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QUANTITATIVE ANALYSIS OF MAGNETIC RESONANCE SPECTROSCOPY TO DIFFERENTIATE HIGH GRADE GLIOMA FROM SINGLE METASTATIC BRAIN TUMOR

Radiology

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ABSTRACT

Introduction: HGG and intracranial metastases are both intra-cerebral malignant tumours. These two types of tumours differ in their neoplastic processes, therapies, and prognosis, which may have an impact on the clinical result. MRS enables noninvasive supervision of metabolites within the target tissue and has the potential to reveal information about the make-up of a lesion and its response to treatment. **Aim and Objectives:** To assess the diagnostic performance of MRS to differentiate HGG from solitary brain MTs. **Materials and Methods:** A prospective cross-sectional study was conducted to differentiate between HGG and single MT using MRS and to assess the accuracy of MRS in differentiating these two pathologies. The tests were conducted utilising an eight-channel receiver head coil and a 1.5T MRI machine. **Results and Conclusion:** In the present study, Diagnostic efficacy of MRS was reported as 97.5%. In this study, 1H-MRS with the additional knowledge from the brain SPECT offered an appropriate pre-surgical diagnosis, answering an important diagnostic conundrum.

KEYWORDS

Magnetic Resonance Spectroscopy, High Grade Glioma, Metastatic Brain Tumor, Peritumoral.

INTRODUCTION

Adults most frequently experience initial HGG and intracranial metastases, which are both intra-cerebral malignant tumours. These two types of tumours differ in their neoplastic processes, therapies, and prognosis, which may have an impact on the clinical result.1,2 Among the HGG (HGGs), a wide range of glial tumours, including WHO grade III and grade IV, are included in Classification of Tumors of the CNS.3

Although the categorization is molecular factors based, it was not utilised in common investigation. Also, 23% of cancer subjects have brain metastases (BMs). Lung, breast, melanoma, and gastrointestinal cancers are the primary tumours that metastasis to the brain most frequently.4 It is simple to distinguish between primary high-grade glioma and intracranial metastatic disease, which frequently develops in individuals with several cause and known cancerous pathology in organs other than CNS.5 Due to the neuroimaging appearance of these two forms of intracerebral lesions being frequently similar, ambiguous, or indistinguishable, standard MRI has low efficacious in differentiating them.6

The technology known as MRS (MRS) enables noninvasive supervision of metabolites within the target tissue and has the potential to reveal information about the make-up of a lesion and its response to treatment.7,8 Ch, Cr, NAA, lactate, myo-inositol, glutamine are the main brain metabolites found.9,10 In comparison to normal tissue, brain lesions exhibit aberrant levels of these metabolites.

The biggest advantage of adding MRS to a clinical evaluation may be including diagnosis with noticeably distinct spectroscopic patterns since malignancies often demonstrate higher Cho and decreased NAA. On the other hand, it may be challenging to distinguish between tumours and acute demyelinating lesions based solely on MRS 2 because both entities commonly exhibit raised Cho and decreased NAA, in addition to frequently increased lactate.11

Widely accessible 1HMRS, which distinguishes between the biochemical traits of initial HGG and cancerous BT, has emerged as a clinical diagnostic technique and holds promise for presurgical screening.12 For instance, significantly high peaks of CHO containing substances have been found in gliomas; lipid peak occurrence is linked to necrosis.12,13

The effectiveness of 1HMRS in separating HGG from MBT, however, is still debatable and being researched.14 With these in consideration, this study was conducted to differentiate between HGG and single MT using MRS and to assess the accuracy of MRS in differentiating these two pathologies.

METHODS

A prospective cross sectional study was conducted on forty cases undergoing MRI brain with clinically suspected metastasis or gliomas to differentiate between HGG and single MT using MRS and to assess the accuracy of MRS in differentiating these two pathologies in the department of Radiology. Ethical committee approval was obtained for this study. The study was discussed to each participant individually, and participants also had the option to decline taking part in the study. The lead investigator used a pre-structured proforma to evaluate all the cases for the demographics and clinical presentation after obtaining written informed consent. MRS was performed after MRI in all cases.

