MAGNETIC RESONANCE SPECTROSCOPY (MRS): BASIC PRINCIPLES AND APPLICATIONS IN FOCAL BRAIN LESIONS

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Pak J Neurol Sci 2007; 2(1):42-46

A spectrum is obtained by splitting a heterogeneous beam of electromagnetic radiation into its components. The individual components are usually displayed in order of their wavelengths. The commonest example is the visible light spectrum where a beam of white light can be split into its component colours. The radiation produced by any substance is dependent on its atomic composition. Spectroscopy is the determination of this chemical composition of a substance by observing the spectrum of electromagnetic energy emerging from or through it.

Initial nuclear magnetic resonance (NMR) experiments were done by Rabi and co-workers in 1938. These efforts were acknowledged by the Nobel Prize in 1944. Later Purcell and Bloch (1952) first detected NMR signals from magnetic dipoles of nuclei when placed in an external magnetic field.[1] First NMR imaging was performed in 1970 on animals followed by human application in the 1980s when whole body magnets of adequate field strength and homogeneity were constructed.[2] Parallel to the introduction of magnetic resonance imaging (MRI) to clinical practice, initial in vivo brain spectroscopy studies were done in the early 1980s. Magnetic resonance spectroscopy (MRS) has rapidly progressed in its clinical utility and recognition. Today, MRS has become a significant non-invasive diagnostic tool and has gained wide clinical acceptability.

BASIC PRINCIPLES

When magnetically active molecules are placed in an external magnetic field they align themselves along the direction of the field and demonstrate a circular oscillation. The frequency of this circular motion (called Larmor frequency) is dependent on the strength of the local magnetic field and the structure of these molecules. When electromagnetic energy (in the form of a radiofrequency, or RF, pulse) is supplied at this frequency, the molecules absorb this energy and change their alignment. When the external energy is switched off, the molecules realign themselves to the magnetic field by releasing their absorbed energy. This released energy is the basis of the MR signal.

Local magnetic fields are dependent on the externally applied magnetic field, the localization gradients applied, and the locally present molecules. The first two factors being constant, the change in the Larmor frequency induced by the locally present molecules may be calculated by detecting the changing MR parameters such as free induction decay (FID), T2 time, T1 time, etc., in response to the applied RF pulse. This change in the local Larmor frequency is used to calculate the amount of any particular molecule within the sample volume. These changes are, however, very small and therefore difficult to detect accurately.

Virtually any nucleus can be interrogated using this technique; however, the two most widely used nuclei are phosphorus (31P) as it is a marker of energy metabolism, and hydrogen (1H) as it is the most magnetically active particle in the human body. Hydrogen-based MR spectroscopy, which is also called proton MR spectroscopy, is now the most widely used and its application in neuro-imaging will be the focus of the rest of this article.

TECHNIQUE

MRS can be performed by two methods - single-voxel spectroscopy (SVS), where a single sample volume is selected and a spectrum obtained from it, or multi-voxel spectroscopy where spectra are obtained from multiple voxels in a single slab of tissue. SVS gives a better signal-to-noise ratio and is a more robust technique. The disadvantage is that only a single spectrum is obtained. The placement of the volume of interest (VOI) becomes critical[3] and may lead to errors of interpretation if not done correctly. With multi-voxel MRS, a much larger area can be covered, eliminating the sampling error to an extent. This is however done at the expense of a significant weakening in the signal-to-noise ratio and a longer scan time. Both SVS and multi-voxel imaging utilize specialized MR pulse sequences. The two most widely used are the Point Resolved Excitation Spin-echo Sequence (PRESS) and the STimulated Echo Acquisition Mode (STEAM) technique. Details of both these techniques are beyond the scope of this article.

OBSERVABLE METABOLITES

MRS provides biochemical information of compounds present in human tissues and cells. Human brain contains hundreds of metabolites but proton MRS can only detect a few of them as at least milli-molar concentrations are necessary for the metabolites to be detected. The major brain metabolites detected are choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate, myo-inositol, glutamine and glutamate, lipids, and the amino acids leucine and alanine.[1-10]

N-Acetyl Aspartate (NAA) is an amino acid found exclusively in neurons. It is regarded as a non-specific marker and is thought to be involved in Coenzyme A interactions and lipogenesis within the brain. It is a marker of neuronal viability. Normal NAA concentration is in the range of 8-9 mmol/kg in healthy adult brain. Concentrations are decreased in conditions leading to axonal injury or neuronal loss. The mechanism of injury, however, is not important, and decreased concentrations are seen in tumors, infarction, and inflammatory conditions such as multiple sclerosis. NAA peak is seen at 2.0 ppm (parts per million) on MR spectra.

