

Magnetic resonance spectroscopy in evaluation of cerebral chemical changes in fibromyalgia patients

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Introduction

Fibromyalgia (FM) is a clinical syndrome defined by the presence of chronic widespread musculoskeletal pain and the presence of at least 11 of 18 body tender points and these features are often accompanied by other symptoms such as fatigue, poor sleep quality, loss of memory, and mood disturbance. The aim of this work was to investigate the role of magnetic resonance spectroscopy (MRS) to detect the differences in cerebral chemical changes between FM patients and control participants. Thirty patients with primary FM (27 females and three males) were selected from the outpatient clinic of the Department of Rheumatology and Rehabilitation, Faculty of Medicine, Zagazig University Hospitals. Patients with primary FM fulfill the American College of Rheumatology criteria for diagnosis of FM. Ten persons were needed as healthy control participants with the same age and sex as the included patients. ¹H-MRS unit was used to assess *N*-acetyl aspartate (NAA), choline (Cho), creatine (Cr), and their ratios from both hippocampi. Our results showed the following: there was a significant difference in the level of l-hippocampal (NAA) and right hippocampus Cho and the levels of hippocampal glutamate/glutamine (Glx) in the patient group compared with the control group. There is a highly significant difference between the level of Rt and Lt hippocampal Glx in the same patient, highly significant difference in the level of Rt and Lt hippocampal NAA/Cr, NAA/Cho, and left hippocampal Cho/Cr ratios between cases and controls, and there was a negative correlation between the number of tender points and the level of Lt hippocampal Cr. Moreover, there was a significant difference between the number of tender points and the level of Rt hippocampal NAA and Lt hippocampal Ch/Cr ratios, highly significant difference between the level of Rt hippocampal NAA/Cho, NAA/Cr, and Lt NAA/Cr and number of tender points, and a highly significant difference between the level of Rt hippocampal NAA/Cho, Rt NAA/Cr, Lt NAA/Cr, and number of tender points ($P < 0.001$). There was a highly significant difference between the level of Rt hippocampal NAA/Cho, Lt hippocampal NAA/Cr, and visual analogue scale, and there was a significant difference between the level of Rt hippocampal NAA/Cho, Lt hippocampal NAA/Cr, and fibromyalgia impact questionnaire.

Conclusion

These findings outline the possible nature of FM as a systemic disorder that is mainly expressed through sensorineural dysfunction and abnormal neuroendocrine stress responses.

Keywords:

brain metabolites, fibromyalgia, MRI spectroscopy

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Introduction

Fibromyalgia (FM) is a condition that appears to involve disordered central afferent processing the major symptoms of FM including multifocal pain, fatigue, sleep disturbances, and cognitive or memory problems. Other symptoms may include psychological distress, impaired functioning, and sexual dysfunction. The pathophysiology of FM remains uncertain, but it is believed to be largely central in nature [1].

FM is characterized by heightened pain perception, including widespread hyperalgesia, in particular deep-pressure stimuli, enhanced temporal summation, and reduced pain-inhibiting effects of heterotopic noxious stimulation [2].

Although converging data support the hypothesis that dysregulation in brain regions processing pain has a primary role in the pathophysiology of FM, the detailed mechanisms underlying this disorder are still unknown [3].

Magnetic resonance spectroscopy (MRS) provides a noninvasive method for characterizing chemical and cellular features *in vivo*. MRS can be used to measure the chemical composition of tissues, characterize certain tissue metabolic processes, and identify unanticipated chemical or metabolic relations with disease. In brain tissue, the concentrations and mobility of MRS-visible low-molecular-weight chemicals are measured as spectral peaks and can be used to detect abnormalities in brain regions that seem normal in

MRI and to elucidate the pathology underlying MRI-visible abnormalities [4].

Aim of the work

The purpose of this study is to investigate the role of MRS to detect the differences in cerebral chemical changes between primary FM patients and control participants.

