ISSN : 0974 - 7532 Volume 9 Issue 6

Research & Reviews in

BioSciences

Regular Paper

RRBS, 9(6), 2014 [214-218]

Evaluation of Cho, Cr and NAA in brain tumor diagnosis using MR spectroscopy

V.Changizi[1,2]*, F.Azarakhsh[1], M.Kazemi[1]

[1]Technology of Radiology Department, School of Allied Medical Sciences, Tehran University of Medical Sciences, (IRAN)

[2]Management of Information of Health Research Center, Tehran University of Medical Sciences, (IRAN)

E-mail : changizi@sina.tums.ac.ir

ABSTRACT

Brain tumors have the high mortality rate especially in children. Therefore it is required to improve early diagnosis of them. At this moment biopsy is to characterize them as a gold standard. However it is an invasive method. Since mr spectroscopy data is specific, we decided to study if we could make differentiation between brain tumors and normal tissues with metabolites concentrations using MRS without biopsy. **Material and Methods :** Totally 25 people including 8 normal person and 17 patients were studied using a Siemens 3T symphony magneton. Individuals were subjected to the pulse sequence of point_resolved surface coil spectroscopy (PRESS) with TE of 135 ms and the pulse sequence of Stimulate echo method (STEAM) with TE of 35 ms. FOV was selected as 160 ×160 mm for both of them. **Conclusion** : Cho, Cr, NAA, Cho/Cr and Cho/ NAA were compared between two groups of patient and normal cases usingKuskal – Wallis test with spss software. Cho and Cr metabolites obtained by STEAM pulse sequence could be as biomarkers for differentiation between brain normal tissues and tumors.

INTRODUCTION

Brain tumors have the high mortality rateespecially in children[1,2]. Therefore it is required to improve early diagnosis of them. Some scientists declare MRScould revealpathology and tissue specificityinformation's ofbrain[3,4].

Nowadays MRI is widely used in medical diagnostic. However it shows only anatomic information without information about tissue biochemistry and metaboliteindices[5].Therefore MRI information mostly are not only enough for early detection but also for characterizingof brain tumors. At this moment biopsy is to characterize them as a gold standard. However it is an invasive method. In addition some tumors are not in access for biopsy. For example low gradeglioma may occur throughout the brain and we should pay attention to the site, age and presence of disseminated disease[6,7].

Fortunately magnetic resonance spectroscopy (MRS) has ability to provide metabolic information in vivo. This technique uses radio frequency waves and magnetic field to provide metabolites spectrum such as Cho, NAA, Cr, Myo-inositol and lactate in safe and non-invasive condition for patient.

In Magnetic resonance spectrum the horizontalx-axis illustrates frequency chemical shift localizing the metabolite in parts per million (ppm). The vertical y-axisillustrates concentration for the metabolites[8]. Since this type of spectrum is specific, we decided to study if we could make differentiation between brain tumors and normal tissues with metabolites concentrationsusing MRS without biopsy.

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Integration of MRI and MRS findings including anatomical and metabolism information respectively could guide us toward this main goal. Some studies put stress to this idea.

Hollingsworth et al (2006) and Ahmad shokry (2012) used MRS for differentiation between low grade and high grade glioma[9,5].

Martin Wilson et al (2013) found the combination of lipids, glutamine and Myo-inositol could predict survival in a cohort of children with brain tumors[2].Tina young poussaint, and Diana Rodrigues found a linear relationship between Cho signal and tumor cell abundance[10]. Stadelbar et al (2006) showed a correlation between the tumor infiltration and changes in NAA, Cho and Cho/NAA ratio[11]. Cohen et al (2005) showed NAA fall in high grad glioma[12].

