

Proton MR Spectroscopy

Amir A. Zamani, MD

INTRODUCTION

Nuclear magnetic resonance spectroscopy (MRS) has been in use in biochemistry labs for more than 50 yr. In its earlier years, it was used primarily for in vitro chemical analysis of small samples. Magnetic resonance imaging (MRI) is a powerful imaging technique that combines exquisite sensitivity to soft tissue contrast with the ability to demonstrate anatomy in many different planes and projections. MRS as a technique for in vivo sampling of biological tissue provides another piece of information, revealing the biochemical changes occurring in the pathological region. The advantages of MRS in comparison with other techniques that provide metabolic information (such as positron emission tomography [PET] or single-photon emission computed tomography [SPECT]) lies in the fact that MRS can be obtained during the same session as MRI. With newer MRS techniques it is possible to sample the entire lesion and its surroundings and cross-reference them to MR images; this enables us to obtain spectra belonging to many small region of the lesion (generally about 1 cm³). The spectra obtained with this whole brain technique can be compared with spectra obtained from the same exact location after therapeutic intervention, thus allowing us to see the effect of certain therapeutic interventions.

MRS can be used in differentiation of similar-appearing pathology (infarct from tumor, tumor from abscess). In certain pathological conditions the MR spectrum is virtually diagnostic. Moller-Hartmann et al. (1) report that added information provided by spectroscopy led to approx 15% more correct diagnoses and 6% fewer incorrect diagnoses.

In our current discussion, we consider only proton MRS. Sodium, carbon, and phosphorus MRS have yet to find wide clinical application.

PHYSICS OF SPECTROSCOPY

Spectroscopy is based on chemical shifts. A proton (hydrogen nucleus) in a magnetic field (for example, 1.5 T) has a precession frequency governed by Larmor's equation (64 MHz at 1.5 T). In fact, the local magnetic field experienced by the proton is not exactly the same as the external magnetic field. This is because the adjacent orbiting charged particles (for example, electrons)

produce their own magnetic field, which add to, or subtract from, the external magnetic field. Thus the resonance frequency of a proton is different (shifted) from what is expected in the given external field. The degree of shift, expressed in parts per million (ppm), depends on the chemical structure of the material. For example, the chemical shift of a proton in the radical $-\text{CH}_3$ is different from that of a proton in the radical $-\text{CH}_2-$.

Like conventional MRI, imaging in MRS begins with the MR signal. Radio waves at an exact frequency will cause the protons in the magnetic field to go to higher energy levels. These higher energy levels are unstable, and protons give up the extra energy in the form of a signal, the amplitude of which diminishes with time (free induction decay). In order to produce spectra on which the differences in chemical shifts are recorded, the received MR signal is subjected to Fourier transform to change it from a plot of intensity vs time to a plot of intensity vs frequency (change from time domain to frequency domain). To ensure that the shifts in frequency reflect different chemical structures only, one has to ensure the homogeneity of the external magnetic field over the imaging region. Indeed, ensuring that the magnetic field is homogenous is key to obtaining good spectra (2).

To obtain spectra from important metabolites in the brain, it is essential to suppress signal generated by water. In biological specimens the concentration of water is 1000–10,000 times greater than that of these metabolites; thus its signal, if not suppressed, will overwhelm the spectrum. A variety of water suppression techniques are available.

From what has been said so far, it is clear that successful spectroscopy depends on good suppression of water as well as achieving external field homogeneity (2). The process of doing both has been simplified in most modern scanners by performing a *prescan*. At the end of this, the imager measures the degree of water suppression as well the homogeneity of the field. If these are satisfactory, the actual acquisition of spectra is allowed to begin.

Contrast enhancement is an essential part of MR evaluation of many lesions. Spectroscopy usually begins after this enhancement. Does this process change the spectra in a way detrimental to identification of the peaks? The effects of enhancement on spectra are subject to much debate, but overall it is believed that in most instances, these effects are negligible.

The important metabolites detected by MRS include *N*-acetyl aspartate (NAA), creatine, choline, lactate, myoinositol, and mobile lipids (3,4).

NAA is a marker of neuronal population and function, and this metabolite in adult brain is confined to neurons. Whenever neurons die (for example, in ischemic infarction) or are displaced by other elements (for example, in tumors), the NAA peak is diminished.

Creatine is in constant equilibrium with phosphocreatine and is a marker of oxidative metabolism of the cells. The concentration of creatine is tightly regulated and is not easily affected by disease processes. For this reason, it acts as a yardstick against which other peaks are measured. Brain does not produce its creatine; it is transported to the brain from liver and kidney.

