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Role of MR Spectroscopy in the Evaluation of Intra Axial Brain Tumours

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Abstract: ***Aims and objectives: To determine biochemical markers of intraaxial brain tumors using MR spectroscopy. To evaluate role of MR spectroscopy in diagnosing and grading of intraxial brain with histopathological co-relation. To evaluate role of MR spectroscopy in determining the infiltrative nature of the intra axial brain tumor. Study Design: Hospital based descriptive study. Materials and methods: MRI of 30 patients with spectroscopy correlation during December 2014 to June 2016 was analysed. Results: Out of 30 patients 42 were males and 8 of them were females. The sensitivity, specificity, PPV and NPV was calculated (in%). For Glioblastoma Multiforme it was 90.91, 87.5, 83.33, 93.33, for Anaplastic Astrocytoma it was 33.33, 95.83.50.92, for Diffuse Infiltrative/Astrocytoma it was 100, 96, 66.67, 100, for Oligodendroglioma it was 50, 100, 100, 96..15, 96.3, for Gliomatosis Cerebri it was 100, 100, 100, 100, for Ependymoma it was 50, 100, 100, 96.15, for Medulloblastoma it was 100100, 100, 100, for Metastasis it was 100, 100, 100, 100, for Choroid plexux Papilloma it was 100, 100, 100, 100, and for Lymphoma it was 0, 96.15, 0, 96.15, respectively.***

Keywords: MR spectroscopy, choline, myoinositol, creatinine, choline/creatinine ratio, brain tumor, gliomas, NAA/Cr ratios

1. Introduction

Intra axial brain masses are a significant health problem and present several imaging challenges. These lesions include primary neoplasm (high and low grade), secondary (metastatic) neoplasm, lymphoma, tumefactive demyelinating lesions, abscesses and encephalitis. We are witnessing a shift in imaging from merely providing anatomical information towards providing information about tumor physiology.

Imaging plays an integral role in intracranial tumor management. Magnetic resonance (MR) imaging in particular has emerged as the imaging modality most frequently used to evaluate intracranial tumors, and it continues to have an ever expanding, multifaceted role. In general, the role of MR imaging in the workup of intraaxial tumors can be broadly divided into tumor diagnosis and classification, treatment planning, and post treatment surveillance. In addition to conventional MR imaging techniques, a variety of advanced techniques have found their place in clinical practice or are the subject of intense research. These advanced techniques offer more than the anatomic information provided by the conventional MR imaging sequences. They generate physiologic data and information on chemical composition. The current advanced techniques include perfusion imaging, diffusion-weighted imaging (including diffusion tensor imaging), MR spectroscopy, blood oxygen level-dependent (BOLD) imaging, and the largely experimental molecular imaging.[2]

Discrimination between extra axial and intra axial brain tumors is relatively easy with only anatomic imaging: however, the major diagnostic challenge is to reliably, noninvasively, and promptly differentiate intraaxial tumors to avoid biopsy and follow-up imaging studies. Integration of diagnostic information from advanced MR imaging techniques can further improve the classification accuracy of conventional anatomic imaging.

Magnetic resonance spectroscopy allows the non-invasive measurement of selected biological compounds in vivo. Proton spectroscopy has been recognized as a safe/and noninvasive diagnostic method that, coupled with magnetic resonance imaging techniques, allows for the correlation of anatomical and physiological changes in the metabolic and biochemical processes occurring within previously determined volumes in the brain. Magnetic resonance spectroscopy (MRS) provides information about the possible extent and nature of changes on a routine MRI scan by analyzing the presence and/or ratio of tissue metabolites such as NAA, creatine, choline, and lactate etc.

Widespread usage of faster MRS applications with higher signal-to-noise ratio (SNR) and spatial resolution, allows us to detect functional metabolic changes, which provides more data to understand the exact nature of the tumor and the morphological and physiological changes occurring in the surrounding brain parenchyma. Longitudinal studies have demonstrated that H1 MRS is useful in monitoring disease progression and treatment effects. MR spectroscopy also has a prognostic implication.[3]

2. Methodology

Patient and Methods

A prospective study was conducted at the department of radiology in Chalmeda Ananda rao institute of medical sciences and hospital during the period December 2014 to June 2016.Thirty patients (30brains) were examined, 22 patients were males and 8 patients were females their ages ranging from (2-75) years presented with clinically

suspected brain tumors were referred from General Medicine Department in Chalmeda anada rao institute of medical sciences and hospital.

