JMSR
Journal of Medical and Surgical Research

Review Article

ISSN: 2351-8200

JMSR 2017, Vol III ; N°3 : 345-352

PROTON MAGNETIC RESONANCE SPECTROSCOPY IN BRAIN TUMORS: LITERATURE REVIEW

B. Alami 1&2, Y. A. Lamrani1, S. Boujraf 1&2, A. Housni3, M. Boubbou1, M. Maaroufi1
1 Radiology Department, Hassan IId University Hospital, Fez, Morocco.
2 Biophysics and clinical MRI Methods, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco
3 Institut Supérieur des Professions Infirmières et Techniques de Santé, Fez, Morocco.

ABSTRACT

MR spectroscopy obtains biochemical information noninvasively from biologic tissue. Within a defined volume of interest, signals may be registered from chemical nuclei within the body; the most commonly used nuclei are protons (hydrogen).
It differs from conventional Magnetic Resonance Imaging (MRI) in that spectra provide physiological and chemical information instead of anatomy.
In this article, we aimed to show the usefulness of MRS in differentiating brain tumors and non-neoplastic diseases mimicking brain tumors in conventional MRI. Additionally we illustrated MRS usefulness to characterize the most common intra-axial brain tumors

Keyword: Brain tumors, Proton magnetic, Resonance spectroscopy

Corresponding author:
Dr. B. Alami
Department of Hepatogastroenterology ,University Hospital Hassan II, Faculty of Medicine and Pharmacy of Fez, University Sidi Mohammed Ben Abdellah, Fez, Morocco

INTRODUCTION

MR spectroscopy obtains biochemical information noninvasively from biologic tissue. Within a defined volume of interest, signals may be registered from chemical nuclei within the body; the most commonly used nuclei are protons (hydrogen).
It differs from conventional Magnetic Resonance Imaging (MRI) in that spectra provide physiological and chemical information instead of anatomy.
In this article, we aimed to show the usefulness of MRS in differentiating brain tumors and non-neoplastic diseases mimicking brain tumors in conventional MRI. Additionally we illustrated MRS usefulness to characterize the most common intra-axial brain tumors

PHYSICAL BASIS

Many nuclei may be used to obtain MR spectra, including phosphorus (31P), fluorine (19F), carbon (13C) and sodium (23Na). The ones mostly used for clinical MRS are protons (H-MRS). The brain is ideally imaged with H-MRS because of its near lack of motion. The hydrogen nucleus is abundant in human tissues. H-MRS requires only standard radio-frequency (RF) coils and a dedicated software package.
There are different field strengths clinically used for conventional MRI, ranging from 0.2 to 3T. Since the main objective of MRS is to detect weak signals from metabolites, a higher strength field is required (1.5T or more). Higher field strength units have the advantage of higher signal-to-noise ratio (SNR), better resolution and shorter acquisition times.
H-MRS is based on the chemical shift properties of the atom. When a tissue is exposed to an external magnetic field, its nuclei will resonate at a frequency (f) that is given by the Larmor equation:
$f = \gamma B0$
Since the gyro-magnetic ratio (γ) is a constant of each nuclear species, the spin frequency of nuclei (f) varies according to the external magnetic field (B0) and the local microenvironment. The nuclei's

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

electric shell interactions with the surrounding molecules cause a modification in the local magnetic field inducing a change on the atom's spin frequency (a phenomenon called chemical shift). The value of this difference in resonance frequency gives information about the molecular group carrying 1H and is expressed in parts per million (ppm). The chemical shift position of a nucleus is expressed in ppm because it is independent of the field strength (choline, for example, will be positioned at 3.22 ppm at 1.5T or 7T). The MR spectrum is represented the x axis which corresponds to the metabolite frequency in ppm according to the chemical shift and the y axis which corresponds to the peak amplitude (Fig. 1) [1, 2].

