Hippocampus Dysfunction May Explain Symptoms of Fibromyalgia Syndrome. A Study with Single-Voxel Magnetic Resonance Spectroscopy

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ABSTRACT. ***Objective.*** (1) To investigate dysfunction of hippocampus in patients with fibromyalgia syndrome (FM) using proton magnetic resonance spectroscopy (^{1}H-MRS), and to compare these findings with healthy controls. (2) To correlate levels of metabolites obtained with aspects of cognition, depression, and sleep symptoms in the patient group.

Methods. The case-control study was performed in 15 female patients, who met American College of Rheumatology criteria for classification of FM, and 10 healthy age-matched female controls. Patients and controls were receiving no medications known to affect cognitive functioning or central nervous system metabolites before their participation in the study. In all patients and controls, ^{1}H-MRS was used to assess N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and their ratios from both hippocampi. Levels of metabolites and their ratios were determined and the findings compared between the groups. All patients and controls underwent psychological assessment to assess cognitive function, depression, and structured sleep interview with sleep diary; Fibromyalgia Impact Questionnaire (FIQ), number of tender points, and visual analog scale (VAS) for pain were assessed in all patients.

Results. NAA levels of right and left hippocampi differed significantly between patients and controls ($p < 0.05$). Cho levels in the right hippocampus were higher in the patient group than in controls ($p = 0.005$), while no differences were found with respect to Cr levels in both hippocampi. NAA/Cho and NAA/Cr ratios differed significantly between patients and controls ($p < 0.05$), while the Cho/Cr ratio showed no differences. Significant correlations were found between language score and right Cho and right Cr levels ($p = 0.041$, $p = 0.006$, respectively), while no significant correlations were found between metabolites and their ratios with FIQ, VAS for pain, or number of tender points.

Conclusion. The hippocampus was dysfunctional in patients with FM, as shown by lower NAA levels compared to controls, representing neuronal or axonal metabolic dysfunction. As the hippocampus plays crucial roles in maintenance of cognitive functions, sleep regulation, and pain perception, we suggest that metabolic dysfunction of hippocampus may be implicated in the appearance of these symptoms associated with this puzzling syndrome. (First Release May 15 2008; J Rheumatol 2008;35:1371–7)

Key Indexing Terms:
FIBROMYALGIA SYNDROME
HIPPOCAMPUS DYSFUNCTION
PROTON MAGNETIC RESONANCE SPECTROSCOPY
HIPPOCAMPAL METABOLITES

Fibromyalgia (FM) is a syndrome of unknown origin[1]. Whether it is possible to separate FM from other pain disorders is not clear [2,3]. Chronic widespread pain is the defining feature of FM, but patients may also exhibit a range of other symptoms including sleep disturbances, fatigue, irritable bowel syndrome, and headache and mood disorders. The syndrome is thought to arise from factors such as stress, medical illness, and a variety of pain conditions in some, but not all, patients in conjunction with a variety of neurotransmitter and neuroendocrine disturbances[1].

The hippocampus plays a role in memory and cognition, 2 functions that may be influenced by prolonged stress. The hippocampus also inhibits brain centers associated with the stress response, i.e., the hypothalamic paraventricular nucleus, central amygdala, and locus ceruleus[4].

Regional brain metabolism can be monitored by specific metabolic markers using proton magnetic resonance spectroscopy (^{1}H-MRS). MR spectroscopy has been used for the

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study of many physiological and pathological processes in the brain and elsewhere. With ^{1}H-MRS one can detect cerebral metabolites *in vivo*, most commonly N-acetyl aspartate (NAA) and choline (Cho) and creatine (Cr)-containing compounds. 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[5].

Our hypothesis was that hippocampal dysfunction may be responsible, at least in part, for symptoms seen in patients with FM. Our objective in this case-control study was to investigate hippocampal dysfunction; using proton magnetic resonance spectroscopy (^{1}H-MRS), we measured different metabolites within the hippocampus in patients with FM and compared the findings with those in healthy controls.

MATERIALS AND METHODS

Inclusion criteria. A total of 15 consecutive female patients who met American College of Rheumatology criteria for diagnosis of FM[6] were invited to participate in the study and all consented; all patients were recruited from the Department of Rheumatology and Rehabilitation outpatient population. Ten healthy female controls matched with patients for age were recruited with permission from another study[7].