A choline peak at 3.2 ppm is a combination of multiple metabolites (free choline, phosphocholine, phosphatidyl choline, and glycerophosphocholine). Some of these metabolites are degradation products of cell membranes; some others are metabolites used in the synthesis of membranes. Because of increases in cell membrane turnover, the choline peak is elevated in all brain tumors. Many investigators point to a high choline/creatine ratio as nonspecific spectroscopic evidence of neoplasia.

Lactate is normally produced in small amounts. These small amounts are usually undetected by MRS. Whenever the glucose metabolism becomes essentially anaerobic, lactate in detectable amounts is produced. Lactate at 1.3 ppm is a doublet peak at TE of 140 ms. With a TE of 40 ms, the lactate peak is all entirely above the baseline. This change with different TEs is essential in positive identification of the lactate peak.

Plasma membrane lipids are seen in conditions associated with necrosis. The peak owing to these may extend over a large segment of the spectrum and overlaps the lactate peak. They do not have the characteristic doublet appearance of lactate and become far less noticeable with a longer TE (for example, 270 ms).

Glutamate is an abundant amino acid and a metabolite related to detoxification of ammonia. It is also an excitatory neurotransmitter.

Myoinositol at 3.6 ppm is a cerebral osmolyte. It may be a degradation product of myelin and possibly a marker for glial cells.

NORMAL SPECTRUM

The postprocessing of data produces spectra with a typical appearance, although there are some variations related to the age of the patient and the site of sampling (Fig. 1). The NAA peak at 2.00 ppm is the dominant peak; the choline peak at 3.2 ppm and the creatine peak at 3.0 ppm are almost half as tall as the NAA peak. There is no lactate peak. Myoinositol at 3.6 ppm and glutamate peaks may be discernible.

PATHOLOGICAL CONDITIONS

Infarction

One of the common questions encountered is differentiation of an infarct from a tumor. Some tumors such as low-grade astrocytomas and anaplastic astrocytomas may have an appearance similar to an infarct and can be erroneously diagnosed as infarcts under these conditions. Correct diagnosis can be aided by obtaining spectroscopy. Another scenario is development of an infarct around the time of resection of a tumor. Apparently, this is not uncommon; some authorities believe the incidence of this event to be as high as 10%. In these situations, positive identification of an infarct can usually be accomplished with diffusion-weighted imaging. Spectroscopy can also be helpful.

Neurons are very sensitive to ischemia. As soon as delivery of oxygen and nutrients ceases, anaerobic glycolysis takes over. As a result, lactate is produced and is easily detectable by spectroscopy by its characteristic doublet appearance at 1.3 ppm.

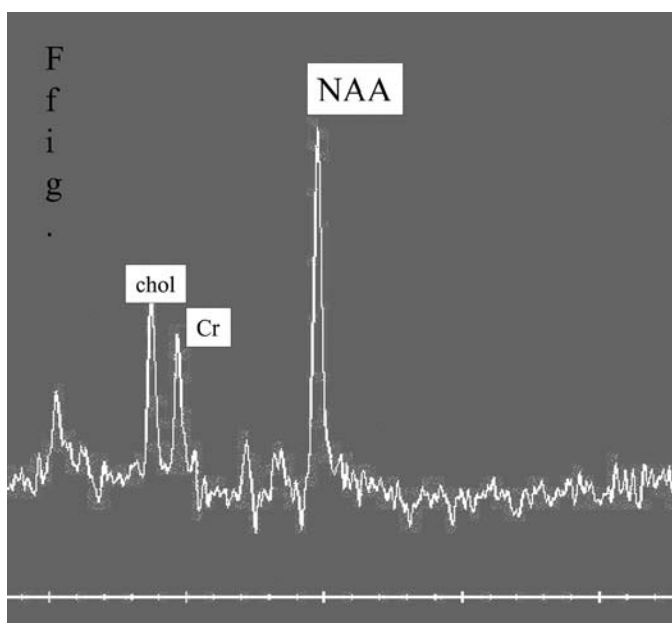


Fig. 1. Normal spectrum. chol, choline; Cr, creatine; NAA, *N*-acetyl aspartate.

Soon after this (in about 30–60 min), the NAA peak begins to diminish (6). Loss of neurons is irreversible, and as a result, the NAA peak remains low while the lactate peak gradually diminishes only to increase again in the subacute and chronic stages because of migration of macrophages that are naturally rich in lactate. Figure 2 demonstrates an acute infarct. Figure 3 demonstrates a tumor that was erroneously diagnosed as an infarct initially. MRS revealed the true nature of the lesion.

