ORIGINAL RESEARCH PAPER

Radiology

KEY WORDS:

ROLE OF MRI SPECTROSCOPY IN EVALUATION OF BRAIN TUMOURS

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ABSTRACT

Focal intracranial masses are routinely assessed on conventional MR examination. Their diagnosis, characterization and differentiation into various grades remains challenging. However, their diagnosis remains indefinite in proportion of cases and Magnetic resonance spectroscopy is an useful adjuvant in reaching a definitive diagnosis.

MR spectroscopy enables imaging at the molecular level, providing information about brain tissue that was previously available on biopsies only enabling the radiologist to start differentiating between benign and malignant processes. The technology, however, is not infallible and should be considered an adjunct to anatomical imaging rather than a replacement for histopathological evaluation.

The main aim of the study is to find out the biochemical changes in various brain tumours and determining the efficacy of choline/ creatine ratio in assessing the grade of malignancy.

INTRODUCTION:

Magnetic resonance spectroscopy (MRS) has rapidly progressed in its clinical utility and recognition and thus become a significant non-invasive diagnostic tool and has gained wide clinical acceptability. improvements in MR equipment enabling the use of small voxels has made MRS applicable to focal pathologies.

Spectroscopy is the determination of the chemical composition of a substance by observing the spectrum of electromagnetic energy emerging from or through it. The spectrum is obtained by splitting a heterogeneous beam of electromagnetic radiation into its components. The individual components are usually displayed in order of their wavelengths.

The main aim of the study is to find out the biochemical changes in various brain tumours and determining the efficacy of choline/ creatine ratio in assessing the grade of malignancy.

AIMS

1. To study the biochemical changes in brain tumours and assess their diagnostic utility.
2. To differentiate neoplastic from non-neoplastic pathologies.
3. To determine the efficacy of choline/ creatine ratio in assessing the grade of malignancy.

MATERIALS AND METHODS

We studied 80 patients; who were found to have focal or diffuse intra cranial pathologies on routine MRI.

46 of these patients had brain tumors while the rest had a variety of non-neoplastic conditions such as infective granulomas, demyelinating plaques, infarcts and some rare ones like intracranial hydatid and dysplastic cerebellar gangliocytoma. The cases were included in a longitudinal study conducted over a period of approximately 2 years.

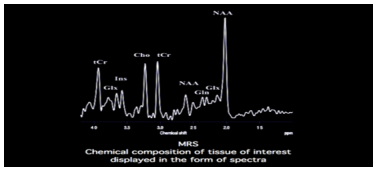
The study was carried out on GE 1.5 Tesla MRI MACHINE. Single and Multi-voxel Spectroscopy performed on the various intracranial lesions as per requirement and data analysis was done on workstation using specialized post processing software.

DISCUSSION

MR Spectrum: The information from the ROI (Voxel) is in the form of a Graph called the MR spectrum. It has two axes.

1. **The horizontal axis:** It is also called the frequency axis or chemical shift axis. The frequency at which a particular neurochemical would resonate is determined by its chemical structure.

2. **The vertical axis:** The height of the peak is directly proportional to the amount of metabolite in the given voxel. It is derived by multiplying the width and height of the peak.



The normal MR Spectrum: Positions of the various metabolites on the chemical shift axis.

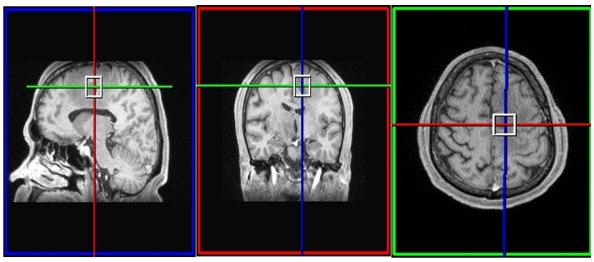
Metabolite	Peak position (ppm)
N-acetyl aspartate	2.02
Creatine	3.03
Choline	3.22
Lactate	1.33
Lipid	1.33
Myo-inositol	3.56
Glutamate	3.65
Alanine	1.48
Pyruvate	2.5
Succinate	2.4
Glucose	3.4
Mannitol	3.8

Single-voxel spectroscopy (SVS) and Multi-voxel Spectroscopy (CSI)

MRS can be performed by two methods - single-voxel spectroscopy (SVS), and Multivoxel spectroscopy also called as chemical shift imaging (CSI).

