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Clinical MR spectroscopy of the brain

CLINICAL REVIEW

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Magnetic resonance spectroscopy (MR spectroscopy) provides information on various tissue metabolites and is a supplement to standard diagnostic MR imaging. This article describes MR spectroscopy findings for those disorders for which the technique has greatest clinical relevance.

The technological and physical principles behind MR spectroscopy are to a large degree the same as those behind MR imaging (MRI). Protons (hydrogen nuclei) display magnetic properties when in a strong magnetic field, and are the source of the signal in both methods. All protons in a water molecule have the same magnetic properties and are the main source of the signal in MRI. Protons in different molecules have slightly different magnetic properties, and this difference enables small molecules in the body to be detected by MR spectroscopy. An MR spectrum will thus reveal the molecules within tissues, provided that the molecules are mobile and present in measurable quantities (> 1 mmol/l) (1). Molecules can be differentiated on the basis of frequency differences along the x-axis, while the area of the peaks corresponds to the concentration of the molecule (Figure 1). Some diseases have characteristic MR spectra, which contain molecules that are not normally seen in healthy tissue, or where the relative concentrations of metabolites differ from those seen in equivalent healthy tissue (1, 2). In addition to the water signal, the dominant peaks in MR spectra of the brain are from creatine, choline and N-acetylaspartate. Depending on the test conditions, metabolites that are present at lower concentrations in normal brain tissue, such as myo-inositol and

glutamine/glutamate, can also be detected. In normal brain tissue, the amount of lactate is usually too low to be detected by MR spectroscopy. Similarly, lipids are bound in fixed, immobile structures and therefore cannot usually be detected with this technique.

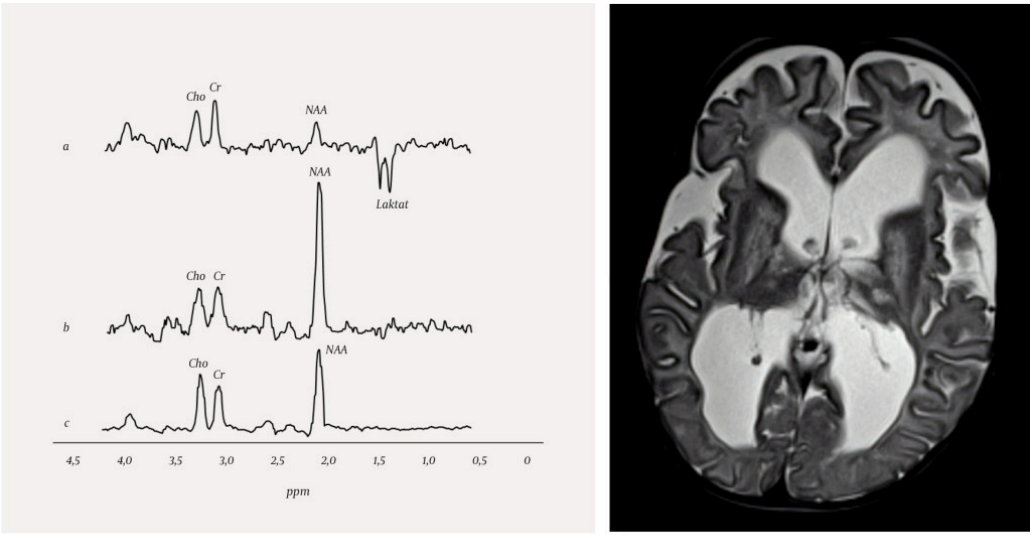


Figure 1 MR spectra from a) a patient with Leigh syndrome, b) a patient with Canavan disease and c) a healthy person, and d) T2-weighted MRI of a patient with Canavan disease. All spectra are recorded with long echo time (135 ms). Choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) appear in all spectra, and changes in these signals can often be linked to pathology. The presence of lactate can be seen in Leigh syndrome (a). In Canavan disease (b), the signal from N-acetylaspartate is far more dominant than in the spectrum from the healthy control (c). Water provides a strong signal at 4.7 ppm (parts per million) that is suppressed and outside the range shown. Spectra are scaled relative to the creatine signal.

MR spectroscopy can reveal metabolic changes that precede pathological structural changes in brain tissue (1). When MRI came into use for clinical diagnosis in the mid 1980s, it was expected that also MR spectroscopy would become a key diagnostic tool, especially in oncology. The reality fell somewhat short of these initial expectations. The technique is now used as a supplement to MRI, primarily in diseases of the central nervous system. For a few conditions, findings from MR spectroscopy may have direct consequences for the follow-up and treatment of the patient. The method has greatest clinical utility in cases of suspected neurometabolic disorders or brain tumours (2). At St. Olavs hospital, MR spectroscopy is used routinely for the diagnosis and follow-up of patients with such conditions. In this article, we describe findings from MR spectroscopy for these diseases based on our own experience and selected literature.