Brain Tumors

According to some authors, spectroscopy is abnormal in every case of brain tumor. This is probably too optimistic, as every practitioner of MRS will testify. It is safe to state that spectroscopy is abnormal in the great majority of brain tumors.

Tumors of the brain are either extraaxial or intraaxial and in each case, they replace the normal neuronal population. As expected, there is a reduction in NAA. Some tumors show spectra in which there is a peak at 2.0 ppm. This is probably because they contain material structurally akin to NAA. NAA is strictly confined to adult neurons.

Tumors also cause a large peak of choline, apparently caused by rapid turnover of cell membranes with accumulation of material used in the synthesis of membranes, or material generated by degradation of cell membranes. A high peak of choline is seen in both intraaxial and extraaxial tumors. In the intraaxial tumors, it can be seen in both tumors of glial origin and others, for example, metastases and lymphomas. A high choline peak, however, is not confined to neoplastic conditions and can be seen in other diseases, for example in

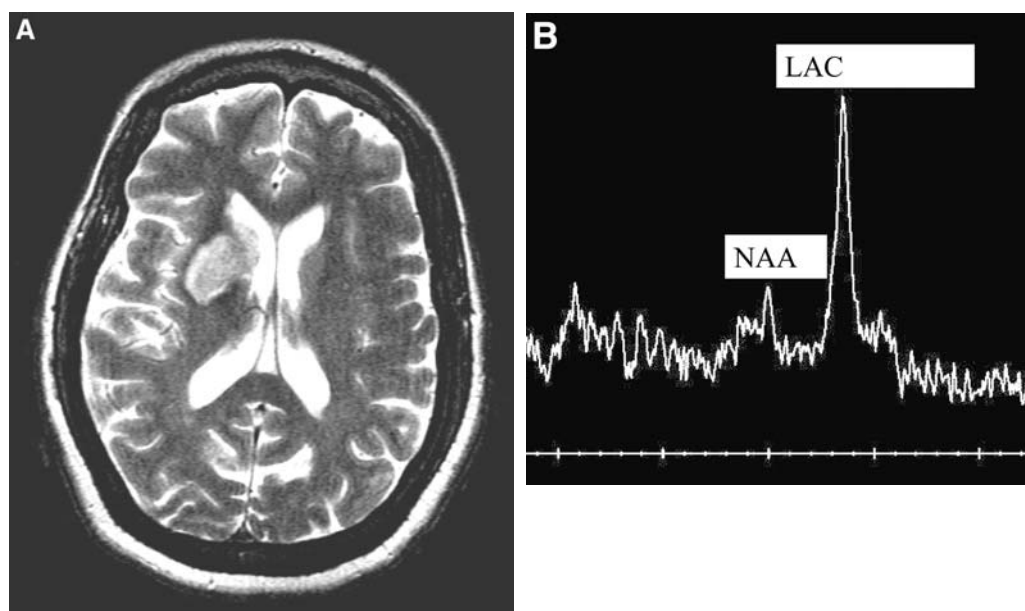


Fig. 2. (A) Right basal ganglionic acute infarct. **(B)** The corresponding single-voxel spectroscopy shows decreased *N*-acetyl aspartate (NAA) and a prominent lactate (LAC) peak. A TE of 40 ms was used.

demyelinating plaques of tumefactive multiple sclerosis (*see* Demyelinating Disease following). Among gliomas, the choline peak may be higher in anaplastic astrocytomas than glioblastomas. One important observation made by many investigators is that in tumors, the site with the highest choline peak does not necessarily correspond to the site of enhancement; this site may reside outside the enhancing portion of the lesion. This fact is potentially significant in choosing an appropriate site for biopsy.

Lactate peak and mobile lipid peaks are seen in more malignant tumors and in those with necrosis. The cystic spaces within a tumor are high in lactate. One note of caution is that even in more benign lesions, after a therapeutic intervention (radiation and/or surgery) a lactate peak may appear (7–10).

Different portions of tumor may have different spectroscopic signatures. Tumors tend to be inhomogeneous, and a complete spectroscopic picture cannot be obtained with single-voxel spectroscopy, hence the need to develop 2D and 3D spectroscopy methods that are more complicated. In many centers, these are fairly routine now, and with 3D volume spectroscopy, the entire brain can be sampled in less than 20 min.

Figures 4 and 5 demonstrate spectroscopy of a glioma and a meningioma, respectively.

