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ORIGINAL ARTICLE

Role of Proton-Magnetic Resonance Spectroscopy (H^1-MRS) in Evaluation of Spinal Cord in Multiple Sclerosis Patients.

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ABSTRACT

BACKGROUND: Proton MR spectroscopy (H1-MRS) is currently considered a useful technique for evaluating axonal damage and demyelination in MS; however, only few spectroscopic cervical MS studies have been published because of the technical difficulties.

To assess the diagnostic role of MRS in evaluation of MS patients and to evaluate metabolic profile in spinal cord MS plaques as well as NAWM.

METHODS: a comparative study between MS cases and control group in which twenty patients with multiple sclerosis were encountered in the study and subjected to clinical assessment including full history taking, clinical examination and imaging assessment by conventional MRI and functional MRI. Additional 20 healthy control individuals of the same age and gender group were included in the study. We determined the metabolic profile of each case and compared it with the control group.

RESULTS: comparison of the main metabolite ratios between different studied groups (MS cord plaque group and control group), Cho/Cr, NAA/Cr, mI/Cr ,and NAA/Cho of control group were 0.52 ± 0.1, 1.1 ± 0.15, 1.4 ± 0.13, and 3.9 ± 0.9, acute MS group were 0.62 ± 0.08, 1.3 ± 0.02, 2.3 ± 0.2, and 2.0 ± 0.04, relapsing MS group were 0.55 ± 0.06, 1.4 ± 0.1, 1.6 ± 0.3, and 1.4 ± 0.08 and progressive MS group were 0.59 ± 0.02, 0.9 ± 0.03, 2.08 ± 0.04, and 1.2 ± 0.06 with P value < 0.001.

CONCLUSIONS: to evaluate the diagnostic role of MRS in the evaluation of MS patients and to evaluate the metabolic profile in spinal cord MS plaques as well as normal-appearing white matter.

KEYWORDS: Spinal cord; Multiple sclerosis; Proton MR spectroscopy (H1 MRS).

INTRODUCTION

Multiple sclerosis (MS) is an auto-immune disease that affects the brain and the spinal cord with a complex relapsing and remitting course, includes inflammation, demyelination, remyelination, axonal loss, and gliosis, alternating or present at the same time; these pathological changes happen in lesions and in normal-appearing white matter (NAWM) and normal-appearing gray matter **(**NAGM) **[1].** Non-conventional MRI techniques as proton MR spectroscopy have been applied to improve our understanding of the pathophysiology of MS. These techniques may provide information on the structural and biochemical changes occurring within and outside macroscopic MS lesions (inflammation, demyelination, axonal loss), namely in the normal-appearing white and grey matter **[2].** T1- and T2-weighted MR imaging is currently the diagnostic reference to define and monitor MS, but it has poor specificity and sensitivity in detecting pathophysiologic MS changes correlated with clinical disability **[3].** Proton MR spectroscopy (H^1-MRS) is currently considered a useful technique for evaluating axonal damage and demyelination in MS**,** however, only a few spectroscopic cervical MS studies have been published because of the technical difficulties **[2].** Quantitative H^1-MRS studies have offered a unique opportunity to evaluate biochemical changes that could shed light on the complex pathophysiology of the disease. The N-acetylaspartate (NAA) peak is thought to be a neuronal marker indicative of axonal integrity, and it is reduced in acute and chronic lesions. An increased peak in choline-containing compounds (Cho), reflecting inflammation, demyelination and remyelination. Last, a myo-inositol (mI) peak increase in MS patients has been interpreted as a possible indicator of gliosis. Reduced GABA level correlates with cognitive impairment in a patient with relapsing-remitting multiple sclerosis **[4].** The

aim of the study is to emphasize the role of MRS in the evaluation of spinal cord in MS patients.