MATERIAL AND METHODS

Totally 25people (12 females and 13 males with ages ranging from 11-81 years, mean age of 48.68±3.7 years) including 8 normal person (2females and 6 males with ages ranging from 11-80 years, mean age of 59.31±8.29 years) and 17 patents with mean age of 43.82±3.58 (10female and 7 mal) were studied using a Siemens 3T symphony magneton. Water suppression was applied before getting spectrum. Patients were subjected to the pulse sequence of point_resolved surface coil spectroscopy (PRESS) with TE of 135 ms andthe pulse sequence of Stimulate echo method (STEAM) with TE of 35 ms. FOV was selected as 160 ×160 mm for both of them. Spectrum was generated by SYNGO software. According to the above pulse sequences, N-acetyl aspartate (NAA) resonating at 2.02 ppm, choline (Cho) at 3.22 ppm, creatine (cr) at 3.02 ppm and myo_inositol (myo) at 3.56 ppm were produced[15]. The metabolites concentrations along with Cho/Cr, Cho/NAA ratios were compared between two groups of patient and normalcases usingKuskal

TABLE 1 : H MRS data of 25 cases for brain metabolites with single voxel spectroscopy in two separate pulse sequences of STEAM and PRESS

Patient no/age (y)/sex	H MRS sequence										Tumor grade
	STEAM TE 30 m se					PRESS TE 135m se					
	Cho	Cr	NAA	Cho/Cr	Cho/NAA	Cho	Cr	NAA	Cho/Cr	Cho/NAA	
1/11/F	41.77	135.00	261.67	.31	.16	51.90	132.00	270.00	.39	.19	N
2/65/M	83.85	101.50	214.00	.83	.39	66.00	59.65	53.95	1.11	1.22	N
3/70/M	70.20	41.60	172.00	1.69	.41	165.50	166.50	179.00	.99	.92	N
4/56/M	19.19	67.85	188.70	.28	.10	41.15	57.00	75.35	.72	.55	N
5/80/M	86.90	4.72	64.80	18.41	1.34	92.20	62.67	52.83	1.47	1.75	N
6/76/M	73.35	50.70	115.00	1.45	.64	25.77	20.61	40.90	1.25	.63	N
7/75/M			61.05			39.33	33.13		1.19		N
8/39/F	4.86	54.60		.09		145.33	32.67	123.33	4.45	1.18	N
9/35/M	204.87	94.53	239.00	2.17	.86	218.00	70.20	40.90	3.11	5.33	Low
10/34/M	239.00	187.00	393.00	1.28	.61	214.00	140.50	222.50	1.52	.96	Low
11/57/F	272.95	122.40	97.70	2.23	2.79	211.63	173.17	75.70	1.22	2.80	Low
12/33/F	108.00	74.30	291.00	1.45	.37	168.00	133.67	106.00	1.26	1.58	Low
13/47/M	215.00	160.00	356.00	1.34	.60	270.67	224.33	132.43	1.21	2.04	Low
14/24/F	46.30	96.40	99.30	.48	.47	37.73	56.40	55.93	.67	.67	Low
15/29/M	121.50	149.00	404.50	.82	.30	130.53	148.00	96.85	.88	1.35	Low
16/60/F	34.10	16.80	105.00	2.03	.32	46.20	47.43	83.60	.97	.55	Low
17/53/M	30.80	64.90	197.00	.47	.16	124.40	20.40	85.50	6.10	1.45	Low
18/51/F	163.67	124.33	231.67	1.32	.71	123.00	85.13	83.33	1.44	1.48	Low
19/57/F	136.00	59.10	52.40	2.30	2.60	95.73	47.71	56.27	2.01	1.70	High
20/32/F	156.00	17.60		8.86		74.70	76.70	90.97	.97	.82	High
21/60/F	86.75	65.25	157.00	1.33	.55	129.60	52.97	64.13	2.45	2.02	High
22/48/M	140.00	4.04	280.00	34.65	.50	119.90	36.05	80.01	3.33	1.50	High
23/56/M	76.65	65.15	162.00	1.18	.47	58.15	57.02	63.80	1.02	.91	High
24/58/F	44.13	82.17	71.79	.54	.61	6.31	2.82	2.28	2.24	2.77	High
25/11/F	156.00	75.50	144.00	2.20	1.15	91.13	71.07	70.17	1.28	1.30	High

