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ARTICLE

Applications of MRS in the evaluation of focal malignant brain lesions

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Abstract

Magnetic resonance spectroscopy (MRS) has clinically been most extensively used for assessing brain disorders, particularly tumors. With 1-H spectroscopy at intermediate echo times, resonances from choline, creatine, N-acetyl-aspartate (NAA), lactate, and free fatty acids can be resolved well enough to assist in diagnosis under routine conditions. Generally, an increased concentration of choline is found in all primary and secondary brain tumors, and the degree of increase correlates with the degree of anaplasia. Further indicators of anaplasia are the presence of lactate, indicating hypoxia, and of fatty acids, indicating necrosis. According to literature, the sensitivity of a combination of proton spectroscopy with contrast-enhanced dynamic susceptibility-weighted imaging for high-grade components in gliomas is better than conventional contrast-enhanced imaging alone. Today, proton spectroscopy is clearly indicated for differentiating radiation-induced damage from recurrences of irradiated brain tumors.

Keywords: *Brain neoplasms; magnetic resonance spectroscopy; radiotherapy.*

Introduction

Magnetic resonance spectroscopy (MRS) has been evaluated in a wide range of applications, including infectious disease, metabolic disorders, drug pharmacokinetic studies, infections, and oncology. Generally, most radiologists are reluctant to use MRS as an adjunct to routine imaging, since it requires additional steps for shimming the magnetic field and adjusting the system, and the spectra require skill to interpret correctly. Undoubtedly, there is also a simple psychological barrier, the radiologist being unfamiliar with interpreting chemical spectra instead of images. However, there are numerous instances where spectroscopic data are valuable for interpreting ambiguous imaging findings. This article will focus on focal brain lesions and examples of the use of proton MR spectroscopy in oncology.

Technical considerations

MRS can be performed as a single-voxel technique, covering a volume of approximately 1 cubic centimeter, or, as is possible on most contemporary scanners, as a multivoxel technique, where a rectangular block measuring several centimeters is measured, with multiple voxels, each again approximately 1 cubic centimeter in size. With this technique, parameters extracted from the spectra can be color-coded for each voxel and the generated parameter maps superimposed on the morphological images (MR spectroscopic imaging, MRSI; or chemical-shift imaging, CSI).

MRS has been investigated for several nuclei, including 1-H, 13-C (for amino acids or as a tracer for pharmaceuticals), 19-F (as a tracer for pharmaceuticals, e.g. 5-fluorouracil), 23-Na (as a marker for cell integrity), 31-P (for assessing energy metabolism)[1,2]. However, most of these applications are technically challenging

Table 1 Metabolites in the brain in proton spectroscopy at 135 ms TE, 1.5 T

Abbreviation	Metabolite	Frequency	Significance
Cho	Phosphocholine [PC], Glycerophosphorylcholine	$\delta = 3.22$ ppm	Membrane turnover, cell proliferation
Cr	Creatine and phosphocreatine	$\delta = 3.03$ ppm and 4 ppm	Temporal store for energy-rich phosphates
NAA	N-acetyl-L-aspartate	$\delta = 2.01$ ppm	Indicates the presence of intact glioneural structures. Exact function unknown
Lactate		$\delta = 1.33$ ppm (inverted) doublet	Anaerobic glycolysis
Lipids	Free fatty acids	$\delta = 1.2$–1.4 ppm	Necrosis

and highly experimental and thus not suitable for routine clinical use. Proton (1-H) spectroscopy, however, can be performed on modern commercial scanners with reliable quality, and has now been sufficiently evaluated to be used in practice. This is to say that spectroscopy is no longer a special method that requires the presence of a physicist, for example, but is now so well implemented on commercial machines that it can be performed by a skilled technician. Furthermore, there is now sufficient experience that the findings at spectroscopy are not only of 'scientific' value, but can be used to draw clinical conclusions and consequences for individual patients.

Table 2 Summary of proton spectroscopic findings in brain neoplasms (according to[3])

Pathology	Cho/Cr	Cho/Cho(n)	NAA/Cr	Cho peritumoral
High-grade glioma	⇑⇑	⇑⇑	⇓⇓	⇑
Low-grade glioma	⇑	⇑	⇑	∼
Radiation necrosis	⇓	⇓	⇓	⇓
Metastasis	⇑	⇑	⇓⇓	⇓
Lymphoma	⇑	⇑	⇓⇓	∼

Cho = choline; Cho(n) = choline in normal tissue; CR = creatine; NAA = N-acetyl-L-aspartate.