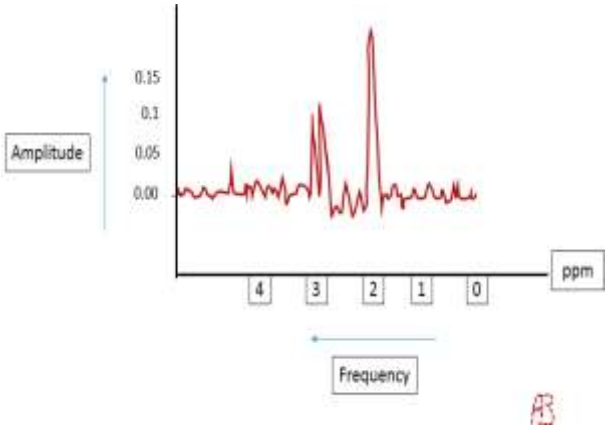


Fig. 1. Normal spectra. y axis correspond to amplitude and x axis to the metabolites frequency

TECHNICAL CONCERNS

Two categories of spatial localization approaches for MR spectroscopy are described: **single-voxel (SV) techniques**: commonly used methods includes 'PRESS'[3] and 'STEAM'[4], which record spectra from one area in the brain at a moment (t), and **multi-voxel techniques ('MR spectroscopic imaging' (MRSI)**, also called 'Chemical Shift Imaging' (CSI) [5]) which simultaneously record spectra from multiple brain areas and thereby map out the spatial repartition of all metabolites within the brain. While SV-MRS and MRSI each have their own advantages and disadvantages (e.g. in terms of spectral quality, scan time, spatial resolution, spatial coverage, and ease of use/interpretation) [6]

MRS can be obtained using different TEs can be used to obtain MRS. Short TE refers to a study in which it varies from 20 to 40 ms. It has a higher SNR and less signal loss due to T2 and T1 weighting than long TE. These short TE properties result in a spectrum with more metabolites peaks, such as myoinositol and glutamine-glutamate, which are not detected with long TE (Fig. 2)[1].

MRS spectra may also be obtained with long TEs, from 135 to 288 ms. Some authors described 135-144 ms as an intermediate TE. Long TEs have a worse SNR, however they have a more simple spectra due to suppression of some signals. Thus, the spectra are less noisy but have a limited number of sharp resonances (Fig. 2)[1].

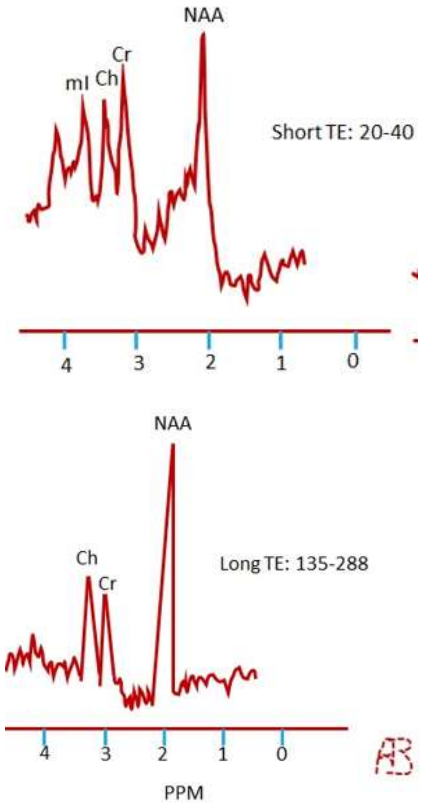


Fig. 2: MR proton spectroscopy in short and long TE sequences displaying different
metabolite peaks

MRS-visible brain metabolites are available in low concentration in brain tissues. Water is the most abundant and its signal in MRS spectrum is too much elevated than others. To avoid this high peak from water to be superimpose on the signal of other brain metabolites, techniques for water suppression are needed. The most commonly used technique is chemical shift selective water suppression (CHESS) which pre-saturates water signal using frequency selective 90o pulses before the localizing pulse sequence [1].For fat, signals can be avoided with the application of a sequence with inversion pulses or simply with placement of a volume selective localization pulse sequence of the region subject to interest. To further eliminate signal from scalp and sinuses, outer volume suppression (OVS) employs

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

the use of very selective suppression (VSS) pulses [7, 8]. The OVS are graphically prescribed using the imaging sequences to guide locations and angles around the scalp by the technologist.
MRS is subject to artifacts. Many factors such as poor water, lipid suppressions, field inhomogeneity and chemical shift displacement may be sources of artifacts into spectra. The homogeneity of the magnetic field is one of the most important predictors of the quality of a spectrum. Regions near bone structures and air tissue- interfaces are more susceptible to artifacts. Therefore, placement of the VOI should be avoided near areas such as anterior temporal and frontal lobes [1, 2]

MR SPECTRUM OF THE BRAIN: METABOLITES AND THEIR BIOMARKER POTENTIAL (Fig. 2)