MRI examination: Instrument
The MR! scan was performed MR GE Signa HDxt. It possesses a Ultra-compact, Superconducting, Active shielded superconducting magnet with a magnetic field strength of 1.5 T.SENSE coils was used for acquisition of images.

Inclusion Criteria
Patients of population (2-75yrs) willing to undergo MRI scanning with clinically suspected clinically suspected brain tumors.

Exclusion criteria
1) Cases with benign lesions after histopathology confirmation.
2) Patient having history of claustrophobia.
3) Patient having history of metallic implants insertion, cardiac pacemakers and metallic foreign body in situ.
4) Patient clinically unstable.

Data Acquisition
Once a patient satisfied the inclusion criteria for this study, he or she was administered the study proforma. The patients were briefed about the procedure. The noise due to gradient coils (heard once the patient was inside the bore of the magnet) and the need to restrict body movements during the scan time was explained to the patient.

Sequences
Conventional spin echo sequences, axial T1, T2, FLAIR, Coronal T2; Sagittal T1; Post contrast T1 GRE, coronal and sagittal; DWI; T2 GRE. SV PRESS 144, SV PRESS 31 Single voxel spectroscopy; 2D PRESS 144 multi voxel spectroscopy was performed at TE of 144ms and 31ms, TR was at 2000 ms. We used PRESS and Tl FFE post contrast sequence as localization sequence with 5 mm thickness. Gadobenate Dimeglumine contrast was used with dosage being 0.1 mmol/kg bodyweight.

3. Study Definition

MR spectroscopy is used as diagnostic test for diagnosing intraaxial brain tumors. An increase choline peak at 3.2ppm, myoinositol peak at 3.6ppm, lipid peak at 0.9-1.4ppm, lactate peak at 1.3ppm and reduced NAA peak at 2.0ppm, creatinine peak at 3.0, 3.9ppm was considered significant for diagnosing brain tumors. We reported brain tumor as high grade if there was increase in choline/creatine ratio of more than 2.3, choline/NAA ratio of more than 1.9, reduced NAA/creatinine of less than 1.5. We reported brain tumors as low grade if choline/creatinine ratio was less than 2.3; this value was used as a threshold value in order to increase the specificity of detecting brain tumors. Astrocytoma tumors were divided as low grade and high grade by using threshold value for myoinositol/creatinine ratio of 0.82 +/- 0.25 for low grade tumors and 0.33 +/- 0.16 for high grade tumors.