Patients and methods

Patients

Thirty patients with primary FM were selected from the outpatient clinic of the Department of Rheumatology and Rehabilitation, Faculty of Medicine, Zagazig University Hospitals. Ten persons were included as healthy control participants of the same age and sex as the included patients. The protocol for this research has been approved by Ethics Committee of the Zagazig University (Egypt) and a written consent from all patients was obtained before entering the study.

Patients with primary FM fulfill the American College of Rheumatology (ACR) criteria for diagnosis of FM [5].

Exclusion criteria

- (1) Pregnancy and lactation, psychiatric disorder, and neurological disorders like cervical disk prolapse and stroke [4].
- (2) All patients with secondary FM were excluded as [6]: early rheumatoid arthritis, systemic lupus erythematosus, hypothyroidism, polymyalgia rheumatica, active polymyositis, myopathies, widespread osteoarthritis (OA), ankylosing spondylitis, diabetes mellitus, liver diseases such as hepatitis C virus and hepatitis B virus.

All patients with primary FM and control persons were subjected to:

- (1) Full history taking with stress on pain, headache, easy fatigue, sleep disturbance, dysmenorrhea, irritable bowel syndrome, morning stiffness, neurocognitive dysfunction, autonomic dysfunction, weight fluctuation.

Visual analog scale (VAS): To measure pain and fatigue, we used a 10-cm horizontal VAS, ranging from 0 (no pain/no fatigue) to 10 (severe pain/severe fatigue) [7].

Fibromyalgia impact questionnaire (FIQ): All patients completed the Spanish version of the FIQ. This is a 10-item self-report questionnaire developed to measure the health status of patients with FM. The

first item focuses on the patient's ability to carry out muscular activities. In the next two items, patients are asked to circle the number of days in the past week during which they had felt good and how often they had missed work. Finally, the last seven questions address ratings of job performance ability, pain, fatigue, morning tiredness, stiffness, anxiety, and depression, as measured using 10-cm VAS scores [8].

- (1) Complete physical examination including:
 - (a) General examination.
 - (b) Musculoskeletal examination: With stress on the number of tender points detected by manual local pressure applied on tender points according to the American College of Rheumatology classification criteria for FM [5].
 - (c) Neurological examination: Including sensory and motor system examination.
- (2) Investigation:

Erythrocyte sedimentation rate: Westergren method, complete blood count, C-reactive protein; rheumatoid factor: latex agglutination test, thyroid function test, antinuclear antibody.

- (3) MRS: All patients and control participants will undergo conventional structural MRI and additional two-dimensional-chemical shift imaging MRS sequences. All participants will be imaged on a 1.5-T MR unit Philips at Achieva (Best, the Netherlands).

Patients and methods

Normal range of the hippocampal metabolites: *N*-acetyl aspartate (NAA) (ppm) ($N = 2.02$ ppm), choline (Cho) (3.2 ppm), creatinine (Cr) (3.0 ppm), glutamate (Glx) (2.1 ppm), and glutamine (Glu) (2.4 ppm) [9].

Their normal ratios are NAA/Cho (1.6), NAA/Cr (2.0), and Cho/Cr (1.2), which will be obtained from voxels studied in the regions of interest selected in the right and left hippocampi in both groups and then compared [10].

Statistical analysis

The data are coded, entered, and checked to Statistical Package for Social Sciences on SPSS, version 10 [11].

Results

There were highly significant differences in the level of Rt hippocampal Cho, Glx, and Lt hippocampal Glx between cases and controls with a mean value \pm SD (3.18 ± 0.02) and with a *P* value of 0.001 (Tables 1 and 2). There is a significant difference in the level of Lt hippocampal NAA between cases and

controls with a mean value \pm SD (2.1 ± 0.1) ($P = 0.04$); however, there is no significant difference between other brain metabolites in cases and controls (Table 3).

There is a negative correlation difference between the number of tender points and the level of Lt hippocampal Cr ($P < 0.001$); moreover, there is a significant difference between the number of tender points and the level of Rt hippocampal NAA ($P < 0.05$). There is no significant difference between the number of tender points and the level of other brain metabolites (Table 4).

