

Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome

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Fatigue is a common symptom of neurological diseases that affect basal ganglia function. We used proton magnetic resonance spectroscopy (¹H MRS) to study the metabolic functions of the basal ganglia in chronic fatigue syndrome (CFS) to test the hypothesis that fatigue in CFS may have a neurogenic component. ¹H MRS of left basal ganglia was carried out in eight non-psychiatric patients with CFS and their results were compared to age- and sex-

matched healthy asymptomatic healthy controls. A highly significant increase in the spectra from choline-containing compounds was seen in the CFS patient group ($p < 0.001$). In the absence of regional structural or inflammatory pathology, increased choline resonance in CFS may be an indicator of higher cell membrane turnover due to gliosis or altered intramembrane signalling. *NeuroReport* 14:225–228 © 2003 Lippincott Williams & Wilkins.

Key words: Basal ganglia; Cell membrane; Choline; Chronic fatigue syndrome; Proton magnetic resonance spectroscopy

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by the symptoms of persistent and overwhelming physical and mental fatigue that typically follows a viral infection (post-viral fatigue) [1]. The pathogenesis of CFS is poorly understood but a central mechanism of fatigue has been proposed [2]. Central fatigue is conspicuous in Parkinson's disease [3] and metabolic changes in the basal ganglia have been observed in fatigued patients with multiple sclerosis [4]. Neuroanatomically, motivational influence of the limbic system on voluntary activities is integrated at the level of the basal ganglia and a failure of this integration may be relevant to the genesis of central fatigue [2,5]. CFS patients do not have any MRI evidence of structural or inflammatory changes in the basal ganglia. However, *in vivo* metabolic functions of basal ganglia in adult CFS patients have not been studied previously. We carried out single voxel proton magnetic resonance spectroscopy (¹H MRS) of the left basal ganglia in eight CFS patients and the results were compared to a matched group of healthy controls. The objective of the study was to identify possible changes in basal ganglia metabolism in CFS with particular reference to the levels of N-acetyl aspartate (NAA), creatine (Cr) and choline containing compounds (Cho).

MATERIALS AND METHODS

Patients and controls: CFS patients strictly fulfilling the modified Centers for Disease Control (CDC) diagnostic

criteria [6] were selected for this study. There were eight patients (M:F = 1:7) between the ages of 32 and 54 (median 42) years with a duration of CFS symptoms of 2–14 (median 4.5) years. None of these patients was depressed. A sex- and closely age-matched group of eight healthy volunteers between the ages of 28 and 59 (median 42.5) years was chosen as a control. None was on medications or supplements known to affect metabolites in cerebral ¹H MRS. All CFS patients were evaluated to exclude chronic viral infections, other fatiguing medical diseases or defined psychiatric disorders fulfilling current criteria. The CFS patients were relatively independent in terms of their daily functions and not severely disabled. Clinical assessments and ¹H MRS were performed on different days. Healthy subjects were asymptomatic. All patients were provided with written information about the study approved by the local ethics committee and consent was obtained before proceeding with the research.

¹H MRS: This was performed on a 1.5 T Siemens Magnetom using PRESS-based single voxel ¹H MRS. A spin-echo (SE) sequence (1500/135 ms) was used and spectra were acquired with (256 averages) and without (one average) water suppression (1024 data points, sample width 500 Hz). No zero filling or line broadening was employed. The volume of interest (VOI) measuring 20 × 40 × 20 mm³ (sagittal, coronal, axial) was positioned using three orthogonal T₁-weighted (SE 500/40) axial scans. It was placed on the left basal ganglia in all the subjects. Baseline and phase

corrections were applied manually to the Fourier transform of the free induction decay and a single observer defined the peak areas. Peak areas of the three metabolites (NAA, Cho and Cr) were calculated. The area of the unsuppressed water peak was also calculated as a reference value to which these metabolite areas could be compared. A two-sample *t*-test with unequal variance was applied to the observed differences between the patient and the control groups in the metabolite and unsuppressed water peak areas.