No patients or controls were receiving drugs known to affect cognitive functions or central nervous system (CNS) metabolites. No patient was wheelchair-bound or used a walking aid.

Demographic data included age and duration of complaints (disease duration).

All patients completed the Fibromyalgia Impact Questionnaire (FIQ)[8] and in all the number of tender points was assessed by the same investigator. To measure pain, we used a marked 10 cm horizontal visual analog scale (VAS) ranging from 0 (no pain) to 10 (severe pain).

MR imaging/proton MR spectroscopy. All MR imaging and spectroscopy studies were performed on a General Electric Signa Echo Speed scanner operating at 1.5 Tesla and equipped with a head coil.

MRI sequences included sagittal T1-weighted standard spin-echo sequences, 600/30/1 (TR/TE). Axial T2-weighted images were obtained using 2900/120/1 (TR/TE) spin-echo sequences. Other images were obtained with section thickness of 5 mm, intersection gap of 0.5 mm, field of view 256 mm, and matrix size 256 × 256. These MR images were used to visualize any white-matter hyperintensities.

^{1}H-MRS imaging data sets were acquired using spin-echo sequences with 1500/272/1 (TR/TE/excitations) and preselection of regions of interest. Voxel placement of the region of interest for spectroscopic analysis was carried out using structural images acquired in the coronal plane (Figure 1) with the following specifications: TR = 10 ms, TI = 250 ms, TE = 4 ms, resolution 1 × 1 mm^2 resolution, and 1.4 mm slice thickness. The spectral sweep width was 2000 Hz. Water suppression was provided by a chemical shift select sequence with a selective pulse of 120 Hz bandwidth.

Data acquisition and processing. Raw spectroscopy data were processed to provide a single-phase spectrum displayed on the image screen and stored in the patient database.

Spectrum display and storage. The spectra were stored in standard format as 512 × 512 images in a spectra series as a part of the patient study. In the autodisplay mode, spectra are displayed on completion of data reconstruction. All image analysis features are available for use with the spectrum. The Probe–SV spectra cover a spectral window from 4.40 parts per million (ppm) to –0.60 ppm relative to water at 4.75 ppm. When images from the display browser are selected, text is displayed in the upper screen over the Probe-SV spectrum. The Probe–SV image display includes the name of the pulse sequence, acquisition parameters, voxel size and location, metabolite signal intensities, and metabolite/reference metabolite ratios.

The metabolites NAA, Cho, and Cr and their ratios NAA/Cho, NAA/Cr, and Cho/Cr were obtained from voxels studied in the regions of interest selected in right and left hippocampi in both groups and compared.

The ^{1}H-MRS investigation was performed by doing single-voxel ^{1}H-MRS to provide spectra with narrower peaks and higher signal-to-noise ratio.

In the patient group, correlations were evaluated between different metabolite concentrations and their ratios and pain VAS data, FIQ, and number of tender points, and different aspects of cognitive functions, sleep symptoms, and depression.

Psychological assessments

Cognitive function assessment. The Mini Mental State Examination (MMSE) was used to assess aspects of cognitive functions among patients and controls. The MMSE questionnaire tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score ≤ 23 is indicative of cognitive impairment. The MMSE takes only 5–10 minutes and is therefore practical to use repeatedly and routinely. It is effective as a screening instrument to separate patients with cognitive impairment from those without[9].

Depression assessment. The Hamilton Depression Scale[10] was used to assess depression among patients with FM and controls. It was developed as a measure of depressive symptoms that could be used in conjunction with clinical interviews. The test includes 17 items; 9 of these are scored on a 5-point scale, ranging from zero to 4 (0 = absence of the depressive symptom being measured, 1 = doubt concerning the presence of the symptom, 2 = mild symptoms, 3 = moderate symptoms, 4 = presence of severe symptoms). There is some consensus for interpretation of the total scores: normal (< 18), mild (18–24), moderate (24–35), and severe (> 35)[10].

Sleep assessment. The structured sleep interview DSM-IV[11], using a sleep diary for 2 weeks, was used to assess sleep among patients and controls.

