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Magnetic resonance spectroscopy of brain in epilepsy

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Abstract The current applications of magnetic resonance spectroscopy (MRS) in the clinical management of epileptic patients are reviewed. A major contribution of MRS to epilepsy is its ability to determine lateralisation before surgical resection of the diseased brain region. Phosphorus-31 and proton single-voxel MRS identify abnormalities in high-energy metabolism, neuronal function and neurotransmitter levels, but information can only be obtained from restricted regions of the brain. Spectroscopic imaging techniques (also known as chemical shift imaging) provide a metabolic mapping of the whole brain. They expand the range of applications of MRS to other types of epilepsy (neocortical, frontal) than temporal lobe epilepsy, which is the most often studied. Also, spectral editing techniques in proton MRS make it possible to detect and monitor drug-induced variations of GABA in the human brain, opening new insights into patient response to drug therapy of epilepsy. MRS is playing an increasing role in the noninvasive characterisation and management of epileptic patients.

Key words Magnetic resonance spectroscopy · Epilepsy · Brain metabolism · GABA · *N*-Acetyl aspartate · Human

Introduction

In vivo magnetic resonance spectroscopy (MRS) makes it possible to assess brain biochemistry noninvasively. It has proved particularly effective in the characterisation of several childhood pathologies such as brain tumors, ischaemia, neonatal asphyxia, infection, neurodegenerative diseases and metabolic disorders [3–5, 29, 44, 45]. Similarly, it is increasingly emerging as a relevant and promising exploratory technique for the noninvasive study of epileptic states [7, 10, 40, 51].

In this report, after a rapid review of biochemical and technical considerations, a survey of the clinical issues pertaining to the characterisation of epilepsy in children by brain MRS is presented.

In Vivo MRS and brain metabolism

Detailed reviews of the metabolic information afforded by brain MRS are available [57]. In a nutshell, ^{31}P-MR spectroscopy provides information about the energetic status of the brain by measuring the intracerebral content in phosphocreatine (PCr), adenosine triphosphate (ATP), phosphomonoesters (PME), phosphodiesters (PDE) and inorganic phosphate (Pi). In addition, intracellular pH and its variations can be directly determined on the basis of the value of the chemical shift of Pi signal. At physiological values of pH, the observed Pi signal is an average generated by two contributing species in fast chemical equilibrium on the NMR time scale: HPO_4^{2-} and $H_2PO_4^-$. The position of the average Pi signal reflects the relative concentrations of the two ionic species and consequently the intracellular pH.

In spite of its informative value, ^{31}P MRS lacks sensitivity, resulting in limited spatial resolution (minimum

voxel size 60 cm^3) and/or poor temporal resolution (large number of scans required to reach a sufficient signal-to-noise S/N ratio). In addition, the unavailability of a commercial ^{31}P head coil and associated electronics limits the scope and the development of cerebral ^{31}P MRS in a routine clinical environment.

The NMR sensitivity of the ^{1}H nucleus is about 14 times that of ^{31}P. As a consequence, metabolic profiles can be obtained from regions of the brain as little as 1 ml in volume within 6 min. ^{1}H MR Spectroscopy enables us to evaluate the energetic metabolism by quantifying the creatine/phosphocreatine signal (tCr), to measure the neuronal status with the *N*-acetyl aspartate (NAA) signal, to assess membrane integrity and turnover based on the choline-containing compounds (Cho), and to detect the presence of anaerobic glycolysis with such markers as lactate (Lac). Depending on the parameters used in the acquisition of spectra (i.e. short echo time or editing methods), it is also possible to assess the glial cell integrity by quantifying the inositol signal (INS), to monitor the evolution of neurotransmitters, such as glutamate/glutamine (Glx) and γ-aminobutyric acid (GABA), and to observe inflammatory and degenerative processes through the variations in the concentration in macromolecules and mobile lipids.

