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Original Research Article

MR Spectroscopic Findings in Brain Tumors and its Correlation with Histopathological Examination - A Prospective Observational Study

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Abstract

Introduction- Modern neuro-radiological advanced technologies like MR spectroscopic technique plays a pivotal role in MR imaging for accurate characterization of various neural pathologies in particular to differentiate brain neoplasms from its mimics.

Aim - To evaluate the role of MRS in patients suspected for brain tumors who are being imaged for MRI brain study and correlate its findings with histopathological examination.

Design- Prospective observational study.

Materials and Methodology - Study was conducted in our Department of Radiodiagnosis among clinically suspected patients for brain neoplasm. MR spectroscopy was performed in cases whose MRI brain findings were in favor of neoplastic etiology and it's correlated with histopathological examination.

Results - Study was conducted in 55 patients. The sensitivity, specificity and diagnostic accuracy of this MRS study were 80.95%, 98.18% and 92.73% respectively. The sensitivity, specificity and diagnostic accuracy of lipid/ lactate levels as a metabolite tool to differentiate between high- and low-grade tumors were 71.43%, 97.06% and 87.27% respectively. Area under ROC curve also showed Lip/Lac levels in our study resulted in AUC of 0.842 at baseline and ($p < 0.001$) in differentiating between low- and high-grade brain tumors.

Conclusion- MR Spectroscopy along with Magnetic Resonance Imaging of Brain at the same sitting in cases of brain neoplasms, helped us in predicting the pathological nature of the lesions and also for grading the lesions as benign or malignant with very high accuracy and higher sensitivity & specificity.

Keywords: Brain neoplasm, MRS, metabolite, diagnostic accuracy.

1. Introduction

Brain neoplasms constitute 1.9% of all malignant tumors in India [1]. Majority of the patients with brain neoplasms have a reasonably typical imaging presentation, however in some cases intra-tumoral hemorrhage and necrosis result in atypical presentation causing diagnostic dilemma [2].

Also, several non-neoplastic brain tumor mimics on imaging necessitates histopathological evaluation for precisely characterizing them for timely neurosurgical intervention [3,4].

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The observation of unique spectrum in brain tumors significantly differs from that of normal brain parenchyma, forming the basis for Magnetic Resonance spectroscopy (MRS). Commonly employed methods for spatial localization in MRS are Single Voxel (SV) and Multi Voxel Spectroscopic Imaging (MRSI) techniques.

2. Material and Method

This is a hospital based prospective observational study with a sample size of 55 subjects, conducted in our Department of Radiodiagnosis. Study population included clinically suspected patients for brain neoplasms whose MR Brain imaging findings were in favor of neoplastic etiology. Patients with history of metallic implants, foreign body, pacemaker, aneurysm clip, cochlear implant, any electric stimulator, recently implanted prosthetic valve, claustrophobia or with contraindications for contrast administration were

excluded from the study. All MRI scans were performed by 1.5 T MRI machine present in our department.

After obtaining ethical clearance from Institute's ethical committee, patients fulfilling the inclusion criteria were enrolled and written consent obtained. Socio-demographic details such as age, gender was obtained from all the study participants and entered in questionnaire. Detailed history regarding their illness, its duration, family history, past surgical history was obtained.

MRI Brain is performed by the 1.5T MRI machine available in our department and the findings were reported as per standard format. MRI Brain findings favoring neoplasms subsequently subjected to undergo MR Spectroscopy using single voxel technique by PRESS sequence at TE-35/TE-135ms (TE – Time to Echo) and their findings reported as per standard format. These cases had been followed up and correlated MRS findings with histopathological examination (HPE).

2.1 Statistical analysis

Data analyzed using SPSS software version 20 and MedCalc software. The qualitative data expressed in proportions and the agreements between diagnostic tests assessed using Cohen's kappa statistic. The diagnostic tool evaluation done by calculating sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, accuracy and by plotting ROC curve.

3. Results

The present study conducted in 55 patients clinically suspected for brain neoplasms referred to our department for MRI Brain study. MR spectroscopy done in cases whose imaging findings were in favor neoplastic etiology and correlated its findings with their histopathological examination.

N- acetyl Aspartate (NAA) level, Creatinine (Cr) level, Choline (Cho) level and Choline/Creatinine ratio were abnormal in all the 55 patients. Lipid/Lactate (Lip/Lac) levels were normal in majority (70.9%) of the patients and peak observed in 29.1% cases. Alanine (Ala) level was normal in 89.1% of the study participants and raised in 10.9% cases. Myoinositol (mI) level was normal in 92.7% of the study participants and raised in 7.3% cases. Glutamine/glutamate complex (Glu/glx) was normal in 90.9% of the study population and raised in 9.1% cases.

