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Evaluation of the imaging aspects of brain tumors by Magnetic Resonance Spectroscopy

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ABSTRACT

Background: Magnetic resonance spectroscopy (MRS) is an established tool for in-vivo evaluation of the biochemical basis of human diseases. Magnetic resonance spectroscopy (MRS) provides a means to assess functional (metabolic activity) of the brain. On one hand, such lucid depiction of 'live biochemistry' helps one to decipher the true nature of the pathology while on the other hand one can track the response to therapy at sub-cellular level. Brain tumors have been an area of continuous interrogation and instigation for mankind. Our aim was to do valuation of these lesions by MRS. **Methods:** This study was conducted in a tertiary care hospital in which all patients underwent magnetic resonance imaging (MRI) at the same setting as the MRS examination. The MRS examination was performed with the stimulated echo acquisition mode (STEAM) pulse sequence in all children, and occasionally the point resolved spectroscopy (PRESS) sequence also was used. Qualitative spectra were obtained in all patients, and at times quantification data also were obtained. **Results:** We found that our spectra over the brain neoplasms were consistent with the MRS findings of brain neoplasms in the literature. There was markedly elevated choline with markedly decreased or absent N-acetylasparate and at times elevated lactate and lipid peaks. In children with meningiomas, there was also an elevated alanine peak. We found MRS to be extremely useful in 1) characterizing a brain mass as a neoplasm, 2) differentiating radiation necrosis and radiation-induced meningiomas from the recurrent primary tumor, 3) following treatment response of the primary neoplasm, 4) differentiating residual or recurrent primary neoplasm from postsurgical changes, and 5) identifying inactive neoplasms or neoplasms in remission. **Conclusion:** By having a basic understanding of the automated MRS in the normal brain for the different pulse sequences (STEAM and PRESS), it is possible to understand the abnormal MRS spectra seen in brain neoplasms.

Keywords: Magnetic Resonance Spectroscopy, Brain Neoplasm, Imaging.

INTRODUCTION

As per World Health Organization data, brain tumor is classified into four different grades based on several different factors such as histologic feature, immunolabeling, genetic profiles or the severity of penetration.[1] Even though the tumor types, tumor grades and the volume are difficult to evaluate, according to a report published in 2007, grade-1 tumors are considered as low in penetration and non-aggressive while, grade-4 tumors demonstrate high penetration rate.[2] When it comes to the clinical management of brain tumor patients, modern diagnostic neuroimaging takes a critical place. Neuroimaging is non-invasive andoffers unique opportunities to study and diagnose different profiles of patients with intracranial brain tumors such as metabolic features, hemodynamic features, and genetic information.[3] From decades, pre-operative evaluation of brain tumors or intraoperative navigation of surgical methods utilizing these imaging tools for a better understanding of the post operative effect on patients brain. Moreover, the overall purpose of the diagnostic imaging of patients with suspected intracranial tumors includes but not limited to detection of the presence of neoplasm, localization and characterization of the extent of the tumor. The role of the radiologist (neuroradiologist) is to aid in the initial diagnosis and follow-up of these children with a brain tumor. This is accomplished by performing imaging studies, the most accurate of which is magnetic resonance imaging (MRI) of the central nervous system (brain and spinal cord) in these children. Although MRI is an excellent modality, it only provides structural information such as the location of the tumor in the brain, local or metastatic spread via CSF, and compression of central nervous system structures with resultant hydrocephalus or spinal canal block.[4] Magnetic resonance imaging does not provide any information on brain or tumor functioning (metabolic activity). Metabolic activity of the brain