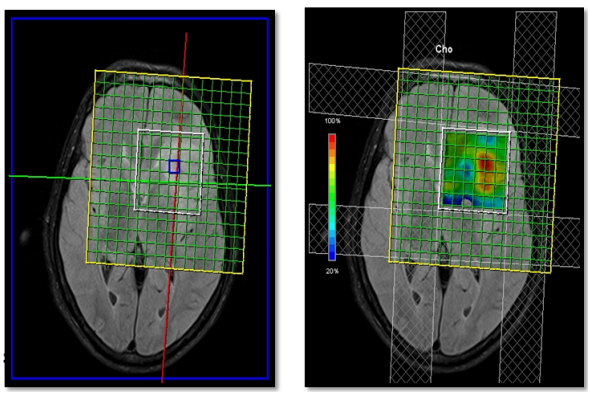
In single-voxel spectroscopy (SVS) a single region of interest is selected and a spectrum obtained from it. SVS gives a better signal-to noise ratio and is a more robust technique. The disadvantage is that only a single spectrum is obtained. The placement of the volume of interest (VOI) becomes critical and may lead to errors of interpretation if not done correctly.

(Single-voxel spectroscopy)



In multi-voxel spectroscopy spectra are obtained from multiple voxels in a single slab of tissue. With Multivoxel MRS, a much larger area can be covered, eliminating the sampling error to an extent. This is however done at the expense of a significant weakening in the signal-to-noise ratio and a longer scan time.

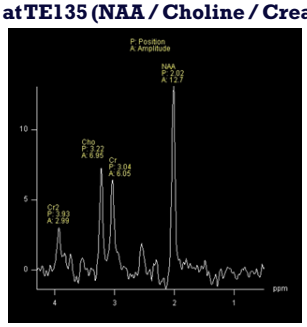
(Multi-voxel spectroscopy)



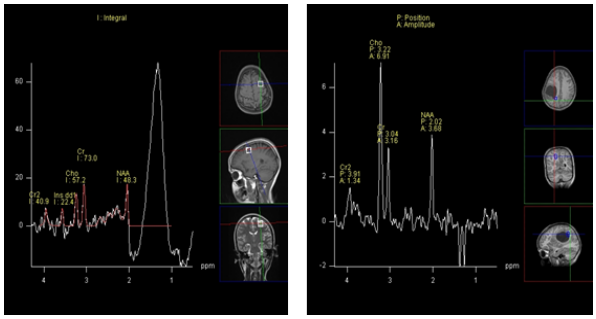
The spectra can be obtained at a low TE 30 or at an intermediate TE 135.

The major metabolites in the spectrum i.e. N-Acetyl Aspartate (NAA), choline (Cho), Creatine (Cr) resonate best at TE135. Hence when these metabolites are to be assessed the spectra are obtained at TE135 as in tumors. When the lipid / lactate signals are to be assessed as in infective granulomas or the central necrotic portions of the tumors the spectra is obtained at TE30.

Spectroscopy at TE135 (NAA / Choline / Creatine peaks)



Spectroscopy at TE 30 (Lipid / Lacate peaks)



N-Acetyl Aspartate (NAA): N-Acetyl Aspartate (NAA) is an amino acid found exclusively in neurons. NAA peak is seen at 2.0 ppm (parts per million) on MR spectra. Normal NAA concentration is in the range of 8-9 mmol/kg in healthy adult brain.

Choline (Cho): The Choline (Cho) peak is a heterogeneous peak representing various choline-containing compounds such as acetylcholine, phosphocholine (lecithin), glycerophosphocholine, and various other intermediates of phospholipid metabolism. The choline peak is seen at 3.22ppm on the frequency axis. It is an indicator of cell density and cell membrane turnover. Elevated levels are found in tumors, especially malignant ones, and in certain demyelinating diseases. Choline is a reliable predictor of cellular activity in tumor tissue.