N-acetylaspartate (NAA) represents the tallest peak in the proton MR spectrum, assigned at 2.02 ppm. NAA is produced in the mitochondria of nervous system cells and is present in neuronal cell cytoplasm and axons. It is found in both white and grey matter and can also be detected in neuronal progenitor cells and/or immature neuronal cells. NAA is used as a marker of neuronal density and viability [1, 2]. The NAA resonance is widely regarded as a marker for neuronal injury and death [9].
Choline (Cho) is a precursor molecule to phosphatidyl choline, an important element in cell membrane synthesis. Its spectrum peak, assigned at 3.2 ppm, is the second highest. Choline is considered as a marker of cellular turnover and proliferation. Thus, its elevation can be observed in case of ischemic injury, neoplasm or acute demyelination diseases [1, 2, 10].
Creatine (Cr) is the third largest peak observed at the spectrum, assigned at 3.0 ppm. Because of the fact that creatinine levels in a healthy human brain are constant and stable, creatinine is considered as a form of reference for spectrum metabolite ratios. It's a marker of energy metabolism. A reduced Cr level may be seen in pathologic processes including neoplasm, ischemic injury, infection or some systemic diseases. Gliosis may cause minimally increased Cr which can be explained by the increased density of glial cells (glial proliferation) [1].
Lactate concentration is very low in a normal functioning brain with adequate oxygen supply. In anaerobic condition, lactate levels increase which produces a lactate peak at 1.33 ppm in the spectra. Characteristic aspect of the lactate peak is peak inversion for different echo times (TE). At short echo times (TE = 20-40ms) the peak rises above the baseline, while at long echo times (TE = 135-144ms) it falls below the baseline. This helps to differentiate the lactate peak from the lipid peak, which resonates at 1.2 ppm but does not show peak inversion at long echo times [1, 2, 11].
Lipids
Lipid peaks can occur at 0.8, 1.2. These peaks appear in case of cellular membrane breakdown or necrosis, such as inflammation, neoplasms or infection [1, 12].
Myo-inositol (mI) is primarily synthesized in glial cells and is considered as a glial marker: an augmentation of mI levels is associated to glial proliferation or glial cell-size increase, which corresponds to inflammatory condition. mI may be a breakdown product of myelin. Its augmentation is not specific; it may be reported in gliosis, astrocytosis, and in Alzheimer disease [12].
Alanine (Ala) is an amino acid that has a doublet centered at 1.48 ppm. This peak is located above the baseline in spectra obtained with short TE and inverts below the baseline on acquisition using TE= 135-144 msec [1]. Ala can be synthesized from pyruvate when the normal route of pyruvate into the Krebs cycle is disturbed [12]. Ala concentrations may increase in oxidative metabolism defects and in tumors. It's specific for meningiomas [13].
Glutamate-Glutamine (Glx) : In normal brain MR spectra, multiplet signals of glutamate (Glu) and glutamine (Gln) appear respectively in the spectral areas 2.2–2.4 ppm and 3.6–3.8 ppm. Glutamate has an important role in neurotransmission process, but glutamine seems to have a higher sensibility to disease; for examples, increased cerebral concentration of Gln are detected in Reyes syndrome, hepatic and hypoxic encephalopathy [14].

DISCRIMINATION BETWEEN NON-NEOPLASTIC DISEASES AND TUMORS

If a diagnosis of non-neoplastic brain lesion can be retained, an invasive brain biopsy procedure may be avoided! Some non-neoplastic lesions (such as abscess, ischemic lesions or demyelinating lesions may mimic brain tumors on conventional radiology imaging [15) even after use of a contrast agent. The injection of a contrast agent may also not improve the diagnostic specificity, since various non-neoplastic lesions are usually associated with disruption of the blood-brain barrier, and not all tumors enhance [9]. MRS can provide help in these situations thus avoiding invasive and non-useful cerebral biopsies. Indeed, several studies have evaluated the utility of MRS to differentiate

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

between tumors and non-neoplastic lesions; typical MRS spectrum for a brain tumor is one of high level of Cho, low NAA and minor changes in Cr. But even in non-tumoral lesions we can have high level of Cho, low NAA (Table I), hence the interest of calculating the ratios of metabolites.