There is a highly significant difference of P value less than 0.001 in the level of Rt hippocampal NAA/Cr, Lt hippocampal NAA/Cr, Cho/Cr, and NAA/Cho ratios between cases and controls with a mean value \pm SD (32.89 ± 0.6), P value > 0.0001 ; (0.57 ± 0.55), P value < 0.001 ; (3.3 ± 1.27), P value < 0.0001 ; and (31.19 ± 0.76), P value < 0.001 , respectively. There is a significant difference in Rt NAA/Cho between cases and controls with a mean value \pm SD (-0.7 ± 1.5), P value < 0.03 ; however, there is no significant difference in Rt Cho/Cr between cases and control (Table 5).

There is a correlation among VAS, FIQ, and brain metabolites in Rt and Lt hippocampi in the FM group (Tables 6 and 7).

Table 1 Demographic data

Demographic data	Cases ($n = 30$) [n (%)]	Control ($n = 10$) [n (%)]	χ^2	P
Sex				
Male	3 (10.0)	1 (10.0)	0.0	1.0
Female	27 (90.0)	9 (90.0)		
Age (years)			t	
Range	20–40	25–45	0.35	0.72
$X \pm$ SD	31.4 ± 4.9	32.2 ± 8.2		

Table 2 Comparison between brain metabolites as measured in Rt and Lt hippocampi of fibromyalgia patients and controls

Brain metabolites	Cases ($N = 30$)	Control ($N = 10$)	t	P
Rt NAA	2.0 ± 0.04	1.996 ± 0.01	1.09	0.28
Lt NAA	2.03 ± 0.4	2.1 ± 0.1	2.07	0.04*
Rt Cho	3.18 ± 0.02	3.14 ± 0.03	3.94	0.001**
Lt Cho	3.14 ± 0.1	$3.2 \pm .008$	1.78	0.08
Rt Cr	3.08 ± 0.07	3.08 ± 0.04	0.08	0.93
Lt Cr	3.12 ± 0.1	3.07 ± 0.06	1.34	0.18
Rt Glx	3.78 ± 0.12	2.6 ± 0.09	28.8	< 0.001 **
Lt Glx	3.1 ± 0.07	2.43 ± 0.05	28.5	< 0.001 **

Rt, right; Lt, left; NAA, *N*-acetyl aspartate; Cho, choline; Cr, creatine; Glx, glutamine/glutamate. *Significant at the 0.05 level; **Highly significant at the 0.01 level. There were highly significant difference in level of Rt hippocampal Cho, Glx, Lt hippocampal Glx between cases and controls with a mean value \pm SD (3.18 ± 0.02) and with P value (0.001). There is significant difference in level of Lt hippocampal NAA between cases and controls with a mean value \pm SD (2.1 ± 0.1), p value = 0.04, but there is no significant difference between other brain metabolites in cases and controls.

There is a highly significant difference between the level of Rt hippocampal NAA/Cho, NAA/Cr, Lt hippocampal NAA/Cr, and the number of tender points ($P < 0.001$). There is a significant difference between the level of Lt hippocampal Cho/Cr and the number

Table 3 Correlation between the number of tender points and the level of different brain metabolites in Rt and Lt hippocampi in the fibromyalgia group

Brain metabolites	r	P	Significance
Rt NAA	0.36	$< 0.05^*$	Significant
Rt Cho	0.32	> 0.05	NS
Rt Cr	-0.19	> 0.05	NS
Lt NAA	0.16	> 0.05	NS
Lt Cho	0.12	> 0.05	NS
Lt Cr	-0.55	$< 0.001^{**}$	HS

*Significant at the 0.05 level; **Highly significant at the 0.01 level. There is negative correlation difference between number of tender points and level of Lt hippocampal Cr (p value < 0.001), also there is significant difference between number of tender points and level of Rt hippocampal NAA, (p value < 0.05) there is no significant difference between number of tender points and level of other brain metabolites.

