ORIGINAL ARTICLE

Magnetic Resonance Spectroscopy: Novel Non-invasive Technique for Diagnosing Brain Tumors

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Abstract

Objective: To determine the accuracy of MR Spectroscopy (MRS) in diagnosing brain tumors.
Study Design: Analytical study.
Place and Duration of Study: Neurosurgery Department, Jinnah Postgraduate Medical Centre, Karachi, from November 2010 to April 2011.
Methodology: Fifty cases with brain tumors, who presented to Neurosurgery Department of Jinnah Postgraduate Medical Centre, Karachi, during the study period, were included in the study. All patients underwent MRS and later brain. Those with recurrent disease were excluded. Data was collected with the help of proforma. Data was analyzed using SPSS version 16. Comparison of MRS findings and biopsy diagnosis was done. Sensitivity, specificity, negative and positive predictive values (NPV and PPV) were determined keeping histopathology as the gold standard.
Results: Out of the 50 patients, there were 20 (40%) females and 30 (60%) males with mean age of 37 ±13.24 years. The commonest presenting complaint was headache (76%) followed by weakness (62%) and seizures (30%). MRI had diagnosed 27 (51%) as neoplastic lesion. Spectroscopy reported 44 (88%) as neoplasms, while on histopathology, 42 (84%) were confirmed to have neoplasm. The accuracy of MRS was 94%, with 97.6% sensitivity, 71.42% specificity, 95.45% PPV and 83.3% NPV.
Conclusion: Magnetic resonance spectroscopy can readily help in differentiating neoplasm from non-neoplastic brain tumors, thus an invasive brain biopsy procedure can be avoided.

Key Words: *Magnetic resonance spectroscopy (MRS). Magnetic resonance imaging (MRI). Brain tumor.*

INTRODUCTION

The first assessment of a brain mass aims to determine whether the lesion is really a tumor or a pseudotumoral lesion.[1] An MR imaging (MRI) examination suggesting a pseudotumoral mass would indicate laboratory tests and/or follow-up. On the other hand, if a tumoral mass is suggested, stereotactic biopsy or surgical resection should be considered. Differentiation between tumors and non-neoplastic lesions using conventional MRI may be challenging. Examples of non-neoplastic lesions that may mimic brain tumors on conventional imaging are infectious (including abscess) or ischemic lesions, or demyelinating lesions.

MR spectroscopy (MRS) is a technique that allows non-invasive monitoring of metabolites within the tissue of interest, and has the potential for providing information about a lesion's composition and response to therapy.[2,3] The major brain metabolites detected are choline, creatine, N-acetyl aspartate (NAA), lactate, myo-inositol, glutamine, glutamate, lipids and the amino acids leucine and alanine.[4,5] Brain lesions show abnormal values of these metabolites as compared to normal tissue. Since tumors typically exhibit elevated Choline (Cho) and decreased N-acetyle acetate (NAA), the greatest benefit of adding MRS to a clinical examination may be including (or excluding) diagnoses with markedly different spectroscopic patterns, e.g. strokes or focal cortical dysplasias, neither of which are expected to have increased Cho. Conversely, differentiation between tumors and acute demyelinating lesions, based on MRS alone, may be difficult as both entities typically present with elevated Cho and decreased NAA, as well as often increased lactate, Table I.[6]

This study was conducted to ascertain the diagnostic superiority of MR spectroscopy not only to MRI but also to compare it with histopathological examination.

Table I: 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
ml	3.56	Glial marker, dementia, HIV encephalopathy, high in infant

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Received: April 25, 2013; Accepted: September 22, 2015.

METHODOLOGY

This analytical study was conducted in the Neurosurgery Department of Jinnah Postgraduate Medical Centre, Karachi, Pakistan, from November 2010 to April 2011. Patients with space-occupying brain lesions were included in the study. Patients having recurrent tumors and those who were not eligible for the surgery and biopsy, were excluded from the study.

Data was collected with the help of a proforma including name, gender, clinical findings of the MRI of the brain and of the MRS, operative findings and histopathological findings. Patients with brain tumors, whose MRI has already been done and were waiting for surgery, were advised MRS. For statistical analysis, SPSS version 16 was used to determine specificity, sensitivity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy using histopathology as the gold standard.