In our review of the literature, we did find that several ratios can be calculated, in daily clinical practice. The most common is a Cho/NAA cutoff ratio of 2 which allows separating reliably neoplasms from non-neoplastic conditions. In fact a Cho/NAA ratio greater than 2 is very suggestive of neoplasms

Table I: Typical MRS spectra for a brain tumors and non-tumoral lesions

	Cho	NAA	Lac	Lip	mI	Suc	Acet	Aa
Tumors	↑	↓	+/-	+/-	+/-	-	-	-
Abcess	N	ABS	↑	+/-	-	↑	↑	↑
Demyelination	↑	↓	↑	+/-	+/-	-	-	-
Ischemia	↑	↓	↑	+/-	-	-	-	-

N =normal; Abs= Absent, Cho= Choline, NAA= N-acetyl aspartate, Lac = lactate, Lip= lipids, mI= myo-inositol, Suc=succinate, Acet = acetate, Aa= amino-acid

48 years old woman with left hemiparesis. Axial T2 WI image shows an expansive lesion with low signal intensity on the right parietal lobe surrounded by edema with heterogenous enhancement on post contrast T1WI. Single voxel MRS at a short and long TE show an increased choline and markedly decreased NAA and creatine with marked lipid peak . Chol/Cr:3,5 CHO/NAA:3,4 ;this MR Spectrum is typically founded in High grade Glioma. In this case, the process was histologically confirmed Glioblastoma

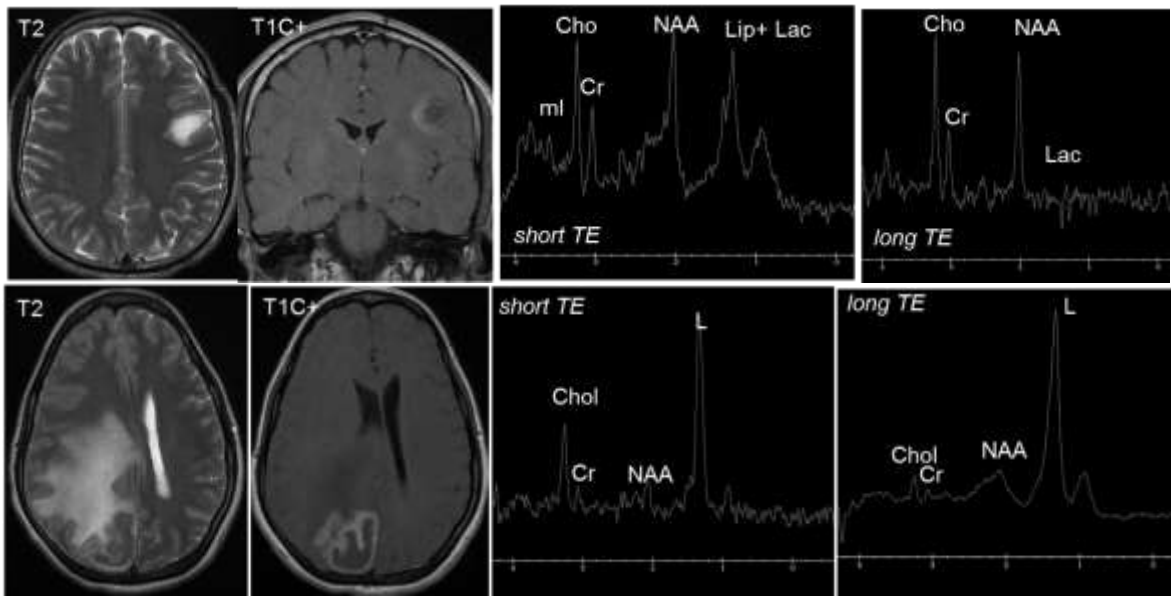


Fig.3: Differentiation between non neoplastic diseases and tumors

34-year-old woman. Axial T2-WI shows well-defined hyperintense left frontal lesion. Post contrast T1-WI shows incomplete ring enhancement of the lesion. Single voxel MRS at a short TE and a long TE show lipid lactate peak, choline peak with normal Chol/NAA ratio which eliminates the malignant origin of the process. According to MRI, the diagnosis of Giant demyelinating plaque has been retained.

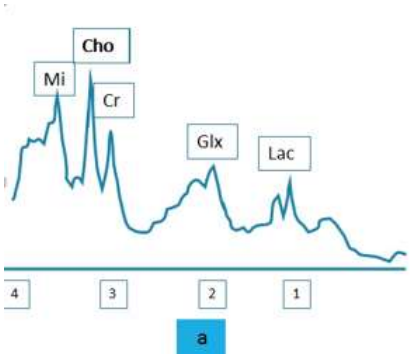
MR SPECTROSCOPY FEATURES OF COMMON BRAIN TUMORS

Primary (non lymphomatous) tumors

The most common primary brain neoplasms are of glial origin and can be classified into low grade (grade I and II, benign) and high grade gliomas (anaplastic gliomas or grade III, and glioblastoma multiforme or grade IV) [6]. Low-grade glial neoplasms occur most often in patients aged 20–40