Table 4 Comparison between brain metabolite ratio in Rt and Lt hippocampi of fibromyalgia patients and controls

Brain metabolites ratios	Cases ($N = 30$)	Control ($N = 10$)	t	P
Rt NAA/Cr	0.57 ± 0.55	1.87 ± 0.07	7.39	0.05**
Lt NAA/Cr	2.89 ± 0.6	1.18 ± 0.01	8.16	0.001**
Rt Cho/Cr	2.0 ± 4.0	0.67 ± 0.03	1.07	0.28
Lt Cho/Cr	3.3 ± 1.27	0.54 ± 0.007	6.83	0.001***
Rt NAA/Cho	-0.7 ± 1.5	0.32 ± 0.02	2.19	0.03*
Lt NAA/Cho	1.19 ± 0.76	2.16 ± 0.007	3.97	0.001**

N-acetyl aspartate/creatinine (NAA/Cr), choline/creatinine (Cho/Cr) *N*-acetyl aspartate/choline (NAA/Cho). *Significant at the 0.05 level; **Highly significant at the 0.01 level. There is highly significant difference in (p value < 0.001) in the level of Rt hippocampal NAA/Cr, Lt hippocampal NAA/Cr, Cho/Cr, NAA/Cho ration between cases and controls with a mean value \pm SD (32.89 ± 0.6), p value > 0.0001 , (0.57 ± 0.55), p value < 0.001 , (3.3 ± 1.27), p value < 0.0001 , (31.19 ± 0.76), p value < 0.001 respectively, there is significant difference in Rt NAA/Cho between cases and controls with a mean value \pm SD (-0.7 ± 1.5), p value < 0.03 , but there is no significant difference in Rt Cho/Cr between cases and control.

Table 5 Correlation between visual analogue scale, fibromyalgia impact questionnaire, and brain metabolites in Rt and Lt hippocampi in the fibromyalgia group

Brain metabolites	r	P	Significance
Rt NAA	0.16	> 0.05	NS
Rt Cho	0.21	> 0.05	NS
Rt Cr	-0.07	> 0.05	NS
Lt NAA	0.17	> 0.05	NS
Lt Cho	0.16	> 0.05	NS
Lt Cr	-0.22	> 0.05	NS

VAS, visual analogue scale; FIQ, fibromyalgia impact questionnaire. There is correlation between VAS, FIQ and brain metabolites in Rt and Lt hippocampi among the FM group.

of tender points ($P < 0.05$), but there is no significant difference between the level of other brain metabolite ratios and the number of tender points (Table 8).

There is a highly significant difference between the level of Rt hippocampal Glx and Lt G hippocampal Lx in the same patient ($P < 0.001$) (Figs. 1–3).

Discussion

FM typically presents in young or middle-aged females as persistent widespread pain, stiffness, fatigue, disrupted unrefreshing sleep, and cognitive difficulties, often accompanied by multiple other unexplained symptoms, anxiety, and/or depression, and functional impairment of daily living activities [12].

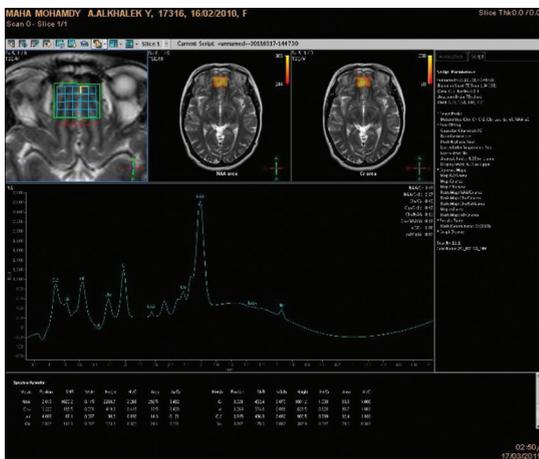
The purpose of our study is to detect the differences in cerebral chemical changes between FM patients and control participants.