The tests were conducted utilising an eight-channel receiver head coil and a 1.5T MRI machine. T2-weighted turbo spin echo axial sequence (TSE), T1-weighted IR, FLAIR, DWI, and T1-weighted SE after medium injection comprised the MRI protocol. Following contrast injection on a VOI location on three reference images utilising PRESS, multivoxel two-dimensional (2D) 1HMRS was carried out for MRS imaging. We used chemical-shift selective water suppression with high-order shimming. To guarantee acceptable quality of the spectroscopic data, the VOI was chosen from within tumour, the peritumoral edoema, and opposite normal white matter as a control. In order to minimise significant interference from the skull's subcutaneous fat and lipids, the VOI was carefully positioned, and saturation slabs were applied in certain regions to bring down the possibility of artefacts.

The spectra were automatically examined for the relative signal intensities of the metabolites NAA, Cho, etc. Using the software package provided by the manufacturer, post processing steps were performed. The window for all spectrum analyses was 0.50 to 4.30 ppm. A single voxel that was collected in the tumour core and peritumoral area was used to quantify the metabolites. All the reports from both cases and controls were entered in the same proforma where clinical presentation was entered by the principal investigator. Excel was used to enter the data, and SPSS was used to analyse it (Version 16). For quantitative data were generated and presented in tables. Sn, Sp, PPV, and NPV were determined to test the hypothesis. Additionally, the Mann Whitney U test and the chi square test were carried out correctly. Statistics were judged significant at p 0.05.

RESULTS

In the present study, 40 cases were included. Among them majority (55%) of cases belongs to age group 41-60 years of age followed by 30% of cases in 21-40 years of age, 12.5% of cases in more than 60 years of age and 2.5% of cases in less than or equal to 20 years of age.(Table 1) Among the study participants, 70% were males and the

rest 30% were females in this study.(Table 2) On assessing the presenting complaints of the study participants, 92.5% of cases had headache, 42.5% of cases had seizures, 32.5% of cases gave history of loss of consciousness and 17.5% of cases had altered sensorium. In the present study, meningeal signs were present in 30% of cases and the rest 70% of cases did not show any meningeal signs.

In MRI T1 weighted imaging showed low, iso and high signals in 55%, 30% and 15% of cases, respectively. Similarly in MRI T2 weighted imaging showed low and high signals in 52.5% and 47.5% of cases, respectively. On assessing the proportion of cases with respect to enhancement pattern in MRI, spotty pattern was noted in 27.5% of cases, heterogenous enhancement pattern was noted in 57.5% of cases and Homogenous pattern was noted in 2.5% of cases. MRI showed edema of grades 1+ in 40% of cases, grade of 2+ in 32.5% of cases and grades of 3+ in 17.5% of cases. Also 10% of cases in the present study had no edema.

MRI diffusion weighted imaging showed low, iso and high signals in 25%, 17.5% and 57.5% of cases, in this study. Contrast enhancement was noted as minimal, moderate and intense in 7.5%, 25% and 67.5% of cases, in this study. On assessing the location of tumor, indigenous frontal, temporal, parietal and occipital lobe involvement was noted in 12.5%, 10%, 10% and 2.5% of cases, respectively. However, fronto temporal, Temporo parietal, Temporo occipital and Parieto occipital involvement was noted in 15%, 22.5%, 15% and 10% of cases, respectively. Also cerebeller involvement was noted in 2.5% of cases.

On assessing the types of tumors, mixed neuronal glial tumors were noted in 5% of cases, ependymal tumors in 7.5% of cases, oligodenroglial tumors in 15% of cases, oligoastrocytic tumors in 27.5% of cases and astrocytic tumors in 45% of cases. In the present study, there were 12.5% of cases with LGG, 80% of cases with HGG and 20% of cases with metastatic lesions.

On assessing the metabolite ratios, in the intratumoral and contralateral area, NAA/Cr was found to be in similar levels in both HGG cases and solitary metastatic lesion cases. However, in pertumoral area cases with solitary metastatic lesion was found to show significantly elevated levels of NAA/Cr.

On assessing the metabolite ratios, in intratumoral and contralateral area, Cho/Cr was found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion. However, in pertumoral area, cases with HGG were found to show significantly elevated levels of Cho/Cr.