RESULTS

There were a total of 50 patients, 20 (40%) females and 30 (60%) males with mean age of 37 ±13.24 years. They presented with main complaints of headache in 38 (76%), weakness in 31 (62%) and seizures in 15 (30%). These patients presented with either right 13 (26%) or left 9 (18%) sided hemiplegia. Five (10%) patients had generalized weakness.

MRI of these patients reported tumors in 27 (54%) and Space Occupying Lesions (SOL) with differential diagnosis of tumor, infection either fungal or tuberculoma in 23 (46%) patients. These were either on the right side 25 (50%) or on the left side 22 (44%); while 3 (6%) lesions were in midline.

On spectroscopy, 44 (88%) patients were diagnosed as having tumor, 3 (6%) had infarction, 2 (4%) had infection and 1 (2%) had benign neoplasm. Out of them, 44 (88%) patients who were diagnosed as having neoplasm, Choline, NAA creatinine and lactate peaks were raised in 41 (93%), 1 (2%), 1 (2%) and 1 (2%) patients, respectively. Peaks of NAA, choline, creatinine and lactate were reduced in 42 (95%), 1 (2%), 4 (9%), 5 (11%) patients each. One (2%) patient had absent lactate peaks and 1 (2%) had normal choline peak. Spectroscopy reported infarction in 3 (6%) patients. Choline, NAA and creatinine peaks were reduced in 1 (33%), 3 (100%) and 1 (33%) patients. Choline peak was absent in 1 (33%) patient. Lactate peaks were raised in 2 (66%) patients. Infection was established in 2 (4%) patients by spectroscopy. One (50%) patient had decreased choline, NAA and creatinine peaks with raised lactate peak. While all the peaks were absent in 1 (50%) of the patient diagnosed with infection. Benign tumor was diagnosed in 1 (2%) patient with reduced peaks of choline and NAA.

On biopsy of the lesions, 42 (84%) patients were diagnosed as having neoplasm, 1 (2%) patient had haemorrhage, 4 (8%) were diagnosed with infection and 3 (6%) patient had infarctions. On sub-diagnosis of the neoplasm out of 42 (84%) patients, 15 (35%) had oligodandroglioma, 5 (11%) had meningioma and 4 (9%) had astrocytoma. Schwannoma and glioblastoma multiforme was diagnosed in 3 (7%) patients each. B-cell lymphoma and hemangioblastoma was diagnosed in 2 (4%) patients each. Metastasis, medulloblastoma, gliosarcoma, chraniopharangioma, chordoma was present in 1 (2%) each. Only one (2%) patient was found to have haemorrhage on biopsy. Infection was diagnosed in 4 (8%) patients. Two (50%) had fungal infection while 1 (25%) had tuberculoma and MRS each. Out of 3 (6%) patients who had benign tumors, 2 (50%) had reactive gliosis.

According to MR spectroscopy, total patients with neoplastic findings were 44 (88%) while biopsy showed 42 (84%) patients with neoplastic findings. According to MR spectroscopy, there were 3 (6%) patients with infarction, 2 (4%) patients with infection while one (2%) case was inconclusive but histopathology showed one patient with infarction, 4 (8%) patients with infection and 3 (6%) patients had gliotic changes. This led to 97.6% sensitivity, 71.42% specificity, 95.45% positive predictive value, 83.3% negative predictive value and 94% accuracy.

