Magnetic resonance spectroscopy of the brain

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In vivo magnetic resonance (MR) spectroscopy is a noninvasive imaging modality useful for obtaining metabolic information complementary to conventional MR imaging. By studying the biochemical and metabolic changes in brain lesions, it is possible to diagnose a multitude of diseases involving the central nervous system and provide information that can be helpful in clinical decision making. This review focuses on the basic proton MR spectroscopy physics, spectroscopy pulse sequences, and the clinical relevance of this modality in neuroradiology. This report discusses its role in neoplastic and non-neoplastic intracranial lesions.

Imaging is routinely used for the diagnosis and follow-up of patients with brain lesions of indeterminate etiology. The standard imaging modalities, such as magnetic resonance (MR) and computed tomography (CT), provide excellent spatial and contrast resolution but are frequently unable to distinguish neoplastic from non-neoplastic conditions, such as radiation necrosis and abscess. In vivo proton spectroscopy is a reliable technique that overcomes the problem of tissue characterization of intracranial lesions.1

Both positron-emission tomography (PET) with 18fluorodeoxyglucose and hydrogen-1 (H-1) MR spectroscopy provide unique physiologic and metabolic information based on different physical principles. The former is based on the glucose metabolism in the tissue of interest and the latter involves identification of metabolites based on the difference in resonance frequency of protons.2

The MR spectroscopy technique aims at determining the concentration of certain nuclei in metabolites and is most frequently based on the resonance frequency of hydrogen protons. Because the concentration of tissue, water, and lipids is several times the concentration of other metabolites, the signal from water and lipids is suppressed to uncover signal from low-concentration compounds.

Whereas MR imaging provides morphological information, MR spectroscopy allows quantification of various metabolites and the study of their distribution in different tissues. It opens a new frontier in imaging in which the distribution of various metabolites can be used for tissue characterization.

Why hydrogen-1 MR spectroscopy?

The different metabolites that can be used with MR spectroscopy include H-1, phosphorus 31, carbon 13, fluorine 19, and sodium 23. The hydrogen and phosphorus concentration in central nervous system tissue is high enough to be useful in clinical MR spectroscopy. At this time, hydrogen is best suited for MR spectroscopy because of its high concentration, favorable relaxation time, and high gyromagnetic ratio.

The relatively lower gyromagnetic ratio and concentration make phosphorus 31 MR spectroscopy less popular than H-1 MR spectroscopy. Using phosphorus 31 on a conventional 1.5 T MR scanner, it is not possible to obtain adequate signal-to-noise ratio (SNR) on a voxel size routinely used in H-1 MR spectroscopy. The minimal voxel size needed to get adequate SNR for phosphorus 31 MR spectroscopy is 30 mL at 1.5 T magnetic fields.

Physics of MR spectroscopy

The spectroscopy technique is based on the principle of chemical shift in which the frequency of precession of a nucleus is directly proportional to the strength of magnetic field experienced by it. The frequency domain spectrum is generated by Fourier transformation of the time domain signal. The resonance frequency of each metabolite is represented on a graph and is expressed as parts per million (ppm). This is because the resonance frequency is in MHz or 10^6 Hz, whereas the difference between various metabolites is only a few Hz. The ratio between the resonance frequency of metabolites is of the order of 10^6 or ppm.
During MR spectroscopy, as the nuclei are exposed to the 90° radiofrequency pulse, the protons rotate (nutate) from the Z axis to the X axis. When the radiofrequency pulse is discontinued, they return to their equilibrium positions at different rates. The decay rate of different nuclei is dependent on the chemical environments they experience, and it allows the visualization of various metabolites as separate spectroscopy peaks.

Because the brain is composed of a multitude of tissues, MR spectroscopy must be obtained from a localized volume of tissue to be useful clinically. The metabolic information is obtained from a localized volume of tissue known as a voxel. In clinical practice, the voxel size can vary from 1 to 8 mL. The spectrum from smaller voxel sizes has the inherent disadvantage of poorer SNR. In practice, a compromise between voxel size and SNR is reached and is most often 1 to 2 mL.