On assessing the metabolite ratios, in intratumoral and contralateral area, Cho/NAA was found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion. However, in pertumoral area, cases with HGG were found to show significantly elevated levels of Cho/NAA.

On assessing the metabolite ratios, in the intratumoral, pertuimoral and contralateral area, Lip+Lac were found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion without any statistical significant difference.

On assessing the metabolite ratios, in the intratumoral, pertuimoral and contralateral area, ADC levels were found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion without any statistical significant difference. On assessing the metabolite ratios, in the intratumoral, pertuimoral and contralateral area, fractional anisotropy (FA) were found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion without any statistical significant difference.

On assessing the metabolite ratios, in the intratumoral and contralateral area, rCBV was found to be in similar levels in both cases with HGG and cases with solitary metastatic lesion. However, in pertumoral area, cases with HGG were found to show significantly elevated levels of rCBV.

On comparing the MRS with the actual diagnosis, 32 cases with HGG were correctly picked by MRS and 7 cases with other pathology (LGG and metastatic lesion) were correctly picked by MRS however one case without HGG was predicted to have HGG by MRS (false positive).(Table 3)

Diagnostic efficacy of MRS was reported as 97.5% in this study with Sn of 100%, Sp of 87.5%, PPV of 96.9% and NPV of 100%, in this study.(Table 4)

DISCUSSION

In the present study, 40 cases were included. Among them majority (55%) of cases belongs to age group 41-60 years of age followed by 30% of cases in 21-40 years of age, 12.5% of cases in more than 60 years of age and 2.5% of cases in less than or equal to 20 years of age. Among the study participants, 70% were males and the rest 30% were females in this study.

On assessing the presenting complaints of the study participants, 92.5% of cases had headache, 42.5% of cases had seizures, 32.5% of cases gave history of loss of consciousness and 17.5% of cases had altered sensorium. In the present study, meningeal signs were present in 30% of cases and the rest 70% of cases did not show any meningeal signs. In MRI T1 weighted imaging showed low, iso and high signals in 55%, 30% and 15% of cases, respectively. Similarly in MRI T2 weighted imaging showed low and high signals in 52.5% and 47.5% of cases, respectively.

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Findings of the present study were comparable with the findings of the following studies. Opstad KS et al.15 claimed that there were substantial variation between the LPA ratios of glioblastomas and metastases. Also in another study, Hollingworth W et al.16 stated that one notable study showed that examination of 1H-MRS increased the DA for ambiguous brain lesions from 55 percent, based on MR imaging, to 71 percent. ZENG QS et al.17 reported that recurrent tumours had much greater in metabolite ratios than radiation-damaged areas. However, Cho/NAA, Cho/Cr, and ADC ratio were discovered by discriminant analysis of MRS combined with diffusion-weighted imaging, and 96.4 percent of all participants were correctly classified. The two discriminant analyses' diagnostic accuracy differed significantly from one another. Oshiro S et al.18 stated that HGG tended to show larger rCBV and signal hyperintensity in DWI and PWI, respectively. Increased Cho to NAA and Cho to Cr ratios have a strong correlation with tumour malignancy. Zeng QS et al.19 stated that in 92.9 percent of the cases, they said, measurable Cho, Cr, and NAA peaks on 1H-MRS could be achieved. They came to the conclusion that in patients with recurring contrast-enhancing lesions close to previously treated gliomas, 1H-MRS could distinguish recurrent tumour from radiation damage. However, Juan M et al.20 in their multi centric study reported that for the majority of the pair wise discrimination issues, MRS accuracies of about 90% were attained. The glioblastoma vs BM discrimination, which was below 78 percent, was the exception. In another study, Josefsen R et al.21 reported that MRS can distinguish between HGG and metastases, particularly with peritumoral measures, which supports the idea that MRS can identify tumour cell infiltration in the peritumoral edoema. Caivano R et al.22 performed a study to discuss the usefulness of MRS in distinguishing between primary HGG and LGG brain metastases. The findings of this study show that MRS can distinguish between LGG, HGG, and BM even in cases those who cannot undergo biopsy.

However, Rehman L et al.23 reported that the 50 patients who were a part of their study and reported headache was the most frequent presenting ailment (76%) followed by weakness (62%) and seizures (30 percent). 51 percent of the lesions were deemed to be neoplastic by MRI.