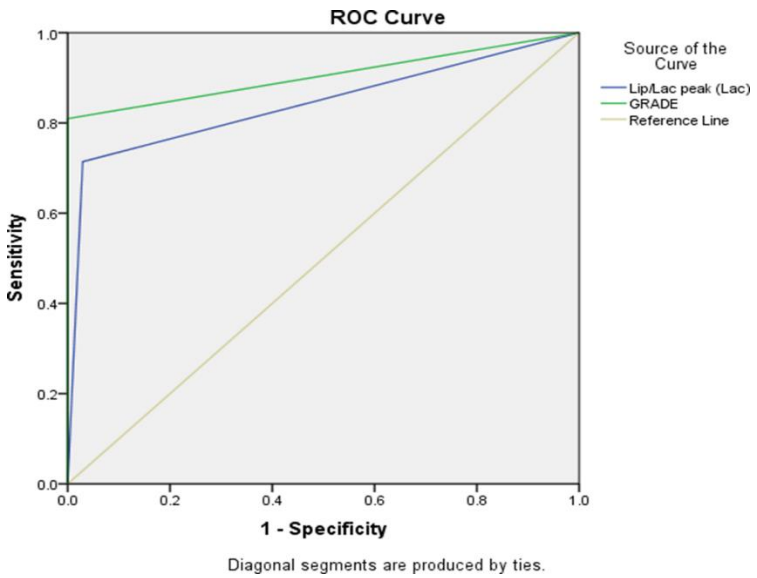
Table -1. Metabolite levels

Metabolites	NORMAL		ABNORMAL	
	n	*%*	*n*	*%*
Lip/ lactate	39	70.9	16	29.1
Alanine	49	89.1	6	10.9
Myoinositol	51	92.7	4	7.3
Glutamine /glutamate	50	90.9	5	9.1

Table - 2. Case distribution based on provisional diagnosis on MRS

Provisional diagnosis	**Frequency**	**Percentage**
Low Grade Glioma	18	32.7
High Grade Glioma	12	21.8
Meningioma	13	23.6
Metastasis	4	7.2
Medulloblastoma	2	3.6
Ependymoma	1	1.8
Atypical Meningioma	1	1.8
Pituitary adenoma	2	3.6
Schwannoma	1	1.8
Pilocytic astrocytoma	1	1.8

As observed, Gliomas (low grade and high-grade gliomas) constituted the most frequent provisional diagnosis on MRS (54.5%).



Graph 1: ROC curve showing the utility of Lip/Lac level and MRS grading as diagnostic tools.

Table -3. Agreement between grade of tumor in MRS diagnosis and HPEdiagnosis

		HPE Grade		Kappa statistic	'p' Value
		High Grade	*Low Grade*		
MRS Grade	High Grade	17	0	0.840	<0.001
	Low Grade	4	34		

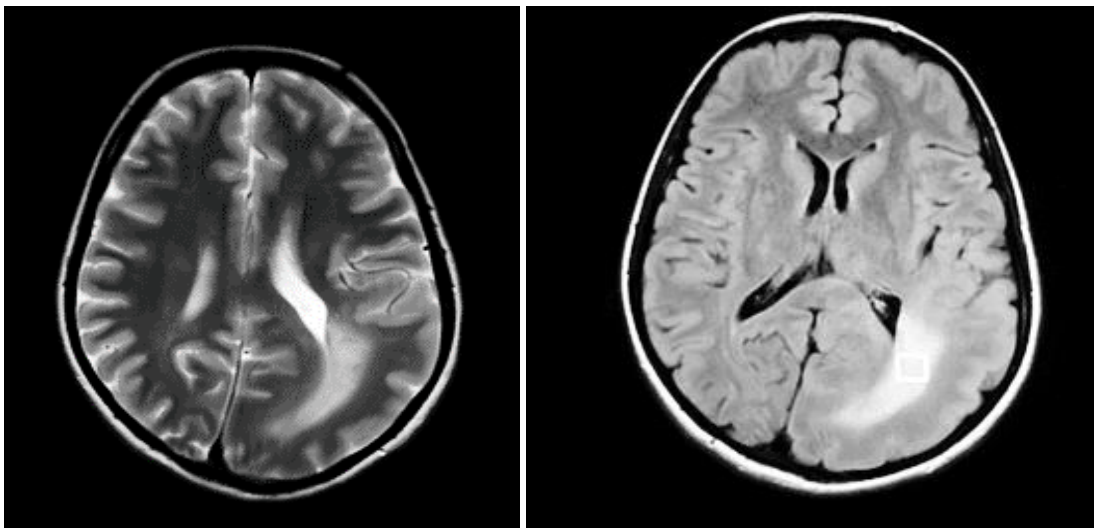
There is a statistically significant almost perfect agreement between MRS grading and HPE grading (K=0.840, p<0.001).

