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The Facets of Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy in Evaluation of Supratentorial Mass Lesions with Histopath Correlation.

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Abstract: Objective: *Evaluation and characterization of MRI and PMRS findings of supratentorial mass lesions and to determine the role of MRI and MRI combined with PMRS in differentiating supratentorial neoplastic mass lesions from non neoplastic lesions. These findings were further correlated with histopath diagnosis.*
Material & Methods: *33 Patients of supratentorial mass lesions were evaluated. MRI including contrast enhanced MRI and Proton (1H) MRS was conducted on 1.5T superconductive unit (Magnetom "Vision") with single voxel multinuclear spectroscopic capabilities using a circularly polarized phased array head coil.*
Results: *In 55% patients MRI rightly differentiated Neoplastic from Non neoplastic lesions, and was equivocal in 45% patients. When MRI was combined with PMRS it helped in differentiating Neoplastic from Non neoplastic mass lesions in 85% of patients and 15% patients remained equivocal.*
Conclusion: *PMRS provides detailed biochemical analysis (metabolites) of the tissue. This information can be interpreted to know the neuronal integrity, cell proliferation or degradation, energy metabolism and necrotic transformation of the brain or tumor tissue. PMRS combined with MRI helped in improving diagnostic capabilities by providing extra information about the chemical nature of the lesion in addition to the structural information provided by the MRI, thus leading to statistically* significant ($p<0.5$), higher proportion of correct *diagnosis and lower proportion of equivocal diagnosis.*

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I. Introduction:

The Magnetic resonance Imaging with its unique multiplanar imaging capability and exquisite contrast and tissue delineation, is a non-invasive method, using Radio frequency (rf) Radiation in presence of a carefully controlled magnetic fields. The annual reported incidence of primary intracranial neoplasms in adults is approximately 12.3 central nervous system tumors per lac population and in children approximately 2.5 central nervous system tumor per lac children [1,2,3]. Central nervous system tumors account for 15 – 20 % of all neoplasm occurring in childhood, under 15 years of age [4,5]. There is evidence that this rate is increasing, especially in elderly [6,7]. 80 – 85 % of all intracranial tumors occur in supratentorial compartment in adults [8,9] whereas in children 52% are supratentorial tumors [5].Few of the Other important intracranial mass lesions are Tuberculomas, Brain abscesses, non-neoplastic cysts and non tuberculous granulomas.

Aim /Objective: The goal of this study was to compare the Magnetic Resonance Imaging features alone, and in conjunction with spectrum of Proton Magnetic Resonance Spectroscopy and subsequent histopathological findings in supratentorial mass lesions and to further evaluate the clinical utility of Proton Magnetic Resonance Spectroscopy along with Magnetic Resonance Imaging for the differentiation of supratentorial neoplastic lesions from non neoplastic lesions.

II. Materials And Methods

The study design was conducted over a period of approximately two years.33 cases of supratentorial mass lesions, referred to the Neurosciences Center of the (Army Research and ReferralHospital)on outdoor and indoor basis were included in the study. All patients had undergone detailed clinical evaluation including neurological examination by neurophysician/neurosurgeon, other relevant investigations as per the proforma, followed by imaging studies.MRI was conducted using a dedicated head coil.Proton (1H) Magnetic Resonance Spectroscopy of the lesion was carried out on 1.5 Tesla Superconductive unit (Magnetom "Vision", Siemens), with multinuclear spectroscopic capabilities using a circularly polarized phased array head coil.All patients were examined in the supine positionT1SE, T2SE weighted and FLAIR Axial images were obtained. T1SE, T2SE