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or the activity of brain lesions has traditionally been provided by the nuclear medicine modality of positron emission tomography (PET), or the newer functional imaging modalities of MRI perfusion/diffusion studies or magnetic resonance spectroscopy (MRS).[5] Position emission tomography scanners and MRI perfusion and diffusion hardware/software are expensive pieces of equipment. However, a few MR manufacturers have developed inexpensive means to perform clinical spectroscopy on existing clinical MR scanners. One of these clinical spectroscopy packages, called the Proton Brain Exam/Single Voxel (PROBE/SV), recently received approval by the Food and Drug Administration (FDA) for clinical use in medical practice.MRI technology, initially described by Felix Bloch and Edward Mills Purcell provides one of the best platforms to capture high contrast-high resolution diagnostic images.[6,7] However, the sensitivity and specificity modalities by which it defines the tumor types and grades have their own limitations. In an attempt to overcome these issues, ongoing investigations on brain tumor imaging invest on clinically proven advanced neuroimaging techniques that can develop, validate and extend the existing imaging technologies. The ongoing investigations also focus on methodologies that highlight the functional and metabolic properties of the tumor.[8] While MRI technology is very appropriate for identifying the correct anatomical position/location of a tumor, in contrary MRS provides a comparative outline of the chemical composition between a normal brains to that tumor compromised brain tissues.[9] Also, unlike MRI where magnetic field and radio waves are used to generate high-resolution images, MRS utilizes a series of consecutive tests that are eventually detected by MRI to determine the chemical composition and/or chemical metabolism of a tumor tissue. Irrespective of these subtle differences between these two technologies, both MRS and MRI are conducted on the same machine and are governed by the same principle of magnetism. Over the past year, we have used the clinical spectroscopy package PROBE that was developed by General Electric Medical Systems (Milwaukee, Wisconsin) for use with our existing General Electric MR Scanner, the Signa 1.5-T, in a variety of abnormalities affecting the pediatric brain. We have found MRS to be an excellent modality because it provides chemical (and therefore functional information) about the tissue under investigation.[10] Here we will outline the variations in brain neoplasm, nature and different stages of brain tumor and tumor grading by emphasizing MRS technology.

MATERIALS AND METHODS

This study is based on the data obtained from 50 patients with brain tumors and long history of headache and vomiting. Parietal and frontal lobe masses were presented with tingling and paresis of opposite extremity. Posterior fossa tumors were presented with cerebellar impairment like head reeling and ataxia. Acoustic Schwannoma in these patients were diagnosed with hearing loss. With few patients, seizure was also observed. The brain tumor was diagnosed with long-echo multi voxel H-MRS in the department of radio diagnosis and modern imaging facility at a tertiary care hospital. The metabolic data of remaining 50 patients were considered and analyzed in this study. Out of 50 patients, 30 cases of glioma, 7 cases of meningioma, 5 cases of Schwannoma, 3 cases of medulloblastoma, 2 cases of metastases and 3 post operation cases exhibited residual tumor. Spectroscopy Before conducting the spectroscopic examination, consent from each patient was obtained. This study utilized 15 Tesla MRI clinical manager (General electronics, Signa Excite). Multi-voxel spectrescopic examinations were guided by T-weighted or T2 weighted images. Postgadolinium TI weighted MRI was also used as and when needed in this study. MRS Setup Under three-dimensional, control the rectangular HMRS voxel was placed on the projection of the solid part of the tumor, avoiding it's cystic and necrotic areas. Eight Cc voxel size was used in this study. Possible contamination with the subcutaneous fat, skull and cerebra 1ventricles was avoided as much as possible. Spatial suppression pulses were applied to the outsides of the voxel to reduce spectral contamination, and global and localized shimming on the water proton and optimization of the water suppression was done. Volume- selected water suppressed long-echo (TR: 400ms, TE: 144 ms, 128-256 acquisitions) spectra were acquired. In each case the reference spectrum with identical size of the voxel was obtained from the normal appearing white matter of the cerebral hemisphere. Metabolic profile Centered at 0.9 and 1.5, metabolite signals from mobile lipids (Lip), lactate (Lac), N- acetylaspartate (NAA), creatine (Cr}, and choline-containing compounds (Cho) were obtained with values of 1.3 ppm, 2.02 ppm, 3.03 ppm, and 3.2 ppm respectively. Not all metabolites could be identified in eachMetabolic profile Centered at 0.9 and 1.5, metabolite signals from mobile lipids (Lip), lactate (Lac), N- acetylaspartate (NAA), creatine (Cr}, and choline-containing compounds (Cho) were obtained with values of 1.3 ppm, 2.02 ppm, 3.03 ppm, and 3.2 ppm respectively. Not all metabolites could be identified in eachindividual case. Differentiation of Lip and Lac peaks with same position, was based on the assumption of their different directions on H-MRS with TE 136 ms. Therefore, any upward directed peak located at 1.3 ppm was considered as predominantly Lip, whereas any downward directed one was defined as Lac. Presence of each metabolite peak was initially evaluated qualitatively by visual

