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# Magnetic resonance spectroscopy: an overview of the method and its application in clinical neuroradiology

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***Background.*** *Magnetic resonance spectroscopy (MRS) is a comparatively new diagnostic method. Brain tissue is very suitable for MRS analysis. In practice, only a small number of compounds present in the brain may be analysed by MRS. The utility of MRS in neuroradiology and clinical practice is constantly growing, since the investigation is of help in the differential diagnosis of pathological processes as well as in assessing the progress of a disease and evaluating the outcome of treatment. In analysing the data obtained, a number of factors that may influence the objectivity of the result must be taken into account. The magnetic resonance scanner located at the Institute of Radiology, University Medical Centre Ljubljana, utilises modern MRS protocols and has proved a valuable tool in the diagnostic evaluation of neurologic diseases.*
***Conclusions.*** *MRS provides spectral analysis of substance in a selected volume of tissue, thereby offering an insight into the metabolic state of the tissue.*

*Key words: nuclear magnetic resonance; nervous system diseases – diagnosis; neuroradiography*

## Introduction

Magnetic resonance spectroscopy (MRS) is a comparatively new diagnostic method. The aim of this paper is to present briefly this new technique. Specific features of the investigation are outlined, special emphasis being placed on its utility in neuroradiology.

MRS appeared as an analytical method in natural sciences already in 1946[1,2] and has remained indispensable to the present. Magnetic resonance imaging (MRI), permitting visualisation of the examined tissue, was developed only in 1973.[3-5] The method was adopted into clinical practice 10 years later, when computer assisted tomographs with sufficiently powerful and adequately homogeneous magnetic fields became commercially available. Further technical advances in the early 90's made it possible to perform MRS analysis of the patient's tissue in the course of magnetic resonance examination, but these in vivo procedures were at first non-standardized.[6] An important milestone in the evolution of the technique was the development of automated MRS sequences in 1995 [7], which increased the clinical utility of the technique and paved the way for new technological so-

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lutions, resulting in progressive shortening of the investigation and increasing application of MRS in daily radiological practice.

The Institute of Radiology, University Medical Centre Ljubljana, has a modern magnetic resonance tomograph (GE Signa Horizon LX 1.5 T), which allows the use of several modern MRS protocols.

## Method

MRS permits in vivo spectral analysis of substance in a selected volume of tissue by means of nuclear magnetic resonance (NMR) and thus offers an insight into the metabolic state of the tissue. In contrast to MRI, which yields information on the distribution of protons in space, displaying the morphology of examined organs, MRS provides chemical analysis of selected tissue.

At present, the majority of clinically applicable MRS protocols employed in neuroradiology make use of the hydrogen nucleus (proton), mainly because of its sensitivity and prevalence in the body. Protons act as small magnetic dipoles in a static magnetic field. If radio-frequency (RF) electromagnetic waves in the form of RF pulses are delivered to tissues in a static homogeneous magnetic field, the tissue receives a certain amount of energy, which may also be absorbed by protons. Protons absorb RF energy only when they are in resonance with a frequency of the delivered RF radiation. This is accompanied by a change in the energy status of the protons, which is a consequence of a different average proton orientation with respect to the direction of the static magnetic field after the RF pulse. On resuming the equilibrium state, the atoms give off the energy in the same form, i.e., as RF radiation, which can be detected by the tomograph with the aid of special RF detection coils. A precondition for high quality signal detection is a strong and highly homogeneous static magnetic field. In MRS the signal is usually acquired from a well-defined volume of the tissue, which is accomplished by the use of special localisation techniques: specially designed sequences of RF pulses [8-12], or with the aid of inhomogeneous RF detection coils (surface coils)[13], or with other less common techniques.[14] Signal detection is followed by computer processing of the acquired data, displayed as spectral analysis of the substance in a selected volume of tissue.