Also, Verma A et al.24 stated that MRS is a crucial tool for the assessment and routine monitoring of brain malignancies. In another study, Caravan L et al.25 claimed that the intratumoral areas of HGGs had mean ADC min values that were noticeably greater than those of BMs. Regarding ADC mean values, no variations between groups were found. Similarly, Wang Q et al.26 performed a study to evaluate the diagnostic accuracy of MRS in distinguishing brain metastases from HGG. They came to the conclusion that MRS had a fair diagnostic performance in separating HGG from metastases.

Furthermore, in the PTR, Cho/NAA ratio outperformed Cho/Cr ratio in terms of Sp and area under the curve.

However, Travers S et al.27 reported that in their study MRS Sn was reported to be 100%, Sp to be 50%, and accuracy to be 81.8%, while PET CT Sn was reported to be 36.4%, Sp to be 66.7%, and accuracy to be 42.9%. They came to the conclusion that MRS is more effective in separating radiation necrosis from recurrent tumour because it is more accurate than PET CT and has a higher NPV.

When compared to those calculated using 2D 1H MRS as published in the literature, the metabolites ratios of the tumour region obtained using 3D 1HMRS in the current investigation were not substantially different. Furthermore, 3D 1H MRS demonstrated substantial changes in the metabolites ratios between the LGG and HGG groups, which was consistent with many other research.28` However, another study found no discernible difference among LGG and HGG.

Another study examined the relationship between the proton MR spectroscopy-measured choline level and the potential glioma proliferation marker Ki-67 labelling index. In gliomas, a significant linear association between Cho value and Ki-67 index was discovered. This finding suggests that a higher level in Cho metabolite indicates an increase in cell turnover, which is consistent with the most cancerous parts of the tumour. Based on our findings, the metabolite ratios, particularly the Cho/Cr ratios, should be a reliable indicator of the glioma grade.

List of Tables and Figures

Table 1: Proportion of cases in different age groups

Age group	Frequency	Percentage
≤ 20 years	01	2.5
21-40 years	12	30
41-60 years	22	55
> 60 years	05	12.5
Total	40	100

Table 2: Proportion of cases with respect to gender

Gender	Frequency	Percentage
Male	28	70
Female	12	30
Total	40	100

Table 3: MRS findings versus Actual diagnosis

MRS	Diagnosis		Total
	HGG	Others	
HGG	32	01	33
Others	00	07	07
Total	32	08	40

Table 4: Diagnostic efficacy of MRS

Parameters	Values
Sn	100%
SP	87.5%
PPV	96.9%
NPV	100%
DA	97.5%

Tissue metabolites identified by ^{1}H-MRS

Compound	Peak position, ppm	Change with malignancies (organ)
Creatine	+4.0, +3.1	↓ (brain)
Myo-inositol	+3.6	↑ (prostate)
Choline	+3.3	↑ (brain)
Citrate	+ 2.6	↓ (prostate)
Glutamine, glutamate	+2.3	↑ (brain)
N-acetyl-aspartate	+2.0	↓ (brain)
Lactate	+1.2	↑ (brain)
Lipids	+1.0	↑ (brain)

Tissue metabolites identified by ^{31}P-MRS

Compound	Peak position, ppm	Change with malignancies (organ)
Phosphomonoesters	+8.0	↑ (bone and soft tissue)
Inorganic phosphate	+5.0	↑ (brain, mammary gland)
Phosphodiesters	+3.0	↓ (brain, mammary gland)
Phosphocreatine	0.0	↓ (brain)
γ-ATP	−3.0	↕ (brain)
α--ATP	−8.0	↕ (brain)
β-ATP	−17.0	↕ (brain)

Figure 1: Tissue metabolites levels in different brain pathologies

Major metabolites of MR spectroscopy and their significance.

