REVIEW

Brain $^1$H-MR spectroscopy in clinical neuroimaging at 3T

Spectroscopie protonique du cerveau en neuroimagerie clinique à 3T

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Summary After more than 10 years of use, clinical neuroimaging spectroscopy has proven to be invaluable in the MRI assessment of several brain diseases. The metabolic characterization of diverse brain lesions and pathological conditions is well established by spectroscopy studies at 1.5T, but recently, an increase in the number of 3T magnets has noticeably improved routine neuroimaging in general. For brain proton spectroscopy, the use of higher magnetic fields has been promising in terms of increasing the signal/noise ratio across the spectrum and widening the frequency bandwidth to allow clearer separation of peaks that are otherwise too close to each other at 1.5T, especially glutamate, glutamine and gamma-aminobutyric acid (GABA). The individual detection and quantification of these metabolites will add more details to the characterization of brain diseases, and allow the inclusion of more brain pathologies. Moreover, the ongoing advances in dedicated hardware and integrated software have led to more accurate and automated postprocessing, offering neuroradiologists a more user-friendly interface. This is an up to date review of the main clinical applications of brain proton MR spectroscopy that are potentially improved at 3T, taking into account the peculiarities of higher magnetic fields. It is based on both the literature and our own clinical experience, starting from July 2005 and including more than 250 scans at 3T (unpublished material), and emphasizes, for every indication, a practical approach to brain MRS to achieve the optimal clinical impact.

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MOTS CLÉS
Spectroscopie protonique ; Tumeurs cérébrales ; Épilepsie ; Aimant à 3T

Résumé Après plus de dix ans d’utilisation sur les aimants cliniques, la spectroscopie a démontré un intérêt certain dans la mise au point par IRM de plusieurs pathologies cérébrales. La caractérisation métabolique de diverses lésions cérébrales a été bien établie par des études réalisées à 1.5T. Au cours de ces dernières années, l’accroissement du nombre d’aimants 3T à usage clinique a significativement amélioré la pratique neuroradiologique globale de routine. Pour ce qui est de la spectroscopie protonique du cerveau, l’utilisation de hauts champs magnétiques a été prometteuse, concernant l’augmentation du rapport signal sur bruit du spectre et, par l’élargissement de la bande de fréquence, la séparation claire des pics dont les fréquences

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Introduction

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that allows the measurement of absolute and relative metabolite concentrations in human tissues and organs in vivo. Brain proton MRS (H-MRS) emerged in the 1990s. Up to now, MRS has been used as both a research and a clinical tool for detecting abnormalities not visible on conventional MRI, and for increasing our understanding of the cellular biochemistry underlying brain pathologies. In clinical practice, brain MRS has always been challenging in terms of its technical requisites (magnet, gradients, coils, hardware and software), as well as examination planning and interpretation as regards pathological processes. Higher magnetic fields have brought some advantages in facing these challenges. This review aims to provide the reader with a practical approach to clinical spectroscopy, both for single voxel (SV) and spectroscopy imaging (SI), using a 3T magnet in routine brain imaging. The clinical indications considered herein have been well documented with 1.5T magnets. However, in their assessments using 3T, radiologists have to deal with peculiarities specific to higher magnetic fields and the new tools and technology. For each indication, the main clinical concerns, scan planning and metabolic findings are discussed.

H³-MRS AT 3T: The tools

Our experience is based on more than 250 scans (unpublished material) using a Philips 3T R2 Magnet (Best, The Netherlands). The tools are generally the same as those used at 1.5T. However, depending on the manufacturer, recent improvements (some available only with 3T magnets) allow more options for optimal acquisitions, postprocessing and spectral analyses. Before considering each of these spectroscopy steps, here are the advantages and some particularities related to the use of higher magnetic fields.

High-field advantages and particularities

The advantages of spectroscopy at higher field strengths are mainly an increased signal/noise ratio (SNR), improved spectral, spatial and temporal resolution, including detection of resonances obscured at 1.5T (such as amino acids), and enhancement of J-coupled spectral resolution [1–3].

Given its linear relationship with magnetic field strength, the SNR theoretically doubles at 3T but, in practice, the gain is 20–50% of that with 1.5T, and mostly at a short echo time (TE) because of interference from many other variables, including the voxel-size, T1 and T2 relaxation times, radiofrequency (RF) pulses and sequence design [2,4,5]. SNR increases with head-coil elements. A phased-array multidetector coil (at least eight coils) has been reported to significantly improve spectral quality at 3T by combining spectra from each channel [6]. Such good results have been obtained for MRSI at 3T in clinical settings and in brain investigations [7].

Spectral resolution

Spectral resolution refers to the broadening of the frequency linewidth, which allows a clear separation of close frequencies such as those for glutamine, glutamate and gamma-aminobutyric acid (GABA). The 0.2-ppm chemical shift between choline (Cho) and creatine (Cr) remains constant, but their separation in absolute hertz frequencies is doubled as well as the whole linewidth.

Spatial and temporal resolution

Spatial and temporal resolution refers to the maximum voxel-by-voxel matching between metabolic maps (SI) and corresponding anatomical sections, with a reduction in acquisition time. Indeed, the use of MRS in clinical practice has been limited because it is time-consuming, and requires a constant balance between time investment and spectral quality. The total scan time includes preparation steps such as shimming (magnetic-field homogenization) and optimal water suppression (both critical for spectral quality) as well as spectral measurements.

Fast spectroscopy techniques

However, hardware advances have permitted faster shimming methods using powerful gradients, so that shimming time has gone from more than three minutes (using the
traditional method of gradients applied in three orthogonal directions and a tuning-in to each direction for current adjustments) to less than 30 s (using first-, second- or third-order shimming). Several reports have described new methods for optimized, fast, automated shimming (dynamic, passive or combined; ferro- or electroshimming) in SV (localized shimming in a target area) and in SI (global or restricted to slice selection), and notably in multislice two-dimensional (2-D) or three-dimensional (3-D) MRSI [6—9]. In brain areas with basically poor $B_0$ homogeneity, such as the posterior fossa and temporal lobes, an alternative to traditional shimming is iterative fast shimming.

In SI, a long scan time is due to phase encoding gradients. Various techniques have been developed to take advantage of what has been done for MRI sequences (parallel imaging and fast k-space sampling) to reduce scan time, particularly for 2-D and 3-D MRSI. Among these, the turbo spin-echo techniques such as turbo spectroscopic imaging (TSE), rapid acquisition with relaxation enhancement (RARE), echo-planar readout gradients in proton echo-planar spectroscopy imaging (PEPSI), sensitivity gradient encoding (SENSE), combined SENSE–PEPSI, and spiral full or undersampling of k-space trajectories are worth mentioning [10—15]. In a recent paper, Schuster et al. described a novel fast-pulse sequence for 3-D MRSI based on the steady-state free precession (SSFP) known as ‘spectroscopy missing-pulse SSFP’ (spMP-SSFP), integrating water and lipid suppression, and applicable to clinical settings [16]. All these acceleration techniques should be parametered on clinical magnets to maintain a reasonable SNR. Another way to shorten the scan time is to reduce the number of excitations ($N_ex$) while balancing this against spectral resolution and SNR (increases as the square root of $N_ex$). We found that an average of 128 $N_ex$ was the minimum for a SV spectrum of good quality.