Table – 4. Agreement between Lip/Lac level and HPE diagnosis

		HPE Grade		Kappa statistic	'p' Value
		High Grade	Low Grade		
Lip/Lac Level	Abnormal	15	1	0.718	<0.001
	Normal	6	33		

There is a statistically significant substantial agreement between Lip/Laclevel abnormality and HPE grading (K=0.718, p<0.001).

Low grade glioma



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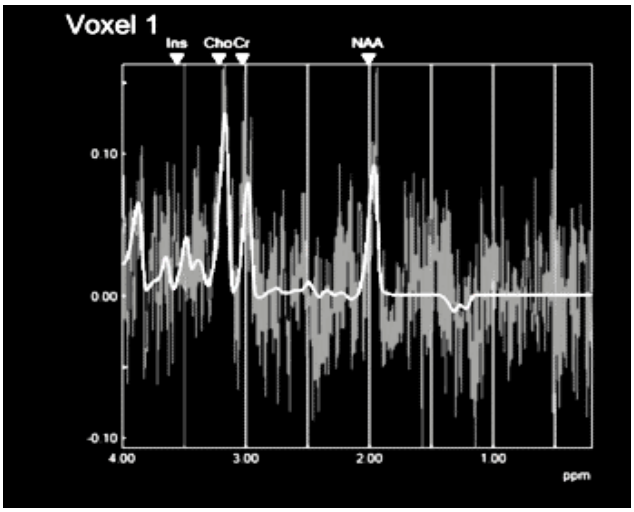
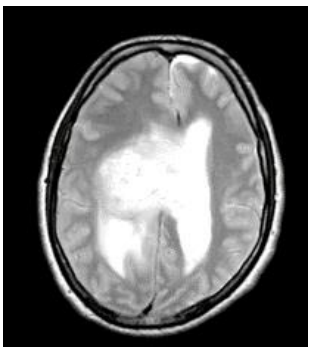


C

Figure -1. Axial T2 (A) & FLAIR (B) sections showing an ill-defined patchy hyperintensity in left peri atrial region. No diffusion restriction / enhancement seen (not shown). (C) single voxel MR spectrum shows choline peak, reduced NAA & Cr levels.

High grade glioma



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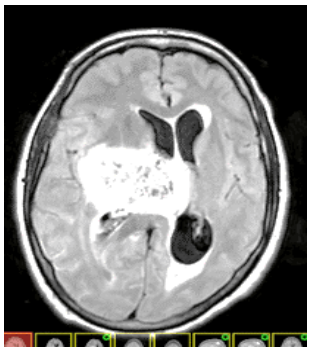

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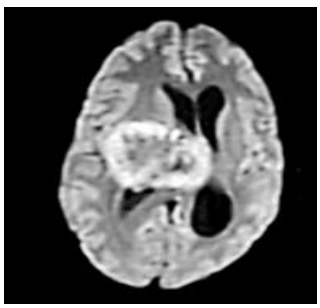

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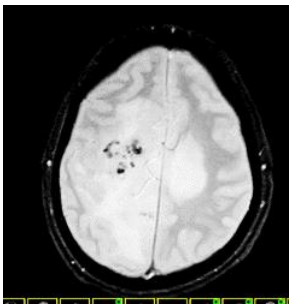

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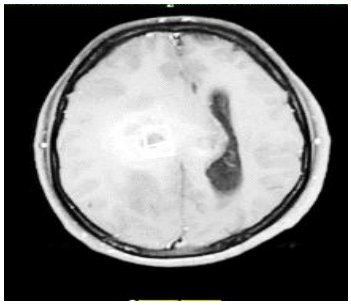

