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ORIGINAL ARTICLE

Can Proton MR Spectroscopy Differentiate Multiple Sclerosis Plaques From White Matter Lesions using Myo-Inositol/Creatine Ratio.

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ABSTRACT

Object: To assess the significance of mI/Cr ratio obtained from MR spectroscopy in differentiating multiple sclerosis (MS) plaques from vascular associated white matter lesions (WML).

Patients and Methods: This study included 23 patients with established diagnosis of relapsing remitting MS (15 females, 8 males, mean age 45±5.7 years) and 18 patients with ischemic WML (10 females, 8 male, mean age 59±5.9 years) who underwent MRI as diagnostic step in case of vascular insult like minor stroke and 12 normal control, all were examined with conventional MRI and single voxel MR spectroscopy. Metabolite ratios for Cho/Cr, Cho/NAA and mI/Cr were calculated automatically then compared between the three groups and compared between MS plaques and WML.

Results: The mean ratio for mI/Cr were (1.57±0.37 , 0.90±0.13 and 0.65±0.05), Cho/Cr were (0.83±0.38, 0.79±0.18 and 1.04±0.07) and Cho/NAA were (0.74±0.33, 0.73±0.23 and 0.61±0.05) in MS plaques, WML and normal control WM (NCWM) respectively. Ms plaques showed significant increase in mI/Cr ratio in comparison to WML (p value <0.001). There were no significant differences in Cho/Cr and Cho/NAA ratios between MS plaques and WML (p value 0.468 and 0.522 respectively).

Conclusion: Increase mI/Cr ratio in MS plaques is of significant value and can be used as an important differentiating point helping in differentiating MS plaques from WML.

Keywords: MS; WML; MRS; mI/Cr ratio.

INTRODUCTION

The detection of focal discrete or confluent hyperintense white matter signals on fluid attenuated inversion recovery (FLAIR) MRI is commonly noticed in daily clinical practice, the major concern is what is their cause as some lesions with different pathologies such as demyelinating disease in particular multiple sclerosis (MS) plaques and white matter lesions of vascular origin (WML) have similar morphological appearance[1].

MS is an inflammatory demyelinating process that affects the brain, spinal cord and optic nerve. It commonly affecting young people and presented with neurological disability [2]. The incidence of MS has been rising in the last few decades with increasing incidence in females [3]. The disease has variable clinical course and multiple subtypes, the most common is relapsing remitting subtype presented by an acute onset of symptoms followed by spontaneous remission , affecting nearly 85% of the patients [2].

WMLs constitute a part of the small vessel disease that comprises small subcortical ischemic and hemorrhagic stroke, vascular lacunae, perivascular spaces, cerebral microbleeds and brain atrophy [4]. Reduced neuronal density was found on histo-pathological examination of both MS plaques and WMLs. In addition, in MS plaques demyelination and gliosis are predominant, while in WML arteriosclerotic changes in the walls of small arteries, incomplete ischemic damage, enlargement of perivascular spaces, as well as fiber loss and myelin rarefaction are prominent [1,5].

This microscopic difference reflected as metabolic changes detected in MR spectroscopy (MRS) in the

form of reduced concentrations of N-acetyl-aspartate (NAA) in both MS and WML due to reduced neuronal density. MS plaques in addition show increase in creatine (Cr) and Choline (Cho), likely due to an increase in cell membrane turnover and/or myelin debris, as well as increase myo-Inositol (mI) concentrations, however, WML shows elevated concentration of lactate (Lac) denoting their presumed vascular origin [6,7].

The most consistent finding in MS is a decrease in the NAA/Cr ratio, whereas an increase in the Cho/Cr ratio was usually, but not always, revealed in active lesions [6].

This study aim to asses if metabolites ratios obtained from MRS can differentiate MS plaques from ischemic WML.

PATIENTS AND METHODS

This study included 23 patients with established diagnosis of MS (15 females, 8 males, mean age 45±5.7 years) who underwent MRI as part of their routine follow up and 18 patients with ischemic WML (10 females, 8 male, mean age 59±5.9 years) who underwent MRI as diagnostic step in case of vascular insult like minor stroke.

Twelve control healthy volunteers (8 male and 4 female, mean age 43±8.65 years) were included with no neurologic deficit or intracranial pathology confirmed by clinical examination and conventional MRI.