and FLAIR Coronal and Sagittal images, too, were obtained whenever deemed necessary.Paramagnetic MR contrast medium, IV Gadolinium enhanced T1 weighted axial images were obtained in all cases, and/or coronal and sagittal images obtained as and when required.Additional MR sequences like Gradient echo sequences and MR Angiography were performed as and when indicated.Single voxel Spectroscopy was performed with Point resolved surface coil spectroscopy (PRESS) sequence. The SVS, SE-135 spectra were used for metabolic ratio calculations.The MR images and MRS spectra were subsequently studied in details along with the Radiologist and Neurosugeons/physicians, keeping the symptomatology of the patient in mind and correlating with other radiological investigations.In cases treated by Radiation, attempt was made to differentiate between the radiation necrosis and tumor recurrence depending on the MRI and Proton Magnetic Resonance Spectroscopy findings. The tissue diagnosis was obtained with the help of stereotactic biopsy or following the excision of the mass lesion, whichever was indicated in the individual case depending on the clinical and radiological outcome.The results of Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy were correlated with the Histopathological findings, and conclusion was drawn in regard to 'p' value for significance of PMRS combined with MRI in relation to MRI findings alone. The statistical analysis was performed using SPSS – 10 software package.

III. Results

Supratentorial mass lesions were divided in different subgroups depending on the age and sex.

Out of the total studied cases (33),12.1% were of paediatricagegroup,rest 63.6% were adults in which Majority of the patients (33.3%) fell into the age group of 20 – 40 years and 40-60 yrs each. Predominantly 63.6% of patients were male(63.6%)21 and females contributed 36.4% of the study group.Intraaxial lesions contributed to 87.9% of the lesions.,followed by extraaxiallesions(9%),and lastly one case of equivocal lesion(3.1%).Neoplastic and non neoplastic cases were distributed(Table -1).The cases were further distributed according to histopathological correlates(Table-2)

Table-1 Neoplastic and Non Neoplastic lesions

S.No	Mass lesions	No. of Cases	Percentage
1.	Neoplastic	24	72.7
2.	Non Neoplastic	5	15.2
3.	Post radiotherapy	4	12.1
	Total	33	100

Table-2 Case distribution of the supratentorial mass lesion on Histopathological examination.

S.No	Mass lesion	No. of Cases	Percentage
1.	Gliomas	14	42.42
2.	Menningioma	4	12.12
3.	Hemangiopericytoma	1	3.03
4.	Lymphoma	2	6.06
5.	Metastases	1	3.03
6.	Pinealoblastoma	1	3.03
7.	Germinoma	1	3.03
8.	Demyelinating disorder	2	6.06
9.	Tubercular	3	9.09
10.	Post radiation recurrence	3	9.09
11.	Post radiation necrosis	1	3.03
	Total	33	100

On Magnetic Resonance Imaging we could diagnose 18 (55%) cases correctly as Neoplastic or Non Neoplastic lesions, and we were inconclusive in 15 (45%) cases.The MR spectroscopic ratios of Cho/Cr, NAA/Cr and NAA/Cho were observed. The lactate and lipid values were also analysed. The results of pathological lesions was compared with age and sex matched controls, studied at our Imaging center to find the normal limits.Mean metabolite ratios (with standard deviations) in normal brain of control group studied at our Magnetic Resonance Imaging center. In cases of doubt we compared the spectral traces with the traces of normal contralateral brain, i.e., mirror image spectra were obtained.Control group consisted of Cho/Cr(1.16,0.18),Naa/Cr(1.88(0.52),NAA/Cho(0.51).

Proton Magnetic Resonance Spectroscopy characteristics of Neoplasms

PMRS characteristics of Grade II Gliomas consisted of 6 cases of grade II Gliomas studied, that included Low grade Astrocytoma (n=4), Oligodendroglioma (n=1). They showed a significant increase in Cho/Cr ratios (maximum of 1.85) and decreased NAA/Cr ratios (minimum of 0.76)(Table-3). Lactate peak was noted in two cases. No lipid peak noted in any case. One case showed normal metabolite ratio.