The resonance frequency of protons is proportional to the static magnetic field, i.e., stronger the field higher is the resonance frequency. However, also protons in different chemical groups may have different resonance frequencies. The resonance frequency depends on the type of chemical binding of protons and the influence of surrounding nuclei within individual chemical groups in a molecule. For instance, hydrogen in the group $CH_2$ has a different resonance frequency from that of hydrogen in the group $CH_3$, and so these two groups are displayed in the spectrum as two different peaks. The phenomena is called chemical shift, and is expressed with the following equation:

$$\text{Chemical shift (in ppm)} = 1{,}000{,}000\ (\nu/\nu_r - 1) \quad (1)$$

Here νr denotes the resonance frequency of the reference standard (plain water) and ppm stands for parts per million.

*The spectrum* is represented as a graph in which the values of the difference in the resonance frequency of chemical groups from the reference value, indicating the type of chemical group e.g. the type of substance, are presented on the *x*-axis. On the y-axis, the surface under individual peaks of the curve reflects the concentration of a specific chemical group and is therefore proportional to the amount of individual substances in the selected volume. The units on both axes are relative. Values on the x-axis are expressed in ppm (parts per million) and on the ordinate in re-

lative concentration (percent). The spectra obtained are the result of a large number of repeated measurements and represent averaging of the measured values. With MRS it is possible to analyse chemical groups with unbound protons. For their detection, the concentration of the substance in the selected volume of tissue must not be less than 0.5-1 mM/kg of tissue.

In addition to the spectrum, the computer calculates and displays also the ratios between selected substances. In standardised protocols, the types of substances to be compared are determined in advance. These ratios are very important in interpreting the results since they allow the elimination of various factors that affect the results of measurements (osmotic status of the tissue, presence of paramagnetic and ferromagnetic substances etc.).

In order to obtain a technically adequate spectrum, we must conduct the investigation in specific phases. Calibration of the instrument involves adjusting the gain of the transmitter to optimise RF pulses in the sequence. Also the gain of the receiver needs to be adjusted to allow the optimal digitalisation of the received analogue signal. Since every sample spoils homogeneity of the static magnetic field due to its magnetic susceptibility a correction of the static magnetic field homogeneity is needed. This procedure is called shimming and is done by the use of various coils in the magnet, which may produce additional inhomogeneous static magnetic fields of adjustable amplitudes to the main static magnetic field. Suitable combination of these fields may improve the static magnetic field homogeneity. Shimming is essential for MRS. Shim adjustment is followed by adjustment of the signal suppression pulses. Namely, predominant substance in the tissue, such as lipid or so-called free water, would have in the spectrum extremely high spectral line that would overwhelm all other spectral lines of much higher interest. Suppression of the predominant substance is therefore necessary. By graphic localisation of the volume of interest in the MR image, we define the site and size of the volume of tissue to be analysed. Sequence parameters set-up is followed by the execution of the pulse sequence in two phases. During the first phase the magnetic resonance signal is excited in the selected volume of the tissue by RF pulses of a special shape, amplitude and duration. This is followed be the second phase during which magnetic resonance signal is acquired. The measurements are repeated many times and the results are averaged. Finally, a spectrum is calculated from the acquired time domain data by the mathematical transformation known as the Fourier transformation. Spectrum post processing is also possible as for example noise filtering, phase correction and line-width measurements. In modern MRS protocols, all important phases are automated, whereby the duration of analysis is appreciably reduced.

The results of investigation are affected by a number of factors. Important technical factors include strength of the basic static magnetic field, size of the selected volume of tissue, number of measurement repetitions, selected technical parameters (echo time, repetition rate) etc. The homogeneity of the local magnetic field in the selected volume of tissue is affected by tissue structure, presence of paramagnetic substances (e.g. contrast medium) and ferromagnetic substances (e.g. blood), and concentration of osmotically active substances and electrolytes (e.g. mannitol).