RESULTS

^1H MRS values of the peak areas for the individual metabolites with references to brain water and choline-containing compounds for each of the patients and her/his matched control are shown in Table 1. Percentage differences in the peak ratios of CFS patients compared with controls are depicted in Table 2. Figure 1 shows a montage of the spectroscopic peaks of Cho and Cr in the VOI of patients and controls. Figure 2a,b offers examples of the spectra from a patient (Fig. 2a) and matched control (Fig. 2b). CFS patients have significantly higher Cho peaks consistent with a low NAA/Cho ratio and high Cho/Cr ratio compared to the healthy subjects ($p < 0.001$). When compared to the unsuppressed water peaks, the increase in Cho was significant at $p < 0.01$ compared with the normal controls.

DISCUSSION

^1H MRS is a relatively new tool for imaging metabolic brain function. NAA levels broadly correlate with the regional neuronal function while Cr is generally considered to be an unvarying metabolic marker, the reason for its use as a reference in the ^1H MRS. In contrast, the Cho peak is believed to be largely derived from the cell membrane lipids [7–9]. In the absence of inflammation and tissue necrosis, elevated Cho resonance may be a marker of increased cell membrane turnover associated with reactive or reparative gliosis [8]. Since choline peaks in the ^1H MRS primarily arise from phosphocholine and glycerophosphocholine, both of which are metabolites of phosphatidylcholine, breakdown

of membrane lipids due to local osmotic events has been proposed as a mechanism for increases in choline resonance [9]. Alteration in the intramembrane signalling is another possible explanation for elevated Cho peaks [10].

Since the severity of fatigue in CFS fluctuates and is easily influenced by normal bodily functions (e.g. exercise, hormonal changes in females, alcohol intake and response to stress and infection), we felt it would be appropriate to use ^1H MRS to study metabolic brain functions in CFS. In a previous report of ^1H MRS in seven CFS patients, reduced levels of NAA were observed in the right hippocampus [11]. Reduction of neuronal NAA has also been reported in the basal ganglia and brain stem among symptomatic Gulf-War veterans who experience symptoms of chronic fatigue [12]. We chose the basal ganglia as the region of interest in our study because central fatigue has been attributed to a failure of the limbic-motor integration of volitional activities at the level of the basal ganglia [5]. CFS patients were selected by using current research criteria and excluding psychiatric causes of chronic fatigue. None of these patients had evidence of ongoing systemic viral infections or clinical depression. No patient was receiving or had received choline supplementation as a treatment before or at the time of their ^1H MRS.

We found no evidence for a loss of functional neuronal mass (which would have been reflected in reduced levels of NAA and a low NAA/Cr ratio) in the basal ganglia of CFS patients included in this study. However, whether referenced to water or other metabolites, the peak of the choline-

Table 2. Percentage difference in the peak ratios of CFS group compared to HC group (ns = not statistically significant).

Peak ratios	% difference	<i>p</i> -value
[NAA]/[Cr]	8.1	ns
[NAA]/[Cho]	-26.5	0.001
[Cho]/[Cr]	48.5	0.001
[NAA]/[H ₂ O]	-5.7	ns
[Cr]/[H ₂ O]	-12.2	ns
[Cho]/[H ₂ O]	31.7	0.01

Table 1. Unsuppressed water and metabolite peaks in the ^1H MRS.

