Original Research Article

Role of magnetic resonance spectroscopy in evaluation of intracranial malignancies

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Abstract

Background: Magnetic Resonance Spectroscopy is a non-invasive technique that enables tissue characterization on a biochemical level surpassing that of conventional MRI. Since its introduction, many trials and studies have been done to assess the usefulness of MRS in brain pathologies ranging from tumors to infections to degenerative processes. This study is aimed at determining the utility of magnetic resonance spectroscopy and assessing whether the information provided in addition to conventional MRI is relevant in patient diagnosis and management. **Methods:** Intracranial space occupying lesions in 50 patients, detected by MRI, were investigated with Proton MR Spectroscopy, using Multivoxel techniques. **Results:** The Sensitivity and Specificity in detecting and characterisation of intracranial tumoral lesions are 95.83% and 92.31% respectively. The Positive predictive value and Negative predictive value 92% and 96% respectively. The Diagnostic accuracy of MRS combined with conventional MRI is 94% keeping Histopathology as Gold standard. **Conclusions:** With the above observations and discussion we conclude that MR Spectroscopy is a highly sensitive tool in differentiating benign, malignant and inflammatory lesions and it can be used as an additional tool prior to biopsy
Key Word: MRS, brain tumor, NAA, Choline, Creatine.

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INTRODUCTION

In vivo H1 magnetic resonance spectroscopy in past 20 years has evolved as a powerful noninvasive technique to determine the molecular metabolites in any given living tissue. They can provide biomarkers of neurologic disorders even in cases where lesions are not seen in conventional MRIs.[1,2] MRI and MRS are based on same fundamental principles[3],the difference being that the radiofrequency signals emitted by nuclei in tissues are used to determine the concentration of different metabolites in the tissue instead of generating anatomic images.[3]

Evaluation Of Brain Metabolites: The metabolites and their spectral pattern depend on echotime.at 1.5 T, metabolites visualized utilizing intermediate to long TE (144-288ms) include N-Acetyl Aspartate(NAA), Choline(Cho), Creatine(Cr), Acetate. Short echo time acquisitions (TE<40 ms) include the above metabolites as well as Glutamate(Glu), Glutamine(Gln), Glucose(Gc), Gamma Amino Butyric Acid(GABA), Myoinositol(MI), Alanine(Ala), lipids and proteins[4,5]

A) N-Acetyl Aspartate(NAA):- peak at 2.01 ppm is the major upfield peak on H-MRS and is used as a reference for determination of chemical shift[6]. This is present only in CNS, primarily in mature neurons and neuronal processes such as axons and is a sensitive marker for neuronal viability and density[7]. NAA concentrations are decreased in many brain disorders, resulting in neuronal and/or axonal loss, such as in neurodegenerative disorders, brain tumors, epilepsy and MS but are increased in Canavan's disease

B) Creatine- peak at 3.02 ppm is a marker for energetic systems and intracellular metabolism. Total Cr concentration is relatively constant throughout the brain and therefore, used as an internal standard. Total Cr

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values tend to be abnormally reduced in brain tumors, particularly malignant ones.[8]

C) Choline-the peak is assigned at 3.2ppm and represents choline-containing compounds that form the phospholipid layer of the cell membrane.it reflects cell membrane synthesis and degradation.[9], Thus, all processes resulting in hyper cellularity (e.g.; primary brain tumors or gliosis) or myelin breakdown (e.g.: demyelinating disease or infarction) lead to locally increased choline concentrations, whereas hypomyelinating disease result in decreased choline levels[8,9].

D) Lactate:-lactate resonance is identified as a doublet and is centered at 1.32 ppm. the presence of a visible Lac signal constitutes a nonspecific indicator of cellular anaerobic glycolysis, which may be seen with brain neoplasms, infarcts, hypoxia, metabolic disorders or seizures[10]. Lactate may also accumulate within cysts or foci of necrosis.[10,11].

E) Lipids and Proteins:- lipids produces multiple resonances, the most important of which are noted at .9 and 1.3 ppm because of methyl and methylene protons of fatty acids, respectively.[12]. It is absent in normal brain, presents only on cellular membrane/myelin sheath breakdown.

F) Myo-inositol:- is a simple sugar assigned at 3.56 ppm. MI is believed to be a glial marker and is absent in neurons[13]. MI concentrations are abnormally increased in patients with demyelinating disease, Alzheimer's disease and low-grade brain tumors.[14].

G) Alanine:- is an amino acid which peaks at 1.48ppm. increased concentration occurs in oxidative metabolism defect; and is specific for meningiomas.

H) Glutamate, Glutamine, GABA:- peaks are located between 2.1 and 2.5 ppm. abnormalities in this signal complex have been noted in schizophrenia and epilepsy.[12].