Table-3 Metabolite ratio in Grade II Gliomas

Group	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Low grade Astrocytoma (1)	1.53	0.96	0.62	-	-
Low grade Astrocytoma (2)	1.85	0.76	0.41	+	-
Low grade Astrocytoma (3)	1.24	1.62	1.31	-	-
Low grade Astrocytoma (4)	2.21	0.64	0.30	-	-
Oligodendroglioma	1.96	.86	0.44	+	-

Magnetic Resonance Imaging findings were inconclusive in 2 cases of Grade II glioma, PMRS helped to confirm the neoplastic nature of one lesion and was inconclusive in the other case, where it showed the spectral traces within normal limits. The tumor was correctly diagnosed in all cases except one, where PMRS and MRI both were equivocal.

PMRS characteristics of high grade Glioma (Grade III and Grade IV) consisted of 9 high grade (Table-4)Gliomas were studied, which included Glioblastoma multiforme (n=6), Anaplastic astrocytoma (n=2). These 8 lesions showed significantly high Cho/Cr ratios and reduced NAA/Cr and NAA/Cho ratios. Lactate peak was noted in all cases except one case of Anaplastic astrocytoma. Lipid peak was noted in all cases, save for one case each of Gliblastoma multiforme, Anaplastic astrocytoma and Anaplastic Oligodendroglioma.One case of Glioblastoma multiforme showed low Cho/Cr and mildly low NAA/Cr ratios. It also showed lactate and lipid peak suggestive of infective etiology, likely tubercular.

Table-4 Metabolite ratio in high grade glioma (grade III and IV)

Lesion	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Glioblastoma multiforme(1)	3.62	0.86	0.24	+	+
Glioblastoma multiforme(2)	1.30	1.03	0.79	+	+
Glioblastoma multiforme(3)	4.13	0.82	0.20	+	+
Glioblastoma multiforme(4)	2.37	1.14	0.48	+	-
Glioblastoma multiforme(5)	3.38	0.75	0.22	+	+
Glioblastoma multiforme(6)	3.50	0.64	0.18	+	+
Anaplastic astrocytoma (1)	2.13	1.02	0.47	-	-
Anaplastic astrocytoma (2)	3.93	0.92	0.23	+	+
Anaplstic Oligodendroglioma	2.25	0.68	0.33	+	-

MRI findings were inconclusive in 3 cases, PMRS helped to reach differential diagnosis in 2 cases and was equivocal in one case, where it was to be differentiated from Tubercular abscess. In these cases tumor type was not correctly diagnosed in two patients, because the spectra of one Anaplstic astrocytoma was corresponding to Low grade astrocytoma, same was for one case of Glioblastoma multiforme where it was diagnosed as a low grade astrocytoma.

Proton MRS characteristic of Extra-axial neoplasms(Table-5)consisted of 5 cases, including 4 cases of menningioma and 1 case of hemangiopericytoma. All the case showed increase in Cho and decreased NAA and Cr levels. None of the lesions showed lactate or lipid peaks. All cases were suggestive of meningiomas.Of the 2 inconclusive cases on MRI findings, PMRS helped to reach the differential diagnosis in both cases. Tumor type was correctly diagnosed in all cases of Menningioma, and one case of Hemangiopericytoma was also diagnosed as Menningioma, where Histology proved the diagnosis.

Table-5 Metabolite ratios in extra-axial neoplasms

Lesion	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Meningioma (1)	6.6	0.77	0.12	-	-
Meningioma (2)	4.8	1.09	0.24	-	-
Meningioma (3)	5.4	0.82	0.15	-	-
Meningioma (4)	7.2	0.64	0.09	-	-
Hemangiopericytoma	3.93	0.53	0.13	-	-

We had 5 cases of miscellaneous neoplasia by Proton Magnetic Resonance Spectroscopy(PMRS) were studied and all showed features suggestive of neoplasm on PMRS, except for one case of Pineoblastoma(Table-6). They exhibit significantly increased Cho/Cr ratios, NAA was mild to moderately decreased, and the creatine was mild to moderately reduced in all cases. Significant Lactate and lipid peak was seen in both cases of Lymphoma and in one case each of Metastates and Germinoma. Normal metabolic peak was noted in a case of Pinealoblastoma.

Table6-Metabolite ratios in miscellaneous neoplasms.