METHODS

Patients: A comparative study has been conducted on 20 patients with a diagnosis of Multiple sclerosis (15 females and 5 males, their ages ranging from 18 to 48 years) and 20 healthy control individuals of the same age and gender group. The MS patients were divided into two groups: MS patients with the radiologically normal-appearing spinal cord (13/20) and MS patients with spinal cord plaques (7/20). The patients were referred from the Neurology Department, Multiple sclerosis clinic in Zagazig university hospitals, to Radiodiagnosis Department, Magnetic Resonance Imaging (MRI unit), Zagazig university hospitals, for MRI diagnosis and follow up, for 11 months in the time frame between April 2018 and Feb 2019. The study was conducted with institutional review based board (IRB) approval and written informed consent was taken from each patients. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patient inclusion criteria: Any age group and gender with Multiple Sclerosis (different clinical subtypes; who were diagnosed clinically and by MRI to have brain plaque lesions).

Patient exclusion criteria: Patients with ferromagnetic vascular clips or spinal metallic prosthesis, "first-trimester" pregnant females (relatively contraindicated), and patients unwilling to complete the study.

Ethical consideration: written informed consent was obtained from all participants; the study was approved by research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the world of Medical Association (Declaration of Helsinki) for studies involving humans.

Methods :all patients were subjected to Complete history taking, full clinical examination (By our colleagues in Neurology Department) and MR Imaging including: conventional MRI and Proton MR spectroscopy (H1 MRS) using TE 34ms, TR 1500ms and voxel was placed on the MS plaques (identified on the PDW or T2WI) and normally appearing cord (Non plaque cases).MR techniques: conventional MRI includes sagittal T1WI (TE 7.8 m/sec and TR 350 m/sec), sagittal T2WI fast-spin echo (TE 120 m/sec and TR 3000-4000 m/sec), sagittal PDW (TE 30 m/sec and TR 5000 m/sec) ,and axial fast spin-echo T2WI (TE 100 m/sec and TR 5000 m/sec). Single voxel MRS was used with NEX

STATISTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered analyzed using Microsoft Excel software. Data were then imported into the statistical package for the Social Science (SPSS version 20.0) software for analysis. According to the type of data, the following tests were used: quantitative data were expressed as mean (M) ± standard deviation (SD) unless otherwise indicated. Independent sample t-test was used for checking difference in continuous measurements, Chi-square test (Fisher's exact test were appropriate) was used for comparing qualitative variables, diagnostic indices (sensitivity, specificity and accuracy) were calculated and then compared with McNemar X2 test and P Value.

RESULTS

Twenty patients were included in our study, who were proved clinically and radiologically to have MS, fulfilling the inclusion criteria. Their ages ranged from 18 to 48 years with a mean age (mean ± SD = 33 ± 8.5), they were 15 females and 5 males. Additionally, 20 control individuals in the same age group were included in the study **[Table 1]**.Comparison of the main metabolites ratios between normally appearing cord in different studied groups (Normally appearing cord MS group and control group) **[Table 2].**Among the normally appearing cord cases (13/20), there were highly significant difference between all metabolites ratios in different studied groups in normally appearing cord compared to the control group (on LSD comparison, the difference is significant on pairwise comparison of each two groups), high significant increase in Cho/Cr and mI/Cr ratios were detected in the acute group compared to the control group, high significant decrease in NAA/Cr and NAA/Cho ratios were detected in the chronic progressive group compared to the control group , and there were significant metabolites ratios changes among different MS groups of normally appearing cord and healthy control ($P<0.001$).

Comparison of the main metabolites absolute values (mmol/L) and ratios between chronic PR MS cases in different studied groups (Normally appearing cord MS group and cord plaque lesion group) Significant increased cr, Cho, and mI in cord plaque lesion group ($P<0.001$).

By statistical analysis of MR spectra of spinal cord in MS patients, we found high significant difference ($P<0.001$) between (acute and chronic), (RRMS and PRMS) and (plaque and normally

appearing cord). Typically in chronic MS lesions in the spinal cord (weather was normally appearing cord or had MS plaques), tNAA was significantly reduced, with mI remained increased, increased Cr and Cho peaks associated with decreased tNAA/Cr, tNAA/Cho, increased mI/Cr and Cho/Cr ratios **[Table 3]**.