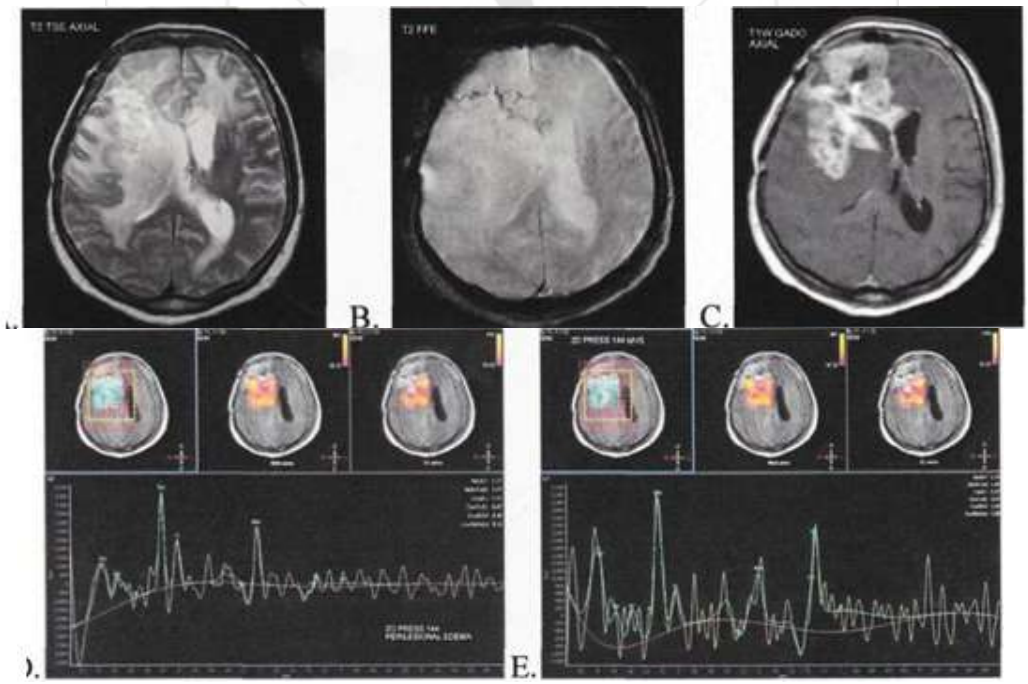

Figure 1: A 63 year old, operated case of GBM is referred for loss of consciousness, sudden in onset

a) T2W FSE AXIAL shows an irregular mixed density heterogeneous mass lesion in right front of temporal lobe with perilesional extensive edema and mass effect. The mass is seen extending and infiltrating the genu of corpus callosum and right internal capsule
b) T2 FSE AXIAL shows linear gradient blooming
c) T1W GADO AXIAL showing heterogeneous post contrast enhancement with stellate shape non enhancing central area suggestive of possible necrosis.

d) 2D PRESS 144 MVS and choline maps; shows increased choline peak, reduced NAA peaks, increased choline / NAA ratio and increased choline/ creatine ratio in the perilesional white matter edema.
e) 2D PRESS 144 MVS and choline maps; shows increased choline peak,