inspection, and type of the pathological H-MR spectra was determined according to the table provided (table-1). Additionally, the peak intensities of NAA, Cho, and Cr in tumors were obtained. Intensity of NAA, Cho, and lip was normalized to Cr of the normal brain (nCr), and the ratios of NAA/Cho, NAA/Cr, Cho/Cr, Cho/NAA, and Cr/NAA were also calculated. This study included 30 males and 20 females with an age range between 5 months and 80 years. The median age was 45 years. Majority of patients were in the age group of 40 to 50 years old.

Table 1: Peak Metabolite Profile

Type of pathological 1HMRS spectra	Predominant metabolite peak	Presence of lac peak	Presence of lipid peak
Type IA	NAA	No	No
Type IB	NAA	Yes	No
Type IC	NAA	Not relevant	Yes
Type IIA	Cho	No	No
Type IIB Cho Yes No	Cho Yes No	Yes	No
Type IIC Cho Not relevant Yes	Cho	Not relevant	Yes
Type IIIA	Lipid(cho preserve)	Not relevant	Yes
Type IIIB	Lipid(cho reduce)	Not relevant	Yes
Type IIIC	Absence of any	detectable metabolite	peak

RESULTS

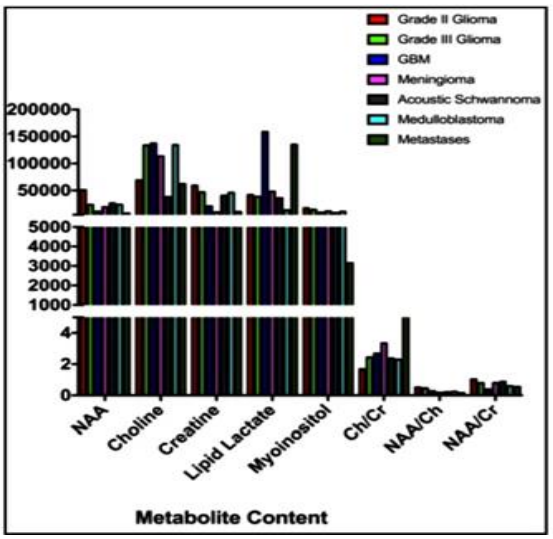

Figure 1: Graph showing different metabolite content in different categories of brain tumor patients.

Out of 50 patients, 30 patients were diagnosed with glioma. Again, out of 30 glioma patients, we found 10 patients each of glioma grade II, glioma grade III and Glioblastoma Multiforme (GBM) category. While grade II and grade III gliomas are typically characterized by elevated choline, low lactate, low lipid and a trace amount of NAA and creatine; the myoinositol levels are normally lower in grade III gliomas than grade II gliomas . On contrary, GBM are typically characterized with high level of choline, lipid, lactate and a trace amount of NAA . Similar to grade III glioma, GBM cases are detected with lower level of myoinositol [Figure 1].