DISCUSSION

Magnetic resonance spectroscopy is an application of MRI that provides chemical information about tissue metabolites.[1] The first clinical use of MRS came in the 1980s.[2] Since then, patients with brain cancer have become the primary focus of MRS applications.[1,2,7]

Early in the development of human brain proton MRS, it was realized that brain tumors exhibited markedly different spectra from normal brain tissue.[8] It was found that nearly all brain tumors have decreased N-acetyl aspartate (NAA) signals, and often also have increased levels of Choline (Cho), leading to increased Cho/NAA ratios. In this group of patients with heterogeneous brain lesions evaluated for suspected neoplasm, analysis demonstrated a high rate of success of 94% accuracy in correctly classifying lesions as tumors and non-neoplastic lesions on the basis of the ratios of NAA/Cho, Cho_{norm}, NAA_{norm}, and NAA/Cr. As expected, elevated levels of Cho were detected in tumors compared with non-neoplastic lesions. Elevated signal intensity in Cho results from increased attenuation of proliferating tumoral cells, with Cho-containing compounds including membrane precursors and products of degradation. Tumoral levels of NAA were presumably originating from residual brain tissue within an infiltrating tumor. The study showed that MRS absolute lipid and macromolecular signals could be helpful in differentiating GBM from metastasis. LM13 class was found to be a

discriminant parameter with an accuracy of 85%. Detection of the MM12-fucose peak may also have a role in understanding molecular biology of brain metastasis and should be further investigated to address specific metabolic phenotypes,[9,10] which were lower than in non-neoplastic lesions. Thus, in agreement with published data.

In a study by Hourani *et al*.[11] 84% of 69 brain lesions (36 tumors) were correctly diagnosed using the ratios NAA/Cho. In this study, 40 (95%) patients were correctly diagnosed as neoplastic following the NAA/Cho ratio.

While 2 (4%) tumors were classified as infarction. Misclassification of tumors as benign lesions can occur either as a result of high tumoral heterogeneity, when regions of spectroscopic sampling differ from the location of the highest tumor grade on histologic examination (which presumably exhibit the highest levels of Cho), or in tumors showing no increase in Cho.[12,13]

On biopsy, 4 (8%) patients were diagnosed as having infections. Out of these 4 patients, spectroscopy reported 2 (25%) as tumors that is because infection tends to resemble low-grade gliomas, with reduction of the NAA signal and elevation of the choline and myoinositol peaks. A lactate peak is an inconsistent finding. MRS can detect subtle differences between low grade brain tumors and should form part of the clinical assessment of these tumors.[14] Lactate, an end-product of anaerobic glycolysis, is often elevated in rapidly growing tumors, in which hypoxic regions may exist.[15] MR spectroscopy may shed light as which organism is responsible for the abscess, because the presence of anaerobic bacteria tends to cause elevated acetate and succinate peaks, whereas absence of acetate and succinate signals are more likely with obligate aerobes or facultative anaerobes.[16] MRS can differentiate high-grade gliomas from metastases, especially with peritumoral measurements, supporting the hypothesis that MRS can detect infiltration of tumor cells in the peritumoral edema.[17]

Second important diagnosis, after differentiating neoplastic from non-neoplastic, is the grade of neoplastic lesion; because of the lack of expertise, we could not differentiate the high grade tumors from low grade tumors by spectroscopy.

However, while differentiating neoplastic from non-neoplastic lesions, our results showing sensitivity (97.6%), specificity (71.42%) and accuracy (94%) are comparable to the previous studies reporting sensitivities of 87%, specificity of 85% and diagnostic accuracy of 88.2%[3] for spectroscopy.[18,19] In this study, PPV and NPV were 95.45% and 83.3%; while one study has found 93% PPV and 70% NPV.[3]

MRS is helpful for differentiating many types of brain tumors.[20] Gliomas of each grade have some specific MRS features that can be used for improvement of the diagnostic value of conventional magnetic resonance imaging in non-invasive assessment of glioma grade.[21]

CONCLUSION

Magnetic resonance spectroscopy can readily help in differentiating neoplasm from non-neoplastic brain tumors, thus an invasive brain biopsy procedure can be avoided.