In acute spinal cord MS demyelinating lesions (whether was normally appearing cord or had MS plaques), there were decrease in tNAA and Cr, while Cho and mI were increased. There were increase in mI/Cr, Cho/Cr, mild decrease in NAA/Cr and decrease in NAA/Cho ratios **[Table 4]**.In RRMS, there was mild reduction of NAA however; more reduction was observed in PRMS.

This metabolic profile was observed in the spinal cord of MS cases whether normally appearing cord or contain plaques; but it were mild in normally appearing cord than cord with plaque lesions.

NAA was reduced in nearly all MS cases relative to normal control group.

Cr was reduced early in the course of the disease; while it was elevated in chronic cases.

mI as well as Cho were persistently increased in MS cases with more elevation in progressive MS cases. **[Table 5&6]**.

Table 1: Demographic characteristics of the two studied groups:

	Cases (n=20)		Control (n=20)		Test	P
Age:						
Mean ±SD	33±8.5		35.42±7.32		-0.366	**0.283**
Range	18-48		18-44			
	NO	%	NO	%	Test	**P**
Gender:						
Female	15	75%	15	75%	0.289	**0.591**
Male	5	25%	5	25%		

Table 2: Comparison of the main metabolites ratios between normally appearing cord in different studied groups (Normally appearing cord MS group and control group):

	Control group	Acute group	Relapsing group	Progressive group	F	P
-Cho/Cr	0.52±0.1	0.62±0.08	0.55±0.06	0.59±0.02	40.536	<0.001*
-NAA/Cr	1.1±0.15	1.3±0.02	1.4±0.1	0.9±0.03	22.33	<0.001*
-mI/Cr	1.4±0.13	2.3±0.2	1.6±0.3	2.08±0.04	34.75	<0.001*
NAA/Cho	3.9±0.9	2.0±0.04	1.4±0.08	1.2±0.06	314.12	<0.001*

Table 3: Comparison of the main metabolites absolute values (mmol/L) and ratios between chronic PR MS cases in different studied groups (Normally appearing cord MS group and cord plaque lesion group):

	Normally appearing cord (n=3)	Cord Plaque Lesion (n=1)	P
NAA	8±1.05	7±1.7	<0.001*
Cho	4±0.56	4.6±0.62	<0.001*
Cr	5.8±1.4	6.7±1.1	<0.001*
mI	7±1.7	7.4±1.2	<0.001*
NAA/Cr	0.9±0.03	0.8±0.05	<0.001*
NAA/Cho	2.0±0.04	1.0±0.79	<0.001*
Cho/Cr	1.2±0.06	0.6 ±0.02	<0.001*
mI/Cr	2.08±0.04	2.2±0.03	<0.001*

* Highly significant values

Table 4: Comparison of the main metabolites absolute values (mmol/L) and ratios between acute MS cases in different studied groups (Normally appearing cord MS group and cord plaque lesion group):

	Normally appearing cord (n=6)	Cord Plaque Lesion (n=3)	P
NAA	10±1.03	9.2±1.1	<0.001*
Cho	4.7±0.34	5.2±0.29	<0.001*
Cr	3.8±0.82	4.5±1.2	<0.001*
mI	8.3±1.3	9±1.7	<0.001*
NAA/Cr	1.4±0.1	1.1±0.11	<0.001*
NAA/Cho	1.4±0.08	2.5±0.09	<0.001*
Cho/Cr	0.55±0.06	0.57±0.06	<0.001*
mI/Cr	2.3±0.2	1.9±0.2	<0.001*

* Highly significant values

Table 5: Absolute metabolites peak changes in normally appearing cord group (13 cases):

Peaks	Acute (n=6)	Chronic RR (n=4)	Chronic PR(n=3)	No (n=13)	%
↓NAA	6/6	1/4	3/3	10/13	76.9%
Normal NAA	0/6	¾	0/3	3/13	
↑Choline(Cho)	6/6	3/4	3/3	12/13	92.3%
↓Choline(Cho)	0/6	¼	0/3	1/13	
↑Myoinositol(mI)	6/6	2/4	3/3	11/13	84.6%
↓or n (mI)	0/6	2/4	0/3	2/13	
↑Cr	2/6	4/4	3/3	9/13	69.2%
↓Cr	4/6	0/4	0/3	4/13	

