ROLE OF PROTON MR SPECTROSCOPY IN NEOPLASTIC AND NON-NEOPLASTIC INTRACRANIAL MASSES

THESIS SUBMITTED FOR PARTIAL FULFILLMENT OF MD. DEGREE IN RADIODIAGNOSIS

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To My Family

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INTRODUCTION AND AIM OF WORK

MR spectroscopy is increasingly receiving more attention from radiologists, neurologists, psychiatrists and other clinicians. In the past, most MR spectroscopy studies were performed by a small and dedicated group of individuals, mostly basic scientists, but recently the availability of commercial software spectroscopy packages have increased its use in daily clinical situations *(Castillo et al, 1998).*

MR spectroscopy does not produce images but results in graphs. Recently, customize software programs that display the level of metabolites as zones of different colors or shades of gray (spectroscopic images) have been developed *(Castillo et al, 1998).*

A definite diagnosis and characterization of intracranial mass lesions, based on structural Magnetic Resonance Imaging (MRI) alone may be difficult. In such cases Proton Magnetic Resonance Spectroscopy (1H-MRS) along with other non-invasive techniques represents an advance in the specificity of brain lesion diagnosis *(Kumar et al, 2003).*

Proton magnetic resonance spectroscopy (1H-MRS) gives completely different information related to cell membrane proliferation, neuronal damage, energy metabolism and necrotic transformation of brain or tumor tissues *(Moller-Hartmann et al, 2002).*

Thus, Proton Magnetic Resonance Spectroscopy (1H-MRS) is superior to MRI in the detection of tumor growth in morphologically normal tissue and in the

differential diagnosis of untreated intracranial space-occupying lesions (SOLs) *(Kumar et al, 2003)*.

MRS provides a detailed bio-chemical analysis (metabolites) of the tissue, allowing direct insight into in-vivo human brain metabolism. The metabolites, reliably mapped using 1H-MRS include Choline {(Cho, 3.20 parts per million (ppm)}, Creatine (Cr, 3.02 ppm), N-acetyl-L-aspartate (NAA, 2.02 ppm), Lactate (Lac, 1.33 ppm) and Lipids (1.28-1.33 ppm). Alanine (1.5 ppm) and acetate (1.92 ppm) were also reported *(Poptani et al, 1995; Kumar et al, 2003)*.

Non-neoplastic lesions such as brain abscesses are marked by decreases in choline (Cho), creatine (Cr) and N-acetyl-aspartate (NAA). In patients with epidermoid cyst, lactate along with an unassigned resonance at 1.8 ppm was reported and could be easily differentiated from arachnoid cyst which shows only minimal lactate. Only lactate is commonly observed in a variety of intracranial cystic masses, except for abscess and cysticercosis, in which resonances of acetate, succinate, amino acids, and/or unassigned metabolites can be seen in addition to a lactate peak. Tuberculous lesions have been shown to exhibit strong lipid resonances, ascribed to mobile lipids within the caseous material, which are minimally visible on MR imaging *(Poptani et al, 1995; Chang et al, 1998; Moller-Hartmann et al, 2002; Kumar et al, 2003)*.

As for brain neoplasms, proton MR spectra obtained from them typically show: 1) decreased N-acetylaspartate (NAA), a marker of neuronal integrity, 2) diminished Creatine (Cr), involved in cellular energetics and osmotic balance, and 3) increased Choline (Cho), involved in cell membrane turnover. Lactate (Lac) and mobile lipids (Lip) can be evident in aggressive tumors, reflecting increased anaerobic metabolism and cellular necrosis, respectively. Gliomas exhibit significantly increased Cho and lipid formation with higher WHO tumour grading. In addition, the Cho/Cr ratio of 1H-MRS provides additional

information to MRI in differentiating residual/recurrent gliomas from non-neoplastic lesions(radiation necrosis) being higher in the former. Metastases have elevated Cho similar to anaplastic astrocytomas, but can be differentiated from high-grade gliomas by their higher lipid levels. Extra-axial tumours, i. e. meningiomas and neurinomas, are characterized by a nearly complete absence of the neuronal marker NAA. Also, patients with cystic meningioma could be differentiated from cystic schowannoma by the presence of alanine in the former *(Poptani et al, 1995; Butzen et al, 2000; Moller-Hartmann et al, 2002; Moller-Hartmann et al, 2002; Ando et al, 2004)*.