Specificity of paediatric MRS

Most of the issues and limitations encountered in paediatric MRS are similar to those experienced in paediatric magnetic resonance imaging (MRI). As a matter of fact, an MRS examination always starts with a conventional MRI procedure, for diagnostic purposes and for three-dimensional referencing of the brain area to be explored by MRS. A successful procedure requires immobility of the young patient in order to obtain high-quality localised spectra or metabolic images. Newborns and infants up to 10 months of age can be kept still in dedicated devices, such as a plastic half cylinder used as a cradle, and put in the head coil of the MR system. Children between 10 months and 5–6 years of age have to be sedated. This requires the on-site availability of adequate physiological monitoring, the presence of an anaesthesiologist and the appropriate equipment to carry out full resuscitation [29]. When their cerebral status allows it, older children can be very cooperative if adequately informed and briefed about the examination. From a practical point of view, the duration of the integrated MRS protocol, including 3D localisation and MRS examination, must not exceed 35 min for it to be readily acceptable as part of a routine MRI/MRS exploration.

The establishment of normal values for metabolite concentrations in various areas of the brain is particularly critical and difficult in children. Normal age-related fast metabolic changes in the developing brain, from postnatal to adult-like brain at 3–4 years of age, must not be mistaken for pathologic deviations. The construction of an age-matched database based on values measured in normal controls is required, albeit difficult due to ethical considerations.

Technical considerations

A major problem to be overcome before proton MR signals can be recorded from brain metabolites is removal of the dominant signal generated by the water protons. The huge difference in relative concentrations between metabolites and water (ratio 1/10 000) cannot be handled by analog / digital converters, since it exceeds their dynamic range limits. A variety of procedures are now available to suppress the water proton signal by saturation / elimination based on dedicated selective pulse sequences during signal acquisition or postacquisition signal processing. A second problem is the accuracy of the 3D localisation of the MRS signal, which must arise from a well-defined brain region. It involves specific constraints on the radiofrequency pulse and must eliminate unwanted spectral contamination from other parts of the brain, like fatty scalp.

Single-voxel MR spectroscopy (SVS) of the brain has been in routine use for more than a decade. It consists in acquisition of a MR signal from a volume of interest (VOI) ranging from 1 to 8 ml in proton MRS and 60 to 120 ml in phosphorus MRS. Two complex sequences of RF pulses are commonly used in the stimulated echo acquisition mode (STEAM) [12] and the point-resolved spatial selection (PRESS) methods [1]. Owing to its theoretical two-fold gain in signal-to-noise ratio (S/N) compared with STEAM at the same echo time (TE), the PRESS method is generally preferred, especially at long echo times (135–270 ms). Under these conditions, NAA, total creatine, choline and lactate are easily detected without overlapping signals from short T_2 species such as fats (from the scalp, but also from the brain in children) and macromolecules. This leads to a straightforward determination of the areas of the metabolite signals and the corresponding relative or absolute concentrations.

Conversely, STEAM sequences allow TE to be made very short (down to 5 ms) without significant degradation of the volume excitation profile. Under these conditions the spectrum is more informative, with the presence, in addition to the signals already observed at long TE, of signals from glutamate / glutamine, aspartate, glycine, inositol, taurine, macromolecules and lipids. Balancing this additional information, short echo spectra are also subject to signal overlaps of short T_2 species, which may cause difficulties in the quantification of metabolites. New developments in postacquisition processing methods tend to minimise the operator-dependent errors in the integration of spectra by using automated quantifi-

cation procedures performed in the time or frequency domains (Amares, Varpro, LC models, maximum entropy).

Despite its robustness and accuracy, single-voxel spectroscopy exhibits some limits. Constraints in acquisition time limit the number of acquired voxels to no more than two during a routine MRS examination, and as a result the metabolic spatial coverage of the brain is reduced. This is not an issue in the exploration of diffuse pathologies. However, in focal diseases the location of the lesion or of the brain anomaly has to be known a priori and determined separately (MRI) to position the volume of interest correctly.