Table 6: Absolute metabolites peak changes in plaque cord group (7 cases):

Peaks	Acute (n=3)	Chronic RR(n=3)	Chronic PR(n=1)	No (n=7)	%
↓NAA	3/3	1/3	1/1	5/7	71.4%
Normal NAA	0/3	2/3	0/1	2/7	
↑ Cho	2/3	1/3	1/1	4/7	57%
↓ Cho	1/3	2/3	0/1	3/7	
↑ mI	2/3	2/3	1/1	5/7	71.4%
↓or n mI	1/3	1/3	0/1	2/7	
↑Cr	0/3	3/3	1/1	4/7	57%
↓Cr	3/3	0/3	0/1	3/7	

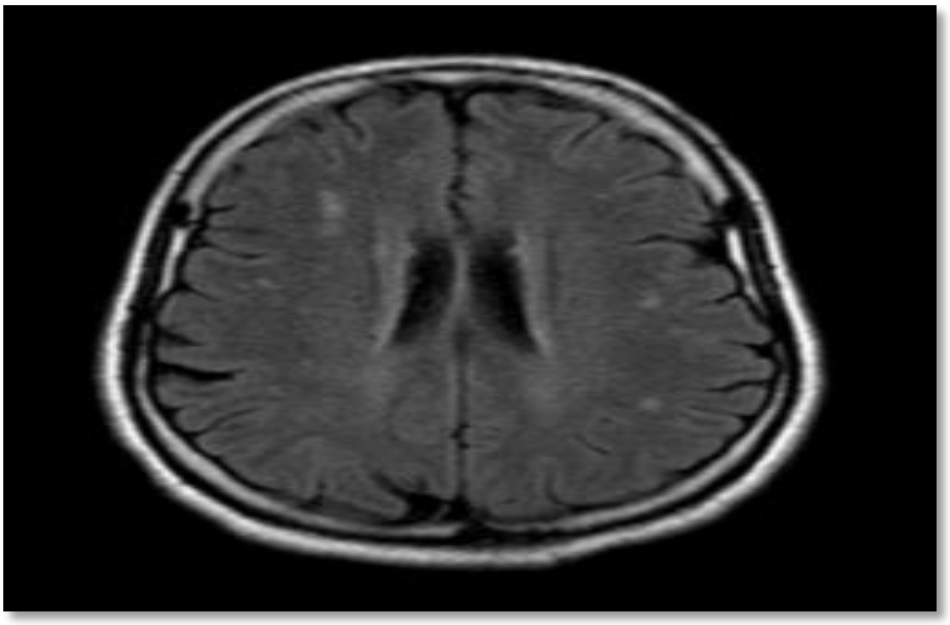

Figure 1(a): A 43-year-old well-known case of RRMS female patient presented by quadriparesis; axial Brain FLAIR shows multiple bilateral hyperintense discrete and confluent plaques seen at the posterior frontal subcortical white matter with one of them is seen at the U fibers seen at the LT side.