Water suppression

Water suppression can be optimized by applying a band-selective inversion with a gradient dephasing pulse (BASING), alone or in addition to a chemical-shift-selective (CHESS) presaturation technique [17]. The use of adiabatic RF pulses (designated as ‘sequence for water suppression with adiabatic modulated pulses’ or SWAMP) with a Philips 3T R2 magnet is also efficient. Moreover, these selective suppression methods are useful for solving some of the inconveniences inherent with 3T such as incomplete lipid saturation (which causes demodulation of baseline between 0.9 and 1.1 ppm, and at 1.3 ppm, with a short TE) and J-modulation anomalies (which cancel out the lactate signal at 1.3 ppm, with TE = 144 ms) [18,19]. Also, it should be borne in mind that complete saturation of the lipid signal will suppress macromolecules resonating between 0.9 and 1.1 ppm in some pathological conditions.

J-coupling

The J-coupling behavior for lactate (Lac) does not change when going from 1.5T to 3T. However, due to weakly coupled resonances (a doublet at 1.33 ppm for a methyl group and a quartet at 4.1 ppm for a methine group, respectively) when the excitation-pulse bandwidth is too narrow and fails to excite the methine spins, the coupling is lost and, in addition, a chemical-shift misregistration artifact could lead to signal misregistration for all metabolites [20]. The solution, in this case, is to increase the RF bandwidth (BW) by using high BW pulses (such as GTST1203 and Spredrex) or to increase the B1 field [18]. Another peculiarity of 3T is splitting of the myoinositol (mI) peak at 3.55 ppm into two smaller peaks, which makes it difficult to visually estimate the amount of mI.

Acquisition tools

To adequately design the MRS study for each condition, the neuroradiologist and/or trained MR technologist needs to be aware of the peculiarities and differences related to the tools used to perform the scan. We now consider each of these in the logical sequence used in designing and planning an MRS study.

Volume selection and sampling methods

First of all is the volume selection or localization technique. In localized $^1$H-MRS, stimulated echo acquisition mode (STEAM) and point-resolved spectroscopy (PRESS) pulse sequences have long been proven to be the voxel localization methods of choice [21]. In PRESS, transverse magnetization generated by the 90° pulse is refocused by the first 180° pulse and again by the second. The signal acquired with PRESS is T2-weighted. In STEAM, the initial 90° pulse is followed by a spoiler gradient, then by the second 90° pulse; a further spoiler gradient eliminates the transverse component and a final 90° pulse refocuses the spins in the transverse plane to generate the (stimulated) echo. The STEAM signal is T1-weighted. In terms of signal-selection efficiency, contamination avoidance and outer volume suppression, the recently improved hardware offers an equivalent performance with either technique. In clinical practice at 3T, however, STEAM works better for shorter TE (10—19 ms) and gives a better metabolite signal with short T2 relaxation [22], while PRESS works better for longer TE (272—288 ms) and MRSI multislice, with less sensitivity to physiological brain movements [23]. Due to variations in metabolite ratios depending on the localizing technique and TE, comparative studies should be performed using exactly the same study design. Another volume selection technique is image-selected in-vivo spectroscopy (ISIS), which is mostly used for $^{31}$P-MRS, but can be implemented for $^1$H-MRS as well [21,24].

Single voxel (SV) and multivoxel (MV) are sampling methods for MRS, and define the geometry of the volume of interest (VOI). SV acquires a spectrum from a small volume of tissue located at the intersection of three orthogonal slices. SV is simple and rapid in planning and acquisition (2—4min), but has a size limitation that typically ranges from 2—8 cm$^3$ at 1.5T, although this size can shrink to less than 1 cm$^3$ at 3T, but still offers a spectrum of good quality. For reliable metabolic information, the voxel should contain as much of the lesion or structures being investigated as possible. SV does not allow investigation of a larger area (decreased spatial resolution) or different contiguous or distant areas of the brain in one measurement. MV helps to
overcome this limitation by covering the entire lesion with one or more slices, including normal-appearing brain areas. Within the VOI, voxel size can be reduced to 0.34 cm³ with a reasonable acquisition time (9.5 min) [25]. We have been able to maintain sufficient spectral quality in clinical practice with a nominal spatial resolution of 0.27 cm³ (0.65-cm cubed) with a 12-min acquisition time. Another advantage of 3T over 1.5T is the possibility of 3-D MRSI, with a third directional phase encoding to cover the largest volume of the brain with a partitioned field of view in four to eight contiguous transverse slices. The gain in SNR is 23—46%, and the spectral resolution (flat baseline for local spectra) is improved with fewer chemical-shift errors and a reduced acquisition time [5,25,26].

Short TE

Basically, a short TE (12—36 ms) allows a signal with the maximum number of detectable metabolites, notably those with short T2 relaxation times. The metabolites detectable on ¹H-MRS classically include the resonances of N-acetyl aspartate ([NAA], 2.02 ppm), creatine ([Cr], 3.04 ppm), choline ([Cho], 3.20 ppm), taurine/scyllo-inositol ([Tau/sc-I], 3.33 ppm), myoinositol or glycine ([mI/Gly], 3.54 ppm), and glutamine and glutamate (respectively Gln and Glu = Glx, 2.10—2.45 ppm and 3.75 ppm; Glu, 2.35 ppm) [27,28]. Depending on the pathology, other metabolites may be detected: (Lac, 1.33 ppm) in mitochondrial disorders; phenylalanine ([Phe], 7.36 ppm) in phenylketonuria, guanidinoacetate ([Gaa], 3.8 ppm) in guanidinoacetate methyltransferase deficiency [2,29], galactitol ([Gal-ol], 3.67—3.74 ppm) in galactosemia [30], alanine ([Ala], 1.48 ppm) in meningoima [31], and macromolecules ([M], 0.9—1.1 ppm) in metabolic diseases and tumors. As already mentioned, a 3T magnet allows a clear separation of these peaks and, therefore, facilitates their quantitation.

Long TE

Long TE (136—288 ms) allows sampling of only the signals of the three major metabolites—NAA, Cho and Cr—but results in, for a given magnetic field and sampling method, better SNR and spectral resolution as well as the maximum intensity of the metabolites. A long TE also shows the best reproducibility independent of magnetic field or coil technology [32]. Thus, there is no variation in metabolite ratios from long TE at 1.5T in comparison to 3T. In clinical practice, it is recommended to use both short and long TE to acquire full metabolic characterization of a disease, except in cases where only short TE is required for the diagnosis. SV and SI can be performed at both short and long TE. For NAA, Cho, Cr, mI and Lac detection in brain tumors, for example, short-TE MRSI is preferable to long-TE MRSI, according to a recent study [33]. However, in our experience, short-TE SI is still a ‘work in progress’ and not applicable as easily as SV for the detection of short T2 metabolites in routine brain spectroscopy.