To conclude, compared to CT and MRI, well-established morphological diagnostic tools, MRS provides information on the metabolic state of brain tissue. So, it is useful to arrive at a more definitive diagnosis in doubtful intracranial space-occupying lesions with similar morphological imaging patterns *(Burtscher and Holtas, 2001; Kumar et al, 2003)*.

The primary aim of this study is to evaluate the utility of proton MR spectroscopy (reporting characteristic spectral patterns) in various neoplastic and non-neoplastic (congenital, inflammatory, post-operative. . . . . etc) brain masses for obtaining the most accurate diagnosis, guided by other studies (CT or conventional MRI) for lesional localization. Reference to the operative and histopathological results will be searched for as well (whenever possible).

BASIC PRINCIPLES OF MR SPECTROSCOPY

INTRODUCTION AND HISTORY

Medical imaging techniques, beginning with the x-ray in 1895 and followed more recently by ultrasound(US), computed tomography(CT), and magnetic resonance imaging (MRI), have provided high temporal, spatial, and contrast resolution methods to assess structure. However, the need to assess beyond the purely anatomic aspects, such as biochemistry and tissue physiology, required the development of functional techniques such as functional magnetic resonance imaging (fMRI), perfusion weighted imaging (PWI), diffusion weighted imaging (DWI), and magnetic resonance spectroscopy (MRS). *(Brandáo and Domingues, 2004)*

Purcell et al and Bloch et al first elucidated the principles of nuclear magnetic resonance in 1946.The technique of spectroscopy is widely applied in chemistry for the analysis of compounds in solution, and is a powerful tool for determining the structure of biological macromolecules. Similarly, MR spectroscopy can be used to identify important molecules in living tissue. *(Purcell et al., 1946; Bloch et al., 1946; Mheshwari and Mukherji, 2002)*

In 1995, a new era in neuroradiology emerged with the approval of MRS by the united States Food and Drug Administration (FDA). *(Brandáo and Domingues, 2004)*

MRS is most useful when augmented with a comprehensive patient evaluation that includes a clinical history and imaging studies. MRS does not replace cMRI but complements the information provided by it. MRS may provide additional

information as a prognostic indicator, while following the progression of the disease and evaluating the response to treatment. ***(Adamson et al., 1998; Brandáo and Domingues, 2004)***

With the potential to record biochemistry in vivo, MR spectroscopy is useful in imaging tumors, infarcts, and epileptic foci in the central nervous system. ***(Mheshwari and Mukherji, 2002)***

MR spectroscopy is a non-invasive means of obtaining metabolic information. MRI is a technique used for the noninvasive detection and anatomical mapping of water protons (hydrogen), whereas MR spectroscopy records protons in intrinsic phosphorus-containing metabolites, sodium, potassium, carbon, nitrogen, and fluorine. ***(Castillo et al., 1996; Ross and Blum, 2001)***

The most useful nuclei for human spectroscopy are hydrogen, phosphorus, sodium, and, to a lesser extent, carbon. Proton (hydrogen) MR spectroscopy (HMRS) has a greater signal-to-noise ratio (SNR) and better spatial resolution than phosphorus spectroscopy and is more easily integrated with MRI in a single examination. HMRS has the potential to record biochemistry in vivo, which can help in tissue characterization. ***(Mheshwari and Mukherji, 2002)***

Protons often are used for MR spectroscopy because of their high natural abundance and high nuclear magnetic sensitivity. Despite the huge number of biomolecules in tissue, relatively few are identifiable in vivo because only freely mobile compounds that are present in substantial concentrations give enough signals to be detected. The concentrations of metabolites of interest are in the millimolar range; water protons are a thousand times as common. For this reason, water resonance has to be suppressed so that the other molecules can be detected. The diagnostically resolvable hydrogen MR spectra may be obtained using clinical instruments (1.5 T or greater) and routinely used surface coils. ***(Lenkinski and Schnall, 1991; Kwock, 1998a; Mheshwari and Mukherji, 2002)***

Conventional MRI and MRS rely on the same physical principles to collect signal but differ the way the data is processed, displayed, and interpreted. Instead of images, a plot with peak amplitudes compared with a respective frequency is obtained. ***(Cousing, 1995; Van der knapp and Valk, 1995; Danielsen and Ross, 1999)***

These metabolites are detected in the spectrum because of the following:

1.They consist of hydrogen protons (H).
2.They exist at concentrations ≥0.5mmol/L.
3.They resonate at different frequencies along the horizontal, chemical shift axis.
4.The hydrogen signal from water is nulled.