MATERIALS AND METHODS

This study was carried out in the Radio-diagnosis Department of Mahatma Gandhi Medical College and Hospital and NIMS Medical College and Hospital, Jaipur, Rajasthan. Total 50 patients were included in this study. All these patients were studied with 1.5 Tesla MRI and proton MRS. In some patients contrast study were also performed using Gadolinium. The patients included in this study came from medical, neurology and neurosurgery OPDs. Some patients had known primary tumors.

RESULTS

We found that MR Spectroscopy has potential application in the diagnosis and characterization of various intracranial space occupying lesions. Besides differentiation of benign from malignant lesions, it also enables the grading of malignancies. It not only compliments the information available by conventional imaging, but can also predict the prognosis and help in management of these lesions.

In the present study,

- Most of the patients presenting with intracranial space occupying lesions were of the 40 to 59 years age group. This was also the most common age group of tumours.
- The majority of patients were males, forming 56% of the study population.
- We found the predominant cause of intracranial space occupying lesions to be tumours (52%) being the most prevalent. Infections formed 48% of the population.
- Irrespective of cause, the predominant presenting symptom was headache, seen in 90% of the patients, followed by seizures (33%).
- The most common cause of intracranial space occupying lesions detected in the study were Gliomas (30%) and tuberculoma (30%).
- The most common tumours detected in the study were Gliomas (57%).
- Total of 50 patients were included in the study. On MR Spectroscopy, diagnostic spectrum was obtained in 47 patients (94%). In the remaining, spectrum obtained was poor due to interference from haemorrhage within the lesion (in 2 cases) or due to peripheral location close to bone (in the remaining 1).
- Mean Cho/ Cr ratio was high in gliomas, metastasis, PNET and meningiomas, while it was normal in infections.
- Highest Mean Cho/Cr value was seen in Glioma (3.19).
- Mean Cho/NAA ratio was high in all the lesions, with highest values seen in the Gliomas (2.70).
- Mean NAA/Cr ratio was below normal in all the lesions, lowest values seen in the meningiomas (1.19) and Gliomas (1.03).
- Lipid-lactate was seen in all high-grade Gliomas and in Metastasis, and only in 66% of the meningiomas.
- Lipid-lactate peak was found in the high-grade Gliomas, particularly in grade IV gliomas (100%).
- Alanine was seen all the meningiomas, but not in any other malignancy
- Decrease choline levels resulting in Cho/NAA and Cho/Cr ratios lower than astrocytoma with peaks of lipid at 1 to 2ppm were seen in PNET.

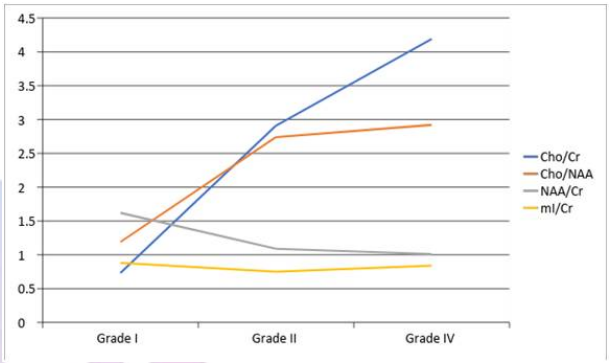
- Elevated choline, decreased NAA and taurine peak at 3.4ppm was seen in Medulloblastoma.
- Lipid lactate peak was seen at 1.3ppm with high Cho/Cr ratios than astrocytomas in Ependymoma.
- Ethmoidal sinus Plasmacytoma with intracranial extension was included in our study as a follow up case post chemotherapy. MR spectroscopy in the intracranial part showed high Cho/NAA peak with high lipid lactate peak showing necrosis.
- The Cho/Cr and Cho/NAA ratios show increase with increasing grade of malignancy, with maximum mean Cho/Cr ratio (4.19) and Cho/NAA ratio (2.92) seen in the Grade IV gliomas.
- NAA/Cr ratio was lower in the high-grade gliomas (1.01) than in the low-grade gliomas, lowest in grade IV gliomas (1.01).
- MI/Cr ratio in the low-grade gliomas was higher (0.88) than in the high-grade gliomas (0.84).
- Increased Cho/Cr (2.70±0.281) ratios were observed in neoplastic lesions as compared to non-neoplastic lesions Cho/Cr (1.59±0.146) with significant p value of 0.0012.
- Increased Cho/NAA (2.49±0.249) ratios were observed in neoplastic lesions as compared to non-neoplastic lesions Cho/NAA (1.40±0.147) with significant p value of 0.0006.

