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PROTON MAGNETIC RESONANCE SPECTROSCOPY IN INTRACRANIAL SPACE OCCUPYING LESIONS: POTENTIAL ROLE IN IMPROVING DIAGNOSTIC ACCURACY

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ABSTRACT Proton Magnetic Resonance Spectroscopy(MRS) is a recent neuroimaging advance allowing non-invasive analysis of in vivo metabolites. The study focuses on assessing accuracy of Proton MRS in diagnosis of intracranial space occupying lesions (ICSOLs), differentiating benign from malignant lesions, grading of tumors and comparing to conventional imaging in diagnosis and characterization of the same. MRI and MRS (single and multivoxel) were performed on 52 patients selected during one year period, clinically suspected of ICSOLs and followed up by biopsy, surgery or imaging. Spectroscopic findings were evaluated for pathologic spectra. The commonest cause of ICSOLs was gliomas followed by metastases. Mean Cho/ Cr ratio was high in gliomas, metastasis and normal in infections. Cho/Cr and Cho/NAA ratios showed increase with increasing malignancy grade($p<0.05$). MRS enables differentiation of malignant from benign lesions with reliable grading of gliomas and hence confidently directs diagnosis and treatment.

KEYWORDS : spectroscopy, intracranial space occupying lesions

Introduction

The term "Intra-Cranial Space Occupying Lesion" (ICSOL) is generally used to identify any lesion, whether vascular, neoplastic, or inflammatory in origin, which increases the volume of the intracranial contents and thus leads to a rise in the intra-cranial pressure. Non-invasive and accurate differentiation between neoplastic and non-neoplastic brain lesions is important in determining the correct treatment and, in some cases to avoid a biopsy. Magnetic Resonance Spectroscopy (MRS) is an analytical method used in chemistry that enables the identification and quantification of metabolites in samples.

Materials and methods

This prospective observational study was performed in department of Radiodiagnosis of Dr.S.N. Medical College for a period of 1 year from January 2016 to December 2016. A total of 52 patients who were referred for specific neurological symptoms and suspected of ICSOLs were selected after fulfilling the essential criteria. The examination was done after ruling out the presence of cardiac pacemakers, ear implants, any metallic implants or bony prosthesis in these patients. Magnetic resonance imaging was performed on Philips Achieva 1.5 Tesla MRI scanner using standard head coils. Single voxel (SVS) and multi-voxel spectroscopy (Chemical shift imaging, CSI) were performed on the voxels of interest selected in the lesions. Corresponding contra lateral areas were also analyzed for the metabolite ratios as control. The SVS spectra were used for metabolite ratio calculations. The area under the curve of a metabolite was considered as relative concentration (integral values) and was measured in terms of ratios. As reference standards, values of Cho/Cr > 1.5, NAA/Cr < 1.6 and Cho/NAA > 0.8 were taken as abnormal.

The metabolites and ratios assessed were: NAA/Cr, Cho/Cr, Cho/NAA, Lactate and Lipids, and other prominent peaks in the spectrum. Based on these ratios the lesions were characterised as: Benign/malignant, grade of malignancy and intralesional morphology (using metabolite maps). The patients were followed up by biopsy, surgery or imaging (treatment response).

Statistical analysis

The MR spectroscopic data in our study was assumed to follow normal distribution. The level of significance was determined using the Student 't' test. For comparison of the three groups (grades) of gliomas, ANOVA test was applied. Probability value (P) <0.05 was regarded as significant. Based on these criteria and indices, a detailed pro forma was prepared and followed for each patient.

Observations and Results

Out of 52 cases selected, diagnostic spectrum was obtained in 48 patients (92%). In the remaining, spectrum obtained was poor due to interference from haemorrhage within the lesion (in 1 case) and due to peripheral location close to bone (in the remaining 3). In the present study, most of the patients presenting were in 20 to 39 years age group forming around 30% of the cases, followed closely by 40 to 59 years age group (29%). The majority of patients were males (62%). Headache was the chief presenting compliant (78.8%) followed by seizures (30.76%). Supratentorial lesions were seen in 82% cases, amongst which single lobe involvement was commoner than others. Most of the lesions were solitary (77%). Haemorrhage was absent in 88% of cases and necrosis was seen in 54% cases.