Neurometabolic disorders

Neurometabolic disorders are a large and heterogeneous group of congenital conditions. The incidence of each individual condition is very low, while the combined incidence is estimated to be 1 per 800–2 500 births (3, 4). Most patients with neurometabolic disorders show developmental delay or

neurological signs and symptoms in the neonatal period or early childhood. Exceptionally, neurometabolic disorders may also have adult onset. Many neurometabolic disorders give rise to non-specific structural changes in the central nervous system that can be characterised with MRI, but it can be difficult to make a definitive diagnosis on the basis of imaging alone. The ability to describe the metabolite composition of brain tissue therefore makes MR spectroscopy useful in certain neurometabolic disorders. A small number of diseases have an entirely disease-specific profile on MR spectroscopy (5), while others have an MR spectroscopy profile that is specific for the condition when viewed in combination with imaging and results from clinical testing (2). Common changes in pathological MR spectra are reduced levels of N-acetylaspartate, decreased or increased levels of choline, increased levels of myo-inositol, and the presence of lactate. Examples of neurometabolic disorders that can be characterised with the aid of MR spectroscopy are mitochondrial diseases and enzyme defects (Figures 1a and 1b).

Enzyme defects

Enzyme defects may lead to failure of cellular processes if a specific enzyme is deficient or defective. Disease severity depends on which enzyme is defective, and diseases in this group have a highly variable clinical picture. Canavan disease is a leukodystrophy, in which white matter becomes oedematous and fluid-filled cavities are formed (Figure 1d). Patients with Canavan disease have specific gene mutations that lead to deficiency of the enzyme aspartoacylase, which is essential for cleavage of N-acetylaspartate into aspartate and acetate. The enzyme deficiency leads to accumulation of N-acetylaspartate in the brain and impaired myelin synthesis. The most common form of the disease has onset at six months of age and causes extensive neurological impairment (6). Signs of the disease are irritability, hypotonia and poor upper body control. The disease greatly impairs the child's development, and can give rise to increased head circumference, poor oculomotor control, blindness, epilepsy, muscle stiffness and spasms. Life expectancy is about ten years. MR spectroscopy of patients with Canavan disease shows a strongly elevated N-acetylaspartate signal (Figure 1b). Canavan disease is the only known metabolic disorder to cause an increase in N-acetylaspartate levels.

Mitochondrial diseases

Mitochondrial diseases are a heterogeneous group of disorders that give rise to progressive or intermittent brain damage (7). MRI shows varying findings with oedema and tissue loss, but bilateral involvement of the basal ganglia is typical. Together with MRI and clinical findings, MR spectroscopy can help identify and characterise mitochondrial diseases. The most common finding on MR spectroscopy is the presence of lactate owing to altered intracellular energy production, often followed by decreased N-acetylaspartate, which indicates cell loss. Leigh syndrome is a mitochondriopathy that can cause developmental delay, spasticity and brainstem dysfunction. MRI typically shows symmetrical signal changes in the basal ganglia, thalamus and brainstem. Lactate in MR spectra from these areas strengthens suspicion of Leigh syndrome (Figure 1a).

Brain tumours

Each year, about 300 patients in Norway are diagnosed with a malignant primary brain tumour, of which about 250 are high grade gliomas (8). MR spectroscopy can help distinguish brain tumours from other types of lesions such as abscesses or subacute infarcts (9). In general, brain tumours have elevated levels of choline, lactate and mobile lipids as well as reduced levels of N-acetylaspartate and creatine compared with equivalent normal tissue. Choline levels increase with the degree of malignancy, and the ratio of choline to creatine, and of choline to N-acetylaspartate, is significantly higher in high grade than in low grade gliomas (Figure 2) (10). Lactate and mobile lipids may be detected in glioblastomas, but are also common in metastases.