For a given spectrum, the position of the metabolite signal is identified on the horizontal axis by its chemical shift, scaled in units referred to as parts per million (ppm). With the appropriate factors considered, such as the number of protons, the relaxation times, and so froth, a signal can be converted to a metabolite concentration by measuring the area under curve (**Fig.1**). ***(Brandáo and Domingues, 2004).***

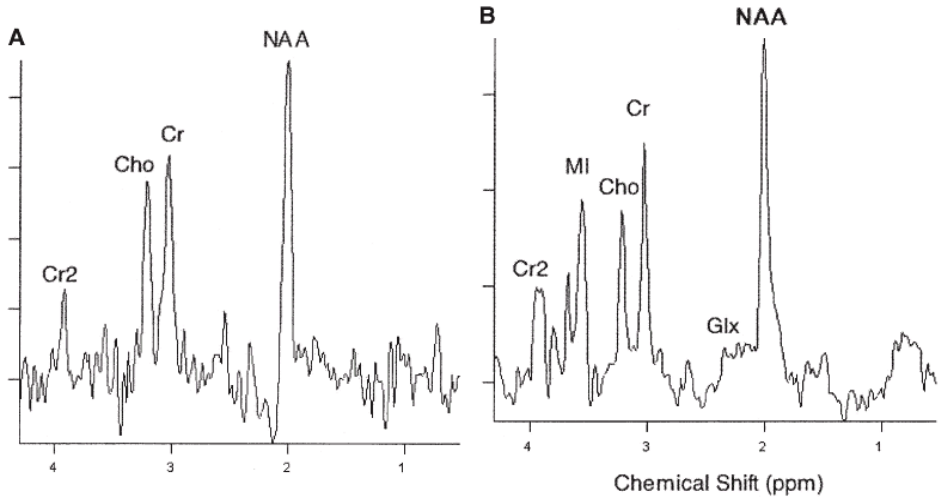

Fig.1. Proton MRS from normal brain tissue using (A) long echo time (TE = 135 msec) PRESS and (B) short echo time (TE = 30 milliseconds) STEAM techniques. On long echo time spectra (A), peaks from Choline (Cho), Creatine (Cr) and N-acetylaspartate (NAA) are clearly visible. The spectra are somewhat noisy because of the small volume. On short echo time spectra (B) additional metabolites normally seen include myoinositol (MI) and glutamate and Glutamine (Glx) peaks, along with a second peak from creatine (CR2). ***(Smith et al., 2003)***

BASIC PRINCIPLES

TIME DOMAIN VERSUS FREQUENCY DOMAIN

MR imaging and MR spectroscopy are basically one and the same technique, differing only in the manner in which the data are processed and presented. Both are governed by the same physical principles. *(Shaw, 1988)*

Hydrogen protons (H1) are commonly used for MRS because of their high natural abundance in organic tissues and high nuclear magnetic sensitivity compared with other magnetic nuclei. *(Castillo et al., 1996)*

When placed inside the strong magnetic field of the MR imaging system, nuclei with net nuclear spin (which includes the hydrogen nucleus) will align their axis of spin preferentially parallel to the direction of the main magnetic field. After nuclei have been aligned to this magnetic field, they can be stimulated with a radio-frequency pulse that perturbs the axis of spin away from the main field. When this pulse is turned off, nuclei return to their original alignment. The relaxation time, or the time it takes nuclei to return to their original position, is governed by the strength of the main magnetic field, and by intrinsic properties of the nuclei. The receiving coil of the MRI unit detects voltage variations as the nuclei precess during this recovery period. A plot of this voltage variation (signal intensity versus time) is termed "free induction decay" and is a function in the time domain (**Fig.2**). *(Smith et al., 2003)*