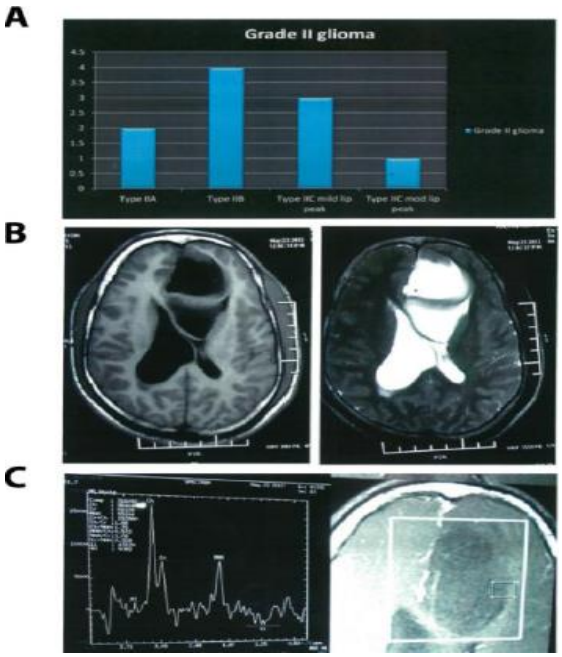

Figure 2: (A) Graph showing Spectra profile for the four different types of Spectra in all grade-II glioma patients (n=10). (B) T1 and T2-weighted MRS in 10 different grade II glioma cases. (C) Case representation of MRS (Ch/Cr and NAA) in grade-II glioma patients.

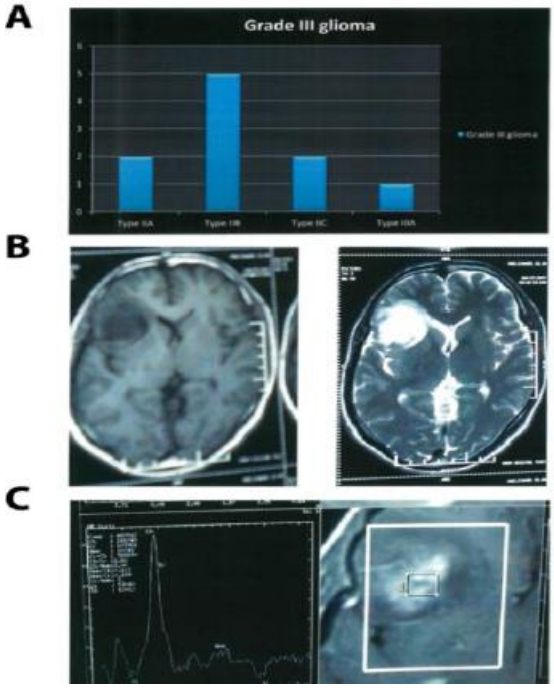

Figure 3: (A) Graph showing Spectra profile for the four different types of Spectra in all grade-III glioma patients (n=10). (B) T1 and T2-weightedMRS in 10 different grade III glioma cases. (C) Case representation of MRS (Ch/Cr and NAA) in grade-III glioma patients.

In our study, out of 10 cases of grade II gliomas, 2 cases were ependymoma, 2 cases were CPP, 2 cases were pilocytic astrocytoma, 2 cases showed type IIA spectra, 4 cases showed type IIB spectra, 3 cases showed type IIc spectra with mild elevation of lipid peak. One case showed type IIC spectra with moderate elevation of lipid peak [Figure 2]. Sometime it gets hard to differentiate a true MRS response to that of false positive or non-response MRS as the enhancement in the signal may be of subtle difference that is hard to distinguish. To overcome this issue, usage of T1 subtraction map is pretty standard in the field. Application of T1 maps reduces the variability in the data and also helps identifying the progression in real time.