The spectra produced by metastases, lymphomas, and malignant gliomas may be quite similar. It is noteworthy that spectra obtained in peritumoral regions in glioma show increased choline. This increased choline is not seen in peritumoral regions of metastases (11). Castillo et al. (12) report that myoinositol

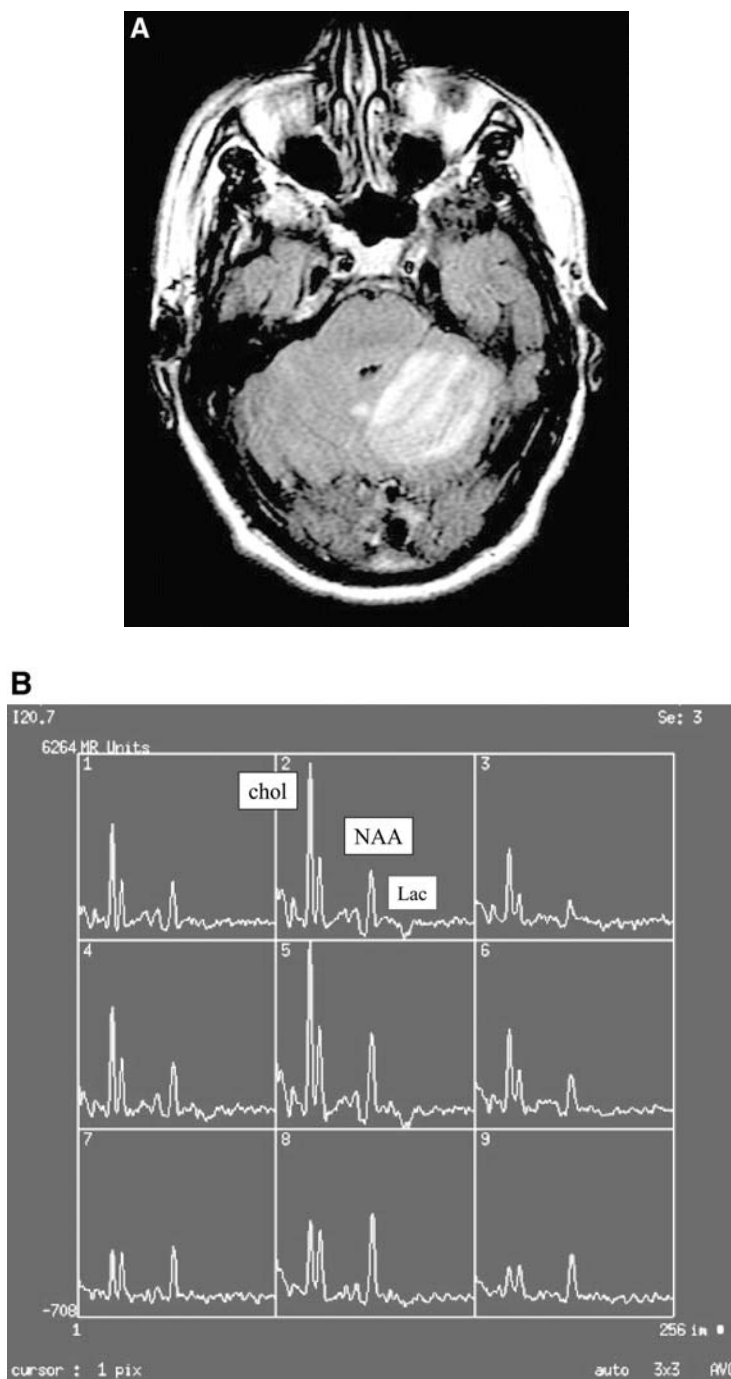


Fig. 3. Medulloblastoma of left cerebellum. **(A)** A left cerebellar lesion with sharply defined margins and a quadrilateral shape, suggesting an infarct. Note mild mass effect in the fourth ventricle. **(B)** Corresponding spectra from a multivoxel study with a TE of 140 ms shows increased choline (chol), a depressed *N*-acetyl aspartate (NAA) peak, and a small lactate (LAC) peak. The spectra are strongly in favor of a neoplastic process. Compare with surrounding normal voxels, for example, voxel #9 in the bottom right.