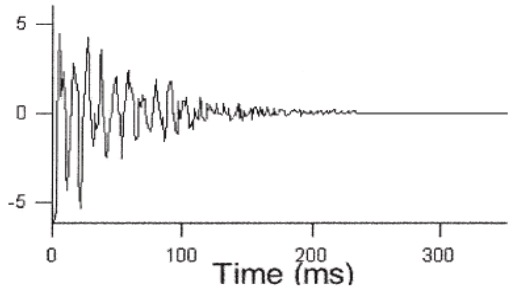

Fig.2. Free Induction Decay (FID) signal recorded from a multivolume spectroscopy of brain. X axis is time, Y axis is signal intensity. Note the complex signal, with multiple different frequencies present. *(Smith et al., 2003)*

In MR imaging, the signal obtained in the time domain is used to generate an image, whereas in MR spectroscopy the Fourier transform of MR signal in the time domain is used to generate a frequency domain spectrum of components that make up the image. ***(Kwock, 1998b)***

T1-weighted spin echo image of a phantom that contains 10% ethyl alcohol. The free induction decay of the MR signal arising from the protons associated with water and ethanol versus time that is used to generate the image. ***(Kwock, 1998b)***

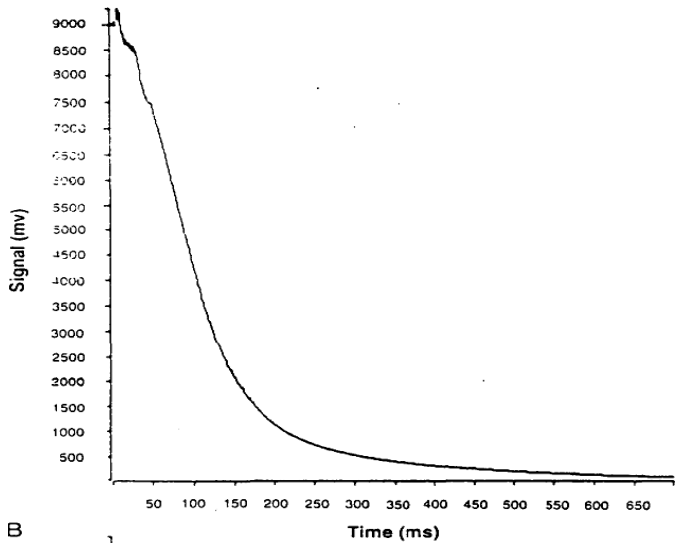

Fig.3. The time domain proton free induction decay process (FID). ***(Kwock, 1998b)***

Fig.3 is the time decay process is characterized by the following mono-exponential function:

$$I = [Nu]e^{-kt/T}$$

where I is the intensity of the signal at time t; [Nu] is the concentration of the nuclei; k is a constant; and T is the relaxation time of the nuclei being excited. (Kwock, 1998b)

It is obvious that one cannot tell what part of the image is composed of protons from ethanol. Fourier transformation of the time domain signal, however, leads to the generation of a frequency distribution of proton

components (frequency domain), which make up the free induction time domain signal **Fig.4.** ***(Kwock, 1998b)***

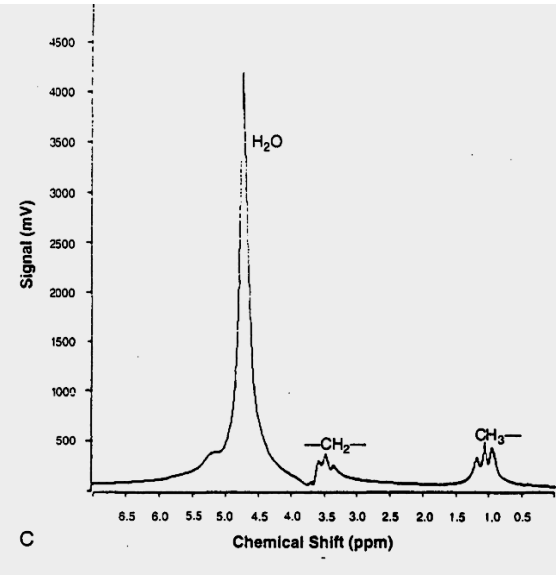

Fig.4. The proton frequency domain Fourier transform of the FID shown in B. ***(Kwock, 1998b)***

This frequency spectrum shows that part of the time domain signal arises from the protons of the methyl (CH3-) and methylene (-CH2-) groups of ethanol. ***(Kwock, 1998b)***

