In Vivo Proton Magnetic Resonance Spectroscopy of Human Spinal Mass Lesions

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Objective: To observe metabolic differences between spinal tumor and other diseases in human spinal mass lesions, in vivo ^{1}H magnetic resonance spectroscopy (MRS) was attempted to obtain metabolic signals in patients with various spinal mass lesions.

Methods: ^{1}H nuclear magnetic resonance (NMR) spectra were obtained from 14 patients before surgery using a receive-only surface coil on a 1.5 T clinical magnetic resonance imaging (MRI) unit. MRS findings were compared with the histopathologic results from biopsy. In addition, tumor spectra were compared with the spectra of other benign diseases including disc herniation, which can mimic spinal cord tumor. In vitro ^{1}H-NMR spectra were also collected from perchloric acid extracts of some spinal tumors.

Results: Typical water resonance line widths were in the 6- to 10-Hz range, but the metabolic signals observed were sufficiently resolved to be assigned from comparison with the ^{1}H spectra of brain tissue. Choline was detected in all tumor spectra (n = 6) except ependymoma, whereas it was absent in other benign diseases including disc herniation (mimicking spinal cord tumors), dermoid cyst, tuberculosis, and non–multiple sclerosis myelitis. Spectral patterns of meningiomas, schwannomas, metastasis from renal cell carcinoma, and ependymomas in the spinal cord were similar to those of central nervous system (CNS) tumors. It was not possible to observe distinctive metabolic differences between benign diseases owing to relatively larger line broadening of some signals compared with that in CNS tissue.

Conclusions: It appeared that acquisition of in vivo ^{1}H-NMR signals was possible in human spinal mass lesions on a 1.5 T clinical MRI unit. Detection of choline only in the spinal tumors may indicate that there is some potential in using in vivo ^{1}H-MRS to distinguish spinal tumors from disc herniation mimicking spinal cord tumors, non–multiple sclerosis myelitis, and dermoid cysts. On the basis of our NMR findings, however, it was not possible to distinguish between benign diseases.

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Despite the potential of magnetic resonance spectroscopy (MRS), few studies of the vertebrate spinal cord have been undertaken.[1–6] This can be attributed largely to the relatively small size of the spinal cord and physiologic pulsation motion at some spinal level sites, which in turn limits our ability to acquire nuclear magnetic resonance (NMR) spectra with adequate signal-to-noise ratio. In particular, only one in vivo study has been reported using ^{31}P-NMR in animals.[6]

Magnetic resonance imaging (MRI) has been instrumental in helping clinicians to diagnose soft tissue lesions correctly, but MRI is still not completely accurate. A number of cases of disc herniation mimicking neural tumor have been reported, both for the lumbar spine and for the thoracic spine.[7–14] It appears that a definitive diagnosis for a spinal lesion cannot be made by conventional radiographic or MRI evaluation alone. Histologic evaluation at the time of surgery is the only way to verify the diagnosis. Application of MRS methodology to such a small tissue sample is unique. Unlike conventional proton MRI, which provides structural information based on signals from tissue water, proton MRS provides localized chemical information, thus providing a noninvasive biochemical assay of tissue in the selected region of pathologic spinal tissue. However, such studies have been subject to problems originating from poor spatial localization and sensitivity, whereas MRS study of brain was relatively well established as a clinical modality. It is thus challenging to acquire in vivo ^{1}H-NMR spectra from human spinal cord lesions. In this report, we present in vivo ^{1}H-NMR spectra that were acquired using a surface coil and obtained from the spinal mass lesions of several patients.

MATERIALS AND METHODS

Patients

Fourteen untreated spinal mass lesions were examined by ^{1}H-MRS before surgery. Three patients were studied to dis-

tinguish tumor from disc herniation with degeneration, and one patient was studied to rule out cyst or abscess from mass-like lesion. Six patients were studied to confirm the presence of tumors diagnosed from MRI alone. The histologic types of the lesions were confirmed by intraoperative biopsy after obtaining proton MR spectra. Normal spinal cords from volunteers (n = 2) and from disc herniation (n = 3), tuberculosis (n = 1), chronic epidural abscess (n = 1), non–multiple sclerosis (non-MS) myelitis (n = 1), meningioma (n = 1), schwannomas (n = 3), ependymomas (n = 1), metastases from renal cell carcinoma (n = 1), and dermoid cyst (n = 2) were examined.