Several types of MRS are known. They can be classified according to observed nuclei, which are most often hydrogen, but carbon, fluorine, phosphorus or some other nuclei can also be observed. The most widely used methods for spatial localisation of the sample are volume methods, such as the STEAM (stimulated echo acquisition mode)[13] and the PRESS (point resolved spectroscopy)[12] spin echo sequences, which utilise selective RF pulses to

define the volume of interest in the sample and compare it to slices in the MR image. At present, PRESS is the preferred method, mainly because of a better signal-to-noise ratio. Tissue can be simultaneously analysed in a single volume of interest (single voxel spectroscopy, SVS) or in several volumes of interest (multi voxel spectroscopy, MVS) in selected planes (2D or 3D). If the results of analysis are superimposed on the morphological image of an organ, we speak of so-called spectroscopic imaging. In this mode of MRS, the computer assigns each metabolite an appropriate, so that the distribution and intensity of colours in the image of an organ illustrate the distribution and concentration of individual metabolites in the tissue being analysed.

In our work, we now use routinely an automated pulse sequence, PRESS-SV (General Electrics) with the following parameters: repetition time TR = 1500 ms, echo time TE = 35/144/288 ms, voxel size 2 × 2 × 2 cm, NEX 8, FOV 24.

Preparation of the patient for the investigation, positioning in the MR tomograph, safety precautions and other measures are the same as for MRI. During the procedure, the patient, or the tissue being examined, must be completely motionless. Therefore restless patients and children are examined in general anaesthesia. Individual spectroscopic analysis at a single volume of interest lasts about 10 minutes. As 6-9 analyses are usually required, the examination may take as long as 90 minutes. Therefore MRS is regarded as a special radiological procedure, which should be undertaken only on the basis of proper indications. Lesions located on the border between tissues of different composition (e.g. brain / skull, brain / liquor space) or close to a bleeding site are difficult to analyse, as the local magnetic field in such regions is very inhomogeneous. Similar problems occur with processes involving tissues with a high content of water or lipids, where suppression of the signal during data processing is difficult and often inadequate. It is important to select a solid segment of pathological tissue that adequately reflects the primary pathological process (e.g. the edge of a lesion) and not an area showing secondary changes (necrosis etc.). Selection of the volume of tissue to be analysed, or its location, is thus of vital importance for the technical quality of the spectrum as well as for proper interpretation of the result.

## Clinical value

MRS can be used for the analysis of all pathological processes in tissues fulfilling the previously mentioned conditions (muscles, parenchymal organs etc.).

### *MRS in neuroradiology*[15,16]

In further text, we will concentrate on the use of MRS in neuroradiology, where the technique has found the widest application. Brain tissue is stationary, mostly homogeneous and therefore suitable for MRS. Moreover, it is not readily accessible for invasive cyto-histological investigations, which carry a substantial risk of procedure-related complications. The main indications for MRS are inborn and acquired metabolic disorders, neonatal hypoxia and other sequelae of ischaemic brain injury, disorders of myelination, degenerative brain diseases, epilepsy, infections, brain tumours and others. MRS provides an insight into the metabolic state of the selected tissue and assists both in the differential diagnosis of pathological processes and in assessing the progress of illness (e.g. tumour malignancy) and outcome of treatment (e.g. evaluation of residual tumour). In practice, only a small number of neurochemical compounds present in brain tissue can be analysed by MRS. The main metabolites (shown with the abbreviations and main resonance frequencies) are: N-acetylaspartate (NAA: 2.0 ppm), choline and choline-rich compounds (Cho: 3.22

ppm), creatine (Cr: 3.0 ppm), lactate (Lac: 1.3 ppm), lipids (Lip 0.9 and 1.3 ppm). In certain pathological processes, other metabolites, which may be typical or non-specific, occur at their resonance frequencies.

*NAA* is found in neurones and is an indicator of the neurone / axon density in brain tissue. Its precise role has not been definitely established.

*Creatine* originates mainly from the intracellular pool of creatine and phosphocreatine and is an indicator of the energy state and activity of cells.

Most of *choline* present in brain tissue is under normal circumstances inaccessible to MRS analysis as it is bound to cell membranes, myelin and other complex lipoproteins and/or lipids. Its two main constituents of choline pool, phosphorylcholine and glycerophosphorylcholine, making the largest contribution to the measured choline value (choline peak in the spectrum), are released in increased quantities during degradation and/or increased turnover of cell membranes and myelin sheaths.

What has been said about choline applies also to free lipids, whose concentration is related to the previously mentioned pathological processes, and which are frequently found in association with altered choline metabolism.