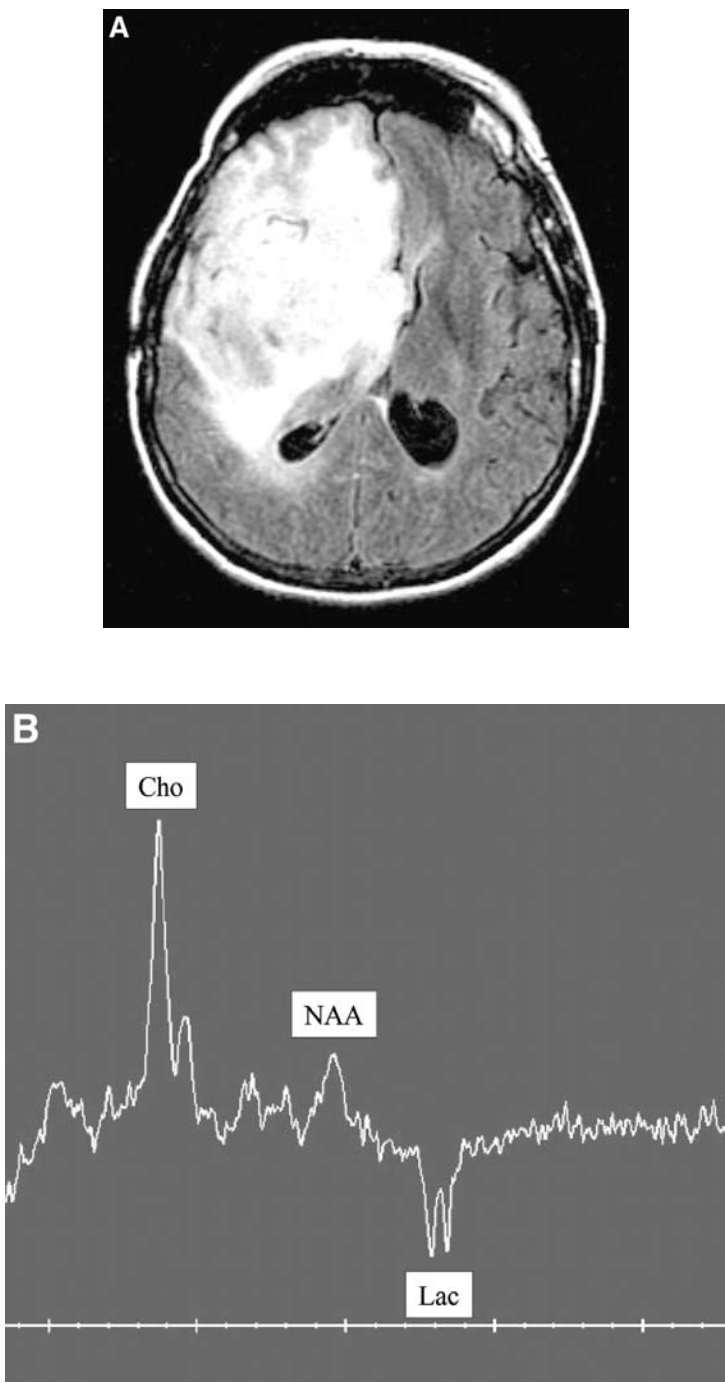


Fig. 4. (A) A large hemispheric tumor with mass effect. **(B)** MR spectroscopy shows elevated choline, decreased NAA, and a lactate peak.