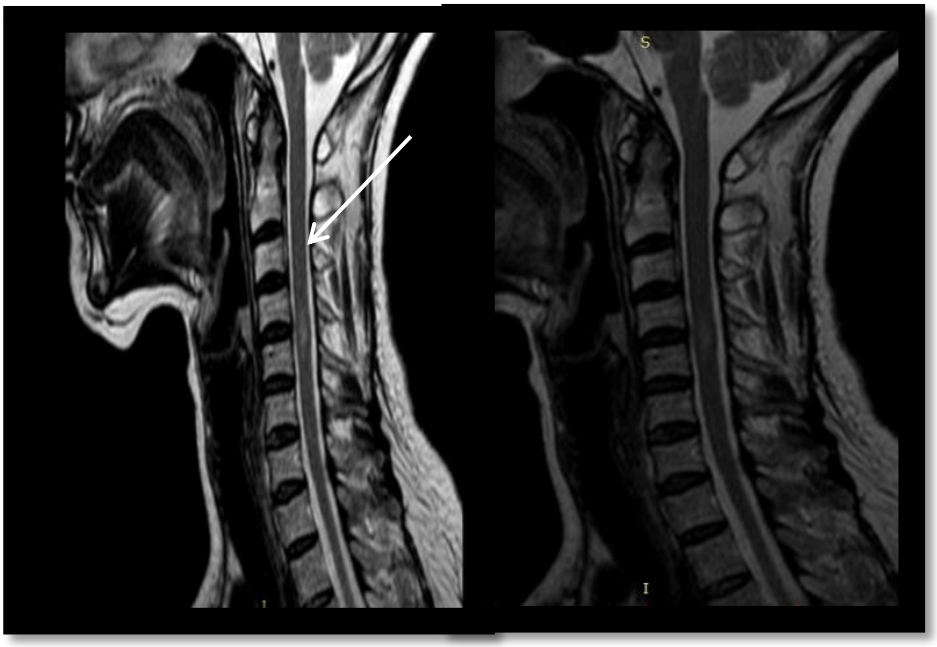

Figure 1 (b): Sagittal Cervical spine T2WI & PDW: sagittal Cervical spine T2WI & PDW show a hyperintense plaque lesion (arrow) involving a short segment of the cervical spinal cord (opposite C4-5 disc level) without cord expansion or atrophy.

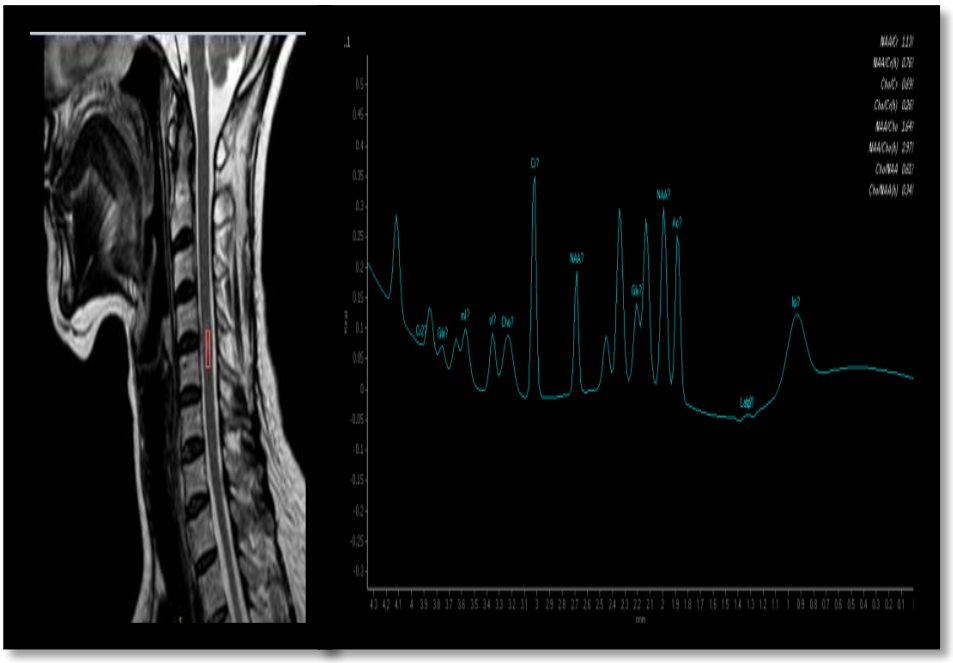

Figure 1 (c): single voxel MRS study (TE=35 ms) on the MS plaque.