Creatine (Cr): Creatine (Cr) is related to cell energy pathways. It is a product of creatine kinase. Its peak is seen at 3.0 ppm. Creatine reflects the energy potential available in brain tissue. Its concentration in normal brain remains very high (7.49± 0.12 mmol/kg) and stable due to high metabolic demands imposed by brain cells. It is highly suitable for the calculation of the metabolite ratios and is taken as the reference.

Lactate (Lac): Lactate (Lac) is absent in normal brain tissue and its presence is indicative of anaerobic glycolysis at the cellular level. The spectral peak lies at 1.33 ppm. It is also noted towards the central necrotic components of brain tumors.

Lipid (Lip): Lipid is also absent normally but can increase in tumors, infections or metabolic conditions. The peak is at 1.3 ppm and it overlaps with the lactate peak. Lipid and lactate both resonate at 1.33ppm.

Factors affecting the signal to noise ratio:

The signal to noise ratio is affected by a number of factors like placement of the voxel, volume of the voxel, TR and TE, shimming (field homogeneity which is achieved by water suppression), frequency of the transmitter and receiver and presence of ferromagnetic materials in the vicinity.

The frequency of the transmitter and receiver and the optimization of the field homogeneity are adjusted for each patient separately because each patient affects the physical properties of the scanner differently. Shimming adjusts the currents in the shim coils so that the magnetic field in the voxel becomes homogenous.

Adjustment of water suppression is very essential since the signal of water is approx. 10,000 times stronger than other metabolites. With perfect water suppression a flat line is seen along the horizontal axis. The residual water peak is seen towards the left of the spectrum.

Size of the voxel significantly affects the signal to noise ratio. The ROI should be as small as possible to fit the lesion; else volume averaging from the adjacent normal brain would

dilute the peaks from the lesion. However when the voxel size is reduced beyond a particular threshold specific for that TE and frequency ;the noise is increased so much that the it is not easy to view the metabolite peaks separately from the noise. So when dealing with the problems of partial volume averaging and signal noise it is better to settle for mild partial volume averaging than risking getting a spectrum with noise contamination.

The presence of ferromagnetic materials such as blood, calcium, air or CSF in the vicinity adversely affects the MR signal. The presence of these substances in heterogeneous tumors is therefore a major factor for failure to get an adequate spectrum in these cases.

MRI SPECTROSCOPY IN BRAIN TUMOURS

Magnetic resonance (MR) imaging is considered to be the reference standard for preoperative diagnostic evaluation and for providing optimal information for clinical decision making.

However, even the current methods of choice—that is, T2-weighted MR imaging and pre- and post-contrast T1-weighted MR imaging (as a technique for visualizing regions where the bloodbrainbarrier is damaged)—are not specific for tumors and can result in ambiguous or misleading results.

Proton MR spectroscopic imaging is a noninvasive tool for investigating the spatial distribution of metabolic changes in brain lesions.

There is increase in the levels of choline containing compounds (Cho) and a reduction in the signal intensity of the N-acetyl aspartate (NAA) and creatine (Cr) in brain tumors.
NAA is regarded as a neuronal marker mainly contained within neurons. Reduction in the NAA signal in neoplasms arises from reduced or absent production of these metabolites because normal neurons have been destroyed or displaced by the neoplastic process.

The Creatine peak is the signal from both Creatine and phosphocreatine. Creatine plays a role in tissue energy metabolism.

The Choline peak is composed of choline, phosphocholine, and glycerophosphocholine. The elevated choline peak is a marker of increased cell membrane turnover caused by tumor growth or normal cell destruction.

The increased anabolism of malignant cells in neoplastic lesions leads to a rapid cell membrane proliferation and thus to a real increase in the Choline concentration.

In proton MR spectroscopy, an elevation in Choline may be due to cell membrane synthesis, destruction, or both. Measurable levels of Cho vary considerably, depending on the cellular attenuation, tumor grade, and presence or absence of necrosis. Choline resonance is most prominent in regions with high neoplastic cellular attenuation and is progressively lower in moderate- and low-grade tumors.

The exponential correlation of the Choline concentration with the percentage of tumor cells could be explained by two different mechanisms.

1. The increased membrane turnover due to tumor proliferation.
2. Increased membrane breakdown due to normal cell destruction.