Statistics. Descriptive statistics are given as mean and standard deviation (SD) unless otherwise indicated. Student t-test was used to compare metabolite levels in both hippocampi of both groups (significance was inferred at $p < 0.05$). Spearman's rho rank correlation coefficient was used to correlate the nonparametric variables ($p < 0.05$ was accepted as statistically significant). The latter correlation is calculated by applying the rho Pearson's correlation formula to the ranks of the data rather than to the actual data values. In doing so, many of the distortions of the Pearson correlation are reduced.

The study was approved by the ethical committee at Dr. Erfan and Bagedo General Hospital.

RESULTS

Fifteen patients with FM and 10 control subjects were studied. The mean (SD) age of patients was 35.7 ± 5.4 years and mean disease duration was 18.1 ± 9.4 months; mean age in the control group was 35.9 ± 5.1 years. All patients showed cognitive functional impairment by MMSE. Eight of 15 patients (35.5%) showed depression (5 mild, 3 moderate) by Hamilton Depression Scale; 9 (60%) patients had sleep disturbance, all had insomnia. No controls showed impaired cognitive function, depression, or sleep disturbance (Table 1).

NAA levels of the right and left hippocampi were lower in the patients compared to controls ($p = 0.05$ and $p < 0.003$, respectively), and therefore were statistically significant. Another statistically significant difference was observed in Cho levels in the right hippocampus (Figure 2), which were higher in the patient group; no difference between patient and control groups was found regarding other measured metabolites in hippocampi on both sides (Table 2).