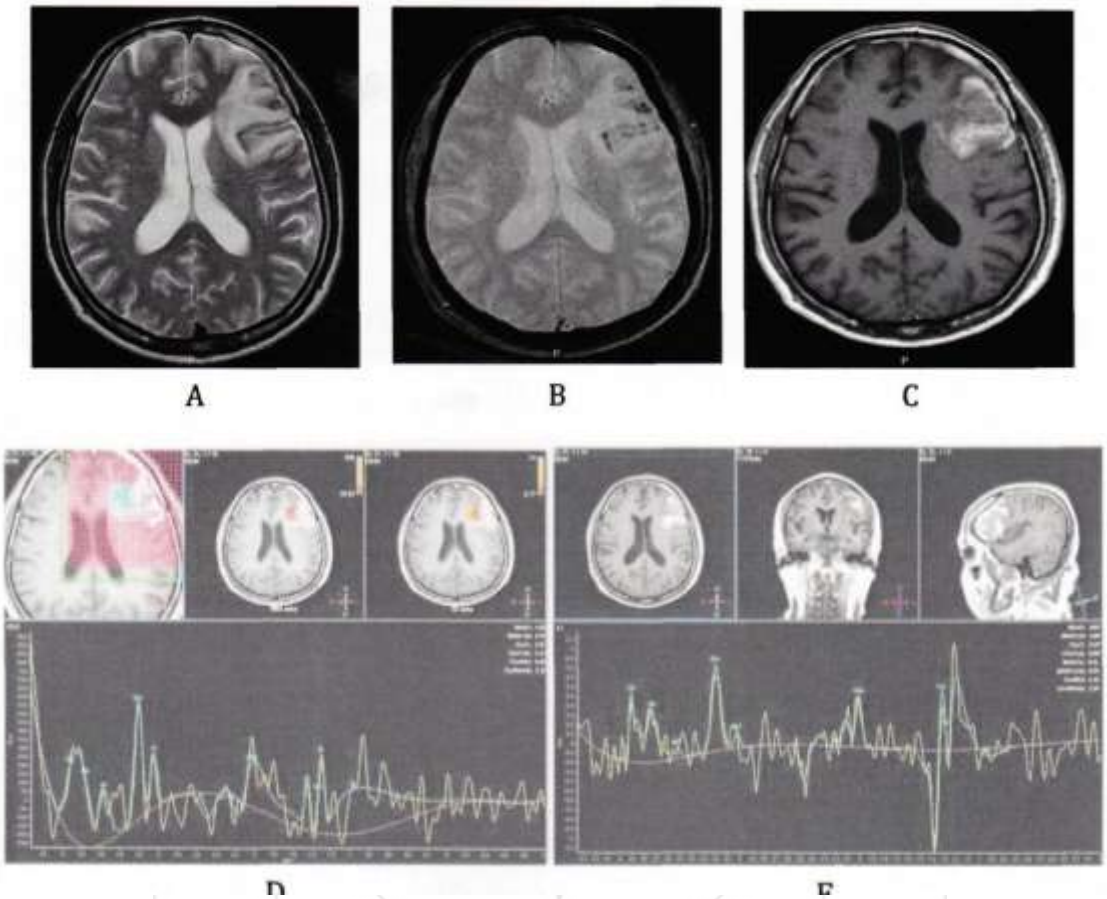

Figure 2: 60 year old referred with seizures.

a) T2 FSE AXIAL shows gyral hyperintensity seen involving left fronto temporal lobe with white matter edema causing sulcal effacement.
b) T2 GRE AXIAL shows multifocal areas of blooming suggestive of petechial hemorrhages.
c) T1W GADO AXIAL shows gyral enhancement in left fronto temporal lobe.
d) 2D PRESS 144 and choline maps; shows raised choline, reduced NAA peaks, increased choline/NAA and choline/creatine ratios in the perilesional white matter edema suggestive of perilesional infiltration.
e) SV PRESS 144 shows raised choline, reduced NAA peaks, lipid inversion, increased choline/NAA and choline/creatine ratios in the enhancing portion of the lesion. The case was finally diagnosed as gliomatosis cerebri.

4. Results

In our study MRI examination was performed on (30) patients with clinically suspected brain tumors. Regarding distribution of sample according to age as shown in (table 1)

Table 3: Distribution of Sample Based on Location

	No. of Cases (n)	Percentage (n%)
Supratentorial	22	73.33%
Infratentorial	6	20%
Both	2	6.67%
Total	**30**	**100%**

	No. of Cases (n)	Percentage (n%)
Mild	**6**	20%
Moderate	**5**	16.67%
Intense	**19**	63.33%
Absent	-	0%
Total	**30**	**100%**

Table 4: distribution of sample based on degree of contrast enhancement of brain tumor

	No. of Cases (n)	Percentage (n%)
Well Defined	16	53.33%
Ill Defined	14	46.67%
Total	30	100%

Table 5: Distribution of sample based on characteristics of tumor margins

S.No.	Brain tumour	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
1	Glioblastoma Multiforme	90.91%	87.5%	83.33%	93.33%	88.89%
2	Anaplastic Astrocytoma	33.33%	95.83%	50%	92%	88.89%
3	Diffuse Infiltrative Astrocytoma	100%	96%	66.67%	100%	96.3%
4	Oligodendroglioma	50%	100%	100%	96.15%	96.3%
5	Gliomatosis cerebri	100%	100%	100%	100%	100%
6	Ependymoma	50%	100%	100%	96.15%	96.3%
7	Medulloblastoma	100%	100%	100%	100%	100%
8	Metastasis	100%	100%	100%	100%	100%
9	Choroid plexus Papilloma	100%	100%	100%	100%	100%
10	Lymphoma	0%	96.15%	0	96.15%	92.59%

5. Discussion

Age distribution

Patients from all age group were included in our study. Brain neoplasms were most commonly found in 31-40 (n=6) years age group. The second most common age group was 41-50 (n=5) and 0-10 (n=5) years age group.

Sex distribution

Out of 30 patients in our present study, incidence of brain neoplasms was more in males 73.33% (n=22).

Location of tumors

In present study of 30 cases, 73.33% (n=22) neoplasms were supratentorial, 20% (n=6) were infratentorial and 6.67%(n=2) were both supra and infratentorial in location. Supratentorial tumors were more common than infratentorial tumors in our study.