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TABLE 2 : Metabolites mean value in normal and tumorcases for both pulses sequences of STEAM and PRESS

HMRS sequence	Signal	Mean value ±standard deviation		
		N	Low	High
STEAM	Cho	51.108±9.59	143.61±28.23	106.181±14.31
	Cr	56.17±11.21	108.96±15.54	52.99±8.96
	NAA	148.45±28.31	241.41±38.03	156.89±27.86
PRESS	Cho	72.77±12.90	154.41±23.65	76.90±12.37
	Cr	55.50±12.96	109.92±19.35	48.14±7.36
	NAA	94.66±20.82	98.27±15.82	57.05±8.47

– Wallis test with spss software. Reports of at least 3 expert radiologists were used for making practical differentiation between two groups and among different tumors.

For PRESS transverse magnetization is produced by the 90° pulse and refocused by the first 180° pulse and then by the second. PRESS is T2_weighted technique. For STEAM three subsequent 90° pulse are used.

RESULTS

TABLE 1 reveals concentrations of three metabolites including Cho, Cr, NAA and ratios of Cho/Cr and Cho/NAA for 18 patients involved with brain tumors and 8 normal individuals. These data were classified on the base of STEAM and PRESS pulse sequences. Grouping of tumors to low and high grades were done on the base of radiologist reports.

Figure 1 shows mr spectroscopy of brain low grade glioma. It is shown low level of NAA and increase of Cho. However data analysis for all patients does not put stress on that.

TABLE 2 mean values of Cho, Cr and NAA for normal and tumor cases with both pulse sequences along with their standard deviations.

TABLE 3 reveals mean values of Cho/NAA and Cho/Cr ratios for normal and tumor cases with two pulse sequences of STEAM and PRESS.

TABLE 4 reveals non parametric statistical analysis results with Kuskal –Wallis test between normal and tumor cases in both pulse sequences of STEAM and PRESS. Only Cho and Cr changes with STEAM and Cho change with PRESS method are significant.

TABLE 3 : Cho/Cr and Cho/NAA ratios for normal and tumor cases with STEAM and PRESS methods

HMRS sequence	Ratio	Mean values ±standard deviation		
		N	Low	high
STEAM	Cho/Cr	2.64±1.55	1.35±0.18	6.01±3.76
	Cho/NAA	0.49±0.11	0.71±0.23	0.84±0.26
PERSS	Cho/Cr	3.81±2.20	1.83±0.52	1.77±0.26
	Cho/NAA	1.18±0.24	1.82±0.44	1.52±0.20

P<0.05, 2 df

TABLE 4 : The results of non-parametric analysis with Kuskal-wallis test between normal and tumor case sincluding STEAM and PRESS methods

HMRS sequence	signal	sig
STEAM	Cho	0.048
	Cr	0.054
	NAA	0.150
	Cho/Cr	0.21
	Cho/NAA	0.32
PRESS	Cho	0.057
	Cr	0.154
	NAA	0.305
	Cho/Cr	0.37
	Cho/NAA	0.11

p>0.05, 2 df

TABLE 5 : The results of parametric analysis with Kuskal-wall is test between normal and tumor cases including STEAM and PRESS methods

HMRS sequence	signal	sig
STEAM	Cho	0.55
	Cr	0.02
	NAA	0.1
	Cho/cr	0.17
	Cho/NAA	0.27
PRESS	Cho	0.4
	Cr	0.64
	NAA	0.07
	Cho/Cr	0.38
	Cho/NAA	0.27