Significantly lower NAA/Cho ratios were observed in the

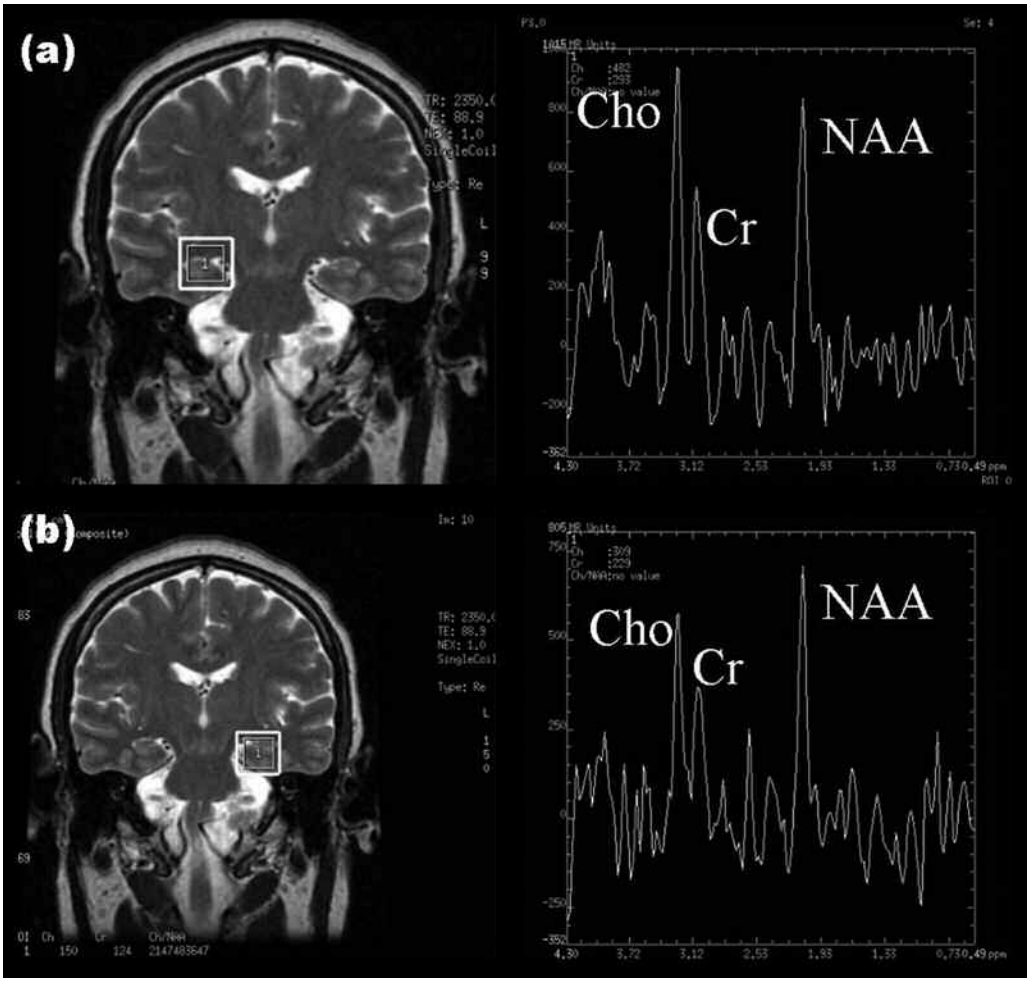

Figure 1. [1]H-MRS of both hippocampi of a female FMS patient, (a) showing reversed NAA/Cho ratio in the right hippocampus with abnormal Cho peak as high as the NAA peak. (b) The left hippocampus metabolite ratios are within normal range. We show in this figure that the voxels were placed in the hippocampus, proving that the spectra are obtained from and can be definitely attributed to the hippocampus.

right and left hippocampi in the patients compared to controls (p = 0.001 and p = 0.002, respectively). Another significant difference was found between both groups regarding right and left NAA/Cr ratios (right NAA/Cr patients mean ± SD = 1.29 ± 0.53, control = 2.32 ± 1.1; p = 0.002; left NAA/Cr patients mean ± SD = 1.64 ± 0.69, control = 2.61 ± 1.6; p = 0.03), while Ch/Cr ratios were not different on both sides (Table 3).

There was no significant correlation between numbers of tender points, FIQ score, and VAS for pain and different metabolites or their ratios among the FM group (Table 4).

Significant correlations were found between language scores and right Cho and right Cr levels (p = 0.041 and p = 0.006, respectively), while no other significant correlations were found between different aspects of cognitive functions as assessed by MMSE and other measured metabolites on both sides (Table 5).

Patients with FM who were depressed did not differ from those who were not depressed regarding sleep disturbances or metabolite measurements.

DISCUSSION

In FM a combination of symptoms frequently exists, including impaired cognition, widespread pain, and disrupted sleep, with no sufficient explanations for these symptoms.

Many theories have been developed and it is not clear whether FM is a chronic stress syndrome caused by many factors, including society and doctors, or just a part of the spectrum of chronic pain[4].

The hippocampus is an integral component of the limbic system, and as such may contribute to the negative affect and avoidance motivation experienced during pain. A substantial body of evidence indicates that the hippocampus processes pain-related information, and some hippocampal neurons respond exclusively following noxious stimulation[12].

Moreover the hippocampus is vulnerable to damage and is particularly sensitive to the effects of adrenal glucocorticoids secreted during chronic stress. The damaging actions of glucocorticoids under such conditions have been termed allostatic load[13]. Thus understanding the status of the hippocampus in