REFERENCES

1. Chris D, Andrew WB, Susan MN, Michael WM, Nicholas MB, Mark RD, *et al.* Pre-operative proton MR spectroscopic imaging of brain tumors: correlation with histopathologic analysis of resection specimens. *AJNR Am J Neuroradiol* 2001; **22**:604-12.
2. Usenius T, Usenius JP, Tenhunen M. Radiation-induced changes in human brain metabolites as studied by 1H nuclear magnetic resonance spectroscopy *in vivo*. *Int J Rad Oncol Biol Phys* 1995; **33**:719-24.
3. Alam MS, Sajjad Z, Hafeez S, Akhter W. Magnetic resonance spectroscopy in focal brain lesions. *J Pak Med Assoc* 2011; **61**:540-3.
4. Bulakbasi N, Kocaoglu M, Ors F, Taytun C, Ucoz T. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. *AJNR Am J Neuroradiol* 2003; **24**: 225-33.
5. Moller-Hartmann W, Herminghaus S, Krings T, Marquardt H, Lanfermann H, Pilatus U, *et al.* Clinical applications of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesion. *Neuroradiology* 2002; **44**:371-81.
6. Ginsberg LE, Fuller GN, Hashmi M, Leeds NE, Schomer DF. The significance of lack of MR contrast enhancement of supratentorial brain tumors in adults: histopathological evaluation of a series. *Surg Neurol* 1998; **49**:436-40.
7. Majós C, Aguilera C, Alonso J, Julià M, Castañer S, Sánchez JJ, *et al.* Proton MR spectroscopy improves discrimination between tumor and pseudotumoral lesion in solid brain masses. *AJNR Am J Neuroradiol* 2009; **30**:544-51.
8. Tate AR, Underwood J, Acosta D. Development of a decision support system for diagnosis and grading of brain tumors using *in vivo* magnetic resonance single voxel spectra. *NMR Biomed* 2006; **19**:411-34.
9. Crisi G, Orsingher L, Filice S. Lipid and macromolecules quantitation in differentiating glioblastoma from solitary metastasis: a short-echo time single-voxel magnetic resonance spectroscopy study at 3 T. *J Comput Assist Tomor* 2013; **37**: 265-71.
10. Negendank WG, Sauter R, Brown TR. Proton magnetic resonance spectroscopy in patients with glial tumors: a multicenter study. *J Neurosurg* 1996; **84**:449-58.
11. Alavi JB, Alavi A, Chawluk J. Positron emission tomography in patients with glioma: a predictor of prognosis. *Cancer* 1988; **62**:1074-8.
12. Herholz K, Pietrzyk U, Voges J. Correlation of glucose consumption and tumor cell density in astrocytomas: a stereotactic PET study. *J Neurosurg* 1993; **79**:853-8.

13. Patronas NJ, Dichiro G, Kufta C. Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg* 1985; **62**:816-22.

14. Orphanidou VE, Auer D, Brundler MA. H magnetic resonance spectroscopy in the diagnosis of paediatric low grade brain tumors. *Eur J Radiol* 2013; **82**:295-301.

15. DeLaPaz RL, Patronas NJ, Brooks RA. Positron emission tomography study of suppression of gray matter glucose utilization by brain tumors. *Am J Neuroradiol* 1983; **4**:826-9.

16. Hölzer T, Herholz K, Jeske J, Heiss WD. FDG-PET as a prognostic indicator in radiochemotherapy of glioblastoma. *J Comput Assist Tomogr* 1993; **17**:681-7.

17. Server A, Josefsen R, Kulle B. Proton magnetic resonance spectroscopy in the distinction of high-grade cerebral gliomas from single metastatic brain tumors. *Acta Radiol* 2010; **51**:316-25.

18. Herholz K, Herscovitch P, Heiss WD. Neuro PET: positron emission tomography in neuroscience and clinical neurology. Berlin, Germany: *Springer*; 2004.

19. Butzen J, Prost R, Chetty V. Discrimination between neoplastic and non-neoplastic brain lesions by use of proton MR spectroscopy: the limits of accuracy with a logistic regression model. *AJNR Am J Neuroradiol* 2000; **21**:1213-9.

20. Ha DH, Choi S, Oh JY, Yoon SK, Kang MJ, Kim KU. Application of (31)P MR spectroscopy to the brain tumors. *Korean J Radiol* 2013 ; **14**:477-86.

21. Bulik M, Jancalek R, Vanicek J, Skoch A, Mechl M. Potential of MR spectroscopy for assessment of glioma grading. *Clin Neurol Neurosurg* 2013 ;**115**:146-53.