*Lactate* is not detected by MRS in normal brain tissue. However, its concentration is increased in anaerobic metabolism or accelerated glyosis.

In some pathological processes, increased concentrations of some additional, non-standard compounds may be registrated. So the concentration of certain amino acids is elevated in infected tissue as a result of metabolism in the presence of bacteria (abscesses), and precursors are elevated as a result of impaired metabolism of normal substances (enzyme defects) etc.

Analysis of the results of investigation requires caution and experience. The spectral peaks of metabolites may overlap because of equal resonance frequencies. The concentration of compounds varies in different parts of the brain (grey matter, white matter, basal ganglia), and so samples from different regions should be analysed. The content of substances depends also on the subject's age. The concentration of metabolites is affected by the presence of osmotically active substances (e.g. mannitol) and drugs in the brain. Ferromagnetic and paramagnetic substances, such as contrast agents (gadolinium, haemoglobin degradation products) affect the MR properties of metabolites. In patients whose brain is not diffusely involved, these problems may be overcome by comparison of spectra from the healthy and affected sides.

At the Institute of Radiology, University Medical Centre Ljubljana, MRS is currently used routinely only in neuroradiology, mainly for neuropaediatric diagnosis and for the diagnostic workup and evaluation of the results of treatment of brain tumours. However, the indications for the investigation are constantly widening.

In the *future*, major advances may be expected to take place in MRS as a result of progressively faster protocols, better signal-to-noise ratio and new combinations of different techniques and types of spectroscopy, exploiting different kinds of reference elements.

## Case report

In a 29-year-old male patient with frequent absence seizures, CT and MRI revealed a space-occupying lesion of undefined aetiology in the left temporal region, which was compatible with vasculitis or a low-grade neoplasm (Figure 2). The patient underwent an operation, comprising uncotomy, hypocampotomy and removal of the medial part of the left temporal lobe. Histological examination of the removed tissue failed to rule out either of the two possible diagnoses. After the operation,

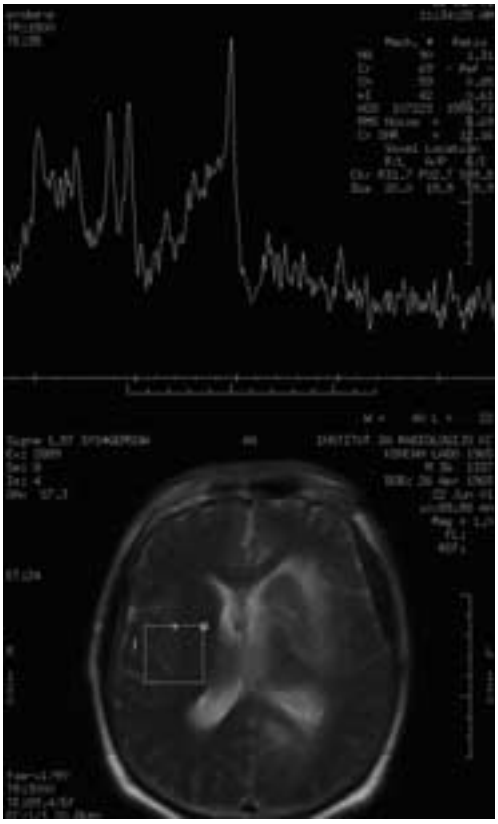

**Figure 1.** Normal, technically appropriate spectrum (above) from the designated area of the brain (below). Values on the *x*-axis reflect the type of compound, and those on the *y*-axis the concentration of this compound. The ratios between selected substances and the technical parameters of the investigation are presented.

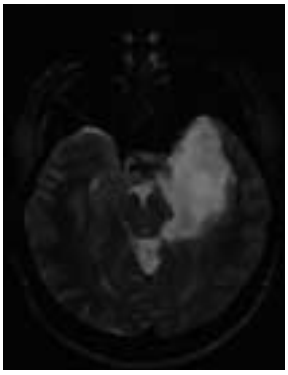

**Figure 2.** T2-weighted MRI obtained prior to surgery, showing oedema of brain tissue in the left temporal region.

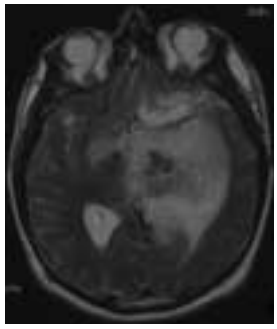

**Figure 3.** T2-weighted MRI obtained after surgery, showing a postoperative defect in the left temporal region. There is persistent oedema within the hemisphere, encroaching upon surrounding structures and causing progressive hydrocephalus.