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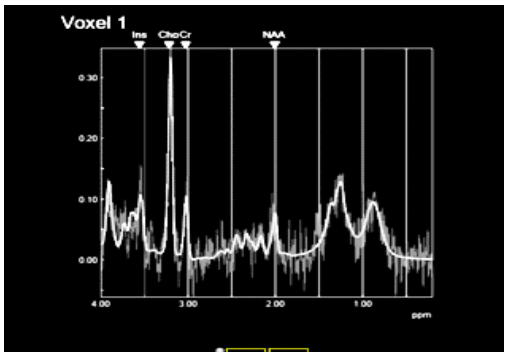

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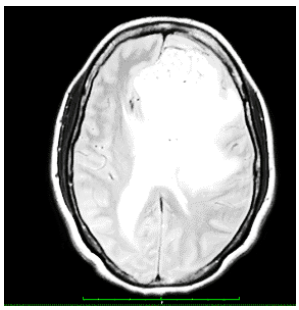
Figure 2: Axial T2 (A) and FLAIR (B) sections showing a large ill defined heterogenous hyperintense infiltrating lesion in right basal ganglia with diffusion restriction & GRE blooming as shown in figures (C & D) respectively. Choline peak, reduced NAA & Cr levels, lip/lac peak on MRS are noted in figures (E & F).



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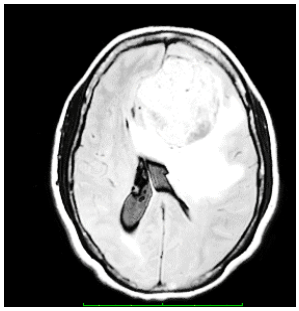

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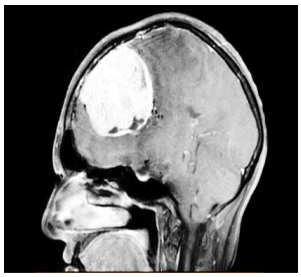

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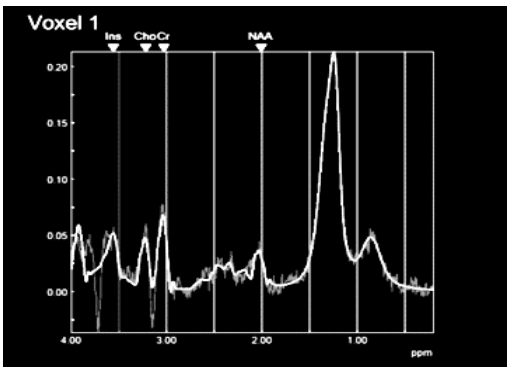

D

Figure 3: Axial T2 (A) and FLAIR (B) shows large well defined extra-axial hyperintense lesion along anterior falx cerebri. (C & D) MRS shows choline peak, reduced NAA & Cr levels, with Alanine peak at 1.4ppm and also myoinositol peak.

4. Discussion

Aim of the study was to evaluate the role of MR Spectroscopy of various brain neoplastic lesions, to grade them into high or low using MR spectroscopy and to correlate these findings with the gold standard histopathological examination. The study comprised of 55 patients (n=55) who underwent MRI Brain with contrast and MR Spectroscopy. Qualitative data expressed in proportions and the agreements between diagnostic tests were assessed using Cohen's kappa statistic. Diagnostic evaluation was done by calculating sensitivity, specificity, positive & negative likelihood ratios, positive & negative predictive values, accuracy and by plotting ROC curve.

Metabolites of MR Spectrum

N- acetyl Aspartate (NAA), Creatine, Choline levels and Choline/Creatinine ratio were abnormal in all the cases. NAA & Cr levels were reduced while Cho levels raised with elevated Cho/Cr ratio which are consistent with the study conducted by Tong Z, et al. [5] who also observed that there was significant reduction in the mean peak height ratios of NAA and Cr in all gliomas ($p < 0.001$).

Lipid/lactate levels were abnormal in 16 cases of which, 15 cases (94.1%) were high grade neoplasms and one case (5.9%) was low grade neoplasm on MRS. On histopathological examination 15 cases with abnormal lipid/lactate levels were high grade. One case was reported as tuberculoma on post-operative histopathological examination, whereas pre-op diagnosis was Glioma due to the choline peak observed on MRS, which was misleading. It is correlating with the study conducted by Mullins et al[6,7] suggesting that lip/lactate peak on MRS signifies higher tumor grade and correlates with tumor metabolic activity.

Alanine peak observed in six cases which were provisionally diagnosed as meningioma on basis of MR morphology & MRS and its further confirmed pathologically, in agreement with study conducted by Kousi E. et al. [8] suggesting that meningioma shows a distinct alanine peak with variable sensitivity.