Gliomas

In present study, glioma cases were reported as low grade (diffuse infiltrative astrocytoma) or high grade astrocytoma (anaplastic astrocytoma and glioblastoma multiformae), oligodendroglioma, ependymoma and gliomatosis cerebri according to the MR characterization of tumors. Both conventional sequences and different parameters of MR spectroscopy was used to optimize for better results. Glioma constituted 70% (n=21) out of the total 30 cases in our study, and was the most common brain neoplasm found in our study. Out of 21 cases of gliomas diagnosed on MRI, 12 were GBM, 3 were anaplastic astrocytoma, 2 were diffuse infiltrative astrocytoma, 1 case of oligodendroglioma, 2 cases of gliomatosis cerebri and 1 case of ependymoma.

In present study 20 out of 21 (95%) cases of glioma had perilesional edema. The only case which did not show perilesional edema was ependymoma (n=l). All GBM showed intense enhancement, anaplastic astrocytoma showed moderate enhancement, and diffuse infiltrative astrocytoma cases had minimal enhancement. Oligodendroglioma, ependymoma and one case of gliomatosis cerebri showed intense enhancement whereas the other case of gliomatosis cerebri showed mild enhancement. Our findings are in agreement with study conducted by R Felix, W Schorner et al.[6]

In present study, all GBM and anaplastic astrocytoma cases and 1 case of oligodendroglioma were heterogenous lesion with both solid and necrotic component. The 2 cases of diffuse infiltrative astrocytoma and 1 case of ependymoma were solid lesions showing no necrotic center. In cases of gliomatosis cerebri, one case was solid and the other was heterogenous with solid and necrotic component.

Histopathology was done in 20 cases of glioma. MRI findings were correlated with histopathology of the tumor in 16 out of 20 cases. First case which did not correlate was of diffuse infiltrative astrocytoma which on histopathology turned out to be anaplastic astrocytoma. Second case was of GBM, which on histopathology turned out to be lymphoma. The third case was of GBM, which on histopathology turned out to be anaplastic astrocytoma. Thefourth case was of anaplastic astrocytoma which on histopathology turned out to be anaplastic oligodendroglioma. Histopathology was not done in one case of brainstem glioma.

Diffuse Infiltrative Astrocytoma

Diffuse infiltrative astrocytoma are grade 2 astrocytomas. There were three patients with diffuse astrocytoma in our study. Two of them were seen in the age group of 11-20years and another case was of 47 year old. On conventional MR sequences, lesions were hypointense on T1WI and hyperintense on T2WI. Lesions were solid to solid and cystic. They showed minimal enhancement. No blooming were observed on T2 GRE sequence.

On MRSI the three tumors showed increased choline peak, reduced NAA, increased ml peak and reduced creatine peak. There was increased cho/creatine ratio of 2.03(±0.42), increased cho/NAA ratio of 1.9(±0.34) and reduced NAA/creatine peak at 0.9(±0.33). ml/creatine ratio was higher at 0.80(±0.25). Both cases showed no choline peak in perilesional edema outside the tumor margin.

One of the case did not correlate histopathologically, it was diagnosed as anaplastic astrocytoma. However we got diagnostic accuracy of 96.3% and a significant association between MRS and histopathology findings with p=0.00854

(p<0.05 being significant). We got 100% sensitivity and 96% specificity. Our findings were similar to study done Mauricio Castilloa et al[16].

We had one case of brainstem glioma. It was in a 5 year old boy. On conventional MR sequences it appeared as a well defined T1 hypointense lesion and T2/FLAIR hyperintense lesion. No blooming on T2 GRE. Minimal contrast enhancement. On MRSI we observed increased choline peak, reduced NAA, increased ml peak and reduced creatine peak. There was increased cho/creatine ratio of 2.03(±0.42), increased **cho/NAA ratio of** 1.9(±0.34) and reduced NAA/creatine peak at 0.9(±0.33). **ml/creatine ratio was** lower at 0.80(±0.25). Both cases showed no choline peak in **perilesional edema** outside the tumor margin. Our findings **were similar to study done** by Broniscer A et al.