Imaging and Spectroscopy

All studies were performed on a 1.5 T Signa clinical MR unit (General Electric Medical Systems, Milwaukee, WI) using a flexible surface coil to receive and body coil to transmit. The general-purpose Signa flex coil design is a linear, receive-only flexible coil consisting of two 13 × 17–cm loops that are serially connected to a co-rotating "saddle coil" pair, configured to form a figure-8 coil circuit. The coil was secured over the back area of patients in supine position. Localizing imaging was obtained by T1-weighted images (repetition time [TR]/echo time [TE]: 489/15 milliseconds, two excitations, matrix size 256 × 192) and T2-weighted images (TR/TE: 4,000/105 milliseconds, one excitation, matrix size 256 × 192) using spin echo and fast spin echo sequences, respectively, on the sagittal or axial plane.

A volume of interest of 0.6–1.3 cm^3 was selected from the center of the lesion with edges of the voxel well within the mass, and the field homogeneity achieved in local shimming resulted in water peak line widths of typically 6–10 Hz. Localized single-voxel proton MRS was performed using stimulated echo acquisition mode[15] (STEAM; TE/TR: 30/2,000 milliseconds) with three chemical shift-selective pulses (CHESS) and subsequent spoiling gradient for water suppression. The bandwidth of the CHESS pulses was 60–75 Hz. The second half of the spin echo was collected using 2,048 data points, a spectral width of 2,000 Hz, with 196–256 acquisitions typically. Time domain data, transferred to a Sun workstation (Palo Alto, CA) and processed with SAGE software from MRI, were zero-filled to 4,096 points, multiplied with exponential or Gaussian exponential function (line broadening, typically 2.5–4.5 Hz), Fourier transformed, phase corrected, and referenced to residual water resonance at 4.7 ppm. The baseline was corrected with a linear tilting algorithm in some cases. Other metabolic peaks were compared with those of normal brain tissues given in the literature.[16,17]

Tissue Extraction and In Vitro NMR Spectroscopy

For some of the tumors, part of the sectioned tissue for biopsy was extracted using the perchloric acid method.[18] A deuterated sample was prepared by dissolving the extracted material in 500–700 μL of D_2O. High-resolution NMR spectra were acquired using a 300- or 500-MHz Varian NMR spectrometer (Palo Alto, CA).

RESULTS

The ^1H spectrum in Figure 1 was obtained from the spinal cord of a healthy volunteer, near L1. We detected *N*-acetyl aspartate, unresolved creatine/choline at 3.0–3.3 ppm, glutamate/glutamine (Glx) at 2.2–2.5 ppm, and signal mixture of myo-inositol with Glx at 3.5–3.8 ppm. In addition, the signal mixture with lipids was relatively widespread at 0.0–1.9 ppm. Line broadening from water resonance in the spinal cord lesion was in the range of 6–10 Hz. The signals detected were assigned by comparing them with the metabolites of brain tissue. The results are summarized in Table 1. In the disc herniation, we observed lipid resonance for only three such patients, as demonstrated in Figure 2. In the dermoid cyst, we found lipids mixed with lactate. Lactate was clearly observed at 4.18 and 1.33 ppm in one cyst, as shown in Figure 3. One patient was diagnosed as having chronic epidural abscess on the lumbar spine, whereas the other patient had transverse myelitis without MS. Choline was not detected in these patients, whereas lipids and unassigned resonances, probably amino acids or degraded lipids, were similarly observed at 0–2.5 ppm in both patients. In the patient with tuberculosis, a very large lipid/lactate mixture was accompanied by a broad but low signal in the region of Glx resonance. Clear resonance assignments in this spectrum were hindered by extensive line broadening.

Two cases of schwannomas demonstrated that myo-inositol was enhanced. The in vivo spectrum was compared