Lesion	n	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Lymphoma (1)		1.63	1.33	0.81	+	+
Lymphoma (2)		1.76	1.24	0.70	+	+
Pinealoblastoma	1	1.16	1.88	1.65	-	-
Germinoma	1	1.91	1.54	0.81	+	+
Metastases	1	3.97	1.09	0.27	+	+

On MRI, one case of Lymphoma was to be differentiated from demyelinating lesion, and Proton Magnetic Resonance Spectroscopy was helpful in reaching the conclusion. However, tumor type could not be established accurately.One case of solitary metastases was to be differentiated from inflammatory lesion and was successfully done so by Proton Magnetic Resonance Spectroscopy, and the tumor type was strongly suggestive of Metastases, Because of prominent Lipid peak.MRI was definitive in diagnosing the neoplastic nature of Pineal region tumors, and PMRS confirmed the neoplastic findings in Germinoma, whereas it failed to show tumor signature in Pinealoblastoma.

Proton Magnetic Resonance Spectroscopy of Non neoplastic lesion

Proton Magnetic Resonance Spectroscopy Characteristics of Demyelinating Lesions

Acute and chronic lesions showed different peaks of Choline and Creatine. In acute lesions (within 10 days of onset of symptoms) there was marked elevation of Choline and normal to mildly raised NAA, however in chronic lesions there was moderate elevation of Choline and moderate reduction of NAA(Table-7). Lactate peak was also noted in the acute enhancing lesions and no lactate peak was noted in the chronic lesion. No Lipid peak was noted in either patients.One case on Magnetic Resonance Imaging was equivocal, where PMRS was helpful to distinguish it from Primary CNS Lymphoma, on the basis of metabolite levels.

Table-7 : Metabolite levels in demyelinating lesions

Lesion	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Multiple Sclerosis (Enhancing lesion)	2.8	1.9	0.68	+	-
Multiple Sclerosis (Non enhancing lesion)	2.1	1.3	0.62	+	-

Proton Magnetic Resonance Spectroscopy characteristics of Tubercular lesion

2 cases showed significantly low Choline, NAA and Creatine, with prominent lipid peak, one of these cases also showed lactate peak. One case showed significantly increased Cho/Cr ratio, and reduced NAA/Cr ratio, Lactate and lipid peaks were also noted and it could not be conclusively differentiated from necrotic Neoplastic lesion(Table-8).

Table 8-Metabolite levels in Tubercular lesions

Lesions	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Tuberculoma	1.20	0.68	0.56	-	+
Tubercular abscess (1)	1.14	0.62	0.54	+	+
Tubercular abscess (2)	1.56	0.76	0.48	+	+

2 cases were inconclusive on the basis of MRI findings. PMRS helped to reach the differential in one case and was inconclusive in one case, where it could not be differentiated necrotic neoplastic lesion. PMRS further confirmed the findings in the Tuberculoma diagnosed on MRI.

Proton Magnetic Resonance Spectroscopy characteristics of Post Radiation lesions: The spectrum was suggestive of recurrence in 2 cases, with increased Cho/Cr and decreased NAA/Cho ratio. One case exhibited normal Cho/Cr and NAA/Cr ratio, and did not suggest of recurrence/recurrent tumor. Recurrent tumors showed lactate peak in 2 cases and lipid peak in one case(Table -9).Whereas it was suggestive of radiation necrosis in the only case of this group, exhibiting decreased NAA, Cho and Cr, with a broad intense peak between 0 and 2.0 ppm consisting of Lipid, lactate level and amino acids.