Proton MRS can be performed at short (20–40 ms), intermediate (135–144 ms), or long echo (270–288 ms) times. Spectra obtained at short echo times contain numerous resonances from substances of lesser importance which distort the spectral baseline and make the spectra difficult to interpret. Due to their short T2 relaxation times, these resonances do not contaminate the spectra obtained at intermediate echo times. Furthermore, glutamate/glutamine shows a resonance around 2.2 ppm, which might overlap with the NAA peak at 2.01 ppm (but only at short echo times). NAA is an important normal neuronal marker (see below). Only myo-inositol, only found at short echo times, may be important in particular neuro-oncological issues, e.g. when low-grade gliomas are investigated. Using long echo times carries no advantage in practice, because of a lower signal-to-noise ratio[3]. Therefore, proton spectroscopy at intermediate echo times remains the technique of choice for most important questions in brain tumor evaluation. Using an echo time of 135 ms, as will be referred to in this paper, has an additional advantage in that the lactate peak at 1.33 ppm is inverted and can more easily be discriminated from a lipid resonance in the same range[1].

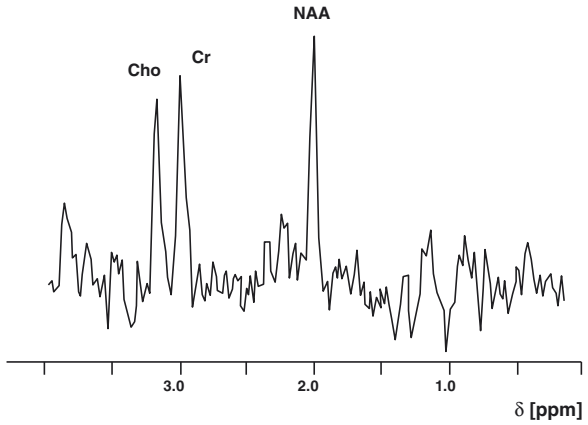

Figure 1 **Proton spectrum of healthy brain obtained with a 1.5 T system and at an intermediate TE of 135 ms. Note that choline has the lowest, creatine an intermediate, and NAA the highest concentration.**

Metabolites

In practice, five metabolites are assessed for diagnosing brain tumors (Table 1). Three of these, choline, creatine, and NAA, are found in the healthy brain (Fig. 1), but the concentrations may deviate in various ways in brain tumors. Two additional metabolites, lactate and lipids, must always be considered pathologic but are not specific for malignancy.

Applications

Interpreting the spectra

The main criteria for interpreting spectra are: the presence or absence of pathologic metabolites, such as lactate or lipids; and the relationships between the concentrations of the three 'physiologic' metabolites, choline, creatine, and NAA. An absolute quantification has been attempted but so far not shown to be stable enough to be done

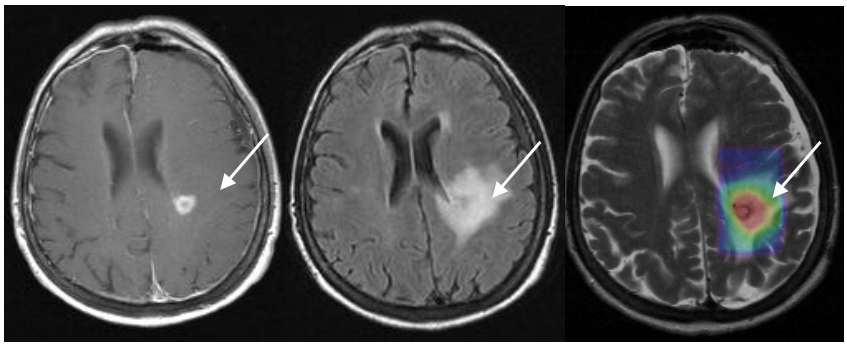

Figure 2 **In an anaplastic glioma which markedly takes up Gd-DTPA, with a T2-hyperintense rim, MR spectroscopic imaging shows an increase in choline not only in the contrast-enhancing center but also in the non-enhancing rim (indicated by a green hue), accompanied by a depression in NAA. This is indicative of infiltration by low-grade components of the tumor. In a metastasis, the T2-hyperintense rim would have the spectrum of normal brain, since the T2 hyperintensity would be caused by vasogenic edema, not by tumor infiltration (see Fig. 4).**

clinically[1]. Spectra are obtained from the lesion itself, from its surroundings, and from presumed healthy tissue, mostly the contralateral hemisphere. It must be borne in mind that the spectra, as they are displayed by the scanner console or with a post-processing program, are usually scaled to the highest peak and that the *y*-axes will usually differ between spectra. This may, for example, cause a cerebral infarct to be mistaken for a tumor owing to a choline peak which is higher than that of creatine and NAA, whereas in fact the NAA and creatine peaks are pathologically low due to the loss of viable neurons. Parameter maps from MRSI (which, for example, encode for the Cho/NAA ratio) will also foster such misdiagnoses. This can easily be avoided if one compares the lesion with healthy brain and carefully checks the scale of the *y*-axes.