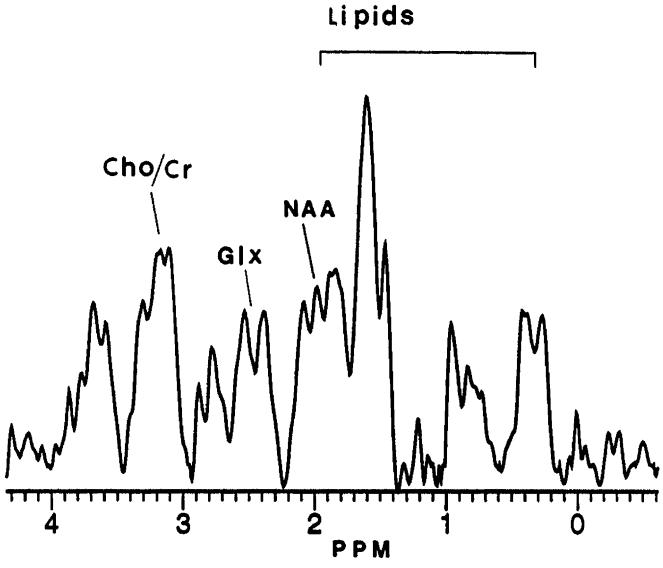

FIGURE 1. STEAM ^1H-NMR spectrum of normal spinal cord.

TABLE 1. Results of Biopsy and Metabolic Features from MRS Studies

Patient No.	Diagnosis*	Biopsy Result	MRS Findings		
			Cho	Lipids/Lactate	Others
1	Mass vs cyst	Dermoid cyst	−	+	
2	Disc herniation vs tumor	Disc degeneration	−	+	
3	Tuberculosis vs abscess	Tuberculosis	−	++	Glx
4	Disc herniation vs tumor	Disc degeneration	−	+	
5	Disc herniation vs tumor	Disc degeneration	−	+	
6	R/o tumor	Chronic epidural abscess	−	+	
7	Mass vs cyst	Dermoid cyst	−	+	
8	Myelitis	N/C	−	+	
9	Ependymoma	N/C	−	+	Glycine↑
10	Schwannoma	Meningioma	+	+	Alanine
11	Tumor	Schwannoma	+	+	mI↑
12	Schwannoma	Schwannoma	+	+	mI↑
13	Metastasis	Renal cell carcinoma	+	+	Glx
14	Tumor	Schwannoma	+	+	Glx↑

*Diagnosed by MRI alone or clinically.
Cho, choline; Glx, glutamine/glutamate; N/C, not confirmed as surgery was not performed; mI, myo-inositol.

with the in vitro NMR spectrum of the tissue extraction obtained from surgical section (Fig. 4). One intramedullary lesion around C5 was suggested to be ependymoma. In this patient, glycine was detected at 3.45 ppm, whereas choline was absent, as demonstrated in Figure 5. Another resonance at 2.12 ppm appeared to be due to lipid rather than Glx, as no accompanying downfield resonance was detected at 3.8 ppm. In the spectrum of one meningioma, enhanced Glx and choline were detected in conjunction with alanine, as shown in Figure 6. A metastatic tumor from renal cell carcinoma also showed enhanced Glx and choline with a large lipid signal.

DISCUSSION

It took around 30 minutes to completely examine a spinal mass lesion of a patient, including scout imaging and two MRS acquisitions. Separate spectral processing took 5 minutes including data transfer to a workstation. As a MRS voxel was given by only square or rectangle type, it was difficult to include a region of interest on normal spinal cord fully within a cursor on any imaging plane. Hence, it may produce potential partial volume effect or signal contamination from surrounding tissue. In contrast, this difficulty was not the problem in the relatively large spinal mass lesion. Relatively large line broadening and low sensitivity of signals from spinal cord and spinal mass lesions were observed compared with normal or diseased brain tissue. This difference can be attributed mainly to the different coil configurations of a spinal surface coil and a brain volumetric coil for acquiring signals. However, it was possible to assign the signals detected by comparing them with those of brain tissue. Spectral amplitude represents the presence of a certain amount of a metabolite with a concentration typically of millimolar order of magnitude in the selected tissue region. Choline signal and creatine signal were not resolved in a spectrum of normal spinal cord, as seen in Figure 1. In some cases such as inflammation or tuberculosis lesions, line broadening was too large to allow unambiguous assignment. Most benign lesions and tumors showed lipid signals in their ^{1}H spectra. Even in normal spinal cord, lipids signals were detected in a relatively spread-out manner as compared with brain tissue. Presently, it is difficult to ascertain whether this observation is the result of contamination from surrounding tissues or represents intrinsic properties. This issue will require further studies with healthy volunteers using the current methodology. The apparent contamination was, however, not serious enough to hinder assignment of other tissue signals between 2 and 4 ppm, as demonstrated in the spectral figures. We have already reported a successful acquisition of ^{1}H-MR spectra from human prostatic lesions using the surface coil used in this study.[19]