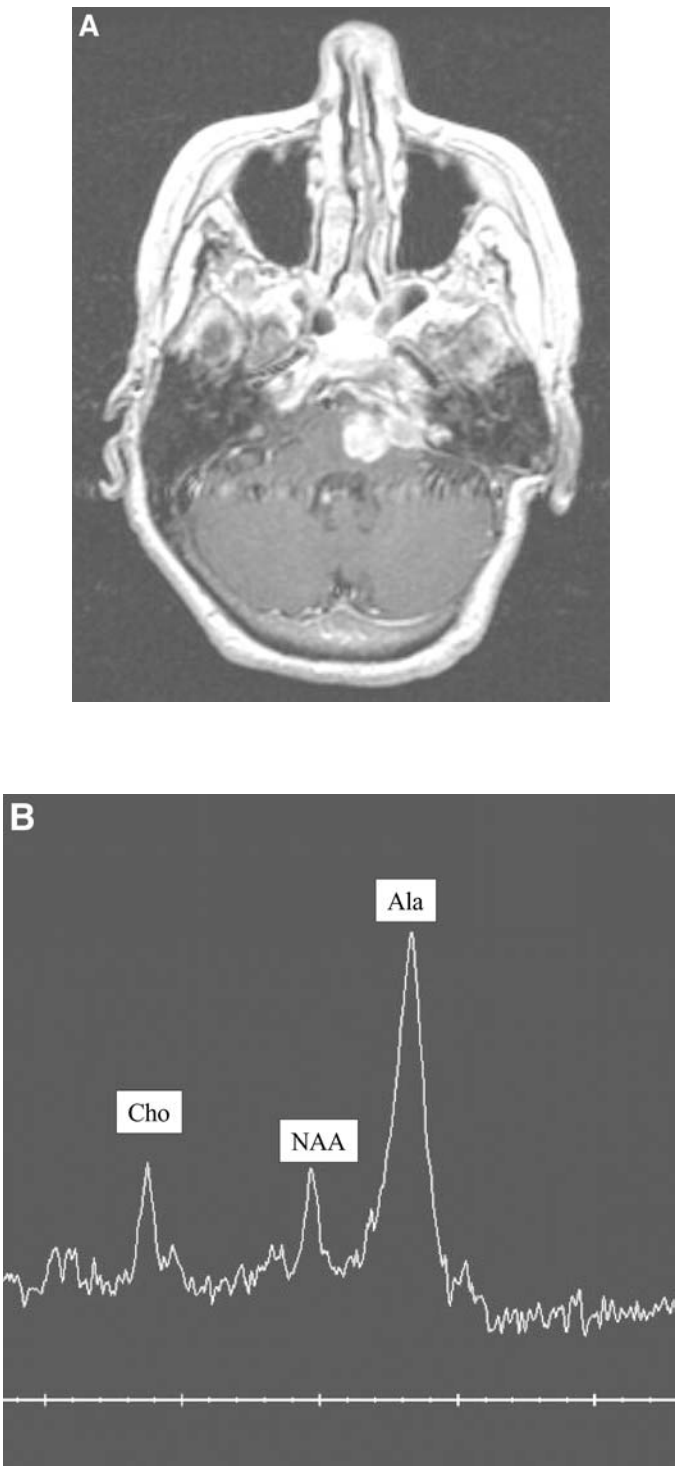


Fig. 5. Spectroscopy of a meningioma. **(A)** A posterior fossa meningioma. **(B)** Spectroscopy demonstrates increased choline (Cho), and decreased *N*-acetyl aspartate (NAA). An alanine (Ala) peak is an inconsistent finding in meningiomas.

is present in all tumors arising from the central nervous system and is absent in metastases. With anaplastic astrocytomas and glioblastomas, there is a trend toward lower myoinositol levels compared with those of low-grade astrocytomas (12). In addition, within the glial family of tumors, it is not currently possible to differentiate between different cell lines, for example, between oligodendrogliomas and astrocytomas.

Radiation Necrosis

Perhaps the purest form of brain radiation necrosis can be seen in patients with head and neck cancer whose brain is injured because of its proximity to the primary site of tumor. Such brain lesions may be seen in temporal and frontal lobes. Radiation necrosis produces a rather flat spectrum because of reduction in the amount of NAA and choline. Lactate may be seen, however. Several investigators have shown that in *severe* radiation necrosis there may be an elevated choline peak. This choline peak makes differentiation of recurrent tumor from radiation necrosis difficult (13).

Abscesses and Other Infections

Necrotic tissue seen in some tumors has a different spectroscopic signature compared with that seen in pyogenic infections. Several investigators have shown this, both in vitro and in vivo. Bacteria producing pyogenic infections possess enzymes that are capable of breaking proteins into amino acids. Identification of cytosolic amino acids (leucine, isoleucine, and valine) by spectroscopy is essential in appreciating the pyogenic nature of a lesion. These amino acids produce a peak at 0.9 ppm (14). This peak, upright when spectroscopy is obtained with a TE of about 40 ms, becomes inverted with a TE of 140 ms. Several authors have shown a similar appearance with cysticercosis. Besides these amino acids, lactate and acetate may be seen. Figure 6 shows spectroscopy of a pyogenic abscess.

Tuberculous infections lack such amino acids. Lipids and lactate may be seen. Herpes simplex encephalitis causes significant reduction of NAA and a lactate peak. With AIDS encephalitis, there is an irreversible loss of NAA (15).

Demyelinating Disease

In active lesions (those with enhancement), there is a mild elevation of choline, and a lactate/lipid peak may be seen (16,17). A highly elevated, towering choline peak may be seen in some case of fulminant demyelination (5). Because of similarities with brain tumors, MRS may not be able to differentiate the two. Decreased NAA is a bad sign that (along with T1 black holes, and low magnetization transfer ratio) may signal loss of neurons and poor prognosis.