Spectral editing techniques

Spectral editing techniques take real advantage of higher field strengths as it allows specific metabolites to be observed and quantified within the acquired spectrum. Good results have been obtained with two-dimensional J-resolved spectroscopy (2D JPRESS) for the selective detection of glutamate. As it employs PRESS for volume localization, JPRESS provides an additional encoding of the J-coupling, improving specificity in detecting J-coupled metabolites and avoiding spectral overlap of resonances [28,34].

Shimming

Shimming methods are selected according to sampling method and the brain area to be investigated. As mentioned above, iterative fast shimming is the best method for the posterior fossa, temporal fossa or frontal base of the brain.

Saturation slabs (REST)

Saturation slabs (REST) are useful for suppressing the outer VOI signals, and are indispensable for SI to avoid lipid signal contamination from the scalp, orbit and skull base. They can also be applied to SV, depending on its location (close to the scalp, orbit or sinuses). Their number, size and geometry need to be adapted to the VOI, keeping in mind that voxels (SI) close to the REST slabs will give a weak signal.

Postprocessing

There are various processing steps that are automated and led by dedicated software (from the manufacturer, home-built, shareware or commercial) implemented on the acquisition console or on an off-line workstation where data are pushed after being acquired. Each of these steps can be manually handled in some systems. The acquired spectrum is postprocessed subsequently in the time domain and, after Fourier transformation, in the frequency domain. In the former, truncation of the first data may be necessary to avoid demodulation of the signal at the beginning and/or at the end. The spectrum resolution can then be artificially improved by zero filling (doubling the number of points within the spectrum), followed by Gaussian filtering (apodization) and noise removal. The next steps include phase, frequency shift and baseline corrections followed by Gaussian and/or Lorentzian peak-fitting and quantitation [35]. Results are displayed as metabolite ratios and, for SI, individual or ratio metabolite maps. These steps can be parameterized using different postprocessing protocols set in relation to each study design. Artifacts coming from eddy currents (small electrical currents that are more prominent at high field strengths due to increased speed and power of gradient coils, causing line-shape distortions and reduced SNR) are avoided by applying appropriate techniques during the scanning process [36].

Spectrum analysis and interpretation

With single voxel spectroscopy (SVS), after the acquired spectrum is displayed, a visual inspection is necessary to directly assess the overall spectrum quality, looking at baseline, SNR, spectral resolution (peak separation, peak sharpness, narrowness of peak base), frequency shift and
phase correction. The criteria for good spectral quality were well defined in 1999 by Vion Dury [37]. For chemical-shift imaging (CSI), the previously mentioned assessment is applied for each voxel during voxel-by-voxel analysis on the metabolite and ratio maps in register with corresponding anatomical images.

To ensure that the acquired metabolic information is accurate, it is essential to use a phantom-based checking system on a regular basis for quality assurance [38,39]. Minimal errors (frequency or phase shift) can often be corrected manually (if allowed by the manufacturer). A web-accessible, quality-control database for brain tumors is also available [40]. The next step is to look at the expected peaks and their relative amplitude and/or areas under the curve (AUC), and to look for and identify unexpected peaks. All of the metabolite ratios given in the figure legends accompanying this review were calculated using the AUC. Knowing whether to take account of metabolite quantification for interpretation is often important in routine brain MRS. In our experience, it depends of what value the numbers could add to the diagnosis or to a baseline study. For example, such numbers are unnecessary when looking for Lac (as its presence is considered pathological) or for Cr deficiency (lack of Cr peak). In other cases such as epileptic focus lateralization, considering the metabolite ratios is essential. Strong, rigorous and reproducible quantification methods have been designed and set for clinical use in many centers, using home-made or commercial software (LC Model) or shareware (jMRUI). In most clinical centers, the quantitation is relative and interpretation is based on metabolite ratios, assuming that Cr is relatively stable in almost all conditions. However, as misinterpretations may arise from variations in both the numerator and denominator in an altered ratio (for example, a decreased NAA and increased Cr in epileptic focus could result in a normal NAA/Cr ratio), absolute quantification is advisable, despite requiring more time and more procedures to be set up [41]. At our center, the integrated ‘Philips advanced tool’ for spectroscopy is reliable and sufficient for postprocessing and quantitative analyses.

As for quantitation, it is indispensable to refer to a control group with normal values (healthy volunteers) if the patient is not able to serve as his own control (having a contralateral normal-looking brain area). Because it is not possible to estimate the extent of metabolic abnormality within the brain, it is preferable not to set a spectrum obtained in an apparently normal part of an affected brain as the normal reference. Although multicenter studies have been published that report normal metabolite concentrations and ratios in the brain of healthy volunteers [42], we believe that the most reliable and rigorous procedure is to build a home-made database as a normal reference once the magnet has been clearly optimally parametered. The radiologist needs a good working knowledge of what each metabolite represents and what its relative variation means to ‘read’ the correct metabolic ‘message’ in a given clinical condition. This knowledge has to include brain metabolite variations in physiological conditions that could affect reproducibility of values and ratios, as well as changes during brain development [43,44]. A recent publication has proposed a computer-based decision-support system developed by the multicenter INTERPRET project to assist radiologists in diagnosing and grading brain tumors [45]. The interpretation should provide the most helpful answer to the question addressed by the clinicians. This means that, before looking at the spectrum, the radiologist should have full clinical information to adapt the spectroscopy scan design, and the MRS findings should be considered along with MRI (performed in the same session or previously) results and other metabolic investigations (such as PET-scan) when available.