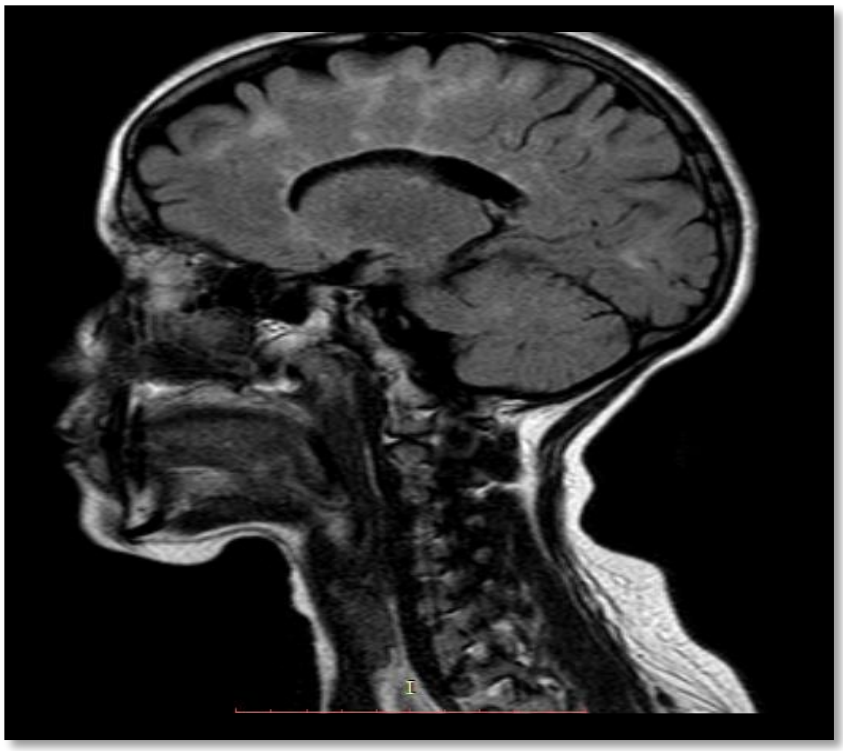

Figure 2 (a): A 48-year-old female patient, who had history of chronic RRMS of 11 years duration. Recently, She developed quadriparesis and urinary incontinence; sagittal Brain FLAIR shows multiple confluent hyperintense plaques seen at the periventricular and subcortical white matter.

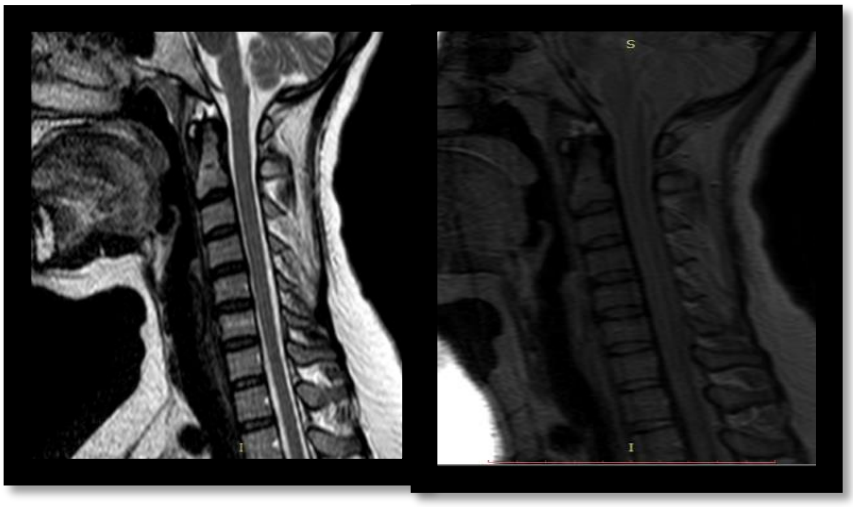

Figure 2 (b): Sagittal Cervical spine T2WI & PDW: Show normal cord signal intensity with no plaques detected, no cord edema or atrophy