Not detecting choline in the disc herniation that mimicked spinal cord tumor revealed that it was feasible to distinguish between this kind of disc degeneration and spinal cord tumor by this technique. Elevated choline was nearly always observed and has been substantiated by chemical assays on tumor biopsies. Therefore, elevated choline does not merely represent the increased membrane synthesis of rapidly proliferating cell but also the breakdown of NMR-invisible phosphatidylcholine, releasing NMR-visible cholines in viable tumor irrespective of malignancy. Observation of lactate in the dermoid cysts demonstrated spectral similarity with brain cysts. It is possible that choline could be detected in the neo-

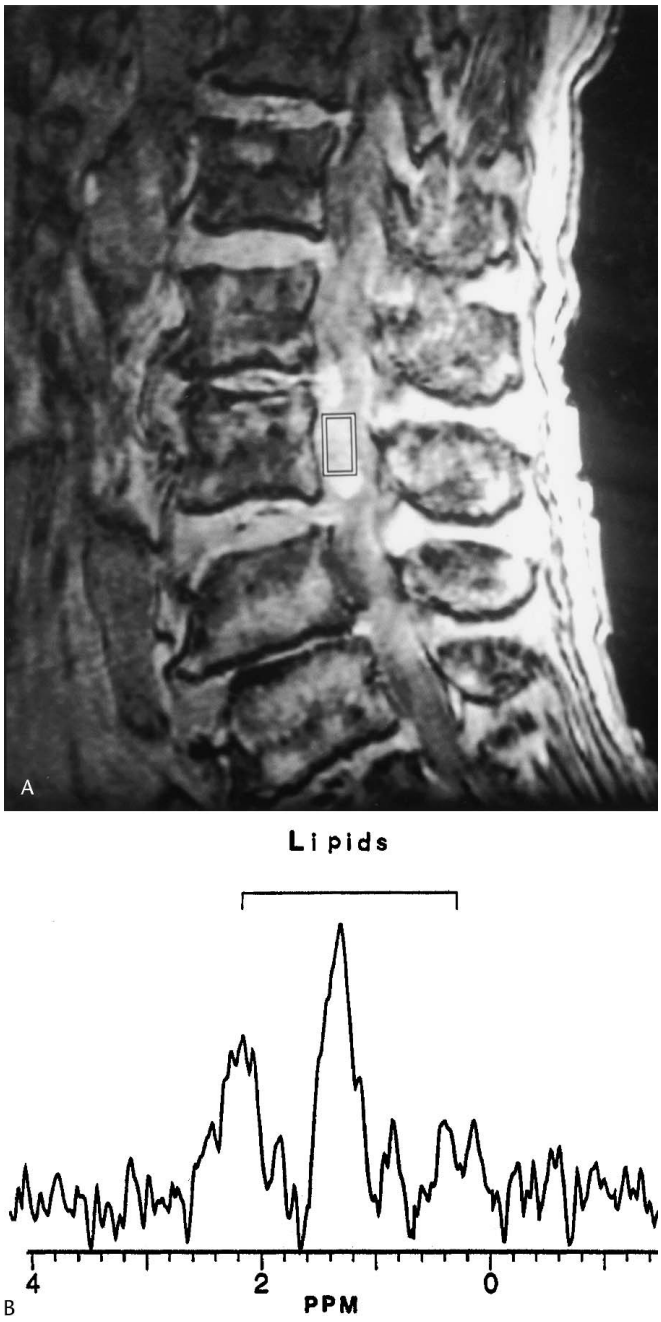

FIGURE 2. T2-weighted fast spin echo image of a patient with disc herniation. Selected voxel for MRS is indicated as a rectangle. Depth of the voxel was given by numerical assignment to contain the lesion as much as possible with sagittal images (A). Also shown is ^{1}H STEAM spectrum of disc herniation (B).