New localisation methods are now available to circumvent those limitations. They are known as spectroscopic imaging (SI) or chemical shift imaging (CSI). These methods allow the acquisition of several contiguous voxels (nominal size of about 1 ml) by phase-encoding a large region of interest in one, two or three spatial dimensions, as is done for the water signal in conventional MRI. The spatial distribution of a selected metabolite can be displayed as a metabolic image, which can be superimposed onto the morphological image obtained by MRI. The S/N of metabolite maps is low relative to water images, but sufficient to detect regions exhibiting abnormal metabolism. However, this attractive method is subject to some restrictions especially at short TEs. First, it is difficult to obtain a good static field and radiofrequency homogeneity across a large volume. This limitation results in distortions, coalescence of adjacent signals and differences in excitation profiles in the spectra obtained in the voxels constituting the grid of the metabolic image. Second, the reduced number of phase-encoding steps in each direction and the subsequent limited number of data points used in the Fourier transform to obtain metabolic maps make the MR signal sensitive to contamination from neighbouring voxels. This is critical, especially near fatty scalp regions. One method of overcoming the problem of fat contamination is to destroy the MR signal from scalp by using judiciously positioned saturation bands (typically 6 or 8) preceding the application of spoiler magnetic field gradients (outer volume suppression, or OVS, technique). It is also possible to optimise the raw data acquisition trajectory (spiral or radial) and to apply different acquisition weightings of the k-space to optimise the spatial frequency response. In any case, these limitations pertain mostly to acquisitions conducted at short TEs, whereas metabolic images are currently rather easy to obtain at long TEs. These new approaches are developed in a research context on conventional MR spectrometers/imagers and should be soon available as commercial products.

MRS and epilepsy

MRS in temporal and mesial temporal lobe epilepsy

Most of the MRS studies on epilepsy conducted during the last 10 years have focused on temporal lobe epilepsy (TLE). The main goal of these studies has been to demonstrate that MRS could help in determining epilepsy lateralisation before surgical resection of the diseased brain region.

^{31}P MRS was used in early studies to lateralise epilepsy [20, 25, 59] during interictal periods, with an increase in inorganic phosphate concentration, a reduced amount of phosphomonoesters, increased pH and no change in ATP in the cerebral lobe involved.

A proton MRS study, using single voxel localisation and PRESS, of 20 children suffering from intractable temporal lobe epilepsy showed that, at long TE, there were abnormalities in the NAA / (Cho+tCr) ratio for 75% of the patients, with 55% cases of correct and none of incorrect lateralisation of seizure focus, and bilateral abnormalities in 45% [8]. The NAA decrease reflects neuronal damage or loss, or altered mitochondrial metabolism [33], while the increase in choline and total creatine concentrations has been related to gliosis [54].

Similar results have been obtained by spectroscopic imaging on adults (75 cases in five studies) [14] and on a large cohort of 100 patients suffering from intractable TLE, demonstrating the reliability and sensitivity of chemical shift imaging techniques to detect metabolic abnormalities in 99% of patients [2].

A very interesting recent observation is the ability of proton MRS to detect metabolic anomalies in patients with normal MR images. In this situation, MRS clearly provides an added value to MRI and enhances the sensitivity of the global MR examination. The NAA/(Cho+tCr) ratio was found to be abnormal on the CSI spectra in five out of seven patients with MRI-negative TLE [6], and in 27% of patients in a study conducted with quantitative short echo time proton SVS located in the hippocampus [58].

Significant differences in metabolic profiles are observed between patients with hippocampus sclerosis and MRI-negative TLE patients. The latter group is characterised by an increase in the glutamate / glutamine signal and a less marked decrease in NAA [58]. Additionally, the extent of hippocampus sclerosis correlates with increased inositol concentrations observed on short echo time proton MR spectra [53, 58]. In five children with TLE, it has been shown that the value of proton MRS lies not only in lateralising hippocampal atrophy, but also in detecting bilaterality and the extent of neuronal loss outside the hippocampi [18].