Clinical applications

Premature babies

The increasing number of preterm births in industrialized countries has boosted both the public and professionals’ interest in this vulnerable population in terms of neurological disabilities such as cerebral palsy, hypotonia/dystonia and sensory impairment [46]. Thus, the main clinical concern has been to predict the neurological outcome with or without brain injury, which requires MR advanced techniques. MRS has been used for this purpose as it allows assessment of early human brain development [44]. However, to our knowledge, no study has yet been published of brain proton MRS in neonates using 3T. Our own experience is lacking such data. Nevertheless, scanning newborns with 3T and using the benefits of advanced techniques (notably, a shorter scan time) is feasible, according to recent studies using the same safety guidelines as with 1.5T and compatible incubators [47—49]. However, particular attention needs to be given to acoustic protection because of increased noise at higher field strengths and heat deposition due to powerful RFs. The feasibility of 3-D MRSI of the neonatal brain has been demonstrated by Vigneron et al. [50] at 1.5T, using a 3-D PRESS sequence covering the entire brain, with TE = 144 ms and an acquisition time of 17—19 min. A technical note from Kim et al. shows that 3-D MRSI is possible at short TE (30 ms) with a 9-min acquisition time, and records the ml signal as well as the Glx [51]. 3-D volume MRSI provides metabolic information from the whole brain in one measurement, but is highly sensitive to head motion during scanning. SV works as well and, although limited in size, can quickly (2—4 min) sample the spectrum in the region of interest (ROI) and is easily repeated if movement occurs. Barkovich recommends two SV scans of about 5.5 cm³ to cover basal ganglia and frontal white matter, respectively [49]. Choosing a long TE (144—288 ms) permits detection of Lac, which indicates a poor prognosis when found in the basal ganglia [49,50]. In premature infants with a 1-year normal outcome, the NAA/Cho ratio increases (increased NAA and decreased Cho) linearly and dramatically between 27.7 and 42.4 weeks, reflecting brain maturation in corticospinal tracts, basal ganglia and posterior white matter [44]. No significant difference was found in Glx between preterm and term neonates [51]. MRS using SV or 3-D SI can, therefore, contribute metabolic information to morphological brain assessments to predict neurological outcomes or to monitor brain maturation.
Hypoxic–ischemic brain injury (HIBI)

In HIBI, the clinician’s expectation from MRI is to assess brain lesions as early as possible and to offer prognostic data for outcomes. Lesions in term infants usually result from mild/moderate hypotension or perinatal asphyxia and classically involve intervascular boundary zones (“watershed areas”). Any subsequent clinical deficit is related to the severity of brain injury, as assessed by imaging or metabolic assessment. Proton MRS is the most sensitive technique (over diffusion) for identifying brain injury during the first 24 h [52], while MRI and diffusion patterns show some variation over time in cases of HIBI [53]. Several studies at 1.5T found a reduced NAA and increased Lac (in metabolite ratios as well as in absolute quantitation) in basal ganglia, which were well correlated with poor neurological outcomes [52–56]. Thus, SV or MV should plan to cover basal ganglia, and a long TE is preferable to a short one.

Metabolic diseases

Radiological diagnosis of inborn errors of metabolism is challenging as the imaging appearances of many disorders overlap, and often vary with the stage and variant of the disease. They are classified in different ways, one depending on predominantly affected white matter (subcortical or periventricular), gray matter (cortex or gray nuclei) or both (basal ganglia), others on biochemical or clinical characteristics and affected organelle. Proton spectroscopy can be extremely useful in confirming suspected pattern recognition and/or response to appropriate treatment at the follow-up. The value of Lac (a doublet centered at 1.3 ppm; both short and long TE) has been stressed in mitochondrial diseases. A broad peak corresponding to branched chains of amino acids (centered at 0.9 ppm; short TE) in neonatal maple syrup disease, a prominent NAA peak in Canavan disease, elevated glycine peak (3.55 ppm; different from mI with both short and long TE) in nonketotic hyperglycemia, Phe peak (at 7.36 ppm; very short TE) in phenylketonuria (PKU), Gal-ol peak in galactosemia (doublet overlaps with Glx at 3.75; short TE) and reduction of NAA (ratios) in normal-looking white matter in asymptomatic individuals carrying X-adrenoleucodystrophy (ALD) are examples of the clinical usefulness of spectroscopy [57–60]. In Cr deficiency due to defects in synthesis (GAMT and AGAT deficiency) or transport across the blood–brain barrier (X-linked defect), the spectrum in the basal ganglia, or in white matter or the cerebellum, will show a low or absent Cr peak and, in the follow-up, an increased Cr peak in response to creatine supplementation [57,58]. Previous examples and cited references are helpful to the radiologist in planning the examination (anatomical location, sampling technique and TE) and in the interpretation of the spectrum of known metabolic disorders. However, children are often sent for MR with a suspected diagnosis. In that case, conventional MRI can serve as a guide for the MRS scan. Spectroscopy can then be used to collect as much biochemical information as possible, covering supratentorial white matter (WM) as well as gray matter (GM) (MV short/long TE) and focusing the lesion or basal ganglia (BG) with SV at a short TE to obtain the widest spectrum of observable metabolites.

Metabolic diseases are progressive with a time course that depends on the type and whether treatment is applied or not. The timing of an MRS scan is therefore crucial for interpretation, as metabolic changes within the earliest stages of a disease often differ significantly from those observed at later stages. Another point to take into account involves metabolite changes due to brain development and myelination. The lack of a clear doublet centred at 1.33 ppm (inverted at 144 ms) to certify the presence of Lac in WM and BG should not be the only basis of ruling out a diagnosis of metabolic disease. Brain Lac concentration has an anatomical and time fluctuation [58,61], so it may be necessary to investigate the entire brain by MRS, including the CSF within the ventricles and the cerebellum and, if possible, to repeat the examination using optimal sequences for Lac detection [18].

Epilepsy

The classification of epileptic disorders from the New Delhi Commission (1989) uses both clinical and electrophysiological criteria to define idiopathic, symptomatic and cryptogenic types on one hand, and diffuse, focal or syndromic types on the other [62]. Symptomatic and cryptogenic epilepsies (diffuse or focal) are indications for MRI, which can detect the underlying structural abnormalities. MR advanced techniques are useful for patients with intractable epilepsy that could be cured by surgical resection of the epileptogenic lesion [63]. Using clinical data and video-electroencephalography (EEG) records, epilepsy can be categorized as either extratemporal lobe (ETLE) or temporal lobe (TLE), depending on the focus [64].