The highest Cho/Cr ratio is recorded. Based on the choline, NAA, Creatine levels, the Choline/ Creatine ratio and presence of lactate it is also possible to get a fair assessment of the tumor grade. The normal Choline/ Creatine ratio at TE 135 is 0.85 in the white matter.

Grade I and II tumors show a Choline/ Creatine ratio of 2.0 + 1.0, for Grade III tumors 2.1 + 1.4 and for Grade IV tumors 2.7 + 1.3. Significant differences exist in the Choline/ Creatine ratios of Grade I/II and Grade IV tumors, however significant overlap is present between Grade I/II and Grade III and between Grade III and Grade IV tumors.

RESULTS:

We studied a total of 80 patients, 46 patients with Brain Tumors and 34 patients with non-neoplastic etiologies were studied

Graph1

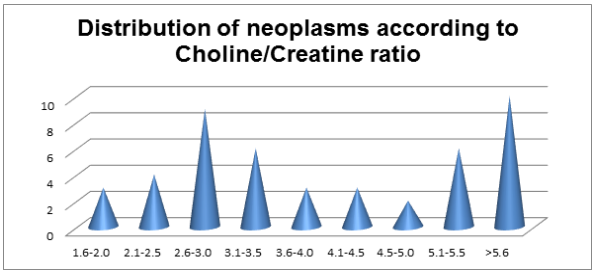


Table 1

Choline/ Creatine ratio	No of patients
1.6-2.0	3
2.1-2.5	4
2.6-3.0	9
3.1-3.5	6
3.6-4.0	3
4.1-4.5	3
4.5-5.0	2
5.1-5.5	6
>5.6	10

The above table and chart shows the distribution of patients with neoplasms according to the maximum Choline/ Creatine ratio. Maximum number of patients 21.7% had a choline a ratio of more than 5.1 followed by 19.5% of patients with ratio of 2.6-3.0.

We classify gliomas on the basis of their histopathology into Grades I-IV. Extra axial tumors like meningioma and schwanoma were considered separately. The gliomas with grade I/II on histopath were classified as low grade gliomas and grade III/IV as high grade gliomas.

Graph 2

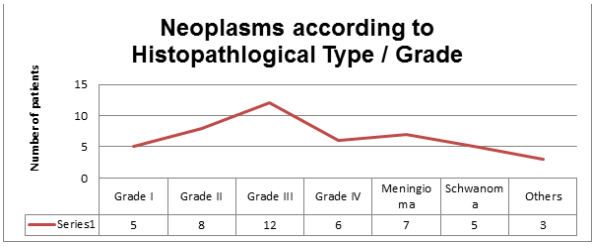


Table 2

Histopathological Grade / Type	No of patients
Grade I	5
Grade II	8
Grade III	12
Grade IV	6
Meningioma	7
Schwanoma	5
Others	3

The above table shows the distribution of patients with neoplasms according to the Histopathological Grade / Type.

We studied 5 patients of grade I gliomas. 3 patients had Choline / creatine ratio between 2.1-2.5 and 2 patientshad

Choline / creatine ratio between1.6-2.0

We studied 8 patients of grade II gliomas. Maximum number of patients had Choline / creatine ratio between 2.6-3.0 and 1 patient each with ratio between 1.6-2.0, 2.1-2.5 and 3.1 -3.5.

We studied 12 patients of grade III gliomas. 5 patients had Choline / creatine ratiobetween 3.0-4.0. 2 patients had ratio between 4.1- 5.0 while 4 patients with ratio between 5.1 – 6.0 and 1 patient had the ratio greater than 6.1.

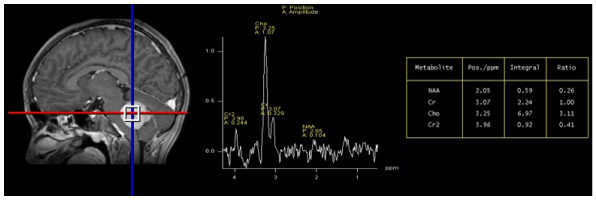
We studied 6 patients of grade IV gliomas. Maximum number of patients (67%) had Choline / creatineratio between 2.5 -3.5 while 33% patients had ratio greater than 3.5