Table-9) Metabolite levels in and Post Radiotherapy cases

Lesion	Cho/Cr	NAA/Cr	NAA/Cho	Lactate	Lipid
Recurrent tumor (1)	1.81	0.80	0.44	+	-
Recurrent tumor (2)	1.93	0.76	0.39	+	+
Recurrent tumor (3)	1.19	1.80	1.51	-	-
Radiation necrosis	1.14	1.23	1.08	+	+

MRI, was inconclusive in 2 cases of recurrent/residual tumor. PMRS helped to reach the diagnosis in 1 cases of recurrence/residual tumor and the other case remained equivocal, left to be diagnosed by biopsy. PMRS

confirmed the diagnosis in one case which was diagnosed on MRI findings. PMRS also helped in reaching diagnosis in the only case of post radiation necrosis.Thus PMRS showed corresponding spectrum in 28 (85%) cases and exhibited inconclusive spectrum in 5 (15%) cases. In 55% patients MRI rightly differentiated Neoplastic from Non neoplastic lesion, and was equivocal in 45% of cases.MRI combined with PMRS it helped in differentiating Neoplastic from Non neoplastic cases in 85% patients and diagnosis in 15% patients remained equivocal. Overall, PMRS was combined with MRI, it helped in 11 cases (33.3%) more to differentiate Neoplastic from Non neoplastic lesion and the number of equivocal cases were also reduced to 12% only.The statistical analysis of the observation was done by (Table-10)Chi² test (f^2 test) for difference between two proportions.

Table10:- Chi² test (f^2 test) for difference between two proportions.

	MRI	MRI + PMRS	Total
Neoplastic lesions	18	29	47
Non Neoplastic Lesions	15	4	19
Total	33	33	66

On statistical analysis the Chi² value was 8.94 ($p=0.0028$) and it was found that there was significant difference between the proportion of Neoplastic and Non Neoplastic lesions detected by MRI, and proportion of Neoplastic and Non Neoplastic lesions detected when PMRS combined with MRI ($p<0.05$).

IV. Discussion

MRI is very sensitive in detection of supratentorial mass lesions.Supratentorial neoplasm treated by Radiotherapy has always been a dilemma on imaging to differentiate between the residual/recurrent tumor from post radiation necrosis.In contrast to MRI, CT and angiography, i.e. methods that provide structural data, Proton Magnetic Resonance Spectroscopy gives completely different information related to the neuronal integrity, cell proliferation or degradation, energy metabolism, and necrotic transformation of brain or tumor tissues. Proton Magnetic Resonance Spectroscopy has been especially helpful in assessing metabolic heterogenicity and regional metabolic variations associated with intracranial mass lesions [16]. On routine Proton Magnetic Resonance Spectroscopy the signals from N-Acetyl aspartate (NAA), Choloine (Cho), Creatine (Cr) and Lactate are studied which are adequately obtained with clinical instruments (1.5 Tesla or greater) [17].The concentration of normal metabolites in the brain varies according to the patient's age [18]. The most striking change is an increase in NAA/Cr ratio and a decrease in the Cho/Cr ratio as the brain matures. N-Acetyl Aspartate is accepted as a neuronal marker, and as such its concentration will decrease with many insults to the brain. NAA is not present in tumors outside the central nervous system[19]. The presence of NAA is attributable to its N-acetyl methyl group, which resonates at 2.0 ppm. In normal spectra, NAA is the largest peak [20]. This peak also contains contributions from less important N-acetyl groups. The exact role of NAA in the brain is not known [17]. Choline is a constituent of the phospholipids metabolism of the cell membranes and reflects membrane turnover, and it is a precursor for acetylcholine and phosphatidylcholine [19]. The latter compound is used to build cell membranes, whereas the former is a critical neurotransmitter involved in memory, cognition and mood. Therefore increased Choline reflects increased membrane synthesis and/or an increased number of cells [17]. The peak of choline occurs at 3.2 ppm and is the second highest peak in the normal spectra [20]. It contains contributions from glycerophosphocholine, phosphocholine and phosphatidylcholine and therefore reflects total brain choline stores. Creatine plays a role in maintaining energy dependent systems in the brain cells by serving as a reserve for high energy phosphates and as a buffer in adenosine triphosphate and adenosine diphosphate reservoirs [20]. Creatine is increased in hypometabolic states and decreased in hypermetabolic states [17]. The peak of Creatine occurs at 3.03 ppm and contains contributions from Creatine, Creatine phosphate and to lesser degree, γ-aminobutyric acid, lysine and glutathione. An additional peak for Creatine may be visible at 3.94 ppm, therefore Creatine peak is reffered to as "total Creatine". Creatine is located to the immediate right of Choline and is the third highest peak in the normal spectra. Because this peak remains fairly stable in the face of the disease, it may be used as a control value[17].