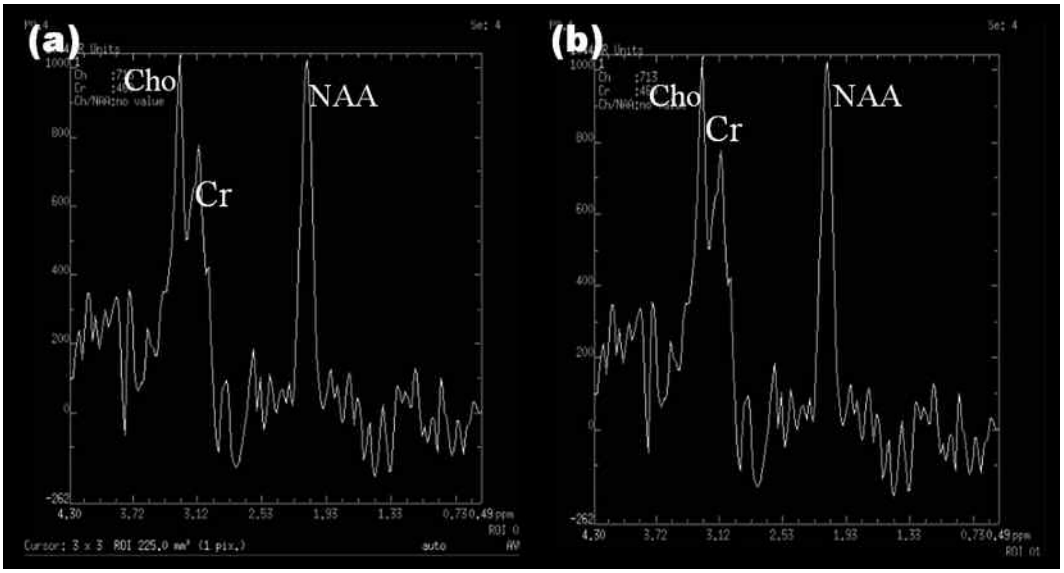

Figure 2. ^{1}H-MRS of right hippocampus (a) and left hippocampus (b) of another female FMS patient showing abnormal spectra. On both sides elevated Cho peaks are found almost similar to the normal high signal of NAA.

Table 1. Demographic features, clinical characteristics, indices, and results of psychological assessment of FM patients and controls. All patients (n = 15) and controls (n = 10) were female.

Characteristic	FM Group	Control Group
Age, yrs, mean ± SD	35.7 ± 5.4	35.9 ± 5.1
Disease duration, mo, mean ± SD	18.1 ± 9.4	—
No. of tender points, mean ± SD	14 ± 2.58	—
FIQ score (range 0–80), mean ± SD	51 ± 5.8	—
Pain VAS score (1–10), mean ± SD	4.5 ± 2.6	—
MMSE score, mean ± SD	12 ± 4.3	27 ± 1.7
HDS score, mean ± SD	18 ± 6.9	8 ± 3.6
Mild depression, n (%)	5 (33.3)	0 (0)
Moderate depression, n (%)	3 (20)	0 (0)
Normal sleep pattern, n (%)	6 (40)	10 (100)
Insomnia, n (%)	9 (60)	0 (0)

FIQ: Fibromyalgia Impact Questionnaire; VAS: visual analog scale; MMSE: Mini Mental State Examination: maximum score is 30, a score ≤ 23 indicative of cognitive impairment. HDS: Hamilton Depression Scale: normal (< 18), mild (18–24), moderate (24–35), severe (> 35).

Table 2. Comparison of NAA, choline (Cho), and creatine (Cr) levels in right and left hippocampi among the FM patients and controls (Student test).

Metabolites	Mean ± SD, mmol	p
Right NAA		
Control	495.53 ± 183.5	0.05
Patients	351.33 ± 209.2	
Left NAA		
Control	583.87 ± 192.38	0.002
Patients	346.20 ± 121.78	
Right Cho		
Control	377.80 ± 100.36	0.005
Patients	547.67 ± 188.35	
Left Cho		
Control	423.0 ± 145.82	0.87
Patients	431.80 ± 161.92	
Right Cr		
Control	231.47 ± 74.10	0.22
Patients	272.47 ± 103.36	
Left Cr		
Control	257.0 ± 80.26	0.35
Patients	227.80 ± 88.132	

patients with FM might prove valuable in guiding future investigations, leading to effective therapy[5].

We investigated possible hippocampal dysfunction that might explain some of the symptoms frequently encountered in FM. We used ^{1}H-MRS to assess hippocampal metabolites (NAA, Cho, Cr and their ratios) among 15 female FM patients and 10 age matched healthy female controls. We studied only women as very few male patients were seen in our clinics.

The hippocampus participates in nociception, a function positively correlated with the activity of hippocampal N-methyl-D-aspartate (NMDA). Several stress-related hormones are known to enhance the activity of hippocampal NMDA receptors, increasing excitatory neurotransmission within the hippocampus[5]. Blocking NMDA receptors in the hippocampal formation reduces nociceptive behaviors; this in turn supports the hypothesis that the hippocampal formation is involved in pain-related neural processing and expression of pain-related behaviors[12].

Wood, *et al*[14] investigated presynaptic dopaminergic function in 6 female FM patients in comparison to 8 age- and sex-matched controls as assessed by positron emission tomography with 6-fluoro-L-DOPA as a tracer. Their findings indicate a disruption of presynaptic dopamine activity wherein dopamine plays a putative role in natural analgesia.