Table 6 Correlation between visual analogue scale and brain metabolites in Rt and Lt hippocampi in the fibromyalgia group

Brain metabolites	r	P	Significance
Rt NAA	0.16	>0.05	NS
Rt Cho	0.21	>0.05	NS
Rt Cr	-0.07	>0.05	NS
Lt NAA	0.17	>0.05	NS
Lt Cho	0.16	>0.05	NS
Lt Cr	-0.22	>0.05	NS

Cr, creatine; Cho, choline; Lt, left; NAA, N-acetyl aspartate; Rt, right; There is no significant between visual analogue scale and level of different brain metabolites in Rt and Lt hippocampi among the fibromyalgia patients.

Figure 1



Magnetic resonance spectroscopy in the brain of normal participant shows typical in-vivo proton magnetic resonance spectrum depicting the localization of major peaks for acetyl aspartate (2.02 ppm), creatine/phosphocreatine complex (3.02 ppm), choline (3.22 ppm), glutamine and glutamate (2.1–2.55 ppm); and myoinositol (3.56 ppm).

We investigate possible hippocampal dysfunction and assess hippocampal metabolites (NAA, Cho, Cr, Glx, and their ratios) among 30 female FM patients and 10 age-matched healthy controls.

We selected age-matched controls to avoid the influence of age. Significant reductions of NAA metabolite ratios in the hippocampus may occur with increasing age, and this must be considered in ¹H-MRS studies of human brain disease [13].

Table 7 Correlation between number of tender points and level of different brain metabolite ratios in both hippocampi of the fibromyalgia patients

Brain metabolites ratios	r	P	Significance
Rt NAA/Cho	0.56	<0.001**	HS
Rt Cho/Cr	0.16	>0.05	NS
Rt NAA/Cr	0.46	<0.001**	HS
Lt NAA/Cho	0.28	>0.05	NS
Lt Cho/Cr	0.36	<0.05*	S
Lt NAA/Cr	0.55	<0.001**	HS

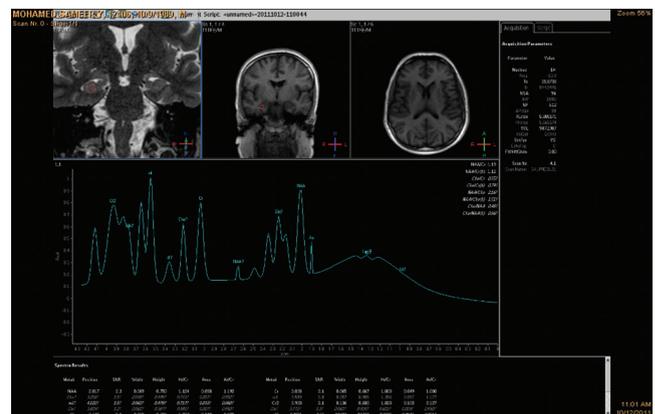
*Significant at the 0.05 level; **Highly significant at the 0.01 level. There is highly significant difference between level of Rt hippocampal NAA/Cho, NAA/Cr, Lt hippocampal NAA/Cr and number of tender points p value <0.001, there is significant difference between level of Lt hippocampal Cho/Cr and number of tender points p value <0.05, but there is no significant difference between level of other brain metabolite ratios and number of tender points.

Table 8 Correlation between levels of glutamate/glutamine in both hippocampi of the fibromyalgia patients

Glutamate/ glutamine	r	P
Rt Glx Lt Glx	0.94	<0.001**

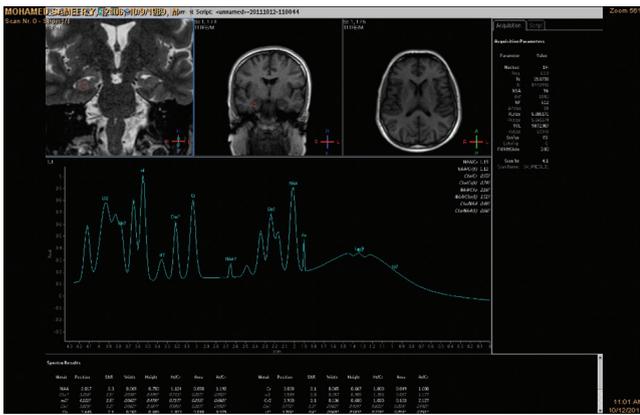
**Highly significant at the 0.01 level. There is highly significant difference between level of Rt hippocampal Glx, Lt G hippocampal Lx in the same patient (p value < 0.001).