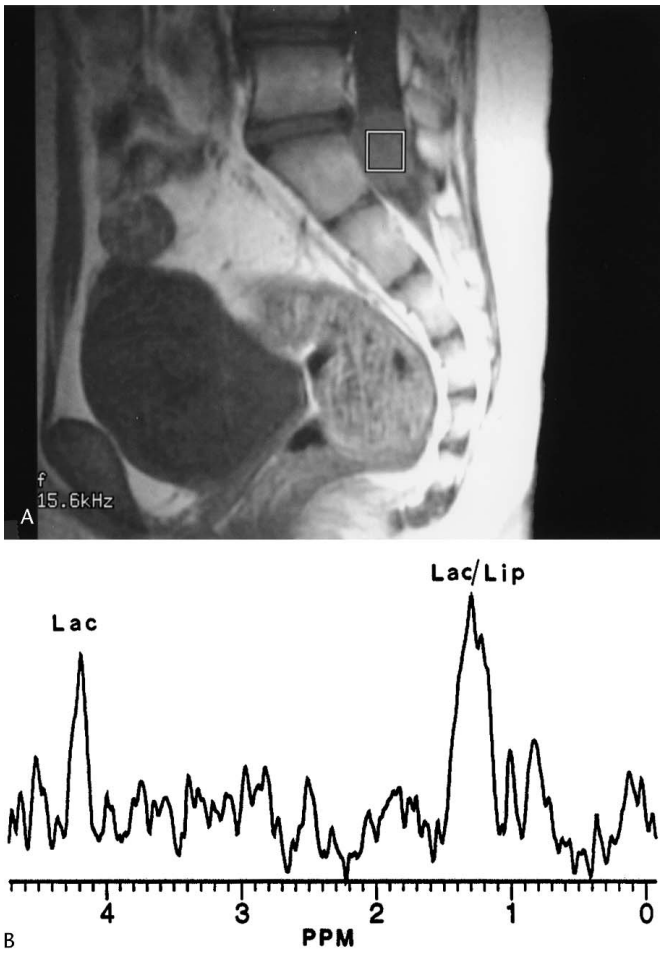

FIGURE 3. T2-weighted fast spin echo image of a patient with dermoid cyst. Selected voxel for MRS is indicated as a rectangle (A). ^{1}H STEAM spectrum of dermoid cyst is also shown (B).

plastic cyst, although it was not observed in this study. Non-MS myelitis patients usually have tumor-like spinal cord lesions.[20] Choline was not observed in this patient. However, this diagnosis was not confirmed by biopsy data because surgery was not done on this patient. Choline was not detected in the patient with chronic epidural abscess. However, it is possible that there was low sensitivity due to the small voxel for this lesion, around 0.6 cm^3.

Enhanced myo-inositol was observed at 3.56 ppm in two cases of schwannoma. This observation is consistent with previous reports by other groups: an in vitro NMR study with cell extract[21] and an in vivo MRS study.[22] Myo-inositol has been suggested originally to be a growth requirement for mammalian cells or even simply the storage form of the inositol polyphosphatide messenger system, because a significant amount of myo-inositol was demonstrated in cells in the undifferentiated state. Free myo-inositol is an important component of both the central and the peripheral nervous systems. Although the cellular localization of the myo-inositol transport mechanism is not known, much of the free myo-inositol in peripheral nerve exists in Schwann cells,[23] and these cells have a relatively high-affinity uptake mechanism for myo-inositol.[24] The