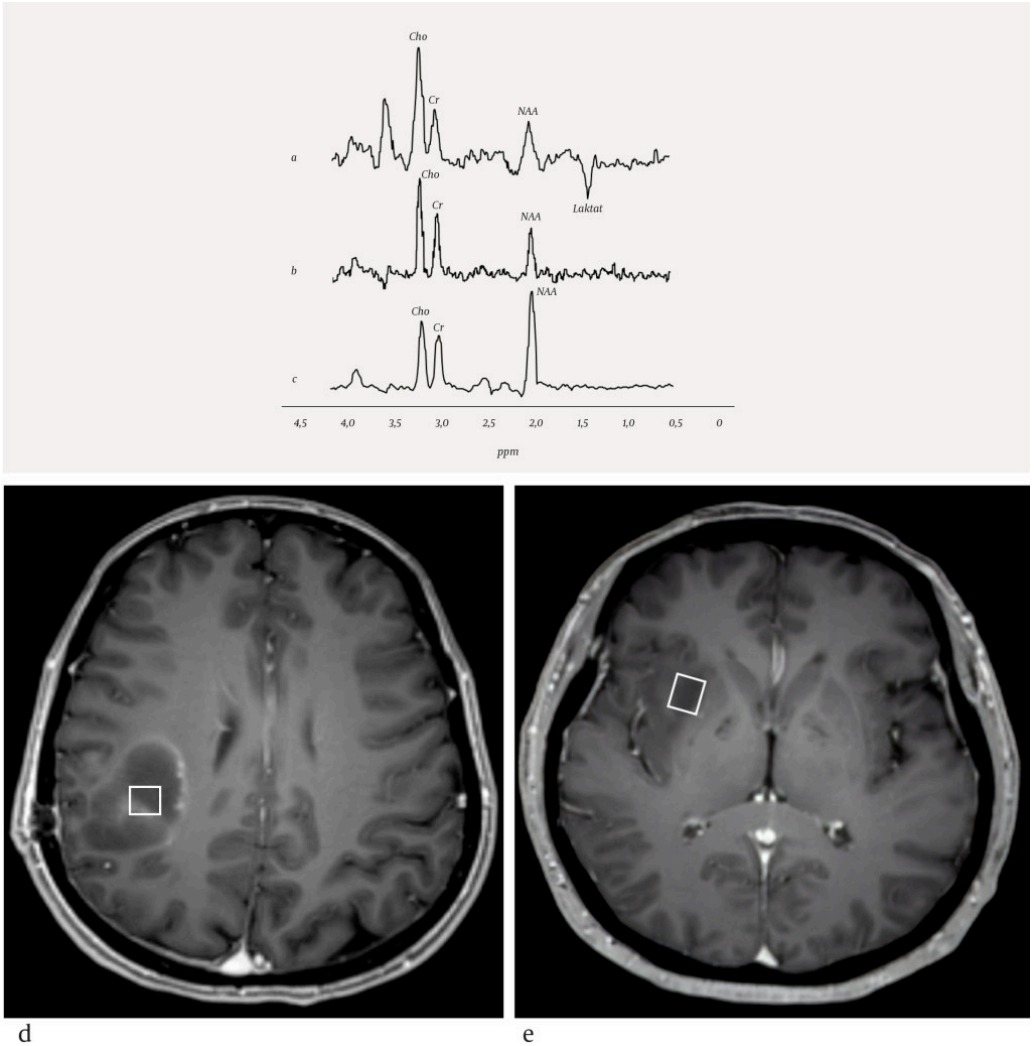


Figure 2 MR spectra of a) high grade glioma, b) low grade glioma and c) a healthy person, and T1-weighted MRI showing volume localisation for MR spectroscopy for d) the high grade glioma (a) with peripheral contrast uptake, and e) the low grade glioma (b), which shows no contrast uptake. All spectra are recorded with long echo time (135 ms). In the spectrum from the healthy control (c), the N-acetylaspartate (NAA) peak has higher intensity than the peaks for choline (Cho) and creatine (Cr), whereas choline, at 3.2 ppm, is the dominant peak in the spectra from both the high grade (a) and low grade glioma (b). In the high grade glioma (a), a negative peak from lactate can also be seen at 1.3 ppm. Spectra are scaled relative to the creatine signal.