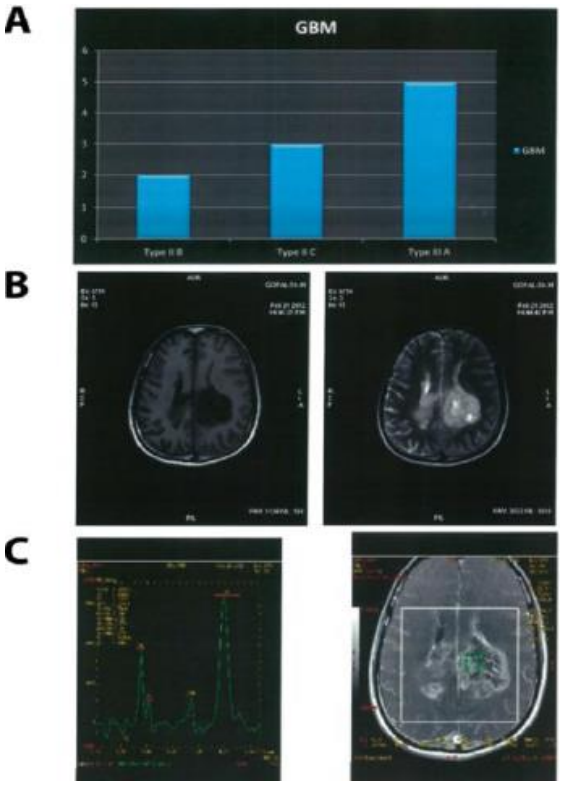

Figure 4: (A) Graph showing Spectra profile for the three different types of Spectra in all GBM patients (n=10). (B) T1 and T2-weighted MRS in 10 different GBM cases. (C) Case representation of MRS (lactate and lipid) in GBM patients.

On the other hand, the source of signal abnormality could be anything from radiation effect to that of postoperative gliosis. A quantitative mapping (here it is called T2) engages analysis of individual voxels relaxation time by acquiring T2-weighed images in order to identify tumors and post-operative outcome more specifically . We have frequently used these two techniques while analyzing all our MRS results. In grade III glioma, 2 cases showed type IIA spectra, 5 cases showed type IIB spectra, 2 cases showed type IIC spectra and 1 case showed type IIIA spectra. Type IIIa spectra is another form of choroid plexus carcinoma [Figure 3]. We also observed lower NAA/Cr and NAA/Ch ratio in grade III glioma patients compared to grade II glioma patients (except 2 cases). In GBM, 2 cases showed type IIB spectra, 3 cases showed type IIC spectra and 5 case showed type IIIA spectra [Figure 4]. It is important to note as presented in Fig. 1 that GBM patients with type IIB and type IIC spectra had higher choline, higher ch/cr ratio, lower NAA/Ch and lower NAA/cr ratio as compared to grade II and grade III glioma patientsMRS (lactate and lipid) in GBM patients. In our study, out of 50 cases, 7 cases were of meningioma patients. As shown in Fig. 1, meningioma patients show high level of alanine peak, which could not be detected in our MRS spectra analysis. Meningioma patients were detected with elevated choline level up to 3 times more than a normal brain. We could not detect NAA peak and creatine peak as meningioma is extra axial. Consistent with the previous report, we observed elevated level of lactate and lipid peak in these patients and [Figure 1]. Out of 7 cases, 2 cases showed type IIA spectra, 1 case showed type IIB spectra and type IIIA spectra each, and remaining 3 cases showed type IIC spectra [Figure 5].

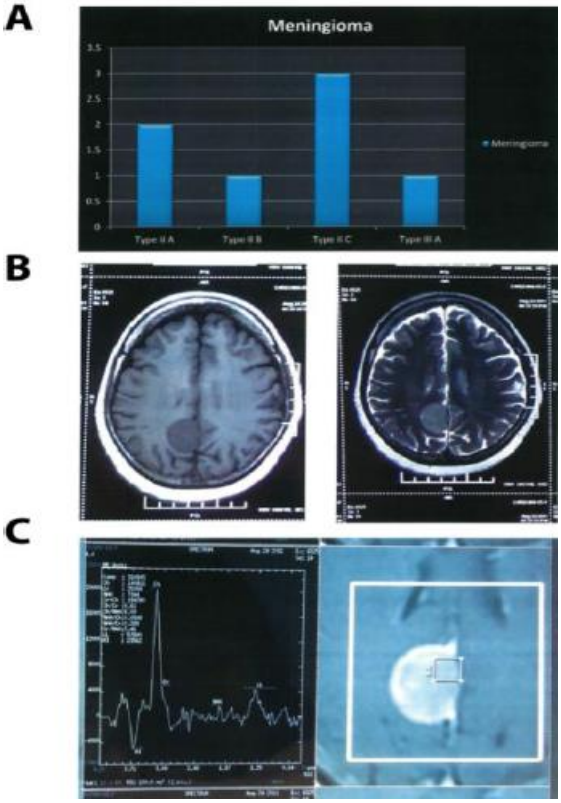

Figure 5: (A) Graph showing Spectra profile for the four different types of Spectra in meningioma patients (n=7). (B) T1 and T2-weighted MRS in 7different meningioma patients. (C) Case representation of MRS (Ch/Cr) in meningioma patients.