The fingerprint of a tumor

In a tumor, the increase in cell turnover will lead to an increase in choline concentration, along with a depression of the NAA peak due to the loss in healthy glioneural structures (Table 2). The creatine resonance may be depressed to varying degrees (depending on the energy status of the tumor) and often serves as an internal reference for calculating ratios. When there are hypoxic components, a lactate resonance may be present. A lipid peak indicates the presence of necrosis and suggests a high grade of malignancy.

Differential diagnosis of suspicious lesions

In addition to differentiation from inflammatory or ischemic lesions, which is not the subject of this article, spectroscopy may help to clarify whether a suspicious lesion is a tumor at all, and whether it is a primary or a secondary brain tumor (i.e. a metastasis of an extracranial primary). A normal spectrum with a low choline and high NAA peak (Fig. 1) makes a tumor highly improbable, and rather suggests a scar, heterotopia, or other benign condition. In patients with a known extracranial primary and an appropriate risk constellation, a contrast-enhancing brain lesion may be confidently diagnosed as a metastasis. In some instances, however, the diagnosis is not very clear, e.g. when no primary tumor is known (or a primary tumor is unlikely to cause brain metastases), or with solitary lesions which are rather irregular but round. Metastases should not contain NAA (if they do, this is mostly due to partial volume effects). High-grade gliomas, which may be morphologically indistinguishable from metastases, usually show some level of NAA, although low. Gliomas and metastases have in common an elevation in choline, a low concentration of creatine, and the presence of lipids and/or lactate (Table 2). Notably, whenever both lipids and lactate are present this cannot be further differentiated since they share a resonance frequency. Usually the lipid peak will predominate.

In some instances, with high-grade gliomas, no NAA will be detected due to necrosis, making the discrimination from a metastasis difficult. Here, it may be helpful to assess the T2-hyperintense, non-enhancing rim. In the presence of a high-grade glioma this rim is usually diffusely infiltrated by low-grade components and will therefore show a depression of NAA and increase in the choline resonance (Fig. 2). With metastases, however, this rim is usually simple vasogenic edema, and the spectrum will be that of normal brain (Fig. 4).

Primary lymphoma of the brain may be morphologically difficult to discriminate from high-grade glioma. As with metastases, the absence of NAA may assist the differential diagnosis[3]. The diffusely infiltrating

Table 3 Performance of MR and MRSI for discriminating between high- and low-grade gliomas (according to[4])

	Criterion	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Cho/Cr	1.56	76	48	81	40
Cho/NAA	1.6	74	63	86	45
Morphology	Contrast enhancement	73	65	86	44

Cho = choline; CR = creatine; NAA = N-acetyl-L-aspartate.

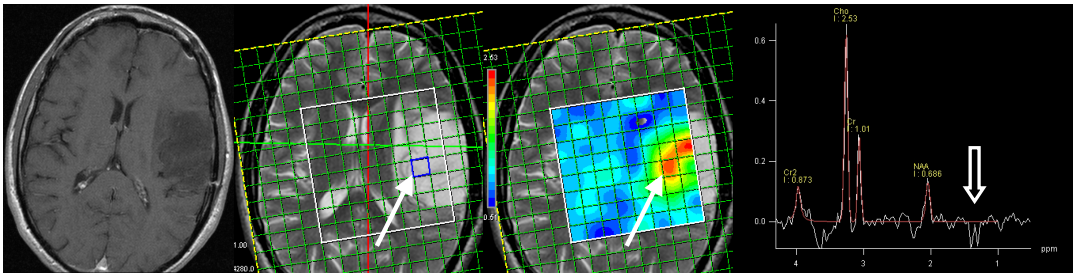

Figure 3 **Glioma without contrast enhancement, according to usual criteria a grade II (i.e. a low-grade) lesion. Spectroscopic imaging, however, indicates a central portion with increased Cho/NAA ratio, possibly indicating anaplastic components. Additional to the pathologic Cho/NAA ratio, the spectrum obtained in the 'hot spot' (solid arrow) shows an inversed doublet at 1.33 ppm (open arrow), indicating the presence of lactate (i.e. hypoxia). This, again, strongly indicates focal anaplasia.**

character in turn will help to distinguish between lymphoma and metastasis.