The Sensitivity and Specificity in detecting and characterisation of intracranial tumoral lesions are 95.83% and 92.31% respectively. The Positive predictive value and Negative predictive value 92% and 96% respectively. The Diagnostic accuracy of MRS combined with conventional MRI is 94% keeping Histopathology as Gold standard.

Table 1: Average Metabolite Ratios in the various lesions

Intracranial Lesion	Cho/Cr	Cho/NAA	NAA/Cr
Gliomas	3.19	2.70	1.03
Metastasis	2.37	1.97	1.63
Meningiomas	1.79	1.51	1.19
PNET*	2.27	1.78	1.27
Infections	1.55	1.47	1.44

*Primitive Neuroectodermal Tumor



Graph 1: Comparison of metabolite ratios in 3 grades of gliomas

Glioblastoma Multiforme

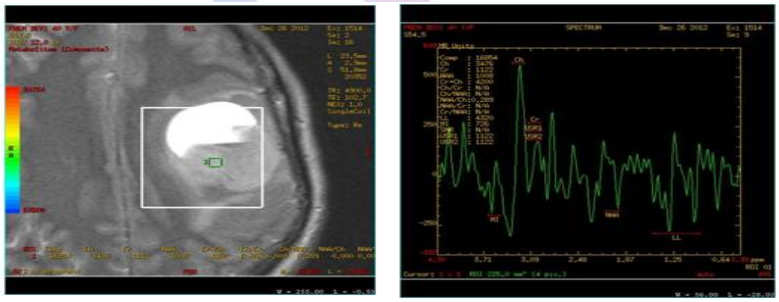


Figure 1: 40 year old lady with left parieto-temporal GBM showing necrosis and high choline peak on MR Spectroscopy

Meningioma

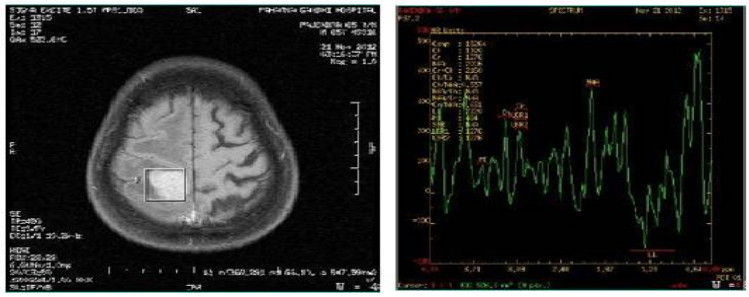


Figure 2: 65 year old man with Meningioma in right high parietal region showing alanine peak at 1.5 ppm on MR Spectroscopy

Medulloblastoma

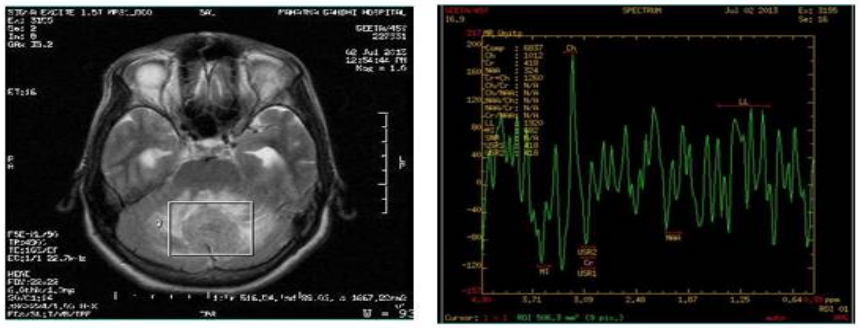


Figure 3: 45 yr old lady with Medulloblastoma in posterior fossa showing taurine peak at 3.4 ppm

