MRS in metabolic disorders

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A. Introduction

Proton magnetic resonance spectroscopy (MRS) is an advanced MR technique allowing in vivo detection of various (normal and abnormal) metabolites in biological specimens. For this reason, it has a well established role in the diagnostic work-up and follow-up of many pathologies of the central nervous system including; metabolic diseases, neoplasms, post-hypoxemic brain damage, degenerative, infectious and inflammatory processes, as well as epilepsy. The technique takes advantage of the presence of small but detectable differences in the resonance frequencies of molecules within the brain tissue, which allows there identification and graphical display on so-called spectra or even quantitative analysis.

B. Technical considerations in MR spectroscopy

Understanding of the underlying biochemical and histopathological processes and the MR spectroscopic “behavior” of the investigated molecules are critical elements in the design and interpretation of a clinical MRS experiment. These will have an impact on the choice of data acquisition (PRESS, STEAM, single-voxel, 2D-3D CSI) and editing techniques (TE), as well as on the size of the sampling volume. Conventional imaging data is also important in the selection of the sampled brain region (e.g. avoid structures interfering with field homogeneity etc.).

1. Acquisition techniques, editing

The different metabolites have different T2 relaxation properties, therefore their detection and spectral appearance may depend on and be modulated by the applied echo time (TE). As a general rule, long echo-time (135 and 270 millisecond) techniques show fewer metabolites, but provide a less noisy background, allowing a more accurate peak analysis. Short echo-time (20-30 milliseconds) acquisition techniques demonstrate more metabolites, but the baseline is noisier.

Some metabolites, such as N-acetyl aspartate (NAA), choline (Cho), creatine (Cr) and lactate, are well assessed on both short and long echo-time spectra. Lactate however, has a peculiar presentation on MR spectroscopy as a function of the applied TE. With 135 millisecond TE, it presents as a negative, whereas with 270 millisecond TE, as a positive peak doublet. This is called the J-coupling phenomenon. Detection of myo-inositol, glutamine, glutamate is best achieved by short echo-time acquisitions. Glycine is best identified on the 135 millisecond spectrum. In order to confidently demonstrate myo-inositol, glutamine, glutamate and branched-chain amino acids, short echo-time (20-30 millisecond) MRS is the technique of choice.

2. Voxel positioning and size

In the clinical practice, the most commonly used forms of MRS are the single-voxel (SV) and the 2D-chemical-shift imaging (2D-CSI) techniques. In neurometabolic
disorders, theoretically the sampling voxel/volume may be placed anywhere in the brain, since abnormal metabolites, if present, are supposed to be ubiquitous within parenchyma. Focal lesion areas, if present, should however be avoided whenever possible, since severely damaged or metabolically compromised (e.g. necrotic) tissue may not be representative of the actual metabolic profile of the rest of the brain. Furthermore, in apparent lesion areas, smaller or larger amounts of lactate are almost always present, due to impaired aerobic energy metabolism, which should not be misinterpreted as an indicator of "mitochondrial disease".

If the voxel size is too small, the baseline of the spectrum may be rather noisy; hence small peaks may not be confidently identified. Typically a 2x2x2 cm or larger voxel provides adequate quality. At higher filed strengths (3T and above), smaller voxels (1x1x1 cm) may yield sufficient signal-to-noise ratios, allowing for consistently diagnostic quality 2D CSI MRS.

C. Normal and abnormal metabolic profiles in the brain.

1. Normal metabolites

In the normal brain, three prominent metabolic peaks are invariably detected; notably NAA (a neuronal marker), Cr (an energy metabolism marker, but also an indirect marker of cellular density) and Cho (an indicator of myelin turnover). Normal absolute and relative concentrations of cerebral metabolites however are region and age specific. For example, in the neonate and very young infant, NAA is a rather small peak (indicating the relative immaturity of the brain), whereas Cho is the most prominent (reflecting the increased membrane production in the context of particularly active widespread myelination of the brain). Later, Cho progressively decreases and NAA increases. By the age of 4 months, NAA becomes the most prominent peak on the spectrum and by the age of 6-12 months, the spectrum reaches its grossly mature "adult" appearance. Lactate should not be present in detectable quantities within normal brain.

2. Abnormal metabolites

Some of the so-called “abnormal” metabolites are actually present in the normal brain too, but in such small quantities that under standard conditions they are undetectable by in vivo proton MRS. Their “conspicuity” on the spectra therefore may be an indicator of a pathological process. Some of these "abnormal" metabolites are non-specific (such as lactate, glutamine-glutamate, GABA), but in certain settings may be suggestive, although not specific of metabolic disorders. For example, increased glutamine concentrations may be found in urea cycle defects but also in acute or chronic hepatic encephalopathy or after hypoxic-anoxic brain damage. Other metabolites appear only in specific disease entities; therefore their detection may be pathognomonic.

D. Brain MRS abnormalities in neurometabolic disorders

In general, MR spectroscopic abnormalities in the brain may be divided into two major groups: process and disease specific metabolic changes. This concept may be applicable to neurometabolic disorders too.

1. Process specific abnormalities

These changes in the metabolic profile of the sampled tissue are not pathognomonic of a given disease, but reflect underlying “generic” biochemical (energy failure, hyperammonemia etc.) and histopathological (demyelination,
inflammation, gliosis, neuro-axonal degeneration, osmotic disturbances etc.) processes. Since many different metabolic disorders may lead to similar, stereotype histopathological changes, the resultant metabolic profile by MRS may be non-specific. This “non-specific metabolic profile” is typically characterized by the decrease of the NAA peak (loss of neuronal integrity) and decrease of the Cho peak (indicating demyelination). Creatine may be decreased (energy failure within tissue) and more or less significant amounts of lipid (tissue breakdown) may appear too. Occasionally the myo-inositol peak may increase (astrogliosis, osmolar changes) and various amounts of lactate (impaired energy metabolism) may be detected.

2. Disease specific abnormalities

Relatively few neurometabolic diseases present with a pathognomonic metabolic profile by in vivo clinical MRS. Those include Canavan disease (pathological increase of NAA), disorders of NAA synthesis (absence of NAA), cerebral creatine deficiency syndrome (absence of creatine), non-ketotic hyperglycinemia (glycine), galactosemia (galactitol), ribose-5-phosphate isomerase deficiency (arabitol, ribitol), HMG co-enzyme A lyase deficiency (HMG?), phenylketonuria (phenylalanine) etc. In some other conditions, (in an appropriate clinical setting), MRS findings may also be fairly specific, such as branched chain amino acids in maple syrup urine disease, succinate in succinate dehydrogenase deficiency or GABA in succinic semialdehyde dehydrogenase deficiency.