Metabolites	Location on spectrum (ppm)	Significance
NAA	2.02	Neuronal integrity
Cho	3.2	Linked to cell membrane turnover
Cr	3.03 / 3.9	Energy storage / stable in metabolic disease
Lipids	0.9 - 1.5	Nectrotic tumor / acute inflammation / not seen in normal brain
Lact	1.32	Not seen in normal brain. Anaerobic metabolism mitochondrial disease, ischemia, inflammation and tumors
mI	3.56	Glial marker, dementia, HIV encephalopathy, high in infant

Figure 2: Major metabolites and its significance

Figure 3: MRS – Diagnostic algorithm of Brain lesions

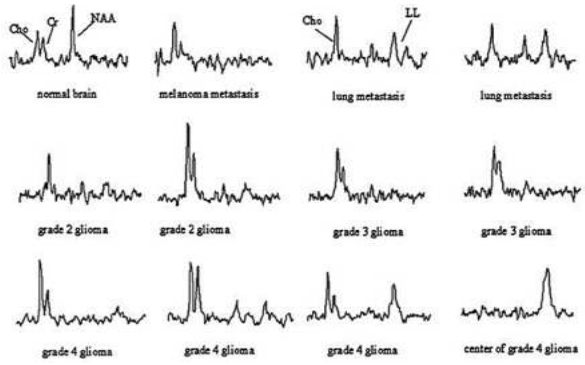

Figure 4: MRS Spectra - Normal brain, brain mets, necrosis, and grades of gliomas

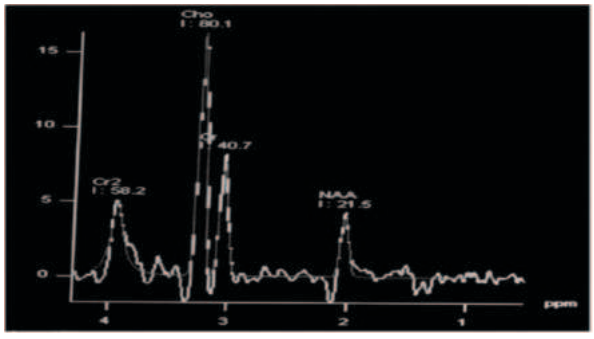

Figure 5: MRS shows elevated ch, decreased NAA and an inverted lactate peak indicates anaerobic metabolism. MRS corresponds to oligodendroglial tumor

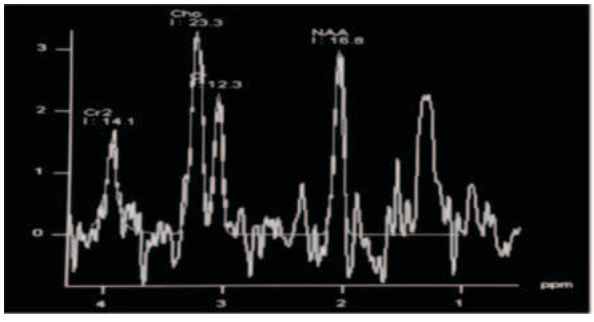

Figure 6: MRS spectra diagnosed as glioma

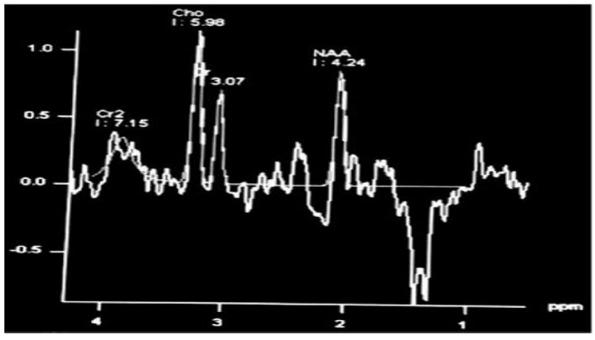

Figure 7: MRS spectra in a suspected metastasis

Figure 8

CONCLUSION

In the present study, Diagnostic efficacy of MRS was reported as 97.5% in this study with Sn of 100%, Sp of 87.5%, PPV of 96.9% and NPV of 100%, in this study. On assessing the metabolite ratios, in pertumoral area cases with solitary metastatic lesion was found to show significantly elevated levels of NAA/Cr compared to HGG cases. However, in the same area, cases with HGG were found to show significantly elevated levels of Cho/Cr and Cho/NAA compared to solitary lesions. Similarly, cases with HGG were found to show significantly elevated levels of rCBV in the peritumoral area compared to cases with solitary lesions. It appears that a multi-modality approach to brain tumour diagnosis would be extremely beneficial for both patients and the doctors engaged in the patient's treatment strategy.

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