Grading of gliomas

The less differentiated the tumor, the higher will be its choline concentration and the lower the NAA peak (Table 3). Additionally, a lipid or lactate peak may indicate some higher degree of malignancy. Naturally, the transition is continuous, and a combination of imaging and MRSI is necessary. Interestingly, when dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MR imaging is included in the protocol to detect highly perfused components, the sensitivity for correctly classifying high-grade gliomas as such may be as high as 90%[4]. As always with gliomas, it must be remembered that histology, whenever only a biopsy is done, is subject to sampling error and may under-grade a tumor.

Tumor heterogeneity

Many gliomas contain areas of different degrees of de-differentiation. By definition, the highest-grade component determines the grade of the entire tumor. The most reliable sign of malignant transformation (i.e. a grade III or IV glioma) is contrast medium enhancement as a consequence of a disturbance of the blood–brain barrier, and tumor angiogenesis (particularly in glioblastoma). Therefore, biopsy is best performed in contrast-enhancing areas because it is there that we are most likely to find possible de-differentiated components. However, it is known that some seemingly low-grade gliomas do contain anaplastic components which do not—or do not as yet—have a disrupted blood–brain barrier, and which may possibly be missed by biopsy. Both spectroscopy and perfusion-weighted imaging may help to locate high-grade areas[4]. In proton spectroscopy, an increase in choline, normalized to creatine or NAA, will indicate anaplastic parts of the tumor (Fig. 3). Dynamic susceptibility-weighted contrast (DSC, perfusion-weighted) imaging will disclose an increased relative blood volume as a consequence of the onset of neoangiogenesis, which may be detectable before an overt breakdown of the blood–brain barrier occurs[5].

Discriminating between tumor recurrence and radiation damage

Radiation damage may become manifest as early as weeks and as late as years after treatment of gliomas. It may present as de novo areas of contrast enhancement, sometimes surrounded by T2-hyperintense areas (vasogenic edema), and may grow in size. The patient may also be symptomatic, depending on the size and severity of the reaction. Even when accounting for clinical data (plausibility of radiation damage by comparison with the radiotherapy target volume), discrimination from

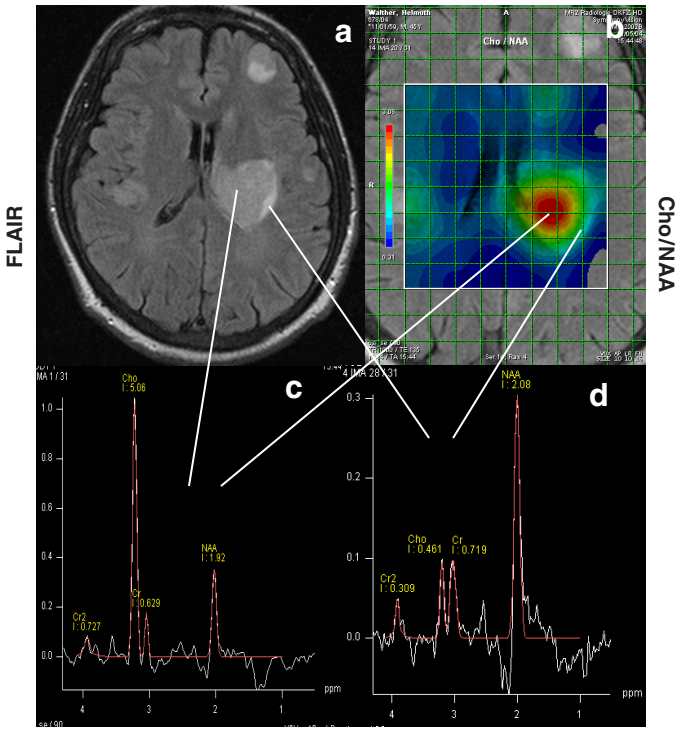

Figure 4 **A 65-year-old man with histologically proven brain metastases from small cell lung carcinoma. Fluid-attenuated inversion recovery image (a), map of choline/NAA (b), spectrum from the center of the metastasis (c), spectrum from a T2-hyperintense rim around the lesion (d). The spectrum from the lesion itself (c) shows, as expected, an elevation of the choline and a depression of the NAA peak, due to replacement of neuronal tissue by the metastasis from a non-neuronal tumor. In the T2-hyperintense rim there is an entirely normal brain spectrum (d, see Fig. 1 for comparison), indicating vasogenic edema rather than infiltrative tumor growth (see Fig. 2 for comparison).**

tumor recurrence may be extremely puzzling. Increased choline/NAA and choline/creatine ratios strongly indicate recurrence (Fig. 4)[6]. Notably, NAA depression and a lipid peak may be present in both entities. In doubtful cases, a repeat study after a due interval may be needed.

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