Lactate levels are normally low in the brain. The presence of lactate generally indicates that the normal cellular oxidative respiration mechanism is no longer in effect, and that the carbohydrate catabolism is taking place [21]. Lactate can play the role of neuromodulator by altering the excitability of local neurons [21]. The lactate peak has a particular configuration; it consists of two distinct, resonant peaks called a "doublet" and is caused by the magnetic field interactions between adjacent protons (J coupling). This Lactate doublet occurs at 1.32 ppm. A second peak for Lactate occurs at 4.1 ppm, because this latter peak is very close to the water it is generally suppressed [17].Lipids in the brain have very short relaxation times and are normally not observed unless very short TEs are used. The protons of lipids produce peaks at 0.8, 1.2, 1.5, and 6.0 ppm [17]. These peaks comprise methyl, methylene, allelic and vinyl protons of unsaturated fatty acids [22]. These metabolites are increased in pathological conditions which reflect necrotic processes [23]. Normal lipid resonances arising

from fat may be the result of voxel contamination by fat located in the subcutaneous scalp.Magnetic Resonance Spectra comprises of several peaks depending on the chemical constituents of the volume of interest. The parameters that characterize each peak include its resonance frequency, its height, and its width at half-height [15]. The resonance frequency position of each peak on the plot is dependent on the chemical environment of that nucleus and is usually expressed as parts per million from the main Magnetic Resonance Frequency of the system used (ie chemical shift). The height (maximum peak intensity) or the area under the peak may be calculated and yield relative measurements of the concentration of protons. The resonance frequency/chemical shift position gives information regarding the chemical environment of protons. The width of peak at half height gives relaxation time information because it is proportional to 1/T2.

On interpretation of the magnetic resonance spectra inference is drawn about the chemical constituents of the lesion and are thus differentiated between neoplastic and non neoplastic lesions and if possible they are further differentiated between the low grade and high grade tumors, keeping in mind the correlation with the Magnetic Resonance Imaging findings.

Numerous studies have been undertaken and many are still in process to define the role of Proton Magnetic Resonance Spectroscopy in conjunction with Magnetic Resonance Imaging. In particular, the clinical utility of PMRS for solving key diagnostic problems like differentiation between Neoplastic and Non neoplastic lesions, and to differentiate between low and high grade tumor. [24,25].

MRS based diagnosis was consistent with pathology results in all cases of astrocytoma, glioblastoma and menningioma. In few cases MR Spectra indicating an inflammatory-demyelinating process correlated with biopsy and clinical course. Thus PMRS proved to be a useful tool in establishing tumor type and differentiating between neoplastic and large inflammatory tumor like lesions (26).

PMRS is useful to arrive at a more definitive diagnosis in doubtful cases with similar morphological imaging patterns. Cho/Cr ratio was a sensitive indicator of tumor grade in Intracranial Gliomas (27).

V. Conclusion

Proton Magnetic Resonance Spectroscopy provides detailed bio-chemical analysis (metabolites) of the tissue, i.e. Choline, NAA, Creatine, Lactate and Lipids levels. This information can be interpreted to know the neuronal integrity, cell proliferation or degradation, energy metabolism and necrotic transformation of the brain or tumor tissue. Proton Magnetic Resonance Spectroscopy used in conjunction with Magnetic Resonance Imaging helped in improving diagnostic capabilities by providing extra information about the chemical nature of the lesion in addition to the structural information provided by the MR Imaging.Present study suggests important role of routine application of PMRS in conjunction with MRI to characterize supratentorial mass lesions, leading to statistically significant ($p<0.5$), higher proportion of correct diagnosis, and lower proportion of equivocal diagnosis. Moreover adequate spectra were obtained in additional 15 minutes only, when combined with MR Imaging.

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