Like meningioma patients, we detected elevated level of choline and absence of creatine in patients

with Acoustic Schwannoma, which represented 10% of total case study (5 patients). Consistent with the previous report, these patients were detected with reduced level of NAA and increased level of lipids.

DISCUSSION

The ability of MRS technology to overcome these issues to some extent made it widely accepted in the field where survival prediction rate of different brain tumor patients became possible. MRS can easily predict survival rate both in adult and infant brain tumors. Recently a series of work has demonstrated this fact.[11] The ability of MRS to predict survival has been evaluated in both adult and pediatric brain tumor populations. To this end, a series of papers have recently been evaluated the role of 1 H MRSI in prediction of survival of GBM patients.[12] The non-invasive diagnosis plays a pivot role in brain tumor patients and it must be accurate as the overall therapeutic plan is mostly depends upon the histopathological grade of the tumor progression.[13] As shown in our study, proton MRS imaging technique definitely helps assisting the surgeons in collecting information on representative samples. MRS is very information in that sense, as surgeons can identify the active tumors easily. Moreoverhaving an overview on the aggressive tumor region prior to execute surgical resection helps in planning of targeted radiotherapy if that is something in the to-do list. In addition, MRS image based preinformation also helps in follow up studies of the same patient.[14,15] However, it is important to keep in mind that multimodality MRI (which includes MRSI) provides additional information that eventually helps in selecting the best and suitable treatment for the patients, as described by Crawford et al.[16] In future studies we are planning to include MRSI in all our clinical investigations. In the study 60% of cases were gliomas which are intra-axial tumors. All glioma patients were showing type II pathological spectra characterized by elevated level of choline, reduced NAA, reduced creatine or preserved creatine. ln this study difference between grade II glioma and grade Ill glioma MRS spectra was the preserved NAA and creatine level in former and reduction in the level in the later and higher myoinositol level in the former than the later.[17-19] GBM showed type Ill pathological spectra due to the presence of lipid lactate peak and significant reduction in NAA and creatine level,myoinositol level as well as more increase in choline level.[20,21] Around 14% cases were meningioma, which are extra axial lesions. In this study meningioma was showing type II pathological spectra. Differentiated from intra axial lesions by significant reduction or absence of NAA and creatine.[22] In addition, myoinositol was absent unlike intra axial lesions. Around 10% cases were schwannoma, an extra axial lesions with significant reduction or absence of NAA, creatine or myoinositol. It is note worthy that schwannoma can be easily differentiated from meningioma with its relatively low choline level and Presence of lipid peak in many cases.[23] All cases were showing type II C pathological spectra. Six percent cases were medulloblastoma and are intra axial lesions. In this study they were showing type II pathologic CII spectra and can be differentiated from gliomas with its marked elevated choline peaks without elevation of lipid lactate peak with marked decreased creatine peak.[24] Four percent cases were metastases and were showing type Ill A pathologic spectra. Like extraaxial lesions, metastases were showing very low NAA and creatine with elevated choline peak and predominant lipid and lactate peak.[25] Remaining 6% cases were post-operative cases showing elevated choline peak and decreased NAA peak, which suggests a possible residual tumor subtype.

CONCLUSION

As it was shown in the present series there is definite variation of the metabolic patterns in neoplasms with the same histological type, whereas more or less similar neurochemical alterations can be observed in completely different diseases. Introduction of the MR scanners with higher magnetic field strength (3Tesla and more) into clinical practice can improve diagnostic efficacy of both structural and spectroscopic neuroimaging and create new options for their combined use. Even though the application of MRS in diagnosis and evaluation of brain tumors is widely accepted by the community and very well documented, we acknowledge that this technique has not been used routinely as a clinical tool. Further work is required in order to collect and analyze data in more organized manner.

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