MRS has proven useful for characterizing lesions in both ETLE and TLE, and in lateralizing the focus in TLE [65–73]. The most common pathology encountered in children with ETLE is malformation of cortical development (MCD). Due to an improved SNR, 3T scans offer better detection and morphological characterization of such lesions [65]. In occult cortical dysplasia, MRSI has been shown to be more sensitive in detecting areas of low NAA/Cho ratios that are well correlated with the epileptogenic focus [66,67]. The scan plan needs to be guided by clinical and video-EEG findings to cover the presumed focus, using single- or multislice SI with long TE (135–144 ms or 272–288 ms, respectively) in conjunction with an SV with short TE to focus on the lesion. Visual inspection of metabolic ratio maps (NAA/Cho; NAA/Cr) and asymmetry index calculation can help to locate the abnormal area that may correspond to the focus in correlation with clinical information. In TLE, MRI and MRS protocols are designed to focus on the temporal lobe and hippocampi. In more than 60% of patients with TLE, seizures are related to mesiotemporal sclerosis (MTS). Several studies have shown good results for both SV and SI in lateralizing the focus, particularly in patients with normal MRI or subtle hippocampal asymmetry [68]. In our experience (results from unpublished material), a combination of SV short TE and SI long TE with MRI focused on the temporal lobes offers a complete assessment in TLE, while keeping a reasonable total scan time of 45 min. SI is acquired with a slice of 83 × 100 × 15 mm (AP × RL × FH) in the axial plane along the hippocampal axis, covering both hippocampi, the
We have used a SV short TE of rectangular shape found, in healthy volunteers (unpublished material), that a restriction of metabolic disturbances in the temporal region (Fig. 1B) restricted to the hippocampus and assessment of the extent parahippocampal gyri and the periventricular WM (Fig. 1A). Postprocessing allows averaging of the spectrum on an area restricted to the hippocampus and assessment of the extent of metabolic disturbances in the temporal region (Fig. 1B and C). We have used a SV short TE of rectangular shape AP/RL/FH = 83/100/15 mm; nominal voxel = 1.25 cc) ; to the hippocampal axis (TE/TR = 288/2000 ms; VOI size AP/RL/FH = 83/100/15 mm; voxel nominal : 1,25 cc); B: From left to right, VOI is the green rectangle, including hippocampi as well as medial temporal lobes; yellow crosses lie in the voxels selected for analysis (within hippocampi); NAA color-coded map shows a decreased NAA signal on the left compared with the contralateral side; Cho/NAA ratio color-coded map also shows asymmetry, suggestive of a decreased NAA in the left hippocampus predominating anteriorly; C: Corresponding spectra in a voxel/voxel comparison shows a decrease of all metabolites, but especially of NAA in the left hippocampus.

**Figure 1** Left mesial temporal lobe epilepsy: A: SI planning using a single slice on the axial plane parallel to the hippocampal axis (TE/TR = 288/2000 ms; VOI size AP/RL/FH = 83/100/15 mm; nominal voxel = 1.25 cc); B: From left to right, VOI is the green rectangle, including hippocampi as well as medial temporal lobes; yellow crosses lie in the voxels selected for analysis (within hippocampi); NAA color-coded map shows a decreased NAA signal on the left compared with the contralateral side; Cho/NAA ratio color-coded map also shows asymmetry, suggestive of a decreased NAA in the left hippocampus predominating anteriorly; C: Corresponding spectra in a voxel/voxel comparison shows a decrease of all metabolites, but especially of NAA in the left hippocampus.

Conventional MRI can provide a full morphological assessment of traumatic brain injury (TBI). Nevertheless, MRI findings, which are critical for patient management, do not often correlate precisely with either the clinical state or neurological outcome. H-MRS allows early detection of biochemical impairment of the brain in cases of TBI as well as better clinical correlation and outcome prediction [74—76]. In this condition, N-acetyl aspartate (NAA) is assumed to be a marker of neuronal wellbeing and viability, and so is a good candidate for measurement. In their study at 1.5T, Carpentier et al. [74] found a decrease in NAA/Cr ratio (<1.50) in the pons of patients with severe TBI, using an SV technique (15 × 15 × 20 mm) at a TE of 135 ms. MRS was positive in some patients with a normal-looking pons on conventional MR, and an NAA decrease was well correlated with a poor neurological outcome. Cohen et al. [76] studied whole-brain NAA at 1.5T in patients with mild TBI. Volumetric measurements of their patients showed a decreased gray-matter volume that, in combination with low whole-brain NAA, strongly suggests damage to neurons and axons beyond MRI-visible lesions. Improved shining techniques with powerful gradients with 3T should enhance the measurement of brain NAA for early assessment and follow-up of patients with TBI.

**Inflammatory diseases**

MRI plays an important role in the diagnosis of multiple sclerosis (MS). High-field MRI results in a significantly higher rate of detection of inflammatory brain lesions (notably in the infratentorial, juxtacortical and periventricular areas), and has a substantial influence on the classification of patients with clinically isolated syndromes (CIS) suggestive of MS [77,78]. Postmortem studies have shown that MS pathogenesis includes inflammation/demyelination, axonal loss and gliosis not only in lesions, but also in apparently normal tissue [79]. The changes outside of lesions are not visible with conventional MRI, whereas MRS has shown metabolic responding asymmetry indices to be effective in lateralizing the epileptic focus (Fig. 2B and C).

According to the literature, MRS can correctly lateralize the focus in up to 80% of patients with TLE—MTS and in about two-thirds of patients with TLE—normal MRI [68]. All studies reported a decrease of NAA in the affected hippocampus associated with neuronal loss or dysfunction. Variations in other metabolites in the epileptic focus are not as well established, although recent studies have described a decrease in ml [68,70]. What is promising with 3T is the use of additional metabolites such as GABA to detect the focus [71]. An epileptic brain is a good example to illustrate why a normal-looking area of brain or hippocampus should not be taken as an internal normal reference in clinical practice. Indeed, studies have shown that metabolite abnormalities can extend far from the lesion in MCD (ETLE) as well as to the contralateral side in TLE [72,73]. Thus, it is preferable to refer to a normative home-made database of healthy subjects who have undergone the same scanning protocol as have the patients.
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Figure 2  Right mesial temporal lobe epilepsy with normal MRI: A: Planning of the SV (TE/TR: 38/2000 ms; 144 exc) using, from left to right, sagittal 3-D T1-weighted image (WI), axial T2-WI and coronal Inversion-recovery T1-WI; the VOI is colored orange (AP/RL/FH = 32/15/10 mm) while the white box (same size) is the water chemical-shift displacement (to improve water suppression); B and C: Spectra from the right hippocampus show a decreased NAA/Cr ratio (1.36) and, from the left hippocampus, a normal NAA/Cr ratio (1.69), respectively; the asymmetry index (21.6%) also favours right lateralization as the epileptic focus.

alterations of normal-appearing white and cortical gray matter (NAWM and NACGM, respectively) in patients with MS [80—84]. The best way to assess these changes is with an MV spectroscopy technique using multiple slices to cover a larger volume of cerebral white matter. The NAA/Cr ratio decreases with neuronal death or dysfunction, while Cho/NAA and Cho/Cr ratios indicate myelin breakdown within MS plaques as well as in apparently normal tissue. The former variations may also be related to the remyelination process within the plaque in the subacute phase. The ml/Cr ratio indicates glial infiltration, present in MS but absent in CIS, the latter probably corresponding to early-stage MS [83]. The metabolic changes may reverse with time, but the precise timing of such a course is not yet established [80]. Combining volumetry of the brain and MRS may improve the accuracy of MR in the follow-up of MS patients.