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans and was approved by our faculty ethical committee. Informed written consent was obtained from all patients during a period from MAY 2021 to APRIL 2022.

All MS patients included in our results were in relapsing phase with newly appeared hyper intense FLAIR white matter lesions (total 25 lesions) while patients with ischemic WML were presented in ischemic stroke (12 patients), transient ischemic attacks (5 patients) and syncope (1 patient) and their MR showed hyper intense FLAIR WML (total 22 lesions).

We excluded MS patients with no newly appearing WML, patients with non ischemic causes of stroke, patients with contraindications to MR imaging (artificial heart valve, cardiac pacemaker, cerebral aneurysm clips, claustrophobia renal impairment and history of gadolinium allergy) .

All MR examinations were done using 1.5 T MR scanner (Achieva, Philips Medical System) using head coil.

Our MRI protocol included pre contrast axial T1WI (TR/TE: 500/8 ms), axial and sagittal T2WI (TR/TE: 2600/102 ms) and axial FLAIR (TR/TE/TI: 6000/120/1900).

In patients with vascular insult, diffusion weighted imaging (TR 4600ms/TE80ms) with ADC map (b-value=1000s/mm2) were added to diagnose an acute ischemic insult.

Post contrast axial and sagittal T1WI (TR/TE: 500/8 ms).

Section thickness = 5 mm, gap 1mm. Field of view = 240 mm in axial images , Matrix 320 X 224.

- MRS was performed using short echo single voxel technique with (PRESS) pulse sequence *(TR: 1500 ms, TE: 30 ms, Spectral width: 1000 Hz, scanning time 4 min)* .

The volume of interest was determined as the area of maximal FLAIR signal abnormality and placed at the anatomic center of the white matter lesion . The voxel size was ranged from 1 cm^3 to 2 cm^3 according to the size of the lesion.

MRS spectra were interpreted qualitatively by assessment of the signal intensity for Cho, NAA, Cr, myo-Inositol and lipid/lactate in every voxel using the integral of each peak as a measure of its intensity and determination of any peak changes compared to the control spectra.

Quantitative assessment using metabolite ratios including Cho/Cr, Cho/NAA and mI/Cr ratios which were automatically calculated in each voxel.

STATISTICAL ANALYSIS

All data were computerized and statistically analyzed using SPSS 22 for windows (IBM Corp., Armonk, NY, USA). To represent quantitative variables, the mean ± SD & median (range) were employed and for qualitative variables the absolute frequencies & percentage were used.

Shapiro Walk test was used to check normality of Continuous data. Three groups of non-normally distributed data were compared using Kruskal Wallis H test while Mann-Whitney U test was used to compare two groups. All tests were two sided. p-value < 0.05 was considered statistically significant

RESULTS

All examined white matter lesions in MS and WML were supra tentorial in location close to the lateral ventricles, in sub cortical and deep white matter of the centrum semiovale.

Normal healthy control spectra obtained from white matter adjacent to body or occipital horns of the lateral ventricles.

Interpretation of spectra obtained from Ms plaques and WML and comparison with normal healthy control was done and revealed that NAA was reduced in all MS and WML spectra, Cho peak was mild elevated in 10 out of 25 spectra of MS patients and mI peak was elevated in all MS spectra.

WML showed reduction of Cho peak in 18 spectra, reduction of Cr peak in 3 spectra elevation of Lip/Lac peak in 19 spectra, while no apparent change in MI peaks was reported.

The mean mI/Cr ratios were (1.57±0.37 , 0.90±0.13 and 0.65±0.05), mean Cho/Cr were (0.83±0.38, 0.79±0.18 and 1.04±0.07) and Cho/NAA were (0.74±0.33, 0.73±0.23 and 0.61±0.05) in MS plaques, WML and normal control WM (NCWM) respectively.

Ms plaques showed significant increase in mI/Cr ratio in comparison with WML (p value <0.001).

There were no significant differences in Cho/Cr and Cho/NAA ratios between MS plaques and WML (p value 0.468 and 0.522 respectively) [table 1 &Fig. 1].