Of the 18 patients of High grade (III/IV) gliomas. Maximum number of patients (44%) had Choline / creatine ratio between 3.1-4.5. 22% patients had ratio between 4.6 -6.0. 17%patients had ratio between 1.5 -3.0 and remaining 17% patients had ratio greater than 6.1

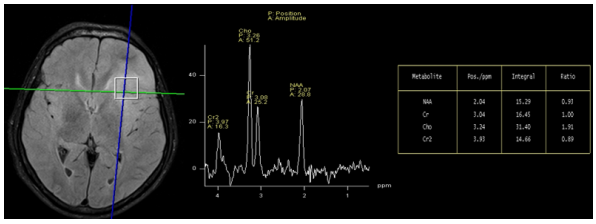
Of the 13 patients of Low grade (I/II) gliomas. Maximum number of patients (5) had Choline / creatine ratio between2.6-3.0; with 4 patients having Choline / creatine ratio between 2.1-2.5. 3 patients had ratio between 1.5 -2.0 and 1 patient had the ratio greater than 3.0.

We studied 34 patients with non-neoplastic etiologies. Maximum number of patients (14) had Choline / creatine ratio between1.1-1.5; with 11 patients having Choline / creatine ratio between 1.6-2.0. 6 patients had ratio between 0.6 -1.0 and 3 patients had the ratio greater than 2.0.

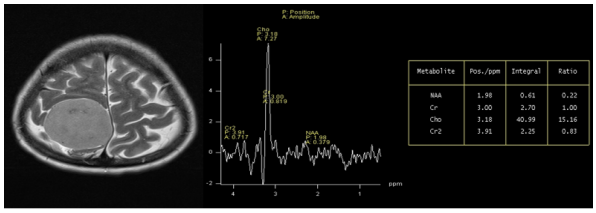
We studied 18 patients of High grade (III/IV) gliomas. 15 patients have a choline to creatine ratio more than 3. Three patients had the ratio below 3. Maximum number of patients (44%) in this group had a choline to creatine ratio between 3.1-4.5.



MRS from a case anaplastic astrocytoma (Grade III) shows significantly raised choline and Cho/Cr ratio with reduced levels of NAA and creatine.



MRS from a case low grade astrocytoma (Grade I) shows raised choline and Cho/Cr ratio with reduced levels of NAA.



MRS from meningioma showing significantly raised choline and very low amounts of NAA and Creatine.

CONCLUSION:

A parallel increase in the choline to creatine ratio is seen within the tumors with increase in the tumor grade. The increase in the ratio is progressive and absolute demarcation between the grades I and grade II tumors or grade III and grade IV tumors is difficult.

Using a choline to creatine ratio of 3.0 as the cut- off, we found that only 1 of the 13 low grade gliomas had a ratio of more than 3.0. In the high grade glioma category 15 out of 18 patients had a ratio more than 3.0 and three patients had a ratio less than 3.0.Using a choline to creatine ratio of 3.0 as the cut off, the sensitivity, specificity, positive predictive valve, negative predictive valve and accuracy of spectroscopy in differentiating high grade tumors from low grade tumors was 83.33%, 92.3%, 93.75%, 80%, 87.09% respectively.

Meningiomas and schwanomas despite being classified as WHO Grade I/ II tumors showed disproportionately high choline to creatine ratios. The extra axial location of these tumors with resultant low amount of Creatine and NAA are most likely account for these findings.

In the 34 patients with non-neoplastic etiologies, 31 patients had a choline to creatine ratio of less than 2.0. Three patients had a ratio in excess of 2.0 of which two were cases of acute infarct and hydatidcyst respectively, which could easily be diagnosed as non-neoplastic taking into the consideration the clinical profile and conventional MR findings. Only one case of tuberculoma falsely presented as metastasis.

In the tumor category out of 46 patients 43 patients had a choline to creatine ratio in excess of 2.0. Only 3 patients (2 with grade I glioma and 1 with grade II glioma) had a ratio less than 2.0.

Using a choline to creatine ratio of 2.0 as the cut off, the sensitivity, specificity, positive predictive valve, negative predictive valve and accuracy of spectroscopy in differentiating neoplasms from non-neoplastic etiologies was 93.47%, 91.17%, 93.47%, 91.17% and 92.5% respectively.

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