Myo-inositol peak reflecting increased glial activity observed in four cases of which, two cases (50%) were low grade astrocytoma, one was atypical meningioma and another was schwannoma. Pathologically the results were same and it correlates with the study by Horská A. et al. [9].

Low grade gliomas: Spectroscopy in these lesions showed elevated Cho levels, reduced NAA & Cr levels with raised Cho/Cr ratio. No lipid/lactate peak noticed which is correlating with the study by Yao et al. [10] who observed a positive correlation between Cho/Cr to the glioma grade, whereas a negative correlation was demonstrated between NAA/Cr or NAA/Cho and glioma grade.

High Grade Glioma: 12 (21.8%) cases of high- grade gliomas on MR spectroscopy with voxel placement on the enhancing solid portion of the lesion showed highly elevated choline peak and reduced / absent NAA & Cr levels with reduced NAA/ Cho and NAA/ Cr ratios and elevated Cho/ Cr ratio. Lipid/ lactate doublet peak noted at short TE-35ms with inversion at intermediate TE-135 ms. Our study is consistent with that of Zeng et al. [11] who also observed that Cho/Cr and Cho/NAA ratios significantly higher in high-grade than in low-grade glioma ($P<.001$).

Meningioma: Fourteen cases of meningioma showed choline peaks with absent/ very low NAA & Cr levels (indicating non neuronal origin of tumor). Among them two cases were atypical meningioma as they showed lipid/lactate peaks on MRS. Alanine peak characteristic for meningioma was seen in six cases and Myo-inositol peak in one case. On HPE, 12 cases were proven as meningioma and two cases turned out to atypical meningioma. Our study is consistent with that of Mustafa et al who also concluded that prominent Cho levels, absent or low NAA & Cr levels and presence of Ala peak were common spectral characteristics of both atypical & typical meningioma.

Metastases: Four cases of brain metastatic lesions with known primary showed choline peak, reduced NAA levels, raised lipid/lactate levels in consistent with study by Andrès Server, Roger Josefsen Et al[12]. ROC analysis of his observation showed sensitivity, specificity, positive (PPV), and negative predictive values (NPV) about 100%, 88.9%, 80.0% and 100% respectively, in differentiating high-grade gliomas from metastases.

Lymphoma: Spectroscopy in a case revealed choline peaks at 3.2ppm with very low NAA & Cr levels. Cho/Cr ratio was raised associated with lipid/lactate peak. This correlates with the study by Harting et al[13] who concluded that significantly elevated lipid resonances constitutes the hallmark of primary central nervous system lymphoma in immunocompetent patients.

Ependymoma: Spectroscopy in one case showed choline peak, reduced NAA & Cr levels and raised lipid/lactate level representing aggressive nature of the tumor. Cho/ Cr ratio was also elevated. Our study correlates with that of Panigrahy et al. [14] who also concluded that ependymoma and anaplastic ependymomas exhibited particularly low levels of N-acetylaspartate with elevated choline level.

Medulloblastoma: Raised choline level, reduced NAA level and lipid/lactate peak observed in two cases of medulloblastoma, consistent with high grade nature as evident by HPE report. Cho/ Cr ratio was also elevated. However, Taurine peak, which is specific to this lesion, not observed in our study (probably due to low sensitivity) which is in contradistinction to the study by Kreiger at al reported that markedly elevated levels of taurine (Tau) was observed in medulloblastomas ($P < .00001$), as also emphasized in the study by Moreno-Torres et al. [15].

The diagnostic accuracy, sensitivity, specificity, positive & negative predictive values of our MRS study in differentiating tumors into low grade versus high

grade are 92.73%, 80.95% , 98.18% 100% and 89.47% respectively .

5. Conclusion

While MR Plain & post contrast study demonstrated classic morphology and enhancement pattern of neoplastic lesions, MR spectroscopic techniques helped in further confirmation and narrowing differential diagnosis by evaluating biochemical composition of the lesions.

MR Spectroscopy study yielded high sensitivity & specificity for detecting brain tumors, to classify their neoplastic nature with an added advantage of grading them as benign or malignant. This novel non-invasive diagnostic tool greatly helpful in improving our ability to predict preoperative histopathological diagnosis. Proton MR Spectroscopy improved the diagnostic accuracy preoperatively in various brain tumors and in addition evaluating its post medical / surgical treatment related changes.

6. Competing interest

The authors declare that there are no conflicts of interest.

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