Epilepsy

The role of spectroscopy in evaluation of patients with medically refractory seizure is controversial. Currently, scalp electroencephalography and tailored MR can be used effectively to localize lesions and help with lateralization. In a certain percentage of patients, these strategies may fail or may provide discordant

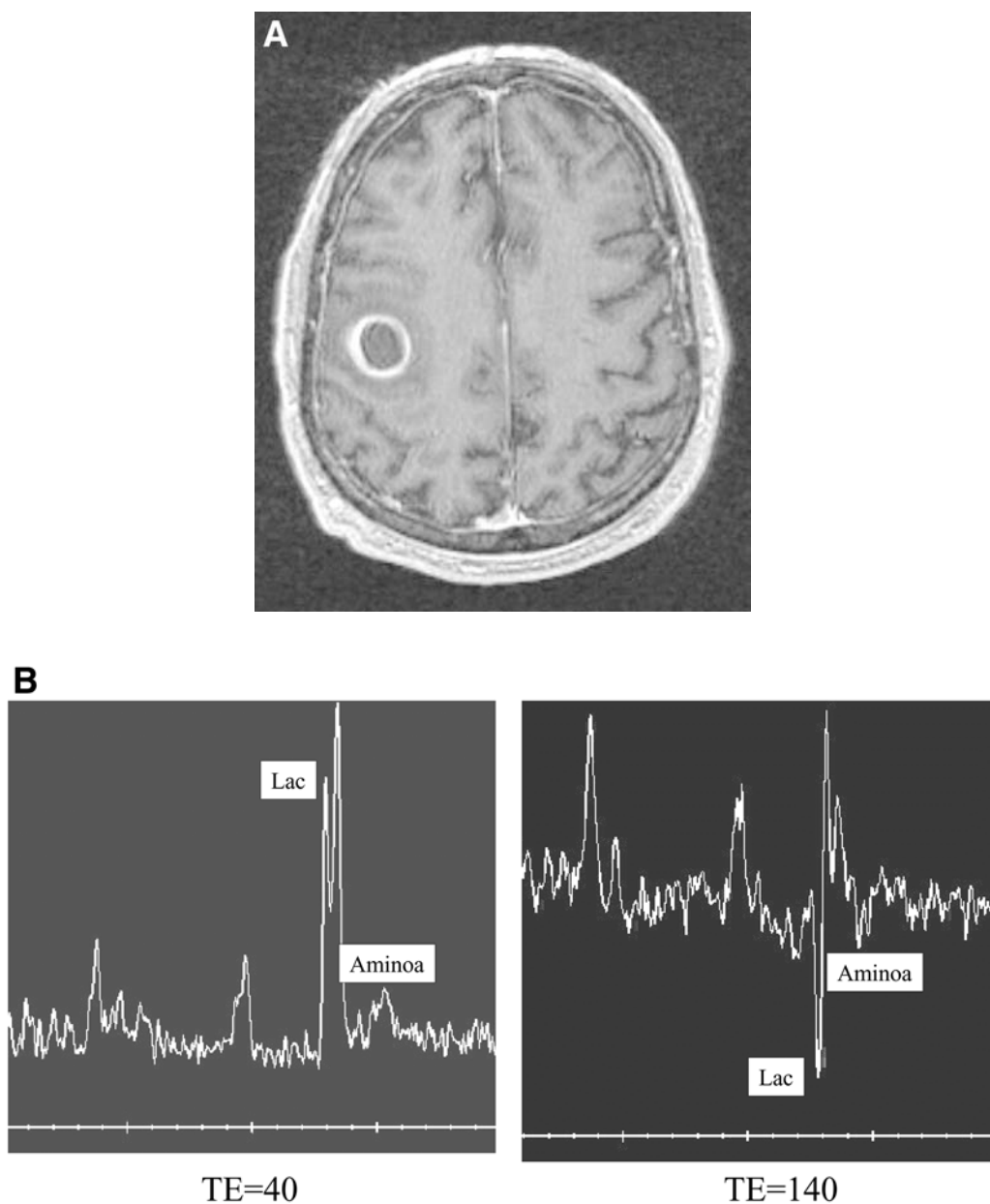


Fig. 6. (A) MRS of a well-defined lesion with a thin rim of contrast enhancement and surrounding edema. Spectroscopy was accomplished with TEs of 40 and 140 ms. **(B)** Note reversal of the peak belonging to cytosolic amino acids (Amino) at 0.9 ppm when TE is switched from 40 to 140 ms. This lesion was a nocardia brain abscess. Lac, lactate.