DISCUSSION

Castillo M *et al*.[15] described the advantages of mutivioxel MR spestroscopy MRSI over SVS .MRSI includes a spatial distribution compared to SVS which acquires spectrum in limited region. The results of the present study also revealed that the multivoxel is superior to single voxel. All malignant tumors, gliomas, metastasis and meningiomas, were characterized by increased Cho, decreased NAA and Creatinine (Cr) along with the presence of lactate (Lac), lactate and lipid (Lip), or lipid resonances in all the cases. Increased Cho has been observed in most brain tumors, attributed to the increased membrane turnover and cell proliferation[16]. In the in vivo proton MRS, the peak at 3.22 ppm is composed mainly of Cho, PC (phosphatidylcholine) and GPC (Glycerol-phosphatidylcholine)[17]. NAA is predominantly located in neurons[18,19]. Higher grade tumors, especially with tissue necrosis, naturally have lower NAA levels due to neuronal loss or replacement. Grading of gliomas has been done on the basis of NAA/Cho[20,21]; Cho/Cr and NAA/Cr[22] ratios. NAA/Cr and Cho/ Cr ratios have shown a consistency in predicting tumor grade[21,23] although Kugel *et al*[20], have not found any significant difference in the metabolite ratios between various grades of tumors. In the present study a significant difference was seen in the Cho/NAA ratios of all three grades of gliomas ($p < 0.05$). Increasing Cho/Cr and decreasing NAA/ Cr values were also seen with increasing grade of malignancy. The NAA/Cr levels in grade IV gliomas were low. However NAA/Cr ratios in low grade gliomas and anaplastic group showed overlapping values. The Cho/Cr levels also showed overlapping values in the higher grade gliomas. From the present study it can be concluded that Cho/Cr, Cho/NAA and NAA/Cr ratios can be used in the grading of malignancies as suggested by Kostas *et al*[24], Ott *et al*[23] and Sutton *et al*[21]. Of these ratios, Cho/NAA appears to be the most significant in determining tumor grade. Lactate may also be formed by anaerobic glycolysis in tumors with hypoxia[25]. Malignant tumors were found to have a higher Lac/Cr ratio than benign tumors. In the present study, lactate was found in all 3 grades of gliomas Similar results were obtained by Kugel *et al*[20] in their study of brain tumors. Lipid resonances have been observed in high grade gliomas in in vivo studies using different echo times[24,26] In the present study, lipid signals were seen in tumors with and without visible necrosis. None of the low grade gliomas showed presence of lipids, while it was present in all the cases of Grade IV and most of the Grade II gliomas, all of which showed varying levels of necrosis on histological examination. Hence it can be concluded that lipid resonances indicate necrosis, and presence of lipid correlates with higher degrees of malignancy. Another metabolite that has been studied for differentiation and grading of astrocytomas is myoinositol.[15] The present study revealed higher levels MI/Cr values (0.88 ± 0.78) in the low grade gliomas than in the high grade gliomas and infections, in concordance with the results of Castillo *et al*[15]. The ratios in the higher grade gliomas were lower (0.84 ± 0.40). Hence myoinositol levels may have implications in the grading of tumors, especially in the identification of low grade gliomas. Reduced or absent NAA peak along with variable signal intensities from Cho, Cr, Lac and Lip have been observed in metastasis.[20,25]. As metastasis often contain non neuronal tissue, a low or absent NAA peak is expected. However in most cases a NAA peak is obtained. This may be explained if the tumor grows invasively or is unable to displace all the neurons or due to partial volume from adjoining brain tissue. Most studies have failed to demonstrate any spectral variations in the different histological types of metastasis, and have not found any difference in metastasis versus glioblastomas or abscesses based on MR Spectroscopy. In concordance with these observations, the present study also revealed spectral patterns in metastasis similar to and hence in differentiable from high grade gliomas. The presence of alanine (Ala) is specific for meningiomas[16,27] In the present study, a prominent Ala peak was seen in all

three cases of meningiomas, along with strong resonance of Cho. One case each of PNET, Medulloblastoma, Ependymoma and Plasmacytoma with intracranial extension were included in the present study. PNET show decrease choline levels resulting in Cho/NAA and Cho/Cr ratios lower than astrocytomas with peaks of lipid at 1 to 2ppm[28] In present study similar findings were found. Ependymoma showed considerable heterogeneity in the spectra. Lipid lactate peak was seen at 1.3ppm with high Cho/Cr ratios than astrocytomas[28,30]. We observed same findings in our study. Medulloblastoma show elevated choline, decreased NAA and may show taurine peak[29,30]. Consistent with earlier studies a prominent taurine peak was observed. Ethmoidal sinus Plasmacytoma with intracranial extension was included in our study as a follow up case post chemotherapy. MR spectroscopy in the intracranial part showed high Cho/NAA peak with high lipid lactate peak showing necrosis. A common clinical problem is distinguishing tumor recurrence from radiation effects several months following surgery, chemotherapy and radiation therapy. Elevated choline is a marker for recurrent tumor[31]. Radiation change generally exhibits low NAA, creatine, and choline on spectroscopy[32,33]. If radiation necrosis is present, the spectrum may reveal elevated lipids and lactate. In the present study 8 patients had come for post treatment follow up, after surgery, chemotherapy and radiation therapy. High Choline levels were found to correlate with tumor recurrence in these patients. Thus the present study has shown that MRS can clearly distinguish the neoplastic intracranial lesions from the nonneoplastic lesions, as well as diagnose various lesions based on the metabolite spectrum and ratios. It has potential applications in grading of malignancies, in directing stereotactic biopsy and in follow up of postoperative patients. It complements the information obtained from conventional MR imaging and contrast studies, proving particularly useful when these studies are inconclusive.

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