Case ^a	H ₂ O	NAA	Cho	Cr	NAA/Cr	NAA/Cho	Cho/Cr	NAA/H ₂ O	Cr/H ₂ O	Cho/H ₂ O
CFS1	501	0.9	0.41	0.45	2.0	2.195	0.911	1.796	0.898	0.818
HC1	436	0.76	0.28	0.34	2.229	2.717	0.821	1.739	0.779	0.639
CFS2	417	0.69	0.47	0.29	2.379	1.468	1.621	1.655	0.695	1.127
HC2	396	0.76	0.32	0.33	2.296	2.346	0.979	1.919	0.836	0.818
CFS3	554	0.89	0.4	0.37	2.405	2.225	1.081	1.606	0.668	0.722
HC3	614	0.9	0.4	0.44	2.05	2.249	0.911	1.469	0.717	0.653
CFS4	442	0.88	0.5	0.37	2.378	1.76	1.351	1.991	0.837	1.131
HC4	466	0.67	0.31	0.36	1.893	2.154	0.879	1.442	0.762	0.669
CFS5	358	0.58	0.33	0.3	1.933	1.758	1.1	1.62	0.838	0.921
HC5	438	0.82	0.29	0.4	2.025	2.810	0.720	1.868	0.922	0.664
CFS6	488	0.87	0.55	0.45	1.933	1.582	1.222	1.783	0.922	1.127
HC6	266	0.62	0.22	0.3	2.066	2.902	0.712	2.346	1.135	0.808
CFS7	442	0.8	0.43	0.36	2.222	1.860	1.194	1.809	0.814	0.973
HC7	384	0.66	0.27	0.38	1.741	2.464	0.711	1.469	0.717	0.695
CFS8	499	0.66	0.31	0.28	2.357	2.129	1.107	1.323	0.561	0.621
HC8	351	0.67	0.25	0.34	1.988	2.720	0.731	1.915	0.963	0.704

^aCFS, patients with chronic fatigue syndrome; HC, healthy control.

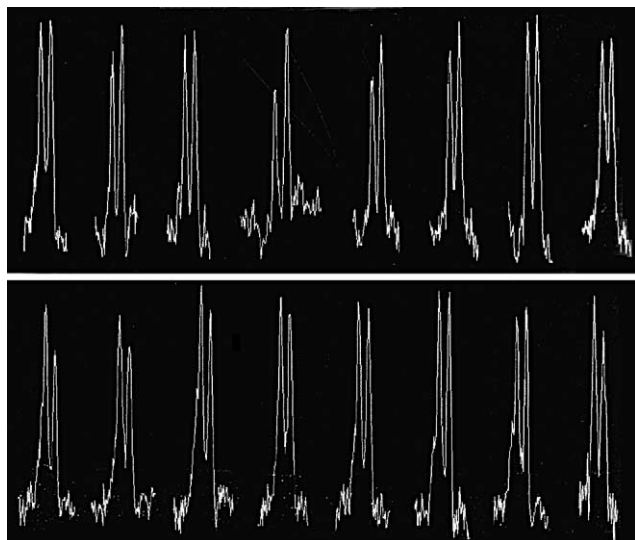


Fig. 1. Choline and creatine peaks in the ^1H MRS of the left basal ganglia in eight normal controls (upper panel) and eight CFS patients (lower panel) shown as a montage.

containing compounds in the ^1H MRS showed increases in the CFS group as compared to the healthy controls. The statistical strength of this association was very significant (Table 2). In the only other ^1H MRS study of the basal ganglia in three CFS children (ages 11, 12 and 13 years), a remarkable elevation of Cho/Cr ratio was similarly observed [13]. None of these cases (ours and the three reported paediatric patients) had focal structural abnormalities of the basal ganglia on MRI. In a more recent study of ^1H MRS in eight CFS patients without psychiatric symptoms, a relative increase in Cho/Cr ratio was observed in the occipital cortex with high statistical significance [14].

At present, there is little evidence to suggest that CFS symptoms are due to persistent or reactivated viral infection. Although persistent Epstein-Barr, enteroviral or human herpesvirus infection has been proposed to explain CFS symptoms, current opinion does not favour this theory [15]. The explanation for the elevated choline levels in patients with CFS is therefore not entirely clear. Continuing reparative gliosis [8] and/or abnormal membrane phospholipid metabolism are possibilities [14]. However, in a different cohort of CFS patients, systemic metabolic studies on lipid and peroxisomal function did not reveal any abnormality (AC, data not shown). It is therefore likely that the increased choline spectroscopic peaks in two different brain areas reported independently by us [16] and other workers [14] in CFS patients indicate local changes in the neural cell membrane lipid composition rather than a systemic disorder of lipid metabolism.