results. In these patients PET imaging, SPECT imaging, and MRS can be used (18). Several studies have demonstrated a reduction in the choline-to-NAA ratio in the temporal lobes responsible for seizure. Achten et al. (19) have found the NAA/chol+Cr ratio to be even more helpful than PET in lateralization. Capiz-

zano et al. (20) report that in patients with mesial temporal lobe epilepsy, in the ipsilateral hippocampus the absolute NAA was 18.5% lower compared with that in the contralateral side. Asserting that metabolic changes can be found in other parts of the temporal lobe and brain, these authors found that lateralization could improve if whole temporal lobe data, rather than hippocampal data, were employed (20). Also, a lactate peak may be seen in the immediate postictal period in the responsible temporal lobe and in lesser amounts in the contralateral temporal lobe. Whether these observations will lead to universal employment of MRS in the evaluation of patients with refractory seizures remains to be seen.

REFERENCES

1. Moller-Hartman W, Heminghaus S, Krings T, et al. Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. *Neuroradiology* 2002;44:371–381.
2. Mukherji SK. *Clinical Applications of MR Spectroscopy*. Wiley- Liss, New York, 1998.
3. Castillo M, Kwok L, Mukherji SK. Clinical applications of proton MR spectroscopy. *AJNR* 1996;17:1–15
4. Miller BL. A review of chemical issues in 1-H NMR spectroscopy: N-acetyl-L-aspartate, creatine, and choline. *Nucl Magn Reson Biomed* 1991;4:47–52
5. Rand SD, Prost R, Li SJ. Proton MR spectroscopy of the brain. *Neuroimaging Clin North Am* 1999;9(2):379–395.
6. Baker PB, Gillard JH, VanZijji PCM, et al. Acute stroke: evaluation with serial proton MR spectroscopic imaging. *Radiology* 1994;192:723–732.
7. Castillo M, Kwok L. Proton MR spectroscopy of common brain tumors. *Neuroimaging Clin North Am* 1998;8:733–752.
8. Burtcher IM, Holtas S. Proton magnetic resonance spectroscopy in brain tumors: clinical applications. *Neuroradiology* 2001;43:345–352.
9. Nelson SJ, Vigneron DB, Dillon WP. Serial evaluation of patients with brain tumors using volume MRI and 3D 1-H MRSI. *NMR Biomed* 1999;12:123–128.
10. Bulakbasi N, Kocaoglu M, Ors F, et al. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. *AJNR* 2003;24:225–233
11. Law M, Cha S, Knopp EA, et al. High-grade gliomas and solitary metastases: differentiation by using perfusion and proton MRI. *Radiology* 2002;222:715–721.
12. Castillo M, Smith K and Kwok L: Correlation of Myo-inositol levels and grading of cerebral astrocytomas. *AJNR* 2000;21:1645–1649.
13. Chan YL, Yeung DKW, Leung SF, et al. Proton magnetic resonance spectroscopy of late delayed radiation-induced injury of the brain. *J Magn Reson Imaging* 1999;10: 130–137.
14. Grand S, Passaro G, Ziegler A, et al. *Necrotic tumor versus brain abscess: importance of amino acids detected at 1-H MR spectroscopy. Initial results.* *Radiology* 1999;213: 785–793.
15. Chong WK, Sweeney B, Wilkinson ID, et al. Proton MR spectroscopy of the brain in HIV infections: correlation with clinical, immunologic, and MRI findings. *Radiology* 1993;188:119–124.
16. Ross B, Michaelis T. Clinical application of magnetic resonance spectroscopy. *Magn Reson Q* 1994;10:191–247.

17. Arnold DL, Matthews PM, Francis GS, et al. Proton magnetic resonance spectroscopic imaging for metabolic characterization of demyelinating plaques. *Ann Neurol* 1992;31:235–241.
18. Castillo, M. Imaging intractable epilepsy: How many tests are enough? Editorial. *AJNR* 1999;20:534–535.
19. Achten E, Santens P, Boon P, et al. Single-voxel proton MR spectroscopy and positron emission tomography for lateralization of refractory temporal lobe epilepsy. *AJNR* 1998;19:1–8.
20. Capizzano AA, Vermathen P, Laxer KD, et al. Multisection proton MR spectroscopy for mesial temporal lobe epilepsy. *AJNR* 2002;23:1359–1368.



<http://www.springer.com/978-1-58829-147-9>

Minimally Invasive Neurosurgery

Proctor, M.R. (Ed.)

2005, 448 p. 318 illus., Hardcover

ISBN: 978-1-58829-147-9

A product of Humana Press