**Water and lipid suppression**

The normal water concentration is 100,000 times the concentration of other metabolites. To detect these metabolites successfully, the signal from water must be suppressed adequately. The water peak located at 4.7 ppm can be suppressed using chemical shift selective excitation (CHESS) or water elimination Fourier transform technique.3

At present, CHESS is the most frequently used technique and involves presaturation of water signal using one or more 90° presaturation pulses centered over the water resonance frequency. Using this technique, the water signal can be suppressed by a factor of up to 1000. In contrast, water elimination Fourier transform technique involves a 180° pulse centered over water and is less efficient than CHESS for water suppression.

During MR spectroscopy, lipid signals in neuroimaging can be eliminated by avoiding excitation of lipid-containing regions. Other methods include the use of radiofrequency presaturation pulses and inversion pulses. The shorter T2 relaxation times of water and lipids result in better suppression using long echo time (TE) compared with short TE pulse sequences.

**Technical parameters**

The two most popular localization methods for MR spectroscopy are point-resolved spectroscopy (PRESS) and stimulated echo acquisition method (STEAM).4 The STEAM technique provides more effective water suppression and shorter TE, thereby allowing visualization of a greater number of metabolic peaks. The disadvantages of STEAM are poorer SNR and increased sensitivity to motion.

The PRESS technique allows better SNR compared with STEAM but shows only the four major peaks, ie, N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and lactate. For long TEs of >135 ms, PRESS is the localization method of choice. The water suppression using CHESS cannot be used with PRESS. Point-resolved spectroscopy for localization and a TE of 135 ms to obtain brain MR spectroscopy scans are used routinely at the author’s institution.

A highly homogeneous magnetic field having width of water peak at half maximal height of <0.2 ppm is required for high-quality spectra. A uniform magnetic field also decreases the acquisition time by increasing the SNR. In practice, either manual or automatic shimming can be used to achieve a uniform magnetic field. Table 1 compares single-voxel technique and chemical-shift imaging for obtaining spectroscopic data.

**Normal metabolites**

The number of metabolic peaks seen on MR spectroscopy varies with the TE used. At higher TEs, such as 136 ms or 272 ms, a smaller number of peaks are seen because of the short T2 relaxation times and/or dephasing effects of J-coupling (Figure 1). At shorter TEs, a greater number of metabolites can be seen (Cho, Cr, NAA, myoinositol [mI], gamma-aminobutyric acid [GABA], glutamate/glutamine) and the spectrum has better SNR. It is difficult to calculate

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**Table 1. Comparison of single-voxel technique and chemical-shift imaging**

<table>
<thead>
<tr>
<th></th>
<th>Single-Voxel Spectroscopy</th>
<th>Chemical-Shift Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echo time</strong></td>
<td>Short or long</td>
<td>Usually long</td>
</tr>
<tr>
<td><strong>Acquisition time</strong></td>
<td>6 minutes</td>
<td>12 minutes</td>
</tr>
<tr>
<td><strong>Water suppression</strong></td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td><strong>Shimming</strong></td>
<td>Localized</td>
<td>Global</td>
</tr>
<tr>
<td><strong>Signal-to-noise ratio</strong></td>
<td>Better</td>
<td>Poorer</td>
</tr>
</tbody>
</table>

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**FIGURE 1.** The proton magnetic resonance spectroscopy of normal cerebral white matter in a 3-year-old boy, obtained with point-resolved spectroscopy technique and repetition time/echo time = 1500 ms/135 ms. The three largest peaks, from left to right, are choline (3.2 ppm, arrow), creatine (3.0 ppm), and N-acetylaspartate (2.0 ppm, curved arrow). The resonance peaks from myoinositol and glutamate/glutamine are not visible at this high echo-time sequence.
the absolute concentration of various metabolites, so the relative concentrations of these metabolites are often used for interpretation. Table 2 summarizes the location of various metabolites seen on MR spectroscopy.

The largest peak seen on MR spectroscopy is due to NAA and occurs at 2.0 ppm. The 2 other minor peaks of NAA are located at 2.5 and 2.6 ppm. In general, NAA is a marker of mature neuronal density and is therefore decreased in many disease states in which neurons are destroyed. These diseases include neoplasm, infarct, demyelinating disease, etc. The only condition where NAA is increased is Canavan's disease. A smaller contribution to the NAA peak is from non-neuronal cell types such as mast cells and oligodendrocytes.