Contrast study with gadolinium was performed in all patients before spectroscopic examination. Enhancement was absent in 9 patients (17%). Most commonly observed enhancement pattern in the ICSOLs was peripheral (42%).

The most common cause of intracranial space occupying lesions was Gliomas, seen in 44% of the cases followed by metastases, which were found in 17% of the patients. The most common infectious etiology encountered was tuberculoma (11.5%). The most common overall age group in which tumours presented was 20 to 39 years (31%).

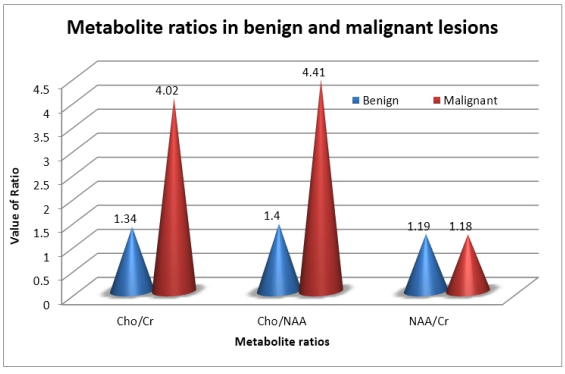
Mean Cho/ Cr ratio was high in gliomas, metastasis, meningiomas and medulloblastoma, while it was normal in DNETs and infections. Highest mean Cho/Cr ratio was seen in gliomas (3.87) and metastases (3.40). The Cho/Cr and Cho/NAA ratios showed increase with increase in grade of malignancy with highest values in Grade IV Gliomas with maximum mean Cho/Cr ratio (6.37) and Cho/NAA ratio (4.68) seen in the Grade IV gliomas.

Lactate and lipid were seen in over 60% of all Gliomas and in Metastases. Lipid-Lactate peak was found in the high grade Gliomas, particularly in grade IV gliomas. In general, there was a considerable overlap of metabolite ratios in the high grade gliomas and metastatic lesions. NAA/Cr ratio was low in all gliomas.

Alanine was seen all the meningiomas, but not in any other malignancy. A distinct glutamate-glutamine peak at 3.8ppm was seen in all meningiomas.

The mean Cho/Cr and Cho/NAA ratios were higher in the tubercular lesions than in NCC and abscesses. Abscesses showed presence of lactate, lipids, amino acids and acetone. Lipid-Lactate peaks were seen in 100% of the cases of Tuberculosis.

Increased Cho/Cr (4.20±0.28) ratios were observed in neoplastic lesions compared to non-neoplastic lesions (1.34±0.05) with significant p-value of 0.001. Increased Cho/NAA (4.41±03.99) ratios were observed in neoplastic lesions as compared to non-neoplastic lesions Cho/NAA (1.40±1.12) with a significant p value of 0.008. Cho/Cr and Cho/NAA ratios were normal in all benign lesions and abnormal in all malignant lesions (graph 1).



Graph 1: Comparison of metabolite ratios in benign and malignant lesions

Discussion

Magnetic Resonance Spectroscopy is a new and emerging imaging modality which offers a level of tissue characterization that can match histological and biochemical diagnosis. In the clinical setting, diagnosis of intracranial mass lesions can be complicated by ambiguous neuroradiological findings, uncharacteristic clinical symptoms or symptom onset. When discussing spectroscopic data of brain lesions, the significance of calculation of signal ratios and the use of these ratios for determining the degree of tumour malignancy or for characterizing histologic tumour types or subtypes is often stressed.