Table (1): Comparison between the studied groups regarding MRS findings

	Group I MS (n=25)	**Group II WML (n=22)**	**Group III Control (n=12)**	**p-vaule[a1]**	**p-value[b2]**
MI/Cr ratio					
Mean±SD	1.575±0.37	0.90±0.13	0.65±0.05	<0.001	<0.001
Median	1.74	0.92	0.64		
(Range)	(0.89 – 1.99)	(0.65 – 1.12)	(0.59 – 0.73)		
Cho/Cr ratio					
Mean±SD	0.83±0.38	0.79±0.18	1.04±0.07	0.003	0.468
Median	0.85	0.76	1.06		
(Range)	(0.15 – 1.71)	(0.55 – 1.12)	(0.89 – 1.14)		
Cho/NAA ratio					
Mean±SD	0.74±0.33	0.73±0.23	0.61±0.05	0.022	0.522
Median	0.75	0.80	0.61		
(Range)	(0.14 – 1.64)	(0.08 – 0.93)	(0.55 – 0.70)		

a: Kruskal Wallis H test; b: Mann Whitney U test; 1: for test between the three group; 2: for test between group I and group II; p-value< 0.05 is significant.

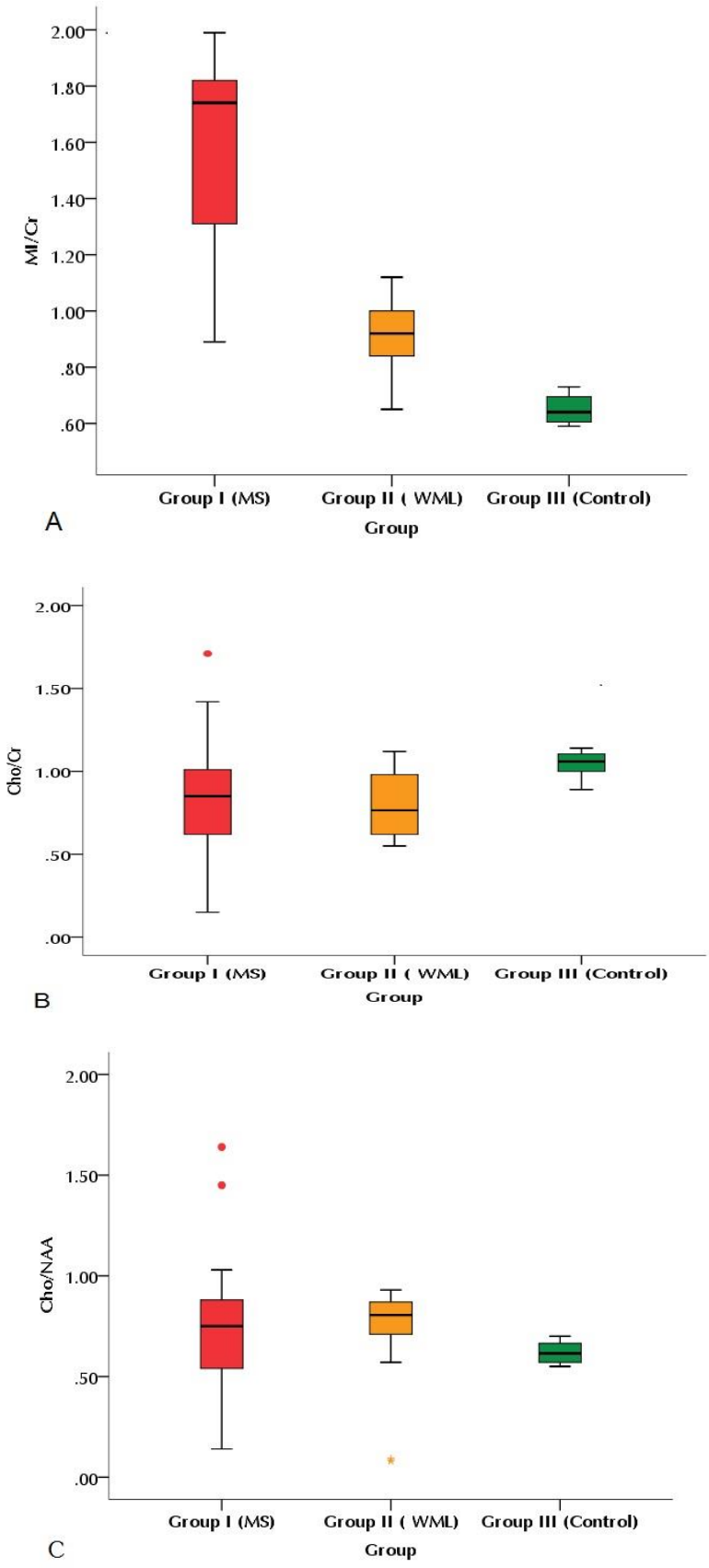

Figure 1: a boxplot for comparison between the studied groups regarding metabolites ratio (A) for MI/Cr ratio (B) for Cho/Cr ratio (C) for Cho/NAA ratio.

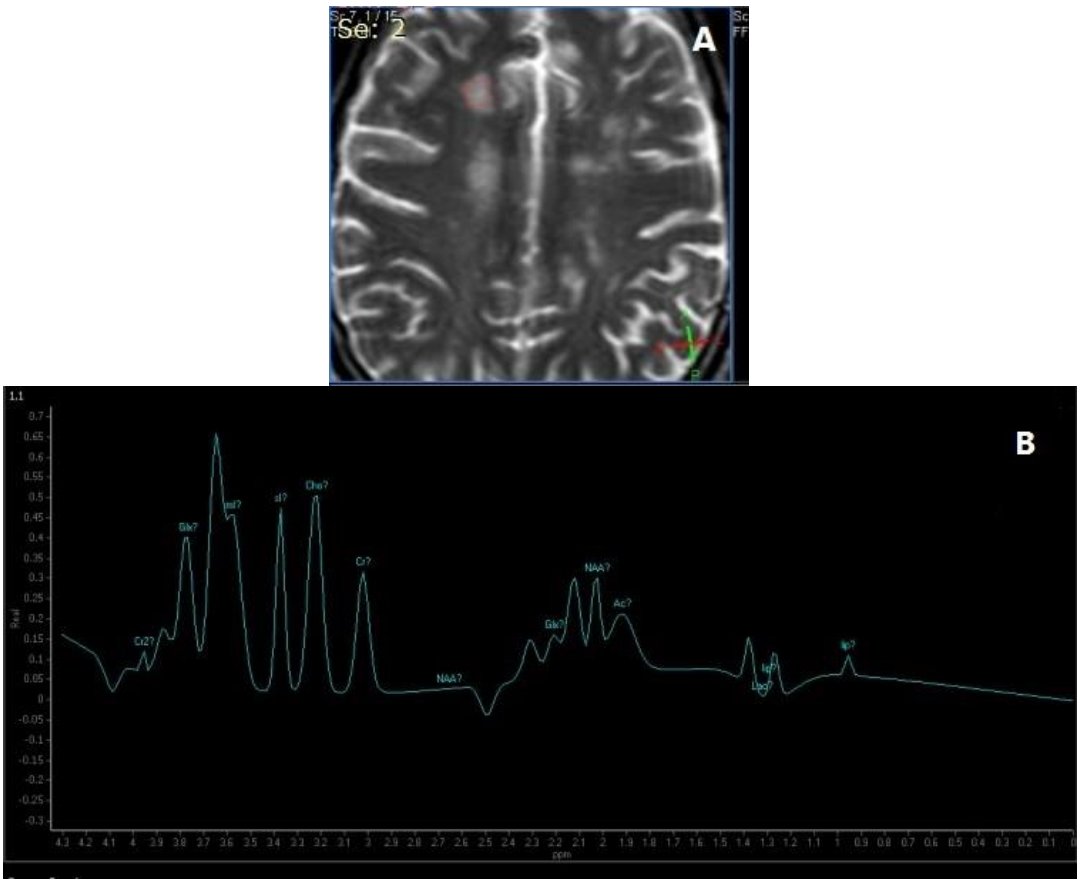

Figure (2): 39 years old female patient with relapsing remitting Ms. Axial T2 (A) showing bilateral fronto-parietal deep and sub cortical white matter MS plaque. (B): MRS depicting decrease of the NAA and Cr peaks, mild elevation of Cho, with elevation of mI peak. mI/Cr ratio 1.75, Cho/Cr 1.42, Cho/NAA 1.82.