Brain tumors

This field has been extensively investigated by numerous studies using H-MRS at 1.5T. Interesting results have been found in the differentiation of tumors from tumor-like lesions (vascular, inflammatory, infectious) [85—89], metabolic characterization of brain tumors correlated with histopathology and the cell proliferation index (Ki-67 or MIB-1) [88,90—93], differentiation of tumor grade [87,90—95], preoperative assessment (biopsy or resection) [96—99], postoperative control and short- or long-term follow-up after surgery, or chemo- or radiotherapy [97—102]. The improvement in spatial, temporal and spectral resolution with 3T results in greater sensitivity of MRS in any of the applications mentioned above. A major advantage is the possibility of 3-D MRSI acquisition integrated with pre- or perioperative neuronavigation [93,103,104]. The tumor border zone is of interest in the evaluation of the extent of a tumor, and to differentiate metastases from high-grade glioma and glioma from nonglial masses. The absolute NAA concentration has shown the best correlation with tumor infiltration [105]. A recent study using 3T found Glx to be elevated in peritumoral brain edema, indicating an energy-linked metabolic alteration of the myelin sheath [106]. Some studies have had better results for tumor differentiation and classification using statistical linear discriminant analysis (LDA) of normalized metabolite concentrations [107,108], or least-squares support vector machines (LS-SVMs) with a radial basis function kernel [109].

Our usual clinical practice, when assessing a brain mass with spectroscopy, is to use SI (long TE 288 ms, PRESS technique) to obtain a Cho map (Fig. 3A). The Cho map intensity is related to its relative concentration. Based on the studies already mentioned, we can assume that, as the highest intensity correlates with the most aggressive part of the tumor, it is possible to use the Cho signal intensity to set the SV (short TE 30—35 ms, PRESS, or 14—25 ms, STEAM) parameters and location (Fig. 3B). When the Cho map is not helpful for this purpose, an apparent diffusion coefficient (ADC) map (of the area with the lowest ADC values), perfusion color map (the area showing an increased rCBV (relative cerebral blood volume)) or postcontrast T1-weighted images
Figure 3 Brain tumor: A: SI planning using a single slice in the standard axial plane (TE/TR = 288/2000 ms; VOI size AP/RL/FH = 131/108/20 mm; nominal voxel = 1.5 cc) with conical alignment of REST slabs opened up; B: SV planning [TE/TR 31/2000 ms; 128 exc; VOI, colored orange (AP/RL/FH = 32/15/10 mm)], using the Cho map to focus on the most aggressive part of the tumor; C and D: The grid and VOI (green box) on axial T2-FLAIR-WI with the selected voxel for analysis (yellow cross), and the corresponding spectrum show highly increased Cho/NAA (3.75) and Cho/Cr (4.19) ratios as well as high levels of Lac and Lip (0.9 to 1.4 ppm), respectively; E: Spectrum from the SV, focused on the highest signal area on the Cho map, shows a drop in NAA peak, high Cho/NAA (11.84) and Cho/Cr (2.25) ratios, but also an increased ml/Cr ratio (0.9) (arrow), and the presence of Lac and Lip. These findings all suggest a high-grade tumor of glial origin; histopathology found a glioblastoma.

The Cho/NAA ratio and free lipids have proved to be the best markers for tumor diagnosis and grading [83,88,92,94] (Fig. 3C–3E), whereas other metabolites are useful for predicting the histological type: Glx and Ala (meningioma) [31,112] (Fig. 4); ml (gliomatosis, paraneoplastic limbic encephalitis, ependymoma) [87,108,113,114]; and Tau/sc-I (medulloblastoma) [87,108,113]. In our clinical practice, we find that the differential diagnosis of primary central nervous system lymphoma (PCNSL) from high-grade glioma, on the basis of MRS, is challenging. Several studies to identify the characteristic metabolic profile of PCNSL have found hugely elevated lipid resonances to be a hallmark [115]. However, this profile is often similar to the spectrum of glioblastoma. Multimodal imaging is then helpful to overcome this limitation by collecting all findings from various techniques, including perfusion [116,117]. MRS is currently considered as part of a multimodal (conventional MRI, diffusion, perfusion and functional imaging) approach in the MRI-based diagnostic strategy for brain masses, as described by Al-Okaili et al. [118] (Fig. 5). Floeth et al. [119] found that integrating other molecular brain-imaging techniques such as 18F-fluoroethyl-L-tyrosine (FET) positron emission tomography (PET) markedly improved the diagnostic accuracy of targeted biopsies.

Neurodegenerative diseases

Normal aging and senescence are accompanied by a number of well-established structural MRI correlates, but are still not well understood. Numerous studies have attempted to identify specific imaging markers for different types of dementia [Alzheimer’s disease (AD), frontotemporal dementias, dementia with Lewy bodies, dementia associated with Parkinson syndromes, Huntington disease, vascular dementias and mild cognitive impairment (MCI)], including cerebral volumetric measurements, diffusion imaging and spectroscopy, as well as very-high-field MRI scans [120–123]. The clinical objective is to obtain a precise and early diagnosis as well as an understanding of related brain changes that could help to predict or slow the course of the disease. NAA is considered to be the first marker for that purpose as it is a direct product of neuronal impairment [123,124].
Figure 4  A 56-year-old woman with unusual headaches, but a normal brain MRI six months earlier: A: Axial T2-WI shows an apparently extra-axial intracranial mass with hyperintense foci posteriorly (p) and a close relationship with brain tissue anteriory (a); B: Post-contrast T1-WI shows intense enhancement of the mass with slight thickening of adjacent meninges; C: SV spectrum by STEAM technique (TE/TR: 14/2000 ms; AP/RL/FH: 20/20/20 mm; 144 exc) focused on the posterior part of the tumor displays highly increased Cho/NAA (5.34) and Cho/Cr (6.31) ratios, marked elevation of Glx peaks (2.1—2.4 and 3.63 ppm; Glx/Cr ratio = 7.43), large amounts of Lac and Lip, and an Ala doublet centred at 1.5 ppm; D: Spectrum from the same voxel at longer TE (144 ms) shows Ala peak inversion at 1.5 ppm and failure of J-coupling for Lac. All these findings, especially the presence of Ala, favour a meningioma with features of malignancy. Histopathology found a meningioma with a subpial component anteriorly (a), and necrotic areas and signs of cellular malignancy posteriorly (p).

Figure 4  Cas d’une femme de 56 ans, présentant des céphalées inhabituelles et ayant eu une IRM cérébrale normale six mois plus tôt ; A : Image axiale T2 montrant une masse intracrânienne d’apparence extra-axiale, présentant des hypersignaux focaux dans sa partie postérieure (p) et un rapport étroit avec le parenchyme à sa partie antérieure (a) ; B : Images T1 après injection de produit de contraste montrant un rehaussement intense de la masse et un discret épaissement miné à l’endroit ; C : Spectre issu d’un voxel unique (SV) (20 × 20 x 20 mm) utilisant la technique STEAM (TE/TR: 14/2000 ms; 144 exc) et centré sur la partie postérieure de la tumeur, montrant une élévation marquée des rapports Cho/NAA (5.34) et Cho/Cr (6.31), une élévation marquée des pics de Glx (à 2,1—2,4 ppm et 3,63 ppm ; Glx/Cr = 7,43), la présence d’une importante quantité de Lac et Lip ; notez le doublet d’alanine (Ala) centré à 1,5 ppm ; D : Spectre issu du même voxel mais à TE plus long (144 ms), montrant à l’évidence la présence d’Ala sous la forme d’un doublet inversé à 1,5 ppm ; notez l’échec du couplage de spin pour le Lac ; l’ensemble de ces observations, et notamment la présence d’Ala, font évoquer un méningiome présentant des signes de malignité. L’histologie révèle qu’il s’agit d’un méningiome à composante sous-piale à sa partie antérieure (a) et comportant des plages nécrotiques et des atypies cellulaires à sa partie postérieure (p).