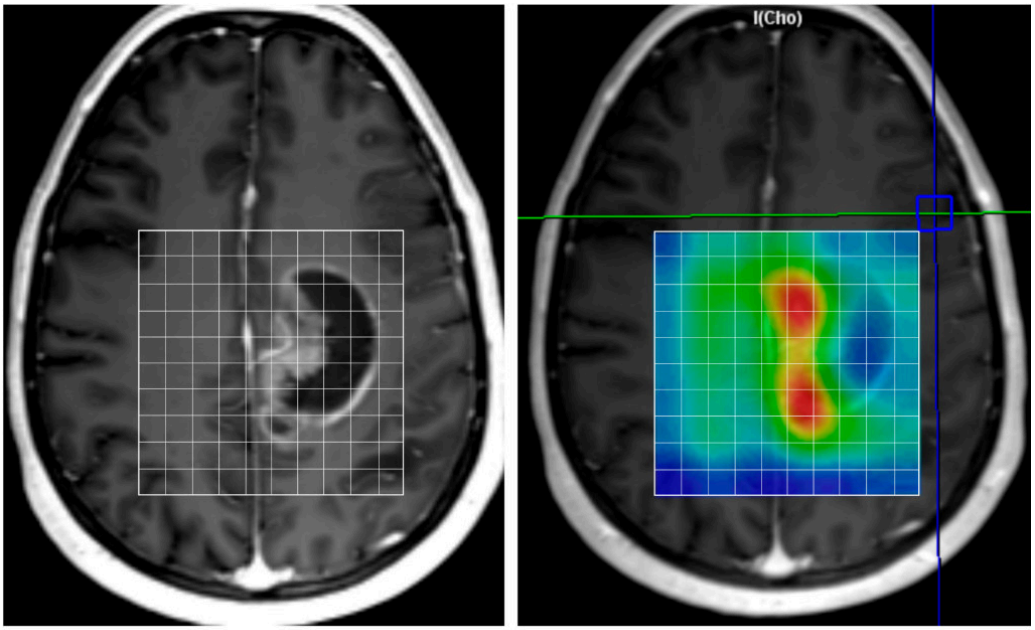
High grade gliomas are usually treated with surgery followed by radiochemotherapy. Radiochemotherapy can lead to oedema with contrast uptake in the operated area, so-called pseudoprogression. This is difficult to distinguish from genuine tumour progression on MRI, but MR spectroscopy can help differentiate tumour growth from a radiation response and pseudoprogression. Typically, the MR spectrum will show high levels of choline in cases of tumour progression, whereas areas with pseudoprogression will show lactate and mobile lipids as a sign of necrosis. Using MR spectroscopy in addition to diffusion MRI has been shown to increase accuracy in discriminating between pseudoprogression and genuine tumour progression (11). As an independent modality, MR spectroscopy has moderate accuracy for diagnosing tumours, but it can be valuable when used in combination with MRI (9).

Practical implementation

The quality of MR spectra and MR images is determined by the same factors, but some of these are more critical for MR spectroscopy. Movements of the patient, and the flow of blood and cerebrospinal fluid, as well as proximity to fat, air and bone can distort the magnetic field to a degree that reduces spectrum quality. The metabolites that are the sources of the signal for MR spectroscopy are present at low concentrations, which sets a lower bound on acquisition time and the size of the volume-of-interest (12). Single-volume proton MR spectroscopy is the most technically straightforward variant of MR spectroscopy, and typically uses a volume of 1–8 cm^3. MR spectroscopy also requires a highly homogeneous magnetic field to be able to differentiate metabolites on the basis of small differences in resonant frequency. It is therefore standard practice to perform additional optimisation of magnetic field homogeneity ('shimming') over the volume selected for MR spectroscopy.

Research and future potential

In our experience, expectations with regard to MR spectroscopy in clinical practice are growing once again. This is happening for two reasons. One is the increased prevalence of MR scanners with high field strength (3 and 7 Tesla). Higher field strength makes it possible to detect metabolites present at low concentrations, and to differentiate between peaks that overlap at lower field strengths. This can be achieved using chemical shift imaging (Figure 3). This method is performed over multiple volumes, typically of 1 cm^3, covers an entire brain slice or volume, and provides information on regional variations in metabolite levels. At St. Olavs hospital, this technique is used in about half of all MR spectroscopy examinations of brain tumours.



a b

Figure 3 Chemical shift imaging of glioblastoma: a) contrast-enhanced T1-weighted image, showing the volume specified for chemical shift imaging, and b) choline map from chemical shift imaging showing the choline level in the volume for spectroscopy. The colour chart illustrates the choline level, from low (blue) to high (red), and in this example, high levels of choline (red) can be seen in the medial portion of the glioblastoma.

The other reason is technological improvements with faster acquisition techniques. A new group of acquisition methods, so-called editing sequences, have been developed to target and specifically detect individual metabolites (13). This type of method can be used, for example, to detect 2-hydroxyglutarate, and thus cancer cells with an isocitrate dehydrogenase mutation. This compound is found in up to 80 % of grade 2 and 3 gliomas (13). Tumours with this mutation are more sensitive to radiochemotherapy, and the mutation is associated with improved prognosis. Another type of technique measures the presence of compounds indirectly by exploiting the fact that the compounds interact with water (14). Specific changes in the water signal, pH and protein content can be identified, which may provide valuable information for the treatment of brain tumours.

The technique of *functional MR spectroscopy*, which is the equivalent of *functional MRI*, opens up entirely new possibilities for investigating dynamic metabolic conditions in normal physiology and pathophysiology. Dynamic MR spectroscopy during presentation of varying stimuli has shown that lactate and glutamate levels in visual cortex increase with visual stimulation and decrease at rest (15). MR spectroscopy is already of considerable and increasing importance for research, and we believe that in the near future it will also acquire greater significance for clinicians.

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