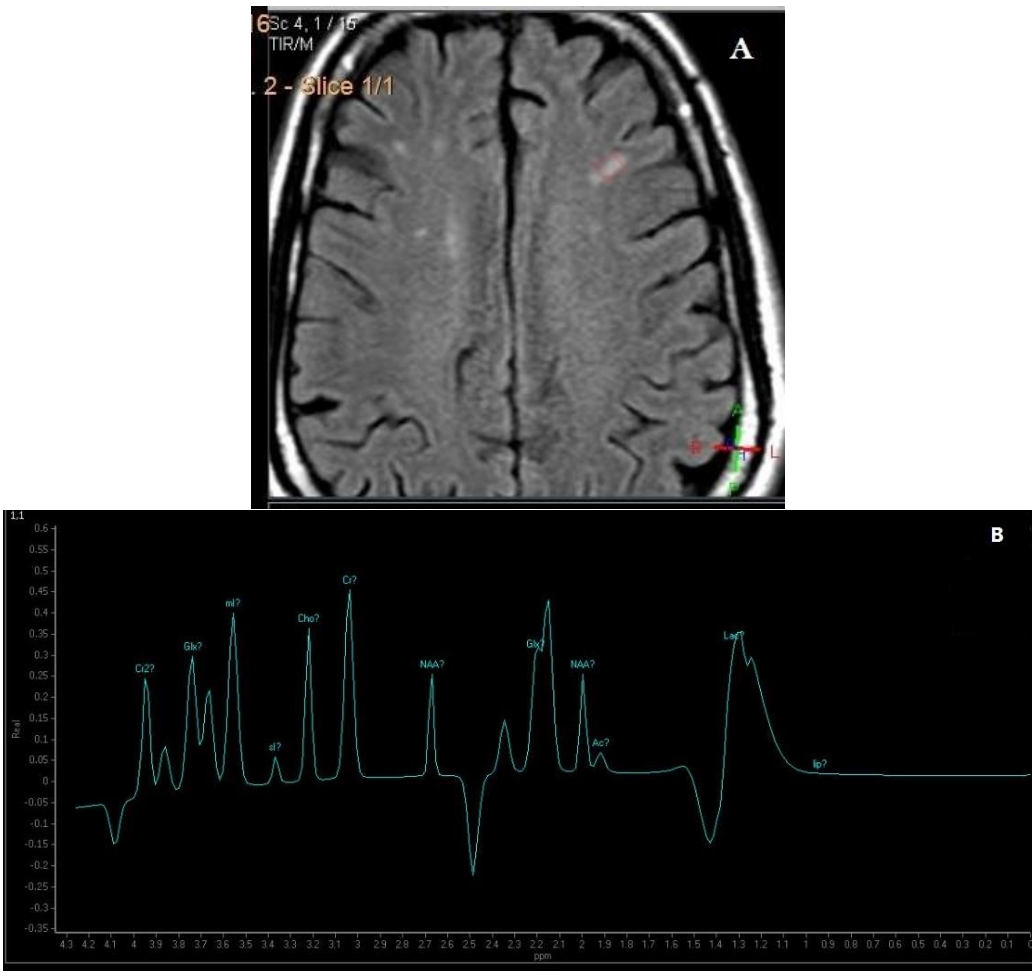

Figure (3): 45 years old male patient presented with ischemic stroke. Axial FLAIR (A) showing bilateral frontal sub cortical WML. (B): MRS depicting decrease of the NAA peak, mild decrease in Cho peak, with elevation of lip/lact peak. mI/Cr ratio 0.91, Cho/Cr 1.12, Cho/NAA 1.61.