The Choline (Cho) peak is a heterogeneous peak representing various choline-containing compounds such as acetylcholine, phosphocholine (lecithin), glycerophosphocholine, and various other intermediates of phospholipid metabolism. It is an indicator of cell density and cell wall turnover. Elevated levels are found in tumors, especially malignant ones, and in certain demyelinating diseases. Choline resonance presents at 3.22 ppm. Studies have shown there is also a direct association between Cho and levels of Ki-67, a protein expressed in all phases of the cell cycle except G0 that serves as a good marker for cellular proliferation. This observation makes Cho a reliable predictor of cellular activity in tumor tissue.

Creatine (Cr) is basically related to cell energy pathways. It is both the substrate and product of creatine kinase. Creatine reflects the energy potential available in brain tissue. Its concentration in normal brain remains very high (7.49± 0.12 mmol/kg) and stable due to high metabolic demands imposed by brain cells. Its peak is noticed at 3.0 ppm. Creatine-Choline ratios are an important indicator of disease states such as demyelination.

Lactate (Lac) is absent in normal brain tissue and its presence is indicative of anerobic glycolysis at the cellular level. Elevated levels are associated with ischemic conditions or metabolic disorders (where anerobic glycolysis predominates) but is also noted at the edges of large brain tumours. The peak is very sensitive to the technique employed and unless the correct echo time is employed, it may be artifactually suppressed. The spectral peak lies at 1.33 ppm. The peak is often inverted or bifid.

Lipid is also absent normally but can increase in tumours, infections or metabolic conditions. The peak is at 1.3 ppm and it overlaps with the lactate peak.

Myo-inositol (Ins) is a naturally occurring sugar. It is the dominant peak in newborn brains and lies at 3.56/4.06 ppm. It is regarded as an astrocytic marker and is a possible marker for intracellular osmotic integrity. Its concentration is decreased in stroke, tumours, lymphoma and some low-grade malignancies.[5]

Glutamate/Glutamine/GABA are neurotransmitters and act as markers for neuronal-glial interaction. Peaks lie at 2-2.5 and 3.4-3.7 ppm.

CLINICAL APPLICATIONS

MR spectroscopic data is presented as a spectrum (Figure 1). A spectrum is the Fourier-transformed information obtained from an MR spectroscopic study. It is presented as a series of peaks along an axis labelled in Hertz (Hz) or parts per million (ppm). The ppm scale describes the shift in Hertz from a reference peak divided by frequency of excitation.[6] In normal adult brain the dominant peak is that of NAA, with Cho and Cr being the other large peaks.

Although the majority of the early work in MRS focused on diffuse brain conditions (such as HIV encephalopathy, demyelinating conditions, neurodegenerative disorders,

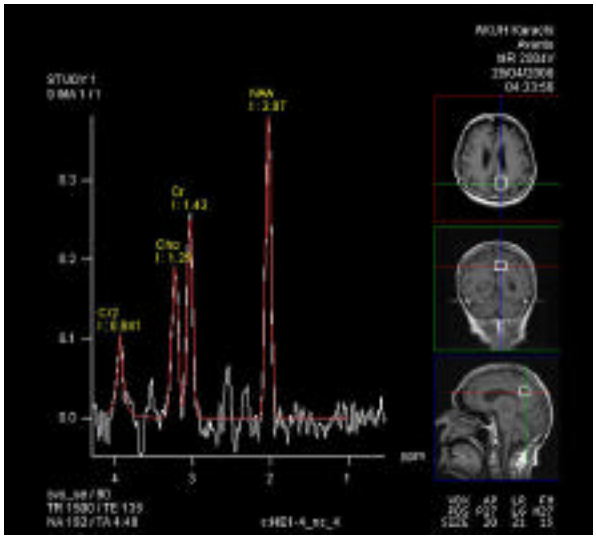

Figure 1: Normal MR spectrum from the cortical grey matter of an adult brain. Note the normal relative values of the NAA, Choline and Creatine peaks. Note particularly the Choline ratio of 1:1.2.

birth asphyxia, and epilepsy), improvements in MR equipment enabling the use of small voxels has MRS applicable to focal pathologies.