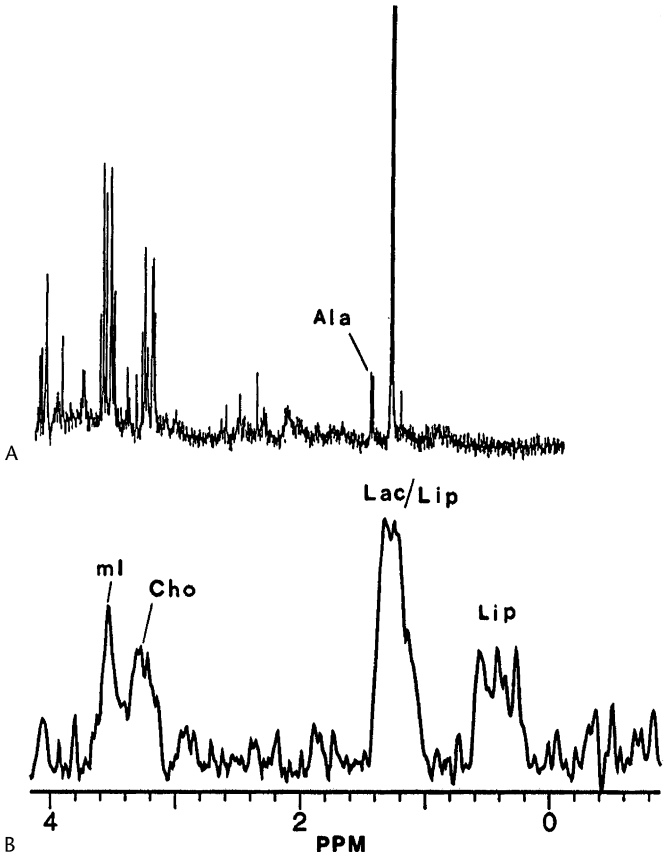

FIGURE 4. A, 300-MHz ^{1}H spectrum of perchloric acid tissue extract of a schwannoma. B, Corresponding in vivo 63.85-MHz ^{1}H STEAM spectrum of a schwannoma. Each in vivo signal showed a larger line broadening compared with in vitro signals due to differences in magnetic field. So, alanine was not resolved in an in vivo spectrum.

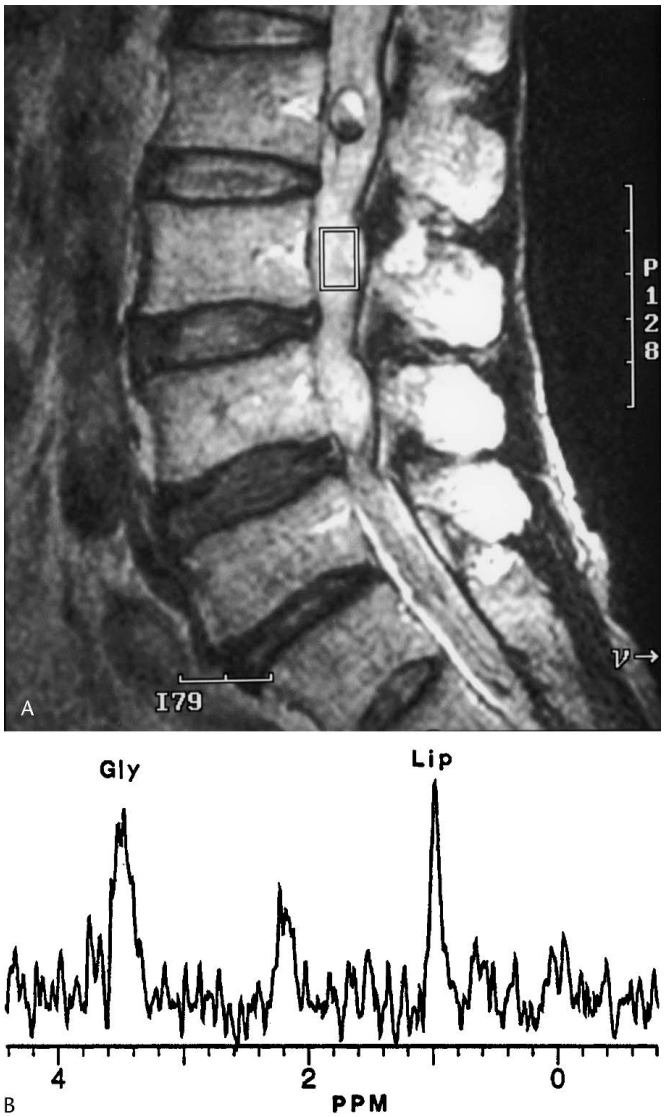

FIGURE 5. T2-weighted fast spin echo image of a patient suggested to have ependymoma. Selected voxel for MRS is indicated as a rectangle (A). ^{1}H STEAM spectrum of its lesion is also shown (B). The most remarkable feature of an ependymoma is the presence of relatively large amount of glycine and little choline on its ^{1}H-NMR spectrum.

reason for the high inositol content in schwannoma is unknown, but recently, myo-inositol has been considered in its role as an osmolyte and astrocyte marker rather than as the neural messenger. Therefore, its enhancement could be associated with the pathologic condition of schwannoma at the time of measurement. Comparison with high-resolution NMR data of tissue extracts revealed a general correspondence between the spectral features of in vivo and in vitro data, in spite of the broadening of in vivo signals, as demonstrated in Figure 4. Relatively small-signal alanine was not resolved in the in vivo spectrum. Lipids detected at 0.2–0.6 and 1.3 ppm were not observed in the in vitro spectrum, presumably because of substantial loss of lipids during the perchloric acid extraction. Therefore, only lactate doublet was apparent at 1.3 ppm in the in vitro spectrum compared with the lipids/lactate mixture signals in the in vivo data. Alanine, an alternative reduced partner of pyruvate derived from glycolysis, have been observed frequently in brain meningiomas.[25–27] Alanine and elevated Glx were also detected in meningiomas of the spinal region as in the brain meningiomas. It suggested the transamination pathway and partial oxidation of glutamine rather than glycolysis in the metabolism of meningiomas. Higuchi et al[28] reported an increase in alanine and Glx in rats subjected to transient global ischemia. Thus, it may be related to pathologic condition of meningiomas, such as tumor necrosis and hypoxia, at the time of measurements. It has been reported from a high-resolution NMR study of extract from an ependymoma cell line that gly-

