degree of malignancy. These observations suggest that decreased Cr concentrations also contributed to the increased Cho/Cr ratios that we have observed. Semiquantitative measurement using external standards will help clarify the influence of changes in individual substances on the overall increased Cho/Cr ratio. Unfortunately, this will extend the time required to study each patient by 50%.

The most likely source of the methylene (CH2) signal at 1.3 ppm in meningiomas is mobile lipid. The intensity of this aliphatic signal has been found to correlate with the extent of necrosis and tumor malignancy. All meningioma cases showing this aliphatic signal in the present study demonstrated necrosis during the histological examination, whereas no necrosis was found in any meningioma from which no methylene signal was detected by MR spectroscopy. This signal also was seen in embolized meningiomas with resulting necrosis. As shown in Fig. 2, a lactate signal appeared immediately after embolization and was superseded by a methylene signal after 3 to 4 days. Production of lactate occurs only when viable cell metabolism is underway in the form of anaerobic glycolysis, which suggests an ischemic change in the tumor. The cell is likely to die from ischemia and the spectral change from the lactate to methylene signal may reflect this event.

Without prior embolization, the presence of necrosis is highly suggestive of tumor malignancy. In the present study, MR spectroscopy showed promise as a clinically important means of detecting tumor necrosis, which sometimes is missed by conventional imaging studies. Histopathological examination revealed intratumoral necrosis in four of our meningioma cases, whereas routine imaging findings in these four cases failed to reveal any necrosis and appeared consistent with a benign diagnosis. Nevertheless, MR spectroscopy examination of these meningiomas detected the presence of mobile lipid and high Cho/Cr ratios and, subsequently, tissue sections of these tumors were found to contain scattered areas of microcrosis. One reason that necrotic change in a meningioma is difficult to detect reliably by using conventional neuroimaging is that, in themselves, inhomogeneous imaging patterns do not necessarily indicate tumor necrosis or malignancy.

The presence of lactate represents a precursor stage leading to tumor necrosis. However, two of the five meningiomas in which lactate was detected proved to be benign on histopathological examination. Thus, the presence of lactate does not necessarily preclude that the tumor is benign. Nonetheless, the MIB-1 SIs in the two benign meningiomas showing lactate signals on MR spectroscopy were 2.95% and 2.3%, respectively—values exceeding mean MIB-1 SIs for the benign group as a whole.
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One of these two meningiomas has not recurred for 2 years, but the other recurred after 1 year. The presence of lactate, therefore, is suggestive of an increased tumor proliferation rate. Although signals of mobile lipid and lactate sometimes can be distinguished from each other on MR spectroscopy, it is important to note that not infrequently these signals are very difficult to separate completely.

Glutamate concentrations in human meningiomas are reported to be three times higher than those in rat meninges. In the present study, most of the meningiomas showed signals ranging from 2.1 ppm to 2.6 ppm, which were thought to be derived from glutamine and glutamate. However, no definitive correlation emerged between these signals and tumor malignancy. Interestingly, although the presence of an alanine signal is fairly specific for meningiomas, our study demonstrated that the absence of such a signal on MR spectroscopy does not exclude the presence of a meningioma. Furthermore, the presence of alanine did not correlate with the proliferation potential of meningiomas.

Conclusions

Both the MIB-1 SI and histological grade of meningiomas could be predicted by noninvasively measuring the Cho/Cr ratio with proton MR spectroscopy. A methylene signal on proton MR spectroscopy correlated highly with Cho/Cr ratio with proton MR spectroscopy. A methylene signal could be predicted by noninvasively measuring the Cho/Cr ratio with proton MR spectroscopy. A methylene signal could be predicted by noninvasively measuring the Cho/Cr ratio with proton MR spectroscopy.

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