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

years, whereas high-grade glial lesions occur in older adults who tend to have shorter survival [16].
Each grade of gliomas have some specific MRS features: low-grade gliomas are generally characterized by a relatively high level of NAA, a low concentration of Cho and an absence of Lac and Lip. The increase in Cr concentration indicates low-grade gliomas with earlier progression and malignant transformation. Progression in the grade of a glioma is reflected in the progressive decrease in the NAA and mI levels and a raise in Cho level up to grade III. Malignant transformation of the glial tumors is also accompanied by presence of Lac and Lip in MR spectra of grade III but mainly grade IV gliomas (**Fig. 4**) [17, 18].



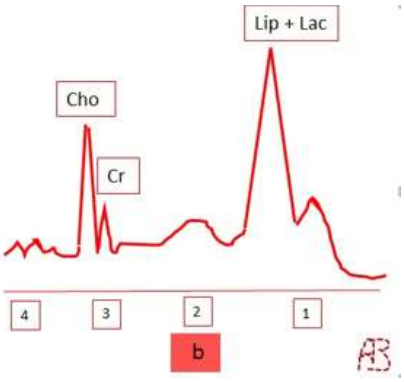


Fig. 4: MR spectroscopy of gliomas, (a) grade II and (b) grade IV gliomas. Elevated Cho/Cr ratio and decreased NAA is apparent in both tumor spectra but Cho/Cr ratio is much higher in high grade glioma. In addition we have a marked Lip+Lac peak in grade IV which is associated with necrosis.

A review of the literature reveals that the significant increase of intra-tumoral Cho/Cr and Lip-Lac/Cr ratios in high grade gliomas (III + IV) compared with low grade (II) at either short or long TE are reproducible observations among many previous studies [19].(Fig. 4)
Some institutions use a threshold value of 2.0 for Cho/Cr to differentiate low-grade from high-grade gliomas; others use a cutoff value of 2.5 [20].

20 years old woman with increased intracranial pressure. Axial T2 WI shows an expansive lesion with high signal intensity on the right occipital lobe which is moderately enhanced on post contrast T1WI
Short-TE monovoxel MRs shows and increased Choline peak, moderate increase in Cho/Cr ratio: 1,4 with absence of lactate and lipid: Histologically confirmed grade II astrocytoma

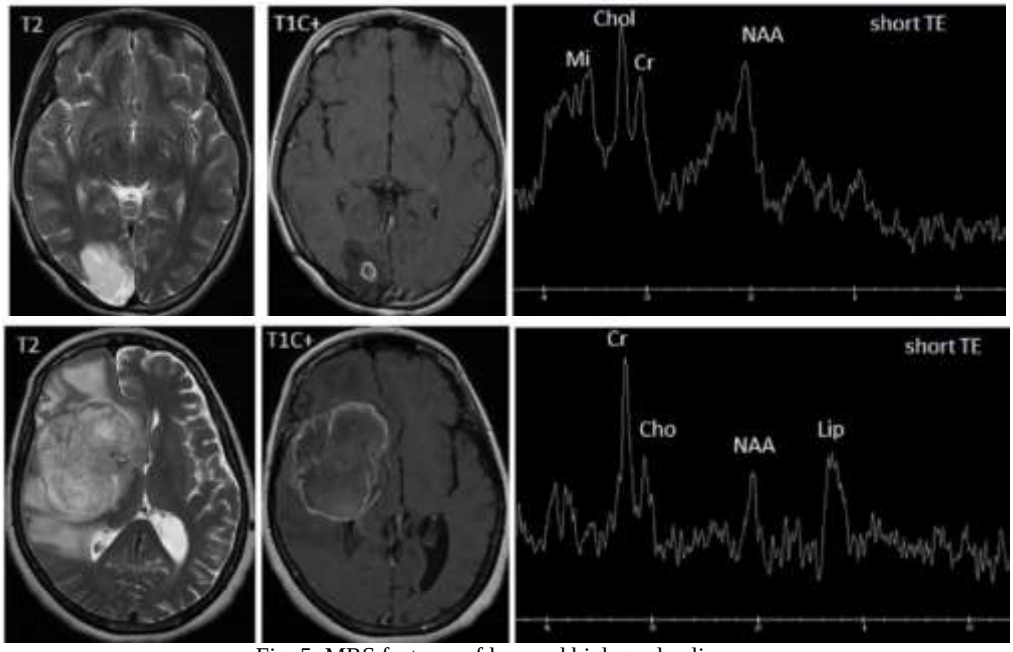


Fig. 5: MRS features of low and high grade gliomas

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

48 years old man with increased intracranial pressure. Axial T2WI shows hyperintense right parietal mass with ring enhancement on post contrast T1WI. MRS shows an increased choline and decreased NAA with lipid peak . Chol/Cr ratio of 2,5: confirmed glioblastoma