Focal intracranial mass lesions (including both neoplastic and non-neoplastic masses) are routinely assessed on conventional MR examination but their diagnosis, characterization and differentiation into various types of pathology remains challenging. Focal lesions are traditionally assessed on the basis of age, clinical presentation, location, peritumoral edema, mass effect, calcification, haemorrhage, necrosis, and contrast enhancement.[7,8] However, the diagnosis remains indefinite and follow-up imaging or histopathology are required in most cases for definitive diagnosis.

NEOPLASTIC LESIONS

The advent of MRS has added to the diagnostic capabilities enabling tissue characterization based on their molecular composition. It provides information about cell proliferation, degradation, neuronal vitality and energy metabolism. Based on these characteristics, MRS attempts to differentiate between benign and malignant brain lesions.[9,10] MR spectral patterns in tumor tissue differ from those of normal brain (Figure 1). Brain tumors usually show an increased choline peak, decreased or absent NAA, and the presence of a lactate and/or lipid peak, which are absent under normal circumstances.[2,4,7,8] Creatine values are usually low in brain tumors, especially malignant ones. Variations in Cho and Cr values can be used to differentiate low-grade astrocytomas from oligodendrogliomas and higher-grade astrocytomas. Rapid proliferation of malignant cells shows up as a high choline peak on spectra. In addition to individual peaks, relative metabolite ratios such as NAA/Cr, NAA/Cho and Cho/Cr are also used for characterizing brain lesions.[7]

Considerable increase in Cho level and Cho/Cr ratio was observed from low-grade astrocytoma to anaplastic astrocytoma to glioblastoma.[8] Highest levels of Cho were also noted in primitive neuro-ectodermal tumors (PNETs). Similarly, an inverse relation is noted between tumor grade and NAA levels. All types of glioma usually demonstrate moderate decrease in Cr level except PNETs, which show a significant decrease in Cr compared with gliomas. Studies also show that lower myo-inositol (Ins)/Cr ratios are associated with high-grade astrocytomas, while low-grade astrocytomas show a high Ins/Cr ratio.

Extra-axial neoplastic lesions such as meningiomas show moderate elevation of Cho, decreased Cr, and almost complete absence of NAA. Unremarkable lipid and lactate resonance peaks are also observed.

Hamartomas seen in neurofibromatosis type 1 may be differentiated from gliomas. Studies show that the Cho/Cr ratio is greater than 2.0 in gliomas, 1.3-2.0 in hamartomas, and less than 1.3 in normal brain tissue.[11]

Differentiation between gliomatosis cerebri (GC) and low-grade glioma (LGG) on anatomical grounds is often difficult. There are, however, subtle MRS variations which may be helpful. GC shows increased levels of creatine compared to low to normal concentration in LGG. There are no significant differences in levels of Cho, NAA and myo-inositol (Ins).[12]

Metastases to brain are more prevalent than primary brain tumors. Law et al[13] demonstrated the value of peritumoral choline measurement to differentiate between high-grade glioma and metastases. Metastases show low peritumoral Cho levels because of vasogenic oedema and increased interstitial water, whereas gliomas show elevated Cho levels on account of infiltrating tumour cells. Metastases can also be differentiated from high-grade glioma by a high lipid peak. NAA and Cr peaks are significantly lower compared to primary brain malignancies (Figure 2).