MRS and frontal lobe epilepsy

The development of the use of MRS in extratemporal epilepsy is directly related to methodological improvements in CSI. Owing to the absence of prior knowledge of the focus location the largest possible brain coverage is necessary, and this is actually provided by CSI. It has

recently been shown that, with the same TE and type of sequence, CSI and SVS give results that are quantitatively similar, while CSI allows investigation of a much larger area of the brain [19].

^{1}H CSI with long TE in patients with nonlesional partial extratemporal epilepsy allowed the detection of significant decreases in NAA/(tCr+Cho); NAA/tCr and NAA/Cho, confirming widespread neuronal damage or dysfunction that was the largest in the region of seizure focus [52]. Similar results were reported a few years ago in eight patients with frontal lobe epilepsy, in whom the NAA/tCr ratio was lower by 27% in the epileptogenic frontal lobe than in the contralateral region [15].

Multislice ^{1}H CSI has demonstrated its advantage in comparison of mesial temporal lobe and neocortical epilepsies (NE) [56]. In contrast to mesial TLE, NAA was not reduced in either the ipsilateral or the contralateral hippocampus to the seizure focus in NE patients. A decrease in NAA was detected in the temporal lobe ipsilateral to the focus for TLE patients, and also in the anterior part of the frontal lobe for patients suffering from NE.

In addition, ^{31}P CSI can give clues to the location of a frontal lobe focus with findings of interictal alkalosis in the epileptogenic focus, and a decrease in phosphomonoesters was found in 7 out of 8 patients [13].

Metabolic description and monitoring of diseases related to epilepsy

Correlated studies of MRS and PET have allowed investigation of the rate of cerebral glycolysis. ^{18}FDG PET reflects the entire glycolytic activity (oxidative and nonoxidative), while MRS detects lactate, the principal product of nonoxidative glycolysis. Two children suffering from congenital lactic acidosis with biochemical evidence of defective mitochondrial respiration have exhibited increased brain lactate and decreased NAA in conjunction with increased glycolysis observed with PET [11]. A correlation between decreased NAA/(Cho+tCr) ratio and decreased interictal glucose metabolism (expressed as the metabolic index: the ratio between regional counts and whole-brain counts for each patient) has been observed in 12 adults with TLE [27], indicating that MRS abnormalities are associated with concomitant quantitative abnormalities of local glucose utilisation. Such a correlation has also been found between ^{1}H MRS abnormalities and perfusion defects seen on interictal $^{99}Tc_m$HMPAO SPECT in 14 children with intractable temporal lobe epilepsy [9]. At short TE SVS an increase in glutamate/glutamine has been observed in the epileptogenic focus located by ^{11}C flumazenil and ^{18}FDG PET [46, 47].

Clearly, MRS has started to be recognised among the panel of methods used in integrated diagnosis and in the decision-making process preceding neurosurgery. A case report on a 16-year-old boy illustrates this cooperative strategy with the demonstration of compensatory cortical reorganisation in dysgenic cortex as a result of complementary information yielded by PET, ^{1}H CSI, cortical mapping, immunocytochemistry and electrophysiology [39].

The metabolic profiles recorded by localised proton MRS in two children with hemimegalencephaly have revealed large abnormalities in the enlarged hemisphere [16]. A dramatic reduction in NAA and glutamate appeared in the white matter, reflecting loss of vital neuroaxonal tissue, but not in cortical grey matter, basal ganglia and cerebellum. In grey matter, inositol and choline have been observed in one child, indicating glial cell proliferation, while abnormalities such as a decrease in NAA were observed to a lesser extent in the contralateral hemisphere.

Localised ^{1}H MRS has been used in an attempt to improve understanding of the apparent brain atrophy that follows adrenocorticotropic hormone (ACTH) therapy. The only change observed to absolute concentrations of NAA, water, tCr and Cho in nine children was a decrease in NAA, suggesting catabolic effects of ACTH on brain tissue, such as cell loss, decrease in NAA synthesis in mitochondria, and leakage of NAA from cell membrane [28].