It has been previously hypothesised that sustained changes in cell membrane function may follow exposure to infections and specific neurotoxins leading to the CFS symptoms [17]. Ciguatera toxin is probably one of the best examples where delayed symptoms of chronic fatigue may be related to the alteration of the membrane ion channels (ciguatera toxin irreversibly inactivates sodium channels in an open mode) [17]. It is also known that the viral

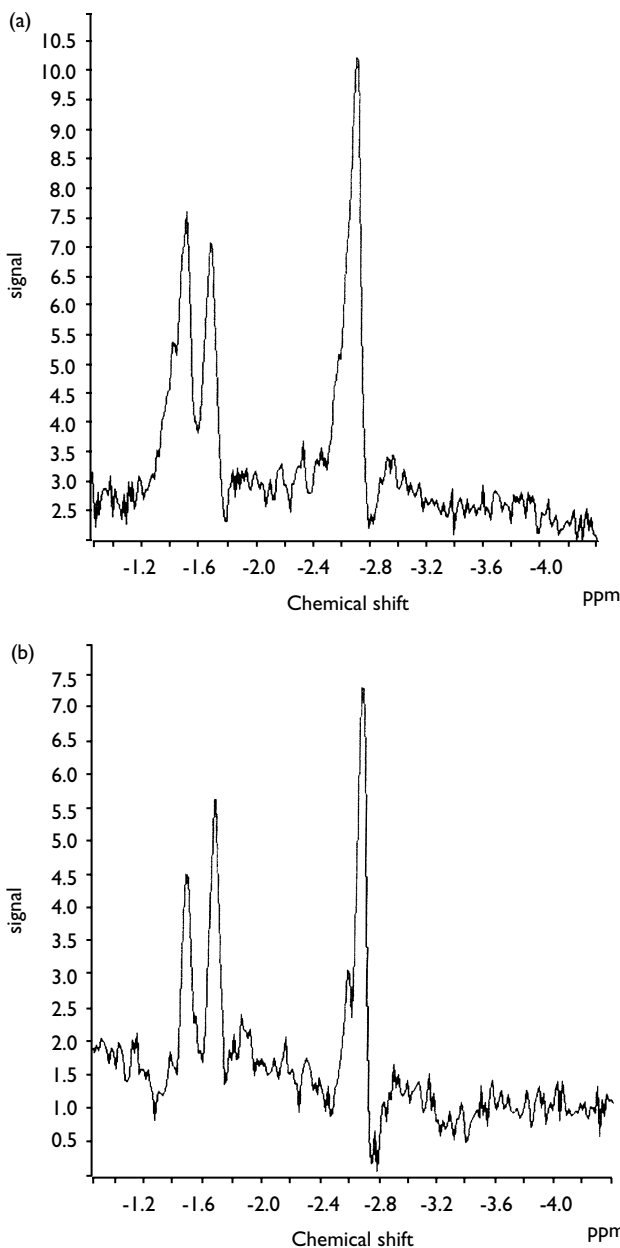


Fig. 2. Examples of the spectra for a CFS patient (a) and a matched control subject (b).

membrane glycoprotein and viroporin molecules induce changes in the host cell membrane permeability, leading to the activation of phospholipases with consequent release of a number of phospholipid moieties including choline [18]. A common route of cellular entry shared by many bacteria, viruses and parasites involves lipid-rich microdomains (caveolae) of the cell membrane. A number of microbes or their exotoxins (in the case of extracellular infections) co-opt the features of the host cell caveolae probably because their cognate receptors are localised within the lipid-rich plasmalemma of host cells [19]. Subsequent adaptations of the host cells to these pathogens and toxin could modify cell

membrane functions that may persist long after symptomatic recovery in some patients.

CONCLUSIONS

It appears that, irrespective of the age of the CFS patients or the duration of their symptoms, choline-containing compounds are elevated in the basal ganglia. Taken together, recent ^1H -MRS observations in appropriately defined, non-psychiatric CFS population objectively confirm an underlying neurobiological process affecting neural cell membrane function. ^1H MRS observations in CFS emphasise the need to explore long-term effects of viral-cell interactions on membrane functions for a better understanding of this common, potentially disabling condition. Additionally, regional brain ^1H MRS has the potential to be used as an objective marker in the research studies of therapeutic interventions in CFS.

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