Radiation-induced necrosis versus recurrent or residual tumour is yet another diagnostic dilemma where MRS may be helpful. Weybright et al[14] demonstrated that a Cho/Cr ratio of greater than 1.79 had a seven-fold increased likelihood of being pure tumor. Additionally Cho/NAA and NAA/Cr ratios are also helpful. MRS is also being used to avoid sampling errors and guide the most appropriate site for obtaining a biopsy when residual tumour is suspected.[15]

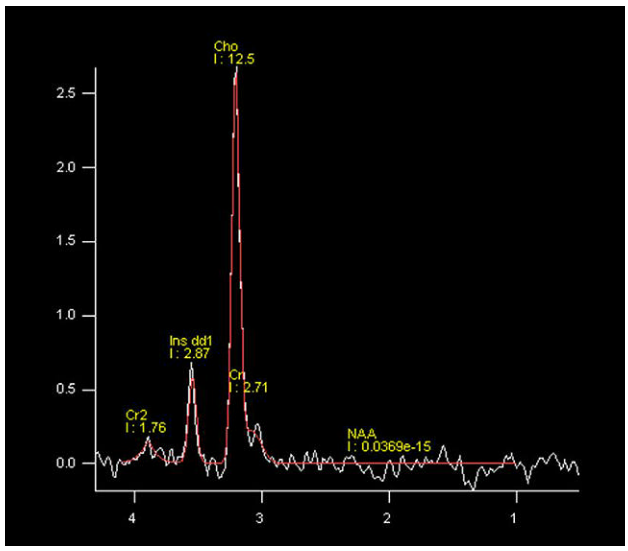

Figure 2: MR spectrum from a metastatic brain lesion. The NAA is virtually absent. The Choline is markedly elevated (ratio: 1:12.5). Significant reduction is also seen in the Creatine peak.

ISCHEMIA AND INFARCTION

All metabolite levels including Cho, Cr and NAA are decreased in cerebral ischemic lesions (Figure 3). Increased Cho/Cr ratio has been reported in brain infarction but this is due to a pronounced reduction of Cr rather than raised Cho values.[16] Prominent Lac and acetate peaks are seen in cerebral infarction. The peak of Acetate, a degradation product of NAA, is particularly characteristic of infarction.

INFECTIONS

Brain abscesses typically show reduced levels of Cho, NAA and Cr. MRS can be used to distinguish pyogenic from tuberculous brain abscess.[17] Pyogenic abscesses usually show increase amino acid (valine, leucine, isoluceine) peaks due to prominent proteolysis, while tuberculous abscess predominantly gives a lipid peak. Intracranial tuberculoma shows lipid resonance at 1.3 ppm, 2.02 ppm, and 3.7 ppm at in vivo MR spectroscopy.

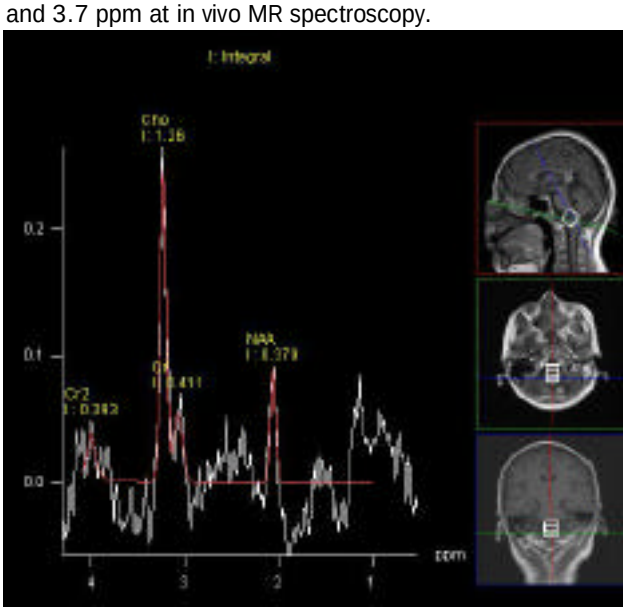

Figure 3: MR spectrum from a focal infarction. NAA is suppressed but still detectable. Choline is normal (compare with choline peak in Figure 1 - the ratio is 1:1.2 in both), however there is marked reduction in the Creatine peak. Additionally there is a broad peak to the right of the NAA peak representing Lactate.

CONCLUSION

MR spectroscopy enables imaging at the molecular level, providing information about brain tissue that was previously available on biopsies only. Its availability on routine clinical MRI systems has given MRS studies wider clinical applicability, thus helping in improved patient care. It is becoming a part of the practice of neuroradiology, enabling the radiologist to start differentiating between benign and malignant processes. The technology, however, is not infallible and should be considered an adjunct to anatomical imaging rather than a replacement for histopathological evaluation.

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