Anaplastic Astrocytoma

Anaplastic astrocytomas are grade 3 astrocytomas. Two patients with anaplastic astrocytoma were evaluated in our study. One was seen in a child of 11years and one in an adult of 37years. On conventional MR sequences, lesion was hypointense on T1W and hyperintense on T2W imaging. Both the cases showed blooming on T2 GRE suggestive of bleed.

On **MRSI both the tumors** showed increased choline peak, reduced NAA, reduced ml peak and reduced creatine peak. There was increased cho/creatine ratio of 4.5(±0.55), increased cho/NAA ratio of 2.5(±0.22) and reduced NAA/creatine peak at 0.9(±0.33). ml/creatine ratio was lower at 0.33(±0.15). Two of the cases showed increased choline peak with raised cho/creatine ratio in perilesional edema probably due to tumoral infiltration. Our findings were similar to study done by Magalhaes A, Godfrey W et al[63] and Mauricio Castilloa et al.[16]

One of the case did not correlate on histopathology, which turned out to be anaplastic oligodendroglioma. We got diagnostic accuracy of 88.89% and specificity of 95.83% but a low sensitivity of 33.33%. There is no significant association between MR spectroscopy findings and histopathological findings, with p=0.2137 (p<0.05 being significant). This may be due to time bound, limited sample study.

Glioblastoma Multiformae

GBM are grade 4 astrocytomas. 12 patients with Glioblastoma multiformae were evaluated in our study. All GBM cases were found in adults between 3 rd to 8th deca'de.

On conventional MR sequences, all cases were heterogeneously hypointense on T1W and heterogeneously hyperintense on T2W imaging. Blooming was a prominent feature observed in all cases. On MRSI all tumors showed increased choline peak, reduced NAA, reduced ml peak at 3.6ppm and reduced creatine. There was increased cho/creatine ratio of 6.5(±0.55), increased cho/NAA ratio of 3.5(±0.22) and reduced NAA/creatine peak at 0.8(±0.33). ml/creatine ratio was lower at 0.15(±0.15). All the cases showed increased choline peak with raised cho/creatine ratio in perilesional edema probably due to tumoral infiltration.

Two cases of GBM did not correlate on histopathology. They were diagnosed as lymphoma and anaplastic astrocytoma on histopathology. However we found a diagnostic accuracy of 88.89%. Significant association between MR spectroscopy findings and histopathological findings with p=0.000076 (p<0.05 being significant). Our study was similar to study done by Magalhaes A, Godfrey W et al[63] and Mauricio Castilloa et al.[16]

We had got one postoperative patient of GBM, who had come for follow up after 7 months. She was in her 6^{l} decade. On conventional MR sequences T1 and T2 shows an irregular mixed density heterogeneous mass lesion in right frontotemporal lobe with perilesional extensive edema and mass effect. The mass was seen extending and infiltrating the genu of corpus callosum and right internal capsule. On post contrast, heterogeneous post contrast enhancement with stellate shape non enhancing central area suggestive of possible necrosis was observed. T2 GRE showed linear gradient blooming. On MRSI showed increased choline peak, reduced NAA peaks, increased cho/creatine ratio of 4.5(±0.55), increased cho/NAA ratio of 2.5(±0.22) and reduced NAA/creatine peak at 0.9(±0.33) ratio in the perilesional white matter edema and in enhancing portion of the mass. Our findings were similar to study done by Taylor JS, Langston JW, Reddick WE, et al.[55]

Metastasis

We had two patients with metastasis. They were in 4th and 7th decade. Histopathology was not done in one. On conventional MR, heterogeneous to hypointense on T1 and heterogenously hyperintense on T2, with perilesional edema. The lesions were illdefined, and showed intense ring enhancement on post contrast SPGR. One of the lesions showed blooming on GRE.

On MRSI, Strong Cho peak at long TE without elevation in surrounding peritumoral edema. Reduced NAA and creatine. Increased lipid/lac peak in one of the tumors. There was increased cho/creatine ratio of 6.5(±0.55), increased cho/NAA ratio of 3.5(±0.22) and reduced NAA/creatine peak at 0.8(±0.33). cho/creatine ratio was not elevated in peritumoral edema.