Other molecules such as ml and Glx have also shown correlated variations [125]. The main spectroscopy finding is a decrease in the relative or absolute concentration of NAA in patients with AD and MCI associated with a significant increase in ml, very likely due to gliosis induced by neuronal loss in the medial temporal lobes, and anterior and posterior cingulated gyri [123—126]. MRS at 3T at short TE, for reasons given above, is better at detecting the glutamine/glutamate complex, which may be a more accurate marker.

As for cerebellar ataxias, including autosomal-recessive Friedrich’s (FA), autosomal-dominant spinocerebellar (SCA), X-linked (FXS), mitochondrial, multiple system atrophy (MSA) and sporadic (paraneoplastic) types of ataxia [127], an appropriate diagnosis is of the utmost importance for prognoses, genetic counselling and possible therapeutic indications. Boesch et al. showed that the NAA/Cr ratio differentiates SCA-2 from SCA-6 [128], and SCA-2 from a cerebellar variant of MSA [129]. In our experience, the NAA/Cr ratio [SV at both short (35 ms) and long TE (144 ms) PRESS] was helpful in a baseline study of patients with cerebellar ataxia with follow-up (unpublished material) (Fig. 6). Other promising markers with 3T are GABA and the glutamatergic pathway [130].

Psychiatric diseases

Advanced neuroimaging techniques have provided clinicians with a better understanding of the morbid anatomy, pathophysiology and chemical pathology of psychiatric diseases such as schizophrenia, addictions, depression and affective disorders, as well as antipsychotic drug effects [131]. Spectroscopy studies of schizophrenia have shown decreases in NAA in the medial temporal and prefrontal regions [132]. The use of higher field strengths and longitudinal studies reveal a progressive excitotoxic glutamatergic process that leads to volume loss and NAA decreases in schizophrenia [132,133], High-field MRS studies of bipolar disorders reveal diminished concentrations of NAA and low NAA/Cr ratios in the basal ganglia at 3T [134], and low glutamine levels in unmedicated patients at 4 T [135]. A recent study with 3T by Shibuya-Tayoshi et al. found that lithium, a first-line drug treatment for acute bipolar disorder, decreases Gln and Glx levels in the bilateral basal ganglia of healthy individuals [136].

Pitfalls

Geometry and positioning of the VOI

The spectrum obtained represents the metabolic profile of the tissue lying within the voxel of interest (VOI). For this reason, the SV technique needs to cover the most informative part of the lesion (the nodular part in the case of tumors, avoiding the necrotic parts; the most recent lesion in multifocal brain disease). However, there is still a certain degree of contamination of the sampled spectrum by lipid (Lip) from the adjacent necrotic areas, giving a broad peak between 0.9 and 1.4 ppm at all TEs. This broad Lac and Lip peak could peak could reduce the signals from other metabolites, making interpretation difficult. The use of REST slabs will avoid lipid contamination from the scalp and areas of necrosis.

Figure 4  Cas d’une femme de 56 ans, présentant des céphalées inhabituelles et ayant eu une IRM cérébrale normale six mois plus tôt ; A : Image axiale T2 montrant une masse intracrânienne d’apparence extra-axiale, présentant des hypersignaux focaux dans sa partie postérieure (p) et un rapport étroit avec le parenchyme à sa partie antérieure (a) ; B : Images T1 après injection de produit de contraste montrant un rehaussement intense de la masse et un discret épaissement miné à l’endroit ; C : Spectre issu d’un voxel unique (SV) (20 × 20 x 20 mm) utilisant la technique STEAM (TE/TR: 14/2000 ms; AP/RL/FH: 20/20/20 mm; 144 exc) et centré sur la partie postérieure de la tumeur, montrant une élévation marquée des rapports Cho/NAA (5.34) et Cho/Cr (6.31), une élévation marquée des pics de Glx (à 2,1—2,4 ppm et 3,63 ppm ; Glx/Cr = 7,43), la présence d’une importante quantité de Lac et Lip ; notez le doublet d’alanine (Ala) centré à 1,5 ppm ; D : Spectre issu du même voxel mais à TE plus long (144 ms), montrant à l’évidence la présence d’Ala sous la forme d’un doublet inversé à 1,5 ppm ; notez l’échec du couplage de spin pour le Lac ; l’ensemble de ces observations, et notamment la présence d’Ala, font évoquer un méningiome présentant des signes de malignité. L’histologie révèle qu’il s’agit d’un méningiome à composante sous-piale à sa partie antérieure (a) et comportant des plages nécrotiques et des atypies cellulaires à sa partie postérieure (p).
**Figure 5**  Multifocal brain pathology using multimodal imaging: conventional MRI by (A) axial T2-FLAIR shows multiple hyperintense areas in the left hemisphere at the level of the vertex, with different signal intensities from three foci: subcortical white matter (WM) in the anterior left frontal lobe (arrowheads); an area posteriorly that is clearly separated from the anterior area (red square); and a subtle area in the deep WM on the right (long arrow); B: Post-contrast T1-WI shows a ‘layered’ enhancement of the left posterior lesion (arrowheads) that is subtle on the right side (long arrow); C: Perfusion imaging [color-coded cerebral blood volume (CBV) map] shows increased relative CBV in both hemispheres corresponding to the enhancing areas (long arrow on right, arrowheads on left); D: Spectroscopy imaging (TE/TR: 288/2000 ms) with color-coded Cho map registered on an axial T2-FLAIR image (made by Osirix; www.osirix-viewer.com) shows high Cho signal intensity that is more intense in the left posterior lesion, suggesting that it is the most aggressive part of the lesion, which extends across the midline; E: The SV spectrum (TE/TR: 38/2000 ms; 128 exc) from the left posterior lesion shows a drop in the NAA peak, a major increase of Cho/NAA ratio and a markedly elevated mI peak; Lac and Lip are also present; F: Diffusion tensor imaging with 2-D cross-sectional tractography projections on the B0 image shows displacement and perhaps disruption of the corticospinal tract on the left (arrowheads), and involvement of the same tract on the right (long arrow); G: Functional MRI (fMRI) helps to locate elective motor areas in relation to the lesions on both sides. This information, from multimodal MRI, helped to make the correct diagnosis of a multifocal high-grade tumor crossing the midline and extending anteriorly into the left hemisphere, and also supported the patient’s preoperative assessment. Histopathology revealed a glioblastoma.