As has been presented in a number of reviews, nuclear magnetic resonance (NMR) is based on the principle that some nuclei have an associated spin property, which allows them to behave like small magnets. In the presence of an externally applied magnetic field, the magnetic nuclei interact with the applied magnetic field and distribute themselves to different energy levels (**Fig.5**). ***(Martin et al.,1980; Koutcher and Burt, 1984;Shaw, 1988; Salibi and Brown, 1998; Kwock, 1998b)***

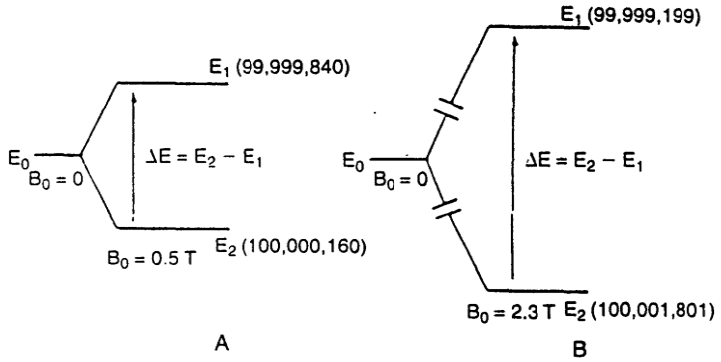

Fig.5. The effect of 0.5 and 2.3 T magnetic fields (B_0) on spin energy levels. Numbers in parentheses represent the number of spins in each energy level, with an initial spin population of 2.0 x 10^8 spins at E_0 before exposure to B_0. ***(Kwock, 1998b)***

Protons, which have a spin quantum number of half the nuclei, distribute themselves into two energy states, which correspond to the nuclei either spinning in the direction of the applied magnetic field or spinning in a direction opposed to the applied magnetic field. The separation between energy levels is proportional to the strength of the applied magnetic field. This means that as the magnetic field strength increases, the intensity of the signal increases. This increase in signal intensity is due to the increase in energy separation between the two states and in the number of nuclei in the lower energy state that can be excited to the higher energy state (**Fig.2**). ***(Kwock, 1998b)***

If energy is applied to the systems shown in Figure 2 in the form of a radiofrequency pulse that exactly matches the energy separation between the two energy states, a condition of resonance occurs. This means that nuclei in the lower energy state can absorb this energy and are promoted to the higher energy state. The equation that describes this phenomenon is known as the Larmor frequency equation:

$$\Delta E = h w_0 = h \gamma B_0$$

where w_0 is the Larmor precessional frequency (cycles/s or Hz), h is Planck's constant divided by 2π, γ is the gyromagnetic ratio for that nucleus (MHz/T, where T = Tesla), and B_0 is the applied magnetic field (T). ***(Kwock, 1998b)***

CHEMICAL SHIFT (THE BASIS OF MR SPECTROSCOPY)

As presented previously, the Larmor frequency equation states that the resonance frequency of a magnetic nucleus (the radiofrequency needed to excite a given nucleus to the higher spin state) is directly proportional to the magnetic field environment it experiences. Atoms such as phosphorus-31 and hydrogen-1 resonate at different Larmor radiofrequencies because of the differences in the magnetic properties in the nucleus of these atoms. This is the basis of the nuclear MR phenomenon (for phosphorus-31 the Larmor resonance frequency at 1.5 Tesla is 25.85 MHz, and for hydrogen-1 it is 63.86 MHz) and allows the identification of magnetic nuclei having different atomic numbers. However, even for a given magnetic nucleus/atom having the same atomic number, chemical compounds containing this nucleus can have slightly different Larmor resonance frequencies. This difference is due to interactions of the electrons that surround the nucleus and forms an electron cloud around it. ***(Kwock, 1998b)***

Electrons are negatively charged species and have spin properties similar to the protons and neutrons in the nucleus of the atom. Thus, when placed in an externally applied magnetic field, electrons precess and induce a small magnetic field, B′, around the nucleus. These local magnetic fields generated by the surrounding electrons can add or subtract from the applied field, $B_\circ$ (normally in the range of parts per million of $B_\circ$). Consequently the nucleus experiences a slightly different magnetic field, B_{eff}, which is equal to ($B_\circ$—B′) (**Fig.6**). ***(Kwock, 1998b)***