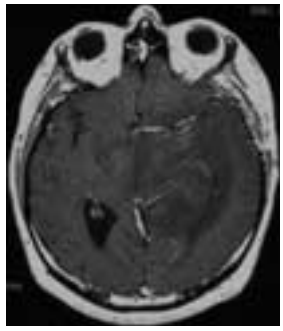

**Figure 4.** T1-weighted MRI obtained after application of contrast medium, showing the state after operation. The lesion does not enhance after gadolinium application.

the seizures persisted, and the patient continued to receive antiepileptic therapy and corticosteroids. Follow-up CT a year after the operation showed persistent oedema in the operated area. Consequently MRI and MRS were repeated as well. MRI confirmed the presence of a space-occupying, partly infiltrative lesion with surrounding oedema in the left temporal region, which extended into the depth of the hemisphere, encroaching upon adjacent structures and causing increasing hydrocephalus (Figure 3). It did not enhance after gadolinium application, which spoke in favour of a low-grade tumour (Figure 4). MRS was pathological, showing a reduced concentration of NAA and significantly increased

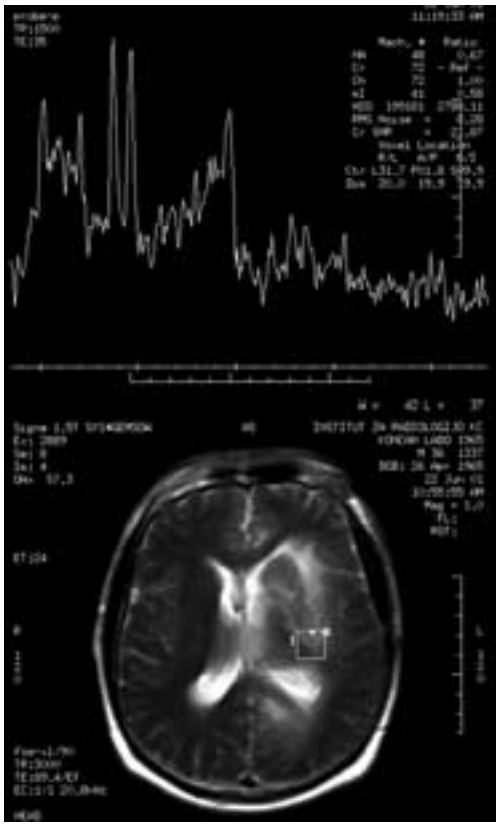

**Figure 5.** Magnetic resonance spectroscopy (above) in a selected volume of pathological tissue (below). The concentration of NAA is reduced, while the concentrations of choline and lactate are significantly elevated. The spectrum is typical of a low-grade malignant process.

concentrations of choline and lactate, compatible with a low-grade tumour (Figure 5). A reoperation was performed, and histological examination of the removed tissue yielded conclusive evidence of a low-grade tumour (glioma).

## Conclusions

MRS provides spectral analysis of substance in a selected volume of tissue, giving information on the metabolic state of the tissue. Brain tissue is very suitable for MRS analysis. In practice, only a small number of compounds present in the brain may be analysed by MRS. The utility of MRS in neuroradiology and clinical practice is constantly growing, since the investigation is of help in the differential diagnosis of pathological processes as well as in assessing the progress of a disease and evaluating the outcome of treatment. In analysing the data obtained, a number of factors that may influence the objectivity of the result must be taken into account. The magnetic resonance scanner located at the Institute of Radiology, University Medical Centre Ljubljana, utilises modern MRS protocols and has proved a valuable tool in the diagnostic evaluation of neurologic diseases.

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