The Cr peak is located at 3.03 ppm and has contributions from Cr, Cr phosphate, GABA, lysine and glutathione. A secondary peak for Cr is at 3.94 ppm. The Cr compounds are involved in energy metabolism via Cr kinase reaction and probably serve as reserves for high-energy phosphates in cell metabolism. Because the Cr peak is relatively resistant to change during disease states when compared with other metabolites, it is usually used in the denominator of Cho/Cr and NAA/Cr ratios. The Cr concentration is increased in hypometabolic disease states and is decreased in hypermetabolic disease states.

The Cho peak is located at 3.2 ppm and contains contributions from glycophosphocholine, phosphocholine, and free Cho. The molecules are located in the cell membranes and reflect the phospholipid membrane turnover, and the peak is elevated in neoplastic and acute demyelinating diseases. The Cho peak elevation in acute demyelinating diseases is due to rapid cell membrane breakdown, whereas in neoplasms it is caused by rapid cell membrane turnover and increased cellular density.

The lactate peak is located at 1.32 ppm and represents the end product of anaerobic metabolism. Usually, lactate is not detectable on human brain MR spectroscopy. Its concentration is increased in certain neoplasms, radiation necrosis, abscesses, mitochondrial diseases, acute infarcts, and cysts. The lactate peak overlaps with lipid peak on STEAM and can be separated from it at a TE of 135 ms when it inverts. The inverted double peak is due to the J-coupling effect from adjacent protons. A second lactate peak at 4.1 ppm is not well seen because it is close to water and is suppressed by the water suppression pulses.

Table 2. Different chemical shifts of metabolites seen in the brain using stimulated echo acquisition method at low echo time (30 ms)

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>1.3</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.32</td>
</tr>
<tr>
<td>Alanine</td>
<td>1.3–1.4</td>
</tr>
<tr>
<td>NAA (first peak)</td>
<td>2.02</td>
</tr>
<tr>
<td>NAA (second peak)</td>
<td>2.6</td>
</tr>
<tr>
<td>NAA (third peak)</td>
<td>2.5</td>
</tr>
<tr>
<td>Glutamate-glutamine</td>
<td>2.4–2.6</td>
</tr>
<tr>
<td>Creatine</td>
<td>3.03</td>
</tr>
<tr>
<td>Choline</td>
<td>3.2</td>
</tr>
<tr>
<td>Myoinositol</td>
<td>3.56</td>
</tr>
</tbody>
</table>

NAA = N-acetylaspartate

FIGURE 2. Radiation necrosis in a 62-year-old man treated with radiotherapy (60 Gy) for high-grade astrocytoma. (A) The magnified contrast-enhanced T1-weighted image shows a thick walled necrotic ring-enhancing lesion. The choline concentration obtained during chemical shift imaging is overlaid on the region of interest. Note that the choline concentration in the necrotic area and the enhancing wall of the lesion is low. (B) The proton magnetic resonance spectroscopy of radiation necrosis (arrowhead) fails to show a discrete choline, creatine, and N-acetylaspartate peak. A broad peak centered at 1.5 ppm is due to a combination of lipids, amino acids, and other breakdown products. Acquisition parameters: Long echo-time spin-echo (point resolved spectroscopy) sequence with repetition time/echo time = 1500 ms/135 ms.
The mI peak is located at 3.56 ppm and is known to decrease in patients with hepatic encephalopathy. It has been suggested that mI be used as a glial cell marker and is increased in Alzheimer’s disease and demyelinating diseases.

The other metabolites identified at low TEs include glutamate, glutamine, alanine, and lipids (Table 2). The cerebral levels of glutamine are increased in patients with hepatic encephalopathy and Reye’s syndrome.

**Developmental and morphologic variations**

A newborn shows low NAA, high Cho, and high mI levels on MR spectroscopy. These metabolites gradually approach the adult pattern by 1 to 2 years of age. The Cho and NAA concentrations are higher in white matter than in gray matter. With aging, the Cho concentration in gray matter is significantly increased. The concentration of Cr is much higher in gray matter than in white matter and is significantly higher in older rather than in younger subjects. The cerebellar levels of Cho are higher than the supratentorial levels.