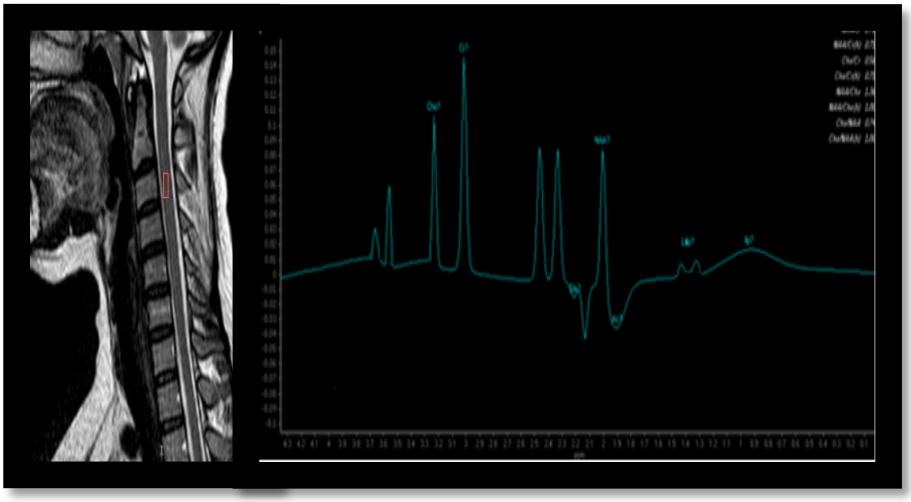

Figure 2 (c): Single voxel MRS study (TE=35 ms) on the normally appearing cord.

DISCUSSION

Quantitative H^1-MRS studies have offered a unique opportunity to evaluate biochemical changes that could shed light on the complex pathophysiology of the disease **[6].**

The pattern of MS plaques may be either discrete or confluent. Statistically talking; we found 5/15 confluent and 10/15 discrete MS plaques lesions. confluent lesions were found with long disease duration or as a progression from many discrete plaques with more regional destruction and axonal loss, the implication of those findings were discussed by **Mohamed et al. [7]** who stated that confluent plaques were more common in PRMS.

Significant decrease of both NAA/Cr and NAA/Cho ratios were found in the acute and chronic progressive groups in comparison with the control group ($P<0.001$) with more reduction in PRMS than RRMS. This was going in line with **Aboul-Enein et al. [5]** who reported that in PRMS, the NAA/Cho ratio and absolute concentrations of NAA were significantly reduced compared to RRMS and to controls.

Illuminating the cause of this metabolic changes in chronic cases, reduction of NAA is due to demyelination with neural and axonal loss, increase Cr as a result of reactive gliosis, increase mI because of glial cell proliferation, increase Cho due to active myelin breakdown, inflammatory changes and edema, the recovery of tNAA to almost normal levels is likely due to the resolution of edema associated with acute inflammation, in addition to remyelination **[8]** By shedding light on chronic RRMS group (7 cases); our results regarding the metabolite values and ratios were hand on hand with that of **Aboul-Enein et al [5] and Abdel-Aziz et al. [9],** *but* stood on the other shore of **[10]** who found no increase in Cho in MS patients in comparison to control group, but it must be pointed out that it was preliminary study with small study population. Using our results, we verified that there were significant reduction in

NAA/Cr and NAA/Cho ratios and elevation of Cho/Cr and mI/Cr ratios in normally appearing cord of MS patients comparing to the control cases. Our results were broadly in line with **Basha et al [11] and Duan et al. [12]** who reported a significantly lower tNAA and NAA/Cr in the normally appearing cord of MS patients than the control cases. A difference between these results can only be attributable to different acquisition methods, number of voxels, TE and voxel localization (selection of VOIs).

There were few limitations of our study; as small sample size, cardiac and respiratory motions.

CONCLUSION

MRS being as an adjuvant tool to conventional MRI, has a crucial role in the evaluation of biochemical and metabolic changes that happen in the normal-appearing white matter as well as in spinal cord plaques. It gives an idea about the pathological changes that happen in spinal cord of MS patients as axonal loss, gliosis, myelin breakdown, and inflammatory changes.

Conflict of interest: No

Financial disclosure: No

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