Secondary neoplasms

Elevated signals of lipid, lactate, and choline and reduced or absent NAA signal are the typical MRS features for secondary neoplasms. Reliability of MRS in differentiation between secondary neoplasms and high-grade gliomas remains low, even though it has been shown by some to be possible by looking for a higher degree of lipid signal in metastatic lesions [21, 22].On the other hand, the high signal intensity on T2 weighted imaging seen in the perilesional area demonstrates elevated Cho/Cr ratio only in high grade gliomas (Fig.6) [23]. This feature is consistent with the pathological findings of infiltrating tumor cells in areas of edema not seen in metastases (Fig. 7).

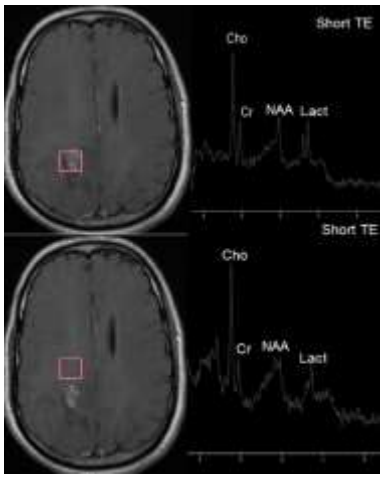


Fig. 6 : Single voxel MRS at a short TE from the centre and the periphery of the confirmed grade III glioma showed elevated signals of choline and lactate with decreased NAA and creatine. Cho/Cr ratio is significantly increased.

Primary brain lymphoma

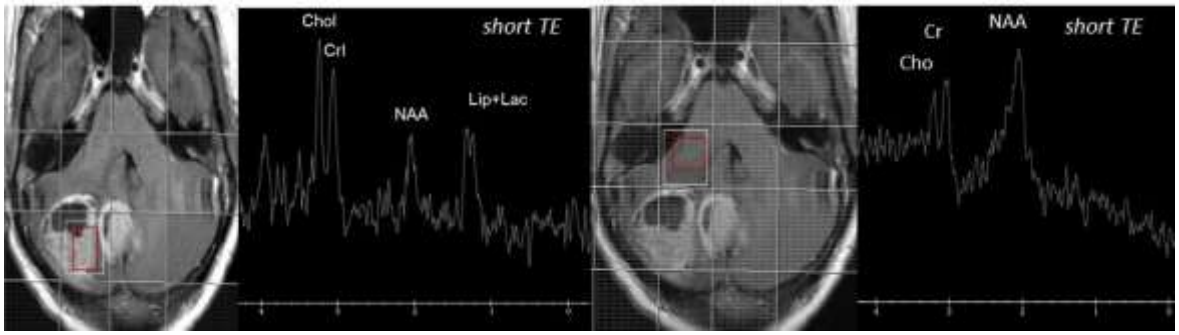


Fig. 7 : secondary neoplasms, Axial T1 post contrast WI of the brain shows heterogeneous lesions in the right cerebellar hemisphere with peripheral enhancement and central necrosis. Single voxel MRS at a short TE from lesion shows elevated signals of lipid, lactate and choline with decreased NAA signal . Single voxel MRS at a short TE from periphery of lesion shows no abnormality of the spectrum

Primary central nervous system lymphomas (PCNSL) historically have accounted for approximately 2% of primary brain tumors. Although the diagnostic Certainty of PCNSL is essentially based on stereotactic biopsy, new imaging techniques may be of great help in diagnosis [24]: diffusion-weighted imaging(DWI)sequence typically shows a restricted diffusion with low apparent diffusion coefficient (ADC) while Perfusion weighted imaging shows hypoperfusion within the tumor.

In addition to other advanced MRI techniques, MRS provides non-invasively a wide spectrum of biochemical information of the lesion. Typical MRS features for lymphoma include elevated signals of lipid, lactate, and choline and reduced NAA signal [16] (Fig. 8, 9).

Elevation of lipid peak is typically a signature of cell death. However, a lipid dominated spectrum is observed in PCNSL that is not macroscopically necrotic due to macrophage content [25, 26].