In the present study, most of the patients presenting with intracranial space occupying lesions were of the 20 to 39 years age group, followed closely by 40 to 59 years age group. This was also the most common age group of tumours. The majority of patients were males, forming 62% of the study population. We found the predominant cause of intracranial space occupying lesions to be tumours, gliomas being the most prevalent. Infections formed a relatively smaller group comprising 19%. Irrespective of the cause, predominant presenting symptom was headache, seen in 79% of the patients, followed by seizures (31%). Even in infections, whether tuberculomas or abscesses, most of the patients presented with symptoms of raised intracranial tension or mass effect. Only a minority had fever or vertigo as the presenting complaint. These observations were in concordance with the findings of **Harada et al. [1], Klug et al.[2] and S Grand et al. [3].**

The results of the present study reveal that the spectral pattern of tumours is markedly different from the normal brain and from other non-neoplastic lesions. We also concluded that histologically different lesions show different spectra, and that histologically similar lesions yield similar spectra with only minor differences. In general, the results are consistent with the earlier studies on brain tumours **(Bruhn et al. [4]; Fulham et al. [5]; Kugel et al[6]; Sutton et al.[7]).** Most of the tumours revealed an elevated Choline (Cho) peak along with a decrease in N-Acetyl Aspartate (NAA) resonance. However these resonances were normal or absent in the non-neoplastic lesions.

All malignant tumours, gliomas, metastasis and meningiomas, were characterized by increased choline (Cho), decreased NAA and creatine (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 tumours, attributed to the increased membrane turnover and cell proliferation **(Bruhn et al. [4])**. Presence of Cho was an essential feature of all gliomas, even when cystic. However, though an elevated choline and hence, Cho/Cr, ratio was seen in the neoplasms, a high Choline level was also noted in few of the infectious lesions such as tuberculomas. The choline pool is expected to increase in tumours because of an increased choline esterase activity which catalyses the first step of phospholipid biosynthesis. On the other hand, increased PDEs (phosphodiesters) containing GPC may be an indicator of the necrotic fraction in tumours as a consequence of phospholipid degradation **(Cabello and Cohen [8]).** Thus the increased Cho may either indicate increased cell proliferation (increased PC) or necrotic process (increased GPC).

Presence of NAA as seen in most of the tumours has been attributed to the difference in the cellular composition and nature of the tumour **(Kuegel et al. [6]).** Higher grade tumours, especially with tissue necrosis, naturally have lower NAA levels due to neuronal loss or replacement.

Proton MRS, with its potential to differentiate lesions, promises to provide a preoperative diagnosis, thus obviating the need for surgical biopsy **(Son et al.[9])**.

Grading of gliomas has been done on the basis of NAA/Cho **(Kugel et al. 6; Sutton et al. [7])**; Cho/Cr and NAA/Cr ratios **(Howe et al. [10])**. NAA/Cr and Cho/ Cr ratios have shown a consistency in predicting tumour grade **(Sutton et al. [7])**. 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 very low, NAA peak being absent in some of the GBMs. 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. [11]**, and **Sutton et al. [7].** Of these ratios, Cho/NAA appears to be the most significant in determining tumour grade.

Malignant tumours were found to have a higher Lac/Cr ratio than benign tumours. In the present study, lactate was found in all 3 grades of gliomas and was not seen in 2 cases of grade IV gliomas (fig. 1). Hence the presence of lactate does not appear to correlate significantly with grade of malignancy. Similar results were obtained by **Kugel et al.** [6] in their study of brain tumours.

Fig. 1: Metabolite maps in a 63 year old male patient with right parieto-occipital glioblastoma multiforme showing elevated choline, low NAA and lactate doublet

Lipid resonances have been observed in high grade gliomas in in vivo studies using different echo times **(Hiroaki et al. 12, Kostas et al. 11)**. Necrosis distinguishes high from low grade tumours in majority of the

histological classification. In the present study, lipid signals were seen in tumours with and without visible necrosis. Only 1 of the low grade gliomas showed presence of lipids, while it was present in most of the cases of Grade III and IV 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.

From the present study it is evident that Cho/NAA and Cho/Cr ratios can be used to determine the histological grade of malignancy. But when used alone, they may prove inconclusive, especially in case of cystic or necrotic gliomas. However, when combined with the presence or absence of lipid signals, and MI/Cr ratios, the grade of malignancy can be predicted with greater accuracy **(Poptani et al. 13, Castillo M et al. 14).**

Reduced or absent NAA peak along with variable signal intensities from Cho, Cr, Lac and Lip have been observed in metastasis **(Fulham et al. 5, Kugel et al. 6).** As metastases often contain non neuronal tissue, a low or absent NAA peak is expected. However, in most cases a NAA peak is obtained. Kugel et al. 6 observed increased lipid signals in metastasis. 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 indifferentiable from high grade gliomas.