The principal findings in our study are the reduction of NAA levels in both hippocampi, being lower in the patient group compared to controls ($p = 0.05$ and $p < 0.00$, respectively), and significantly higher levels of Cho in the right hippocampus in the patient group compared to controls. The reduction in NAA levels may represent a neuronal and/or metabolic dysfunction that may contribute to decreased neuronal viability in hippocampus in FM patients; on the other hand the observed higher Cho levels among the patients may represent a state of demyelination that additionally may impair neuronal viability; this requires further study.

Table 3. Comparison of NAA/Cho, NAA/Cr, and Cho/Cr ratios in both hippocampi in both groups (Student test).

Ratio	Mean ± SD	p
Right NAA/Cho		
Control	1.32 ± 0.44	0.001
Patients	0.69 ± 0.36	
Left NAA/Cho		
Control	1.40 ± 0.33	0.001
Patients	0.88 ± 0.36	
Right NAA/Cr		
Control	2.32 ± 1.1	0.002
Patients	1.29 ± 0.53	
Left NAA/Cr		
Control	2.61 ± 1.6	0.03
Patients	1.64 ± 0.69	
Right Cho/Cr		
Control	1.69 ± 0.37	0.13
Patients	2.33 ± 1.54	
Left Cho/Cr		
Control	1.79 ± 0.75	0.41
Patients	2.03 ± 0.82	

Table 4. Correlation between number of tender points, Fibromyalgia Impact Questionnaire (FIQ) score, and visual analog scale (VAS) for pain and levels of different metabolites among the FM group. Data are Spearman's rho, correlation coefficient (2-tailed).

Metabolites	Tender Points	VAS	FIQ
Right NAA	–0.443, 0.098	0.391, 0.150	0.004*, 0.990
Right Cho	–0.179, 0.524	0.203, 0.468	0.000**, 1.000
Right Cr	–0.269, 0.333	0.193, 0.492	0.347, 0.206
Left NAA	–0.357, 0.191	0.150, 0.593	0.478, 0.071
Left Cho	0.171, 0.541	0.131, 0.641	0.131, 0.641
Left Cr	0.126, 0.653	0.102, 0.718	0.102, 0.718

* Significant at the 0.05 level (2-tailed); ** significant at the 0.01 level (2-tailed).

NAA is an abundant amino acid in the CNS and can be reliably measured by ^{1}H-MRS[15]. NAA has been shown to be predominantly localized in neurons, axons, and dendrites within the CNS[16]. It has been widely used as a marker of neuronal density that may reflect myelination processes in the human adult, so it is a useful *in vivo* marker to assess neurometabolic fitness and neural viability[17]. The Cho signal measured by ^{1}H-MRS is derived predominantly from constituents of membrane phospholipid metabolism. The Cho signal is significantly higher in conditions where there is ongoing breakdown of myelin or glial cell proliferation[18]. Cho is a rate-limiting precursor in the synthesis of acetylcholine and a precursor to cell membrane phosphatidylcholine[19].

Creatine levels as detected by ^{1}H-MRS reflect the sum of phosphocreatine (PCr) and Cr. PCr is present in the brain at high levels, providing a store of phosphate for phosphorylation of ADP and thus maintaining ATP levels[20]. Traditionally, Cr levels are thought to show less interindividual variation and thus are commonly used as the denominator[21]. In our study no differences were found between patient and control groups regarding Cr levels in both hippocampi.

McLean, *et al*[22] used 2D-chemical-shift imaging MR spectroscopy to examine regional metabolite levels in brain regions involved in pain processing, e.g., thalamus, pulvinar region, internal capsule, and frontal, parietal and occipital gray matter. They reported that mean Cho/Cr ratios were significantly higher in FM patients in the left internal capsule, the left pulvinar/thalamic region, and the right prefrontal subcortical region. The mean signal intensity under the NAA peak was significantly lower in the right prefrontal subcortical region. They suggested that the brains of FM patients have regional abnormalities in the concentrations of several metabolites, and that many of these abnormalities are in regions involved in pain processing.

NAA concentrations in patients with posttraumatic stress disorder (PTSD) were found to be decreased[23-25] and pathophysiological changes observed in the hippocampus may be responsible for the clinical picture of PTSD[26].