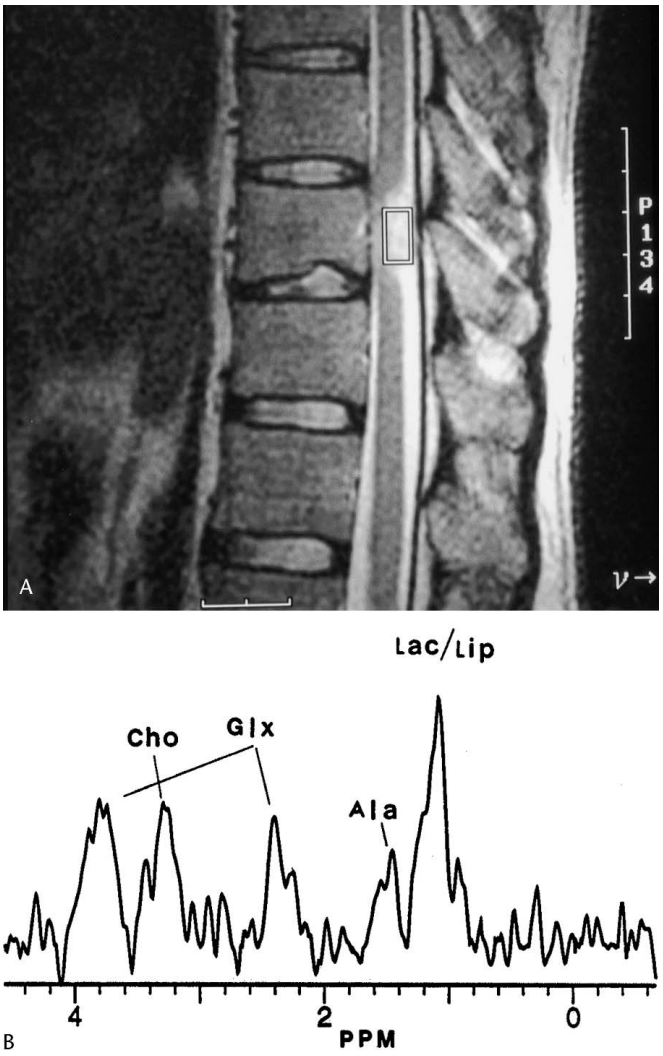

FIGURE 6. T2-weighted fast spin echo image of a patient with meningioma. Selected voxel for MRS is indicated as a rectangle (A). ^{1}H STEAM spectrum of meningioma is also shown (B). The spectrum showed a typical spectral feature of a meningioma, such as presence of alanine and increased Glx. This suggests a transamination pathway and partial oxidation of glutamine rather than glycolysis in the metabolism of meningiomas.

cine was highly enhanced and that, unusually, choline was not elevated.[21] An MRS observation of glycine without choline may suggest that this spinal cord lesion could be ependymoma rather than astrocytoma in this patient (Patient 9). However, this was not confirmed by biopsy because surgery was not performed on this patient. A metastatic tumor from renal cell carcinoma showed a very similar spectral trend to that seen with brain metastases. High lipid signals and enhanced choline have been observed frequently in brain metastases.[22,29] Triglyceride, a form of mobile lipids, was frequently encountered in the MR spectra of actively growing tumors and could be derived from membrane or myelin-lipid breakdown without cell necrosis.[30,31] Observation of choline and mobile lipids simultaneously in actively growing tumors may suggest their attribution also to increased phospholipids metabolism in highly proliferating cells as increased phosphodiesterase was shown in high-grade brain tumors from ^{31}P-MRS studies.[32,33] Triglycerides may play a role as a source of lipid turnover in this metabolic pathway.

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