Figure 2



Spectra detected by magnetic resonance spectroscopy of both hippocampi (boxed areas in ¹H-spectrum images) of a representative patient with fibromyalgia; the first picture reveals that Glx (glutamine/ glutamate) concentrations are higher in the right hippocampus. The second picture shows the left hippocampal metabolite ratios are within normal range.

Figure 3



¹H-MRS of both hippocampi of a female fibromyalgia (FM) patient. The first picture shows abnormal Cho peak as high as the N-acetyl aspartate (NAA) peak. The second picture shows the left hippocampus metabolite ratios are within the normal range.

In this work, we find reduction of Lt hippocampal NAA level in the patient group compared with controls ($P < 0.05$), and the elevation of right hippocampal Cho level in the patient group compared with controls ($P < 0.001$).

This is also in accordance with Fayed *et al.* [4], which found significant difference for Cho ($P = 0.019$) and NAA + N-acetyl glutamate (NAA + NAG) ($P = 0.034$) in the left hippocampus, with levels being lower in the patient group compared with controls.

This is also in agreement with Brooks *et al.* [14]; they observed significantly reduced concentration of NAA in the right hippocampus of patients with cerebrospinal fluid (CSF) ($P = 0.005$), whereas hippocampal volume was preserved. They concluded that it is likely that lower NAA levels reflect reduced neuronal/glial metabolism rather than reduced cell density.

NAA is described as a neuron marker, because it is found at high concentrations almost exclusively in neurons, but is virtually undetectable in various other cell types, including glial cells [15].

Disturbances of Cho have been interpreted as a compensatory response to the increase in intracellular osmolarity caused by the accumulation of glutamine in astrocytes. The reduction in the intracellular Cho levels is also a likely mechanism to compensate for hyperosmolarity. Low Cho levels have been observed in hepatic encephalopathy in stroke and HIV patients [16].

In this work, we find elevation of Rt and Lt hippocampal Glx levels in the patient group compared with controls

($P < 0.001$). There is a highly significant difference between the level of Rt and Lt hippocampal Glx in the same patient ($P < 0.001$).

This is in accordance with Fayed *et al.* [4], who found significantly higher levels of glutamate + glutamine (Glx) ($P = 0.049$) and higher glutamate + glutamine/Cr (Glx/Cr) ratios ($P = 0.034$) in the posterior gyrus of FM patients compared with healthy controls.

This denotes that Glx elevated in multiple areas of the brain in primary FM patients.

This is also in agreement with Harris *et al.* [17], who found significantly higher levels of glutamate in the right posterior insula in patients with FM than in healthy controls.

Valdes *et al.* [18] reported that Glx concentrations are higher in the right amygdala than in the left amygdala in FM patients.

The hippocampus inhibits brain centers associated with the stress response, that is, the hypothalamic paraventricular nucleus, central amygdala, and locus ceruleus. Thus, changes reported in the hippocampus affect the central amygdala.

This is also in agreement with Lutz *et al.* [19], which reported FM patients had significantly higher levels of Glu ($P = 0.009$) and combined glutamate and glutamine ($P = 0.001$) within the right posterior insula as compared with controls.

In this work, we find highly significant difference in the level of Rt and Lt hippocampal NAA/Cr, Rt and Lt hippocampal NAA/Cho, and Lt hippocampal Cho/Cr ratio between cases and control groups being lower in the patient group, but there is no significant difference in Rt Cho/Cr between cases and control.

This is in accordance with Emad *et al.* [20], who found significant differences between patients and controls regarding NAA/Cr, being lower in the patient group; significant differences were found regarding the NAA/Cho ratios of both hippocampi, whereas no significant differences were found between patients and controls regarding Cho/Cr ratios in both groups.

This denotes that Cho/Cr ratio elevated in multiple areas of the brain of FM patients.