In our study significant differences were observed 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, while no significant differences were found between patients and controls regarding Cho/Cr ratios on both sides.

NAA loss resulting in a decrease in the NAA/Cr ratio may primarily be the result of a neuronal dysfunction. A decrease in the NAA/Cr ratio was interpreted to be an indicator of neuronal tissue damage[27].

The NAA/Cr ratio is thought to be a more stable indicator of neuronal and axonal loss or dysfunction than NAA alone[28]. Reductions in NAA/Cr ratios are interpreted as signifying reductions in absolute NAA levels[25].

Some studies were done in patients with chronic fatigue syndrome (CFS)[28,29]. Brooks, *et al*[28] evaluated 7 patients with

Table 5. Correlation between 5 different aspects of cognitive functions assessed by Mini Mental State Examination and NAA, Cho, and Cr levels in both hippocampi in the patient group. Data are Spearman's rho, correlation coefficient (2-tailed).

Metabolites	Orientation	Registration	Attention	Recall	Language
Right NAA	–0.357, 0.191	–0.054, 0.848	0.260, 0.349	0.205, 0.463	0.090, 0.750
Right Cho	0.134, 0.635	–0.450, 0.092	–0.150, 0.594	–0.220, 0.430	0.532, 0.041*
Right Cr	–0.338, 0.218	0.134, 0.633	0.035, 0.902	0.190, 0.498	0.674, 0.006**
Left NAA	0.040, 0.887	0.160, 0.570	–0.046, 0.870	0.363, 0.184	0.371, 0.174
Left Cho	0.433, 0.107	–0.149, 0.595	–0.173, 0.537	0.000, 1.000	–0.123, 0.663
Left Cr	0.066, 0.815	0.033, 0.906	–0.098, 0.728	–0.063, 0.823	0.122, 0.665

* Significant at the 0.05 level (2-tailed); ** significant at the 0.01 level (2-tailed).

CFS and 10 matched healthy control subjects of similar age by ^{1}H-MRS. They observed significantly reduced concentration of NAA in the right hippocampus of patients with CFS ($p = 0.005$), 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.

Chaudhuri, *et al*[29] studied the metabolic functions of the basal ganglia in CFS using ^{1}H-MRS. They found a highly significant increase in the spectra from choline-containing compounds in the CFS patient group ($p < 0.001$). Their findings may indicate higher cell membrane turnover due to gliosis or altered intramembrane signaling.

We selected age-matched controls in order 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 ^{1}H-MRS studies of human brain disease[30].

In our study all patients showed variable degrees of cognitive impairment. Subjective cognitive impairment is a common complaint among patients with FM, the so-called "fibro fog"[31,32]. It was found that patients perform more poorly on tests of immediate and delayed recall, and their ratings of both their memory abilities and sleep quality were lower than those of controls[33].

In our study 9 patients (60%) showed sleep disturbance. Sleep recording abnormalities in FM patients showed increased numbers of awakenings and reduced amount of slow-wave sleep[34], and interventions designed to improve sleep quality may help to improve quality of life for FM patients[35].

Our results are still preliminary, and further studies examining hippocampal dysfunction in larger numbers of FM patients using ^{1}H-MRS are needed to determine the reproducibility and sensitivity of this technique as a surrogate marker in the disease and to redirect novel therapeutic strategies to combat it.

To our knowledge, this is the first report that addresses significantly lower NAA, reduced NAA/Cr ratios, and higher Cho levels in the hippocampus as assessed by single-voxel ^{1}H-MRS among patients with FM, compared with controls. Lower hippocampal NAA levels suggest neuronal or axonal metabolic dysfunction, or some combination of these processes. Yet neuronal loss within the hippocampus was not studied in our series, and this should be assessed in further studies, in order to elucidate whether the reduction in NAA level reflects actual neuronal loss due to atrophic changes within the hippocampus. We suggest that hippocampal dysfunction may be in part responsible for some of the phenomena associated with FM. Our observations are still preliminary and further studies in larger numbers of patients are needed. Our findings may indicate ways to new therapeutic strategies for treatment of patients with this puzzling syndrome.

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