These aspects can also be found in glioblastoma multiform and metastases but may help in differentiating PCNSL from other lesions [25].

We also found a transition zone of abnormal spectra outside the enhancing area reflecting the infiltrative nature of the lymphoma. This feature may help differentiate PCNSL from metastasis but not from high grade glioma [27].

JMSR
Journal of Medical and Surgical Research
Review Article
ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

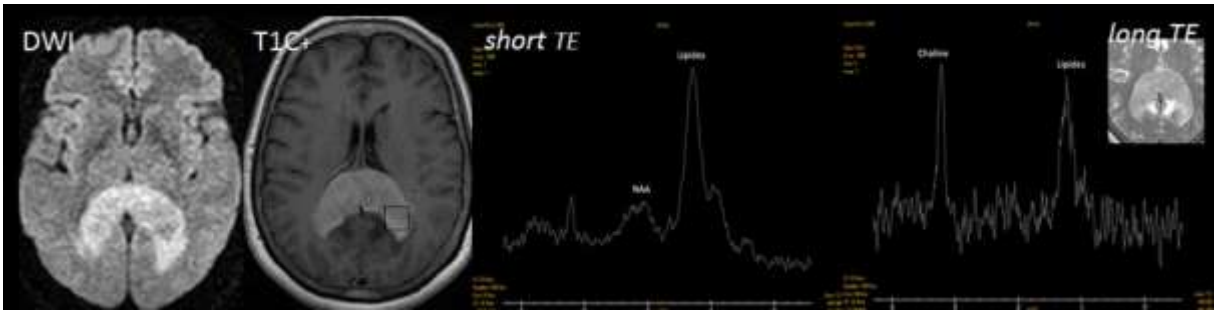


Fig. 8: 62 years old women with increased intracranial pressure. DWI reveals high signal within the mass of the corpus callosum with homogeneous enhancement on T1C+. MRS (TE 35 ms and 144 ms) show an exaggerated lipid peak, increased choline and decreased NAA: confirmed primary brain lymphoma

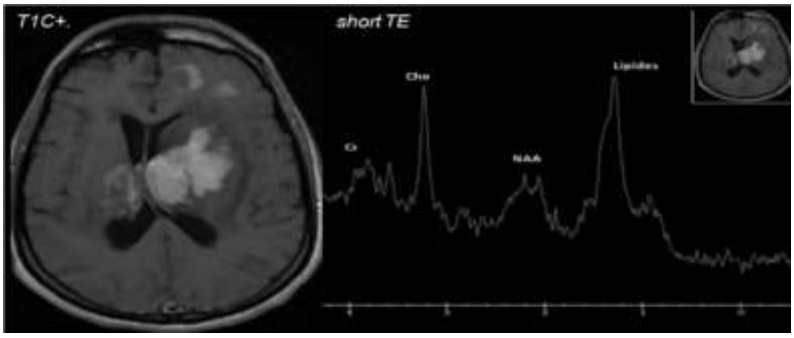


Fig. 9 : 48 years old man with increased intra cranial pressure. Axial T1C+ WI showing multiple lesions in the basal ganglia with Multifocal strong patchy homogeneous enhancement . Single voxel, short TE MRS demonstrates an exaggerated lipid peak in a solid mass with decreasing value of NAA and elevation of choline: confirmed lymphoma

CONCLUSION

MRS provides information on biochemical changes in brain tissue which occur before possible visibility in structural images. Therefore, MRS was elected a non-invasive method for diagnosis and grading of primary brain tumors. The analysis of metabolite peaks and their ratios in MR spectra is a source of useful additional information for characterization of other brain process such as metastases and brain lymphomas.

