^{1}H MRSI Comparison of Chronic Fatigue Syndrome and Generalized Anxiety Disorder

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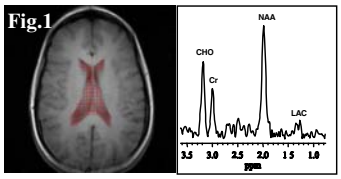
Introduction. Chronic fatigue syndrome (CFS) is characterized by disabling, otherwise unexplainable fatigue of at least 6 months duration. Additional symptoms may include bone and muscle pain, impaired memory and concentration, headache, sleep disturbances, anxiety, and/or depression.[1] Its pathophysiology is poorly characterized, but recent ^{1}H MRSI studies have found significant cerebral metabolic abnormalities in the basal ganglia[2] and occipital cortex[3] of CFS patients. Recently, we reported increased ventricular lactate in a sample of CFS patients, consistent with possible cerebral energy dysfunction.[4] However, the specificity of these findings is unclear, due to considerable symptomatic overlap between CFS and generalized anxiety disorder (GAD). The present study thus used ^{1}H MRSI to explore regional differences between the neurometabolic profile of CFS and that of GAD -- a phenotypically related, yet distinct, disorder (disease control) -- and healthy controls.

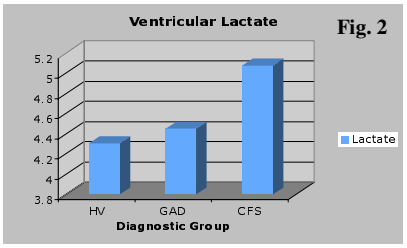
Methods ***Clinical Methods***. Fifteen medically healthy volunteers with no history of psychopathology (9 females, 6 males, mean age = 36.9 , SD= 11.39 and sixteen medication-free patients with GAD (11 F, 5 M, mean age=38.1, SD=13.25) were recruited for ^{1}H MR spectroscopic imaging. Sixteen CFS patients (11 F, 5 M, mean age=37.6, SD = 9.9) were recruited from a private practice; these patients were medication-free for at least 48 hours prior to the scan. Mood state prior to the MRS scan was assessed in all groups using the Hamilton Rating Scale for Depression (HAM-D 17) and the Hamilton Anxiety Rating Scale (HAM-A). There were no significant differences between the three groups in mean age, full scale IQ, body mass index, or years of education (p>0.15 for all).

MRSI Methods. All scans were performed on a General Electric 3.0 T MRI system. Following acquisition of localizer MRI series, a 4-section ^{1}H MRSI scan was performed using the method of Duyn et al[5], with 15-mm thick slices, 3.5-mm gaps, TE/TR 280/2300 ms, FOV 240 mm, 32x32 phase-encoding steps with circular k-space sampling, 512 points along the signal acquisition domain, and a spectral width of 2500 Hz. Raw data were processed using standard fast Fourier transform algorithm, and the peak metabolite areas within each ROI were obtained by frequency-domain spectral fitting. All values were expressed as ratios relative the root-mean-square (rms) of the background noise in each voxel. Groups were compared using ANOVA with post-hoc testing by Tukey HSD test; correlation coefficients were computed to assess relations of clinical measures with MRSI measures. Means are presented ±SD.

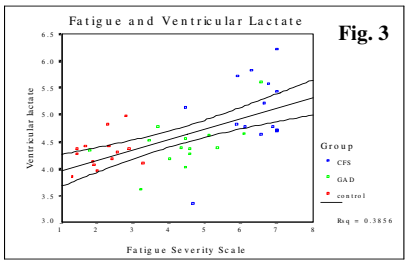
Results and Discussion. ***Fatigue and diagnostic group***. Patients with CFS had significantly higher scores (p<0.001) on the Fatigue Severity Scale (FSS) (6.30± .84) than did GAD patients (4.47±1.15, p<0.001) or healthy controls (2.37±1.00, p<0.001). ***Ventricular Lactate***: As we had previously reported[4], a reproducible finding in the MRSI spectra of CFS is the presence of lactate in cerebrospinal fluid, primarily in the bodies of the lateral ventricle (Fig. 1).