**FIGURE 3.** Acute lymphocytic leukemia in an 11-year-old boy. (A) The contrast-enhanced T1-weighted image shows two areas of enhancing leptomeningeal leukemic infiltration, one of which is associated with parenchymal hemorrhage (arrows). (B) The proton magnetic resonance spectroscopy shows elevated choline/creatine ratio and an inverted lactate triplet at 1.3 ppm. Acquisition parameters: Long echo-time spin-echo (point resolved spectroscopy) sequence with repetition time/echo time = 1500 ms/135 ms.

**FIGURE 4.** Fibrillary astrocytoma in a 3-year-old child. (A) The contrast-enhanced computed tomography shows hydrocephalus due to a large infiltrating tumor involving bilateral thalami (arrows) and extending into cerebral white matter. (B) The proton magnetic resonance spectroscopy obtained from the anterior margin of the neoplasm shows elevated choline and low N-acetylaspartate levels. Acquisition parameters: Long echo-time spin-echo (point resolved spectroscopy) sequence with repetition time/echo time = 1500 ms/135 ms.
Applications

Unlike PET, MR spectroscopy does not suffer from the disadvantage of ionizing radiation and, therefore, can be used to perform serial studies to monitor disease progression. By avoiding surgical/stereotactic biopsy, MR spectroscopy provides a possible noninvasive investigation in the management of neoplastic and non-neoplastic brain lesions. A typical chemical shift imaging sequence takes approximately 12 minutes to complete and can be incorporated with MR examination under the supervision of a neuroradiologist.

The overwhelming number of MR spectroscopy applications in clinical practice is in neuroradiology because of the lack of motion artifacts, absence of free lipids in the brain, and ease of magnetic field shimming. The protean practical and research applications of MR spectroscopy are for neoplasm, radiation necrosis, temporal lobe epilepsy, stroke, Alzheimer’s disease, multiple sclerosis, Parkinson’s disease, AIDS, and a number of metabolic disorders.

Brain tumors

The MR spectroscopy data are often useful in confirming the diagnosis, grading the malignancy, and distinguishing radiation necrosis from residual/recurrent neoplasm (Figures 2 through 5). The accuracy of MR spectroscopy in distinguishing neoplastic from non-neoplastic lesion is greatest when the spectra are obtained from voxels at the enhancing edge of a lesion. A typical astrocytoma shows decreased NAA, decreased Cr, and increased Cho levels. The degree of elevation of Cho correlates with the histologic grade of malignancy and is helpful in distinguishing tumors from non-neoplastic disease processes. An elevated lactate level is frequently found in high-grade malignancies.

In a study of 55 patients with focal brain lesions conducted by the author, MR spectroscopy had an overall accuracy of 90.9% in distinguishing neoplastic from non-neoplastic lesions. The MR spectroscopy spectra of metastases shows increased Cho/Cr and decreased NAA/Cr ratios. The lactate and lipid levels are more likely to be elevated in metastases than in primary brain neoplasms.

The MR spectroscopy of peripherally located neoplasm is more technically difficult to perform because of contamination from fat and susceptibility artifacts. A typical cerebellopontine angle schwannoma will show the absence of NAA along with elevation of phosphoinositide peak at 3.6 ppm. The absence of NAA along with elevation of alanine peak (1.3 to 1.4 ppm) is often seen in meningiomas.

Epilepsy

The MR spectroscopy detection of a decrease in NAA coupled with an occasional increase in lactate is useful in detection of the seizure focus in patients with temporal lobe epilepsy. The decrease in NAA corresponds to neuronal loss on histology in these patients. The localization of the seizure focus is helpful in the surgical planning.
FIGURE 6. Nocardia abscess in a 62-year-old woman. (A) The contrast-enhanced T1-weighted image shows the cerebellar abscess in the midline and on the left side (arrows). (B) The proton magnetic resonance spectroscopy shows amino acids/lipid peak at 1.4 to 1.5 ppm (curved arrow) and a possible inverted lactate peak at 1.3 ppm (arrow). There is decrease in the N-acetylaspartate, choline, and creatine concentration in the abscess. Acquisition parameters: Long echo-time spin-echo (point resolved spectroscopy) sequence with repetition time/echo time = 1500 ms/135 ms.

of temporal lobectomy in patients with intractable seizure disorder.