This is also in accordance with Petrou *et al.* [21], who found that Cho/Cr ratios were markedly different in several regions in the FM group, namely in the right dorsolateral prefrontal cortex (DLPFC) and, to a lesser extent, the left caudate nucleus. This variability

in Cho/Cr levels within the patient group appeared to be a 'widespread' phenomenon, because those with low levels in brain region typically had low levels in the other, and vice versa, whereas no such association was seen within controls.

The NAA/Cr ratio is thought to be a more stable indicator of neuronal and axonal loss or dysfunction than NAA alone. Reductions in NAA/Cr ratios are interpreted as signifying reductions in absolute NAA levels [17].

An increased Cho/Cr ratio could potentially be an indicator of several cellular processes. For example, it could reflect active demyelination that may be too early or too subtle to detect on anatomic imaging; elevated Cho/Cr levels have been demonstrated in the context of active demyelination or ongoing gliosis in patients with multiple sclerosis. Elevated Cho/Cr levels can also be seen in malignant neoplasms as well as in the context of central nervous system infection or inflammatory conditions such as neuropsychiatric lupus erythematosus. Although neither demyelination nor malignant neoplasms are likely to be the cause of these abnormalities in FM, changes in Cho/Cr levels (though nonspecific) do provide a sensitive indication of altered brain metabolic activity [21].

This is also in accordance with Petrou *et al.* [21], where they reported significant correlations between brain metabolite levels and other clinical variables (number of tender points and duration of disease), which were found in patients with FM.

In this study, we found a highly significant difference between the number of tender points and the level of Lt hippocampal ($P < 0.001$); also there was a significant difference between the number of tender points and the level of Rt hippocampal NAA ($P < 0.05$), but there was no significant difference between the number of tender points and the level of other brain metabolites.

This in accordance with Emad *et al.* [20], which reported that there was no significant correlation between the numbers of tender points and the different hippocampal metabolites among the FM group.

This may be due to the difference in the number of selected cases between this study and our study; we selected a larger number of subjects or because that study selected females only, but in our study we selected both males and females or may be because we selected only cases of primary FM but other studies were carried out in FM patients in general.

In this work, we found no significant difference between VAS or FIQ and the level of other hippocampal metabolites.

This is in accordance with Emad *et al.* [20], who found no significant correlation among VAS, FIQ, and different hippocampal metabolites.

This disagrees with that found in Valdes *et al.* [18], wherein it is reported that Glx levels in the right amygdala were related to higher VAS although there were no significant correlations between overall VAS scores for pain and Glx levels.

This may be due to the difference in age and sex of patients and their country and we selected age-matched participants and both males and females and our study was carried out in Egypt but the other study was carried out in Spain.

Finally in this work, we find highly significant differences between the level of Rt hippocampal NAA/Cho, Rt NAA/Cr, Lt NAA/Cr, and the number of tender points ($P < 0.001$). There is a significant difference between the level of Lt hippocampal Cho/Cr and the number of tender points ($P < 0.05$). However, there is no significant difference between the level of other brain metabolite ratios and the number of tender points.

Conclusion

According to our results, we conclude that there are alterations in hippocampal metabolites in the brain of FM patients and controls as there is a reduction of Rt hippocampal NAA and elevation of Rt hippocampal Cho, Rt and Lt hippocampal glutamate/glutamine (Glx), NAA/Cr, NAA/Cho, and left hippocampal Cho/Cr ratio.

These findings outline the possible nature of FM as a systemic disorder that is mainly expressed through sensorineural dysfunction and abnormal neuroendocrine stress responses.

Our findings may indicate ways to find new therapeutic strategies for the treatment of patients with this puzzling syndrome.

Recommendations

Our recommendations include:

- (1) Using brain ^1H -MRS as a noninvasive attempt to obtain an insight into brain metabolism in FM patients and helping in confirming the diagnosis.
- (2) Although the number of participants included in the study is comparable to or larger than other studies investigating FM with functional neuroimaging techniques, it necessary to continue as it may help us in predicting the outcome of the disease and management.

Acknowledgements

Conflicts of interest

None declared.

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