In the present study, we have found that, quantitatively, ventricular lactate significantly differed between the three diagnostic groups (p<0.001), with CFS patients having higher mean lactate (5.08±0.66) vs. both GAD patients (4.45±0.44; p=0.004), and healthy volunteers (4.31±0.31; p<0.001) (Fig. 2). Across all subjects, ventricular lactate concentrations did not correlate with any demographic variable, including age, body mass index, or IQ. However, a highly significant correlation (Fig. 3) was found between ventricular lactate and fatigue severity scores (Spearman rho=0.636; p<0.001, n =42). This significant relationship remained while adjusting for depression severity (r=0.65, p<0.001). No significant correlations were observed between ventricular lactate and key clinical assessments other than the FSS, including the HAM-D17, HAM-A, and the Pittsburgh Sleep Quality Index (PSQI), indicating that lactate and fatigue may be singularly linked.



Basal Ganglia/Thalami and Occipital Cortex. No significant differences were seen in basal ganglia regions; however differences were observed between groups in right thalamic NAA/Cr (p=0.004). CFS patients had elevated NAA/Cr (2.96± .39) compared to controls (2.47± .43, p=0.004) and GAD patients (2.61± .36, p =0.046). However, in the same region, CFS patients also trended towards lower Cr/RMS (8.22 ±2.01) than controls (9.90 ± 2.39, p = 0.069). This may indicate that the increase in NAA/Cr in CFS patients as compared to controls may arise because of a decrease in Cr, the denominator of the ratio, and not because of an increase in the absolute concentration of NAA . In occipital grey matter, NAA/Cr was significantly different between groups (p=0.006), and was higher in CFS patients (3.13±1.04) vs. GAD patients (2.39±0.38, p=0.012) and controls (2.41±0.46, p=0.017). Occipital grey NAA/Cr strongly correlated with FSS scores (r=. 428, p=0.003, n = 45). In the occipital cortical area, group effects were seen across multiple neurometabolites: 1) Cho/Cr (p=0.033), with lower Cho/Creatine in CFS (0.77±0.15) as compared to GAD (1.00±. 36; p=0.026); 2) NAA/Cho (p=0.009), higher in CFS (3.34± 1.04) vs. GAD (2.53± 0.71, p=0.011 and controls (2.66 ± 0.31, p = 0.044); and 3) Cho/rms (p= .031), with lower Cho/rms in CFS (6.90± 2.21) than in GAD (9.15± 2.86, p=.025). Here, a relative decrease in the levels of choline in CFS patients as compared to GAD patients may explain the higher NAA/Cho in the former group.



Conclusion. Consistent with our previous uncontrolled case series, CFS is associated with markedly elevated ventricular lactate, when compared to the matched healthy controls and patients with a phenotypically similar disorder (GAD). The high correlation between lactate and fatigue severity, and not to any other rating scale, suggests a specific relationship between subjective fatigue and brain lactate concentrations. There were also preliminary suggestions of additional distinct neurometabolic abnormalities in CFS, particularly in occipital cortex: elevated NAA/Cr and NAA/Cho, and decreased Cho/Cr and Cho/RMS. The MRS profile observed in this group of CFS patients is potentially consistent with a pathophysiological model of mitochondrial dysfunction that involves oxidative phosphorylation and a resultant shift toward glycolytic energy production. Future studies in larger samples should test the specificity, sensitivity, and positive predictive value of ventricular lactate (and other MRS metabolites) to establish their validity as viable diagnostic biomarkers for this poorly understood condition.

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Acknowledgement. This work was supported by an Investigator-initiated Research Grant from the CFIDS Association of America, Inc. (Shungu), by NIH Grant K23MH069656 (Mathew), NIH Grant MO1-RR-0071 (General Clinical Research Center, Mount Sinai School of Medicine), and by Weill Cornell Medical College New Faculty Development Funds (Shungu).