**Frequency shifts**

When first looking at the spectrum, it is important to check that the frequency shift is correct and, if necessary, to make an additional correction manually. The reference is usually the NAA peak at 2.02 ppm. The Ala peak, a doublet centred at 1.5 ppm and inverted at 144 ms, should not be mistaken for the Lac peak (centred at 1.3 ppm). When Lac and Ala coexist, it may be difficult to discriminate between them.

**Patient movement**

A spectrum of poor quality is often the result of incorrect shimming, high water content (cyst) or a partial volume...
A 16-year-old boy with cerebellar ataxia and normal brain MRI: A: SV planning (TE/TR: 31/2000 ms; 20 × 20 × 20 mm; 144 exc) in the deep left cerebellum hemisphere includes the dentate nucleus (arrowheads); B: spectrum obtained shows decreased NAA/Cr ratio (1.19) compared with the mean control value (1.44), indicating neuronal loss or dysfunction; C: The total Glx/Cr ratio (arrows on B) is significantly increased (P < 0.01) in the patient (2.45 vs 1.56 in the controls), suggesting a disturbance in the glutamate–GABA pathway.

Figure 6 Cas d’un patient âgé de 16 ans, présentant une ataxie cérébelleuse avec une IRM cérébrale normale. A : Positionnement du voxel unique (TE/TR : 31/2000 ms ; 20 × 20 × 20 mm ; 144 exc) dans la profondeur de l’hémisphère cérébelleux gauche incluant le noyau denté (têtes de flèche) ; B : Spectre obtenu : baisse du rapport NAA/Cr (1,19) en comparaison avec la valeur moyenne observée dans un groupe témoin (1,44) indiquant une perte ou un dysfonctionnement neuronal ; C : Image d’un tableau montrant que le rapport de Glx total/Cr (flèches sur (B)) est significativement (p < 0,01) plus élevé chez le patient (2,45 vs. 1,56 dans le groupe témoin), suggérant une perturbation de la voie neurométabolique impliquant le glutamate et le GABA.

Voxel/voxel contamination (CSI)

The spectrum in one CSI voxel is partially affected by the signals from the surrounding voxels. This effect explains why a voxel within the frontal horn of the lateral ventricle, close to the lateral wall, could show an NAA peak even with no NAA source in the CSF. For the same reason, lipid signals from the voxels within necrotic areas of a lesion will affect the spectrum of voxels along the borders.

Peak/peak contamination

This phenomenon affects peaks of molecules with similar resonance frequencies such as Cho and Cr, Lac and Lip, and ml and Glx. A large amount of Cho will lower the signal of Cr, as will a large amount of Lip over Lac, and ml over Glx.

Increased choline as artifact

When an expansive process causes a mass effect in the brain, the apparently normal adjacent white matter is displaced and fibers become packed. The spectrum from displaced and packed fibers shows an increase in the Cho signal (Cho/Cr ratio). However, this does not necessarily mean that the area is involved in the pathological process. In our experience of a case of a giant pituitary adenoma displacing frontal lobes laterally, the brain parenchyma was clearly not affected (no MR signal abnormality), yet showed increased Cho within the displaced and packed white matter.

Gliotic scar

All signals within the spectrum are spoiled and the spectrum not analyzable if the VOI is set within a gliotic scar (due to ischemia or infection).

High-grade tumors with low cell proliferation indices (MIB-1)

These tumors often show mildly elevated Cho/NAA and Cho/Cr ratios (SV and SI, respectively) similar to those seen in low-grade tumors or inflammatory diseases. The surrounding parenchyma may show normal spectra. The differential diagnosis between a high-grade glioma and a metastasis is difficult to make in such cases.

MRS in patients with PCNSL and given steroids

The spectrum of brain lesions in PCNSL has been mentioned above. If a brain mass is suspected, an emergency CT scan may reveal the mass and its surrounding edema. Steroidal treatment to ease brain edema is usually given a few hours to several days before the patient undergoes
Figure 7 Potential effect of corticosteroids in differentiating cerebral lymphoma (PCNSL) and vasculitis (CNSV). In a 75-year-old man with histologically confirmed PCNSL: A: Axial T2-FLAIR-WI shows involvement of the deep periventricular white matter (WM) and basal ganglia (BG); B: SV spectrum (TE/TR: 37/2000 ms; 20 × 20 × 15 mm; 128 exc) within the right BG shows typically increased Cho/NAA and Cho/Cr ratios, and large amounts of Lac and Lip. In a 58-year-old woman with histologically confirmed PCNSL who received corticosteroids (16 mg/day) for three weeks prior to MRI and before the biopsy was taken: C: Axial T2-FLAIR-WI shows a right periventricular hyperintense heterogeneous mass and signal abnormalities in the right subcortical frontal and parietal lobes; D: SV spectrum (TE/TR: 32/2000 ms; 25 × 15 × 15 mm; 128 exc) of the mass shows minor abnormalities, in particular, a slightly reduced NAA/Cr ratio and no evidence of a Lac/Lip peak. In a 42-year-old man with histologically confirmed CNSV: E: axial T2-FLAIR-WI shows bilateral frontal subcortical and BG hyperintense areas, including the right posterior temporal lobe; F: The SV spectrum (TE/TR: 36/2000 ms; 20 × 20 × 20 mm; 128 exc) displays a reduced NAA/Cr ratio, slightly increased Cho/NAA and Cho/Cr ratios, and a large Lac/Lip peak.

MRI—MRS examination. The effect of steroids on the spectrum of such lesions has not been documented. However, in our experience (unpublished material), in all patients (later revealed to have PCNSL) who received steroids prior to MRS, the spectrum showed the same abnormalities as found in patients with cerebral vasculitis (mild increase of Cho/Cr and Cho/NAA ratios, large amount of Lac, no free lipids), leading to misdiagnosis. In all of our patients with histologically proven PCNSL in whom MRS was performed with no prior steroidal treatment, the spectrum showed abnormalities similar to a high-grade tumor (Fig. 7).

Normal spectrum with white-matter MR signal abnormalities

We have observed a normal spectrum in two patients with white-matter signal abnormalities (hypersignals on FLAIR images). The voxels placed over the signal abnormalities displayed completely normal spectra. A possible explanation for such a finding is that an unknown pathological process may have modified the water content or water distribution within the white matter without impairing the normal biochemistry in that tissue. Both patients had normal neurological examinations.

Conclusion

Based on a review of the literature and our own clinical experience with 3T, high-field proton MR spectroscopy can significantly improve the overall diagnostic accuracy of MRI of the brain, leading to more valuable information and more efficient patient management. MRS should be integrated into a multiple-modality approach of brain diseases. As the MRS technique continues to develop, its application in
high-field neuroimaging in clinical settings should certainly become more and more routine.

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