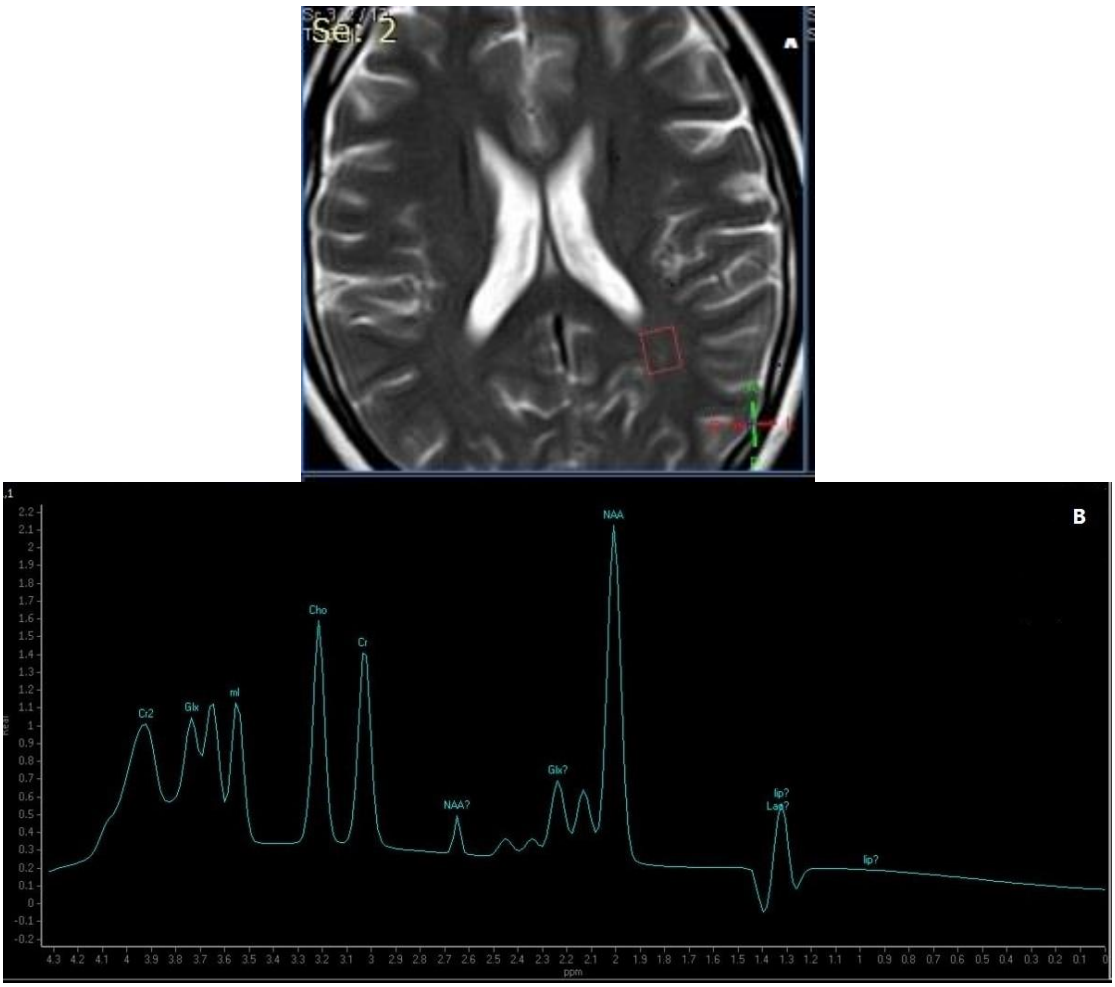

Figure (4): Normal healthy control (A) axial T2 (B) MRS with voxel placed on periventricular occipital white matter reveals normal NAA, Cho, Cr , mI and lip/lac peaks. mI /Cr ratio 0.66 , Cho/Cr 1.04, Cho/NAA 0.56.

DISCUSSION

MRI is an important tool in diagnosing MS as well as in monitoring disease activity and progression. It has a high positive predictive value that exceeds all other tests needed for imaging MS patients [8,9]

.

Multiple pathological conditions are presented by white matter areas of high signals in FLAIR images in the deep and periventricular white matter, which have similar morphological criteria to MS and their differentiation are somewhat so difficult by conventional MR images, one of those common pathologies is WML of vascular origin, that is commonly seen in daily clinical practice.

It is not true that WML are inevitable consequence of normal aging because although it is more common in older people , their prevalence is significantly variable and they are seen also in patients with dementia and stroke and many researchers found that they are associated with multiple risk factors and clinical significance [10,11].

The distinctive pathologic findings in MS are the plaques which represent multiple areas of myelin loss, accompanied by variable degree of gliosis and inflammation [5]. While the pathologic changes in WML were described as ischemic and revealed axonal loss [11].