A very well-documented exploration of a child suffering from guanidinoacetate methyltransferase deficiency has shown creatine deficiency with a low tCr signal on the ^{1}H MRS spectrum, a low PCr signal, and a predominant signal of guanidoacetate phosphate on the ^{31}P spectrum. These deviations were reversed after sustained therapy with creatine monohydrate supplementation [48].

Finally, with ^{31}P CSI it has become possible to quantify improvement of energy metabolism during a ketogenic diet, as seen in seven patients with intractable epilepsy [31]. Ratios of PCr/(γ-ATP) and PCr/Pi measured at baseline (regular diet) and after administration of the ketogenic diet showed a small but significant increase.

Therapeutic follow-up by MRS: editing of GABA signal

We have just described a few selected studies that illustrate the sensitivity of MRS in assessment of the effect of palliative or curative therapies. However, the main focus of the pharmacological studies remains centred around the possibility of detecting the signal of γ-aminobutyric acid (GABA) on the proton MR spectrum of the brain.

GABA is the major inhibitory neurotransmitter in human cortex, and changes in its metabolism may play an important role in the origin and spread of seizure activity [23, 32]. The detection of GABA is particularly difficult owing to its low concentration and the overlapping of its resonance with those of tCr and NAA. However, like lactate, glutamate and glutamine, GABA displays a

J-modulation which can be used for spectral editing. Proper attention has to be paid to editing efficiency, selectivity and strong coupling effects in order to quantify the GABA signal accurately [41].

Since the first in vivo observations of brain GABA and homocarnosine 2-pyrrolidinone by MRS techniques [17, 22, 42, 43], the number of clinical studies using MR editing methods applied to epilepsy has grown rapidly [21, 26, 30, 34, 35, 37, 38, 41, 43, 49]. An interesting ^{1}H NMR study has demonstrated a correlation between seizure control and brain GABA levels [36].

Along the same lines, proton MRS makes it possible to observe drug-induced variations of GABA in the human brain. Several antiepileptic drugs are aimed at the GABA-ergic system, such as topiramate, vigabatrin and gabapentin. They have all been shown to increase the brain GABA level in epileptic patients [4, 34, 36, 38, 55]. Topiramate also increases GABA in healthy volunteers [26], while vigabatrin treatment allows detection of the signal for homocarnosine 2-pyrrolidinone, a lactam resulting from the cyclisation of GABA [21].

Similarly, a recent study on epileptic patients between 1 and 5 years old has shown that vigabatrin also increases brain GABA in children, opening up new perspectives in therapeutic monitoring and in understanding of the role of GABA-mediated inhibition in paediatric epilepsies [30].

A challenging objective is now to find out the cerebral spatial distribution of GABA, glutamate/glutamine and lactate using three-dimensional CSI techniques [50].

Conclusions

Phosphorus-31 and proton single-voxel MRS identify abnormalities in high-energy metabolism, neuronal function and neurotransmitter levels, but information can only be obtained from restricted regions of the brain. Spectroscopic imaging techniques (also known as chemical shift imaging) provide metabolic mapping of the whole brain. They expand the range of applications of MRS to other types of epilepsy (neocortical, frontal) than the type most often studied, i.e. temporal lobe epilepsy. Also, spectral editing techniques in proton MRS make it possible to detect and monitor drug-induced variations of GABA in the human brain, opening new insights into patient response to epilepsy drug therapy.

The characterisation and management of epilepsy relies increasingly on a panel of noninvasive complementary techniques. In the forthcoming research protocols the quantitative metabolic information afforded by brain MRS will be usefully compared with hippocampus volumetry from anatomical MRI, regional brain hypoperfusion from perfusion-weighted MRI replacing radioisotopic techniques like PET or SPECT, water molecular motion abnormalities from diffusion-weighted MRI, damage in tissue structure from magnetisation transfer-weighted MRI and of course noninvasive EEG (the gold standard) coupled with BOLD (blood oxygen level-dependent) contrast in functional MRI [24].

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