The presence of alanine (Ala) is specific for meningiomas **(Bruhn et al. 4, Poptani et al. 13).** In the present study, a prominent Ala peak was seen in all three cases of meningiomas, along with strong resonance of Cho. The NAA and Cr levels were low, giving a high Cho/NAA and increased Cho/Cr ratios. Specificity of Alanine for meningiomas was confirmed.

In the present study, 6% of the patients had been diagnosed with Dysembryoplastic Neuroepithelial Tumours (DNETs). We found normal Cho/Cr and Cho/NAA values in all cases of DNETs. These findings are consistent with earlier reports and indicate a useful role of spectroscopy in confirming the diagnosis, ruling out a more malignant pathology.

In the present study, we found characteristic spectrum in the abscesses composed predominantly of cytosolic amino acids, lactate and acetate. The strong lactate and acetate peaks in abscess may be due to the enhanced glycolysis along with fermentative pathways resulting in turnover of pyruvate to acetate and lactate. Thus from our study it can be concluded that the abscess spectrum can be differentiated from glioblastomas or metastasis. This is in concordance with the results of Harada et al. 15, Kim et al. 16, Chang et al. 17 and Grand et al. 3.

Intracranial tuberculomas show the presence of lipid signals at 0.9 and 1.3 ppm which is due to the presence of caseous material having high lipid content **(Gupta et al. 18)**. In our study also, tuberculous lesions could be identified by the presence of lipid (Fig. 2). Though a prominent lipid signal was seen in the high grade malignancies as well, tuberculous lesions did not show the high Cho/NAA levels or decreased NAA/Cr levels seen in neoplastic lesions. Hence tuberculomas can be differentiated from neoplastic and other ring enhancing lesions by the characteristic lipid peaks.

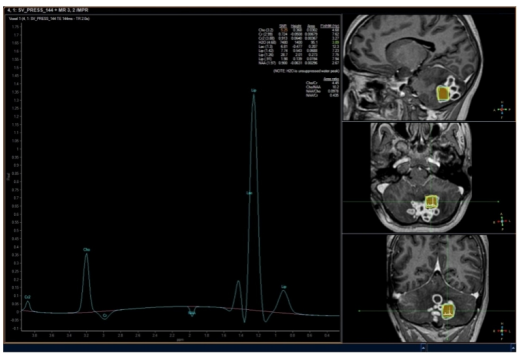


Fig. 2: Metabolite maps in a 15 year old female patient with multiple conglomerated ring enhancing lesions in posterior fossa showing prominent lipid peak suggesting tuberculomas

Proton MRS has been used to predict the presence of histopathological features important for brain tumour diagnosis that can be used to plan stereotaxic biopsies and selective tumour resections **(Dowling C et al. 19, Son BC et al. 9). Dowling et al. 19** found that areas of abnormal spectrum indicating higher degree of malignancy within a lesion correlated with regions of viable cancer. This may be valuable for guiding surgical biopsies and focal therapy. We also found that using metabolite maps of Cho, Cho/NAA and Cho/Cr areas within tumour showing features of higher malignancy correlated with areas of increased rCBV in the perfusion studies. This suggests a potential role for guiding stereotactic biopsy and treatment in brain tumours.

Thus the present study has shown that MRS can clearly distinguish the neoplastic intracranial lesions from the non-neoplastic 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 biopsies 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.

Conclusion

Proton MRS helps in better tissue characterization of different intracranial space occupying lesions. It has a complimentary role to MR imaging not only in providing a better diagnosis, but also in directing treatment and follow up of such lesions. MRS plays a critical role in pre-operative or pre-interventional differential diagnosis of cerebral mass lesions by distinguishing neoplastic from non-neoplastic lesions, by grading neoplastic lesions and by improving the accuracy and confidence level of neuroradiologists in their diagnoses.

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