We got diagnostic accuracy of 100% and significant association between MR Spectroscopy findings and Histopathological findings for Metastasis with p=0.0370 (p<0.05), which are similar to the study done by Law M, Cha S, Knopp EA, et al.[24].

6. Conclusion

Accurate grading of gliomas on the basis of MRS alone may be difficult. Combining MRS with conventional and other advanced MR imaging techniques, grading becomes more precise.

Some features of tumors on conventional MRI (e.g. contrast enhancement, surrounding edema, signal heterogeneity, necrosis, hemorrhage and midline crossing) suggest a high grade. MRS is complementary and helpful for glioma grading. High grade gliomas demonstrate marked elevation of Cho, decreased NAA and presence of Lac and Lip. Myo

is high in low grade gliomas and decreases with increasing grades of tumors.

From our study we can conclude that in vivo MR spectroscopy can be used as a reliable method for glioma grading. It is useful in discrimination between WHO grade II and grade HI, IV astrocytomas as well as other intraaxial brain tumors such as gliomatosis cerebri, ependymoma, medulloblastoma, oligodendroglioma, lymphoma, metastasis and choroid plexus papilloma. Our study also demonstrates that spectroscopic MR measurements in the peritumoral region can be used to demonstrate differences in solitary metastases and high-grade gliomas and also peritumoral infiltrative nature of certain intraaxial brain tumor.

7. Summary

Analysis of spectra of 30 patients with intraaxial brain tumors was done; 11 with GBM, 2 with anaplastic astrocytoma, 3 with diffuse infiltrative astrocytoma, 2 with oligodendroglioma, 2 with gliomatosis cerebri, 2 with ependymoma, 2 with medulloblastoma, 1 with metastasis, 1 with choroid plexus papilloma and 1 with lymphoma. Three other tumors were not histopathologically correlated.

MRS of gliomas shows decreased contents of NAA since neurons are superseded by the neoplasm cells. For the same reason, a decreased level of Cr is observed. Furthermore, astrocytomas show high Cho contents. Some tumours show Lac and Lip signals, which are markers of anaerobic metabolism and necrosis. High Lac-Lip concentration helps to distinguish high and low grade gliomas. Glioblastomas have a higher Lac-Lip concentration than anaplastic astrocytomas. Absence of the Lac-Lip signal does not exclude the diagnosis of high grade glioma. In our study peak Lac-Lip was present in all instances of glioblastoma. Cho contents measured with the Cho/Cr ratio increase with the grade of astrocytoma. The decrease of Cho/Cr ratio in some glioblastoma is explained by the presence of necrosis in these tumours. Our study did not show a statistically significant difference in Cho/Cr ratio, Cho/NAA ratio, there by misclassifying and down grading in 3 cases of astrocytoma out of 21 cases of glioma. This is chiefly due to difficulties in placing the voxel in the representative part of the neoplasm. No significant difference in Naa/Cr ratio was observed in different types of gliomas.

Another potentially useful metabolite is ml. A study on in vitroMRS showed that ml concentration was the only factor discriminating astrocytomas of different grades. It was suggested that ml/Cr level is the highest in WHO grade II astrocytomas, whereas the level observed in anaplastic astrocytoma was greater than the one found in glioblastoma.

Despite certain discrepancies, MRS can distinguish astrocytomas of grade II from grade Ill/and IV with the diagnostic accuracy of 96.3%.

The MRS spectrum of oligodendrogliomas is very similar to that found in astrocytomas: high Cho signal, decreased Naa and Cr with present Lac-Lip and ml. In both oligodendroglioma (WHO grade III), there was high Lac-Lip signal. Hence, the assessment of concentration of these metabolites may be of assistance in distinguishing oligodendrogliomas from anaplastic oligodendrogliomas.

Other intraaxial brain tumors namely Gliomatosis cerebri, lymphoma, ependymoma and medulloblastoma showed elevated Cho/Cr and Cho/NAA ratios as well as decreased NAA/Cr ratios of varying degrees within the areas of hyperintensity on T2-weighted images and in enhancing part of the tumor. In CPP, similar findings were found except for increased Lac peak.

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