Radiation necrosis
This condition typically develops in brain neoplasms that have been irradiated with 4000 or more rads. It is often impossible to distinguish it from viable residual/recurrent neoplasm based on MR imaging. In these patients, MR spectroscopy shows promise in sensitivity and selectivity for differentiation of radiation necrosis from recurrent/progressive brain tumor. The MR spectroscopy spectrum of radiation necrosis shows a broad peak because of fatty acids, lactate, and amino acids centered at approximately 1.5 ppm. MR spectroscopy and PET play a complementary role in classifying indeterminate brain lesions into non-neoplastic and neoplastic.

Multiple sclerosis
In acute multiple sclerosis, there is a decrease in the NAA levels that correlates well with the neurologic impairment. In these patients, there is an increase in the Cho concentration from accelerated myelin destruction. The increase in lactate level seen in these patients is the result of inflammatory infiltrates. In hyperacute demyelinating disease, there is a transient decrease in Cr that returns to normal in subacute and chronic stages.

In chronic multiple sclerosis, there is an irreversible decrease in NAA and inositol levels. The decrease in NAA in the white matter surrounding the demyelinating plaque correlates best with clinical impairment in these patients.

AIDS
There is potential for detection of a decrease in NAA and an increase in Cho even before the development of abnormalities on MR imaging. The metabolic abnormalities increase as the severity of the disease increases. In immunocompromised patients, MR spectroscopy can often be used to distinguish between neoplasm and opportunistic infection. For example, the spectra of toxoplasmosis show large lipid and lactate peaks with virtual absence of normal metabolites. This can be distinguished from lymphoma, which shows marked elevation of Cho and lipids and significant reduction of NAA. MR spectroscopy may play a future role in monitoring the results of antiretroviral therapy and predicting the usefulness of drug therapy.

Stroke
In early stages of stroke, lactate elevation can be identified in absence of MR imaging abnormalities. These areas may represent ischemic zones at risk for infarction. In acute infarcts, there is a decrease in NAA and an increase in lactate concentrations. There is a progressive decrease in NAA and lactate up to 1 week after infarct, indicating the reversibility of neuronal damage during this period. In chronic infarcts, there is a decrease in NAA, Cr, and Cho levels.
Other diseases

In patients with Alzheimer’s disease, there is a decrease in NAA levels and hippocampus atrophy, which may be useful in distinguishing this disease from normal aging. There are reports of a decrease in NAA levels and an increase in mI in patients with Alzheimer’s disease. In patients with hepatic encephalopathy, there is an increase in glutamine, a decrease in Cho, and a decrease in mI concentration. In Parkinson’s disease, NAA, Cr, and Cho levels are unchanged but lactate levels are elevated.

The MR spectroscopy feature of brain abscess includes increased acetate and succinate levels at 1.92 and 2.42 ppm, respectively (Figures 6 and 7). Currently, there are a number of MR spectroscopy research frontiers that include inherited, idiopathic, and metabolic brain disorders.

Pitfalls

Hydrogen-1 MR spectroscopy is a technically demanding investigation and produces low SNR. The possible causes of poor spectral quality on MR spectroscopy include hemorrhage, postoperative changes, less than 200 acquisitions, small voxel size, and automatic shimming. These causes either result in poor homogeneity of the magnetic field or poor SNR, making the interpretation of spectroscopy data unreliable. The presence of hemorrhage and postoperative changes within the volume of interest often leads to poor-quality measurements due to susceptibility effects caused by hemosiderin. The cortical brain lesions located close to the calvaria are often difficult to image on MR spectroscopy because of susceptibility artifacts and contamination from lipids located outside the dura.

Conclusion

Although MR spectroscopy allows detection of only a few of the cellular metabolites at moderate spatial resolution, it remains a unique modality available to neuroradiologists that provides biochemical information not obtainable with CT or MR imaging. Hydrogen-1 MR spectroscopy can be implemented on the widely available 1.5 T MR scanners. With its recent improvements in techniques, MR spectroscopy is already playing an important role in the management of neurologic diseases.

With the advent of high-field MR imaging scanners, it is possible to improve SNR as well as reduce acquisition time and voxel size. In the future, MR spectroscopy research is likely to result in smaller voxel size and improved acquisition time.

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