MRS has the ability to investigate many pathological processes by their characteristic metabolic markers, based on this fact , it is supposed that MS plaques and WML would exhibit different changes in MRS [12].

MRS changes in MS plaques have been discussed in many previous studies, however few studies investigated MRS changes in WML.

The reduction of NAA in MS plaques was a common remarkable finding [1,13,14]. NAA is a marker of neuronal integrity and its reduction is not specific findings as it is seen in any type of brain damages either neoplastic, inflammatory, ischemic or degenerative processes and indicates neuronal loss or dysfunction, so both Ms plaques and WML show reduced NAA levels [15]. That was in keeping with our results as we found that NAA has been reduced in all spectra of MS and WML.

In the last years , conflicting results regarding changes of Cho and Cr were reported in multiple studies dealing with MRS findings in Ms.

Markedly elevated Cho had been reported in acute MS plaques and was explained by active myelin breakdown, inflammation as well as release of cell membrane, and its concentration start to decrease with the relief of the inflammatory process over several months [16, 17].

We found that Cho peak was mild elevated in 10 out of 25 spectra of MS patients and reduced in 15 spectra, we attributed this to the variable duration of the disease among our MS cases.

WML shows reduced NAA, Cr, and Cho levels associated with increased lactate levels which underline their ischemic etiology [1,18]

In our study WML showed reduction of Cho peak in 18 out of 22 spectra, reduction of Cr peak in 3 spectra and elevation of Lac peak in 19 spectra.

In Ms patients Myo-inositol levels were significantly higher in NAWM, acute lesions and chronic lesions in relation to control white matter and this marked increase in myo-inositol in acute cases indicates glial cell proliferation and in chronic cases it is a sign of myelin destruction with gliosis [3]. Elevated myo-inositol in MS cases compared to controls was also reported by **Fernando et al(19)** who performed their study aiming to determine NAWM metabolite concentrations in MS patients.

Our results revealed that myo -inositol was elevated in all spectra form Ms plaques , Keeping with our results, elevation of mI peak in both acute and chronic MS cases was reported by **Kaddah & Khalil [7]** .

Kapeller et al [1] performed their study to investigate the difference in MRS spectra between MS plaques and WML and found a significant reduction in the NAA concentration in both MS plaques and WML and MS plaques additionally showed significant increase in myo-Ins concentration, while no significant changes where detected in concentration of Cho and Cr.

Increased mI concentrations in MS plaques and absence of its increase in WML is a significant finding giving this metabolite a special importance in their differentiation [1]. That was going with our results as we did not detect elevation of mI peak in any of the spectra obtained from WML.

The simpler, widely used approach to interpret the intensity of the most prominent brain resonance is to quantify resonance lines in terms of metabolite ratios. The signal arising from Cr is most frequently taken as a reference. NAA/Cr, Cho/Cr and mI/Cr ratios are the commonest calculated ratio, also Cho/NAA is sometimes used **[20].**

Elevation of Cho/Cr ratio in all acute cases and reduction of NAA/ Cr ratios in all chronic MS cases was reported by **Kaddah & Khalil [7]**.

In the study of **Fernando et al [19]** they found that the ratio of NAWM mI/Cr was significantly higher while NAA/Cr was significantly lower in CIS patients versus controls, however no significant difference was detected in Cho/Cr ratio.

We did not assess the NAA/Cr ratio as we found marked reduction of NAA in both MS and WML which is not a specific findings and as mentioned before seen in any type of brain damage.

Regarding Cho/Cr and Cho/NAA ratios, we found statistically significant differences between MS, WML and normal healthy control, while no statistically significant differences was detected between MS and WML.

We attributed that findings to the effect of decrease NAA levels in all spectra from both MS and WML as well as decrease Cho levels in most of MS and WML spectra in addition to the decrease Cr levels in some spectra from both groups.

In our study, Ms plaques showed statistically significant increase in mI/Cr ratios in comparison to WML and normal control as well as we detected a statically significant differences between MS and WML.

That was explained by the effect of elevation of mI levels in all MS spectra and absence of mI increase in all WML spectra.

We concluded that increase mI/Cr ratio in MS plaques is of significant value and can be used as an important differentiating point helping in differentiating MS plaque from WML.

Conflict of Interest: None

Financial Disclosures: None

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