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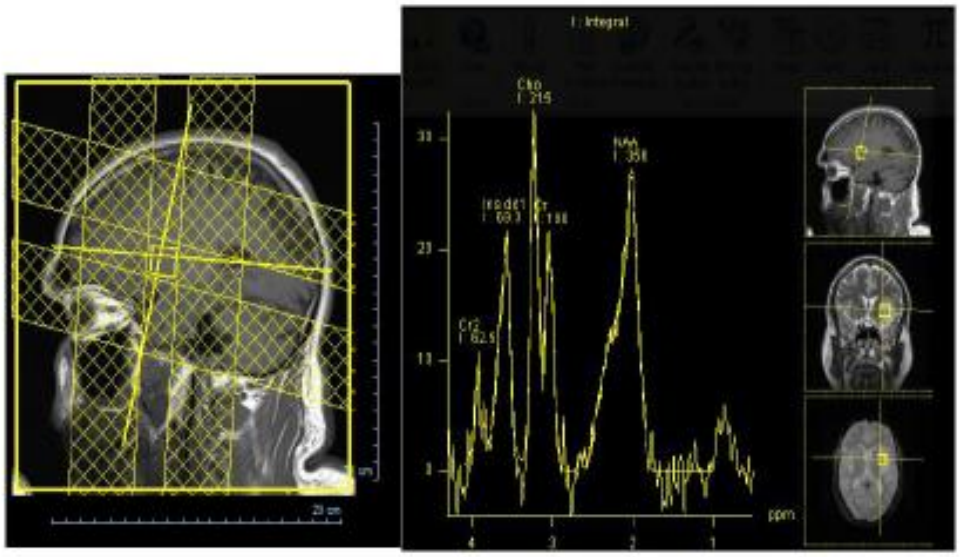

Figure 1 : Forty-seven years old male withlow grade tumor in left temporal lobe of brain figure (A) shows voxel on the lesion; (B) reveals single voxel MR spectroscopy of the left temporal lobe using STEAM sequence for TE=30 msec. It is shown increase of Cho, and decrease of NAA.

TABLE 5 shows the results of parametric analysis with mann withney test between two populations of normal and tumor cases. Only Cho and Cr changes with STEAM method are significant.

DISUSSION AND CONCLUSION

Our study on 25 persons including 17 patientsand 8 normal cases couldn't approve MR Spectroscopy as an accurate signature to differentiate brain tumors from its normal tissues. However it was found Cho and Cr could be as the relevantbiomarkers. Tina Young et al (2009) established linear relationship between Cho signal and tumor cell abundance[10]. It is almost close to our results. Mostly Cho was higher in center of tumor and got down toward peripheral. Increase of choline is due to proliferation and density of tumor cells[17,18]. Also increase of Cho shows cell membrane synthesis. There is a relationship between mitotic activity and malignancy so increase of choline means tumor development[18].However sometimes low grade glioma shows increase of choline[18]. it is due to a high density of cell in tumor with no proliferation and necrosis. Also cerebral infarction, inflammation and MS are other diseases with sign of choline increase. Therefore it is not specific finding[13].Our study revealed Cr changes between normal and tumors cases are significant.

We found the type of pulse sequence is an important factor so that STEAM could reveal the significant changes for Cho and Cr concentrations between normal and tumors cases but PRESS couldn't. Therefore research on pulse sequences could guide scientists toward making a definite decision if MRS is a signature technique or not.

We couldn't find any significant changes for NAA, Cho/NAA and Cho/Cr ratios between under study populations. However malignant tumors make neuron destruction causing a loss of NAA[13]. It was not significant in our study. NAA is resonating at 2_2.5ppm. Glioma could have wide distribution in brain tissue with keeping normal shape in MRI. Therefor it is not true to compare NAA level between two hemispheres in order to get true diagnosis[14]. Some scientists reported NAA, Cho/Cr and Cho/NAA ratios could be indexes for differentiation among brain tissues including normal, low and high grade tumors[12-14]. It couldn't be approved by our study. However it is very complicated and needs more study even with new designed pulse sequences.

We used at least 3 expert radiologists report for classifying tumors to low and high grades. It shows it is soon to judge if we could replace pathology by MRS.

On the whole Cho and Cr metabolites obtained

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by STEAM pulse sequence could be as biomarkers for differentiation between brain normal tissues and tumors.

ACKNOWLEDGMENT

This study has been supported by Tehran University of Medical Sciences.

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