REFERENCES

1. Bertholdo D, Watcharakorn A, Castillo M. Brain Proton Magnetic Resonance Spectroscopy. Neuroimaging Clinics of North America , 2013 Aug; 23(3): 359-562
2. Kim M. Cecil. Proton Magnetic Resonance Spectroscopy: Technique for the Neuroradiologist. Neuroimaging Clin N Am. 2013 August; 23(3): 381–392.
3. Bottomley PA. Spatial localization in NMR spectroscopy in vivo. Ann N Y Acad Sci 1987; 508:333–348.
4. Frahm J. Localized Proton Spectroscopy using stimulated echoes. J Magn Reson 1987; 72 (3):502–508.
5. Brown TR, Kincaid BM, Ugurbil K. NMR chemical shift imaging in three dimensions. Proc Natl Acad Sci U S A 1982; 79 (11):3523–3526.
6. Horská A, Barker PB. Imaging of Brain Tumors: MR Spectroscopy and Metabolic Imaging. Neuroimaging Clin N Am. 2010 August ; 20(3): 293–310.
7. Duyn JH, Gillen J, Sobering G, van Zijl PC, Moonen CT. Multisection proton MR spectroscopic imaging of the brain. Radiology. 1993 Jul; 188(1):277–282.
8. Osorio JA, Xu D, Cunningham CH, et al. Design of cosine modulated very selective suppression pulses for MR spectroscopic imaging at 3T. Magn Reson Med. 2009 Mar; 61(3):533–540.
9. Hourani R, Brant LJ, Rizk T, et al. Can proton MR spectroscopic and perfusion imaging differentiate between neoplastic and nonneoplastic brain lesions

ISSN: 2351-8200
JMSR 2017, Vol III ; N°3 : 345-352

in adults. AJNR Am J Neuroradiol 2008; 29(2):366–372.
10. Licata SC, Renshaw PF. Neurochemistry of drug action: insights from proton magnetic resonance spectroscopic imaging and their relevance to addiction. Ann N Y Acad Sci 2010; 1187: 148–171.
11. Soares DP, Law M. Magnetic Resonance Spectroscopy of the Brain: Review of Metabolites and Clinical Applications. Clinical Radiology 2009; 64:12-21.
12. Van der Graaf M. (2010). In vivo magnetic resonance spectroscopy: basic methodology and clinical applications. Eur Biophys J 39:527-540.
13. Yue Q, Isobe T, Shibata Y, Anno I, Kawamura H, Yamamoto Y, Takano S, Matsumura A (2008) New observations concerning the interpretation of magnetic resonance spectroscopy of meningioma. Eur Radiol 18:2901–2911
14. Ross B, Blu¨ml S (2001) Magnetic resonance spectroscopy of the human brain. Anat Rec 265:54–84
15. Omuro AM, Leite CC, Mokhtari K, et al. Pitfalls in the diagnosis of brain tumours. Lancet Neurol 2006; 5(11):937–948.
16. Riyadh N. Al-Okaili, Krejza J, Wang S, John H. Woo, Melhem E R, Advanced MR Imaging Techniques in the Diagnosis of Intraaxial Brain Tumors in Adults. RadioGraphics 2006; 26:S173–S189.
17. Law M, Yang S, Wang H, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuroradiol 2003; 24(10):1989–1998.
18. Bulik M, Jancalek R, Vanicek J, Skoch A, Mechl M. Potential of MR spectroscopy for assessment of glioma grading. Clinical Neurology and Neurosurgery 115 (2013) 146– 153.
19. Kousi E, Tsougos I, Tsolaki E, Fountas K N, Theodorou K, Fezoulidis I, Kapsalaki E and Kappas C. Spectroscopic Evaluation of Glioma Grading at 3T: The Combined Role of Short and Long TE. The Scientific World Journal. 2012;2012:546171
20. Brandão LA, Castillo M. Adult Brain Tumors: Clinical Applications of Magnetic Resonance Spectroscopy. Magn Reson Imaging Clin N Am. 2016 Nov; 24(4):781-809.
21. Howe FA, Barton SJ, Cudlip SA and al. Metabolic profiles of human brain tumors using quantitative in vivo H-1 magnetic resonance spectroscopy. Magn Reson Med 2003; 49(2):223–232.
22. Moller-Hartmann W, Herminghaus S, Krings T and al. Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. Neuroradiology 2002; 44 (5):371– 381.
23. Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW. (2002). High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. Radiology. 222(3):715-21.
24. Lamrani Y.A, Alami B, Housni A, El Fattach H, Boubbou M, Maaroufi M. Radiological appearances of primary central nervous system lymphoma (PCNSL). Journal of Medical and Surgical Research (JMSR) 2016, Vol III; n°1: 215- 222.
25. Hartmann M, Heiland S, Harting I, et al. Distinguishing of primary cerebral lymphoma from high-grade glioma with perfusion-weighted magnetic resonance imaging. NeurosciLett 2003; 338:119–22
26. Tallibert S, Guillevin R, Menuel C, et al. Brain lymphoma: usefulness of the magnetic resonance spectroscopy. J Neurooncol 2008; 86(2):225-229.
27. Mansour A, Qandeel M, Abdel-Razeq H and Ali Abu Ali H. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. Cancer Imaging 2014,7;14:22