INTRODUCTION

Chronic fatigue syndrome (CFS) is a complex illness, which is often misdiagnosed as a psychiatric illness. In two previous studies, we used $^1$H MRSi to compare neurometabolites in CFS with generalized anxiety disorder (GAD) [1] and major depressive disorder (MDD) [2], common neuropsychiatric disorders with extensive symptom overlap with CFS. In those reports, CFS patients showed significantly elevated ventricular cerebrospinal fluid (CSF) lactate compared to healthy control subjects [1,2] and to patients with GAD [1], while no differences were found between CFS and MDD [2]. Importantly, our replicated finding of significant elevations of ventricular lactate in CFS suggested a potential illness-associated biomarker, whose understanding could shed new light onto the pathophysiology of the illness. In the present third independent cross-sectional study, we aimed to investigate a pathophysiological model of CFS, which postulates that sustained oxidative stress [3] and associated oxidant damage lead to cerebral hypoperfusion and/or to secondary mitochondrial dysfunction that could potentially explain our observed cross-sectional elevations of ventricular lactate. Specifically, this study had two primary objectives: (a) to use $^1$H MRSi to replicate in a new cohort our finding of cross-sectional elevations of ventricular lactate in CFS, and (b) to determine whether the postulated [3] and experimentally documented [4,5] oxidative stress increases in the disorder are associated with antioxidant capacity deficit by using $^1$H MRSi to measure in vivo brain levels of glutathione (GSH), the most abundant antioxidant in CNS. In addition, we used arterial spin-labeling (ASL) MRI to replicate prior observations of decreased regional cerebral blood flow (rCBF) in CFS [6,7] that may explain the observed lactate elevations, and $^{31}$P MRSi to measure regional brain levels of high-energy phosphates (HEPs) as indices of a possible secondary mitochondrial dysfunction in CFS [3], whose presence might also be associated with elevations in lactate.

METHODS

Subjects: Participants included 15 unmedicated CFS patients diagnosed according to the CDC criteria [8], 15 unmedicated patients with major depressive disorder (MDD), as established by DSM-IV-TR criteria who served as “disease controls”, and 13 age- and sex-matched healthy volunteer (HV) subjects.

In vivo Neuroimaging Measurements: A GE 3.0T MR system was used to conduct the following neuroimaging studies in a single 60-90 min session: (a) In vivo brain GSH data were acquired using fast spin echo-J-editing and normalized to the peak area of the lactate peak, expressing for the first time a correlation of occipital GSH and ventricular lactate levels in CFS subjects, and 13 age- and sex-matched healthy volunteer (HV) subjects. Specifically, we found no differences between the groups in any phosphate metabolites, measured by in vivo brain GSH data were acquired using fast spin echo-J-editing and normalized to the peak area of the lactate peak, expressing for the first time a correlation of occipital GSH and ventricular lactate levels in CFS subjects, and 13 age- and sex-matched healthy volunteer (HV) subjects.

RESULTS AND DISCUSSION

(a) Ventricular CSF Lactate: Mean ventricular CSF lactate, measured by $^1$H MRSi and expressed in institutional units (i.u.), differed significantly between the CFS, MDD and HV groups (F$_{2,35} = 16.78$, p < .001) (Fig. 1). Elevated ventricular lactate levels were also found in MDD compared to HV (p = .009). There was a weak trend toward higher ventricular lactate in CFS compared to MDD (p = .114). This finding represents a third independent replication of our previous observation of increased CSF lactate in CFS, suggesting this to be a feature of the disorder.

(b) Cortical GSH: Comparisons of occipital GSH levels measured by J-editing and normalized to the peak area of the unsuppressed voxel tissue water (W) revealed a main effect of diagnostic group (F$_{2,35} = 15.93$, p < .001), which post hoc testing attributed to reductions of GSH/W (Fig. 2, bottom) in both CFS (p < .001) and MDD (p = .004) compared to HV. There was a non-significant trend toward lower GSH/W in HV compared to MDD (p = .086). To our knowledge, this is the first study to document in vivo cortical GSH deficits in CFS (a 36% decrease) and in MDD (a 21% decrease), which supports a role for increased oxidative stress in both disorders, and provides a compelling rationale for investigating treatment strategies, such as supplementation with N-acetylcyesteine (NAC) or other synthetic precursors, that can restore cortical GSH reserves to potentially lower oxidative stress.

(c) Regional Cerebral Blood Flow (rCBF): Following intensity and morphological normalization and statistical analysis using the Statistical Parametric Mapping (SPM) software, Version 5, we found significantly different ASL-derived CBF values at the uncorrected significance level of .001 in two brain regions. The CFS group had lower rCBF values in the left anterior cingulate cortex (p = .039) and in the right lingual (p = .016) regions compared to the HV group. In addition, there was a trend toward lower rCBF in the left anterior cingulate cortex in MDD subjects compared to HV (p = .08). There were no significant differences in rCBF values between CFS and MDD in any brain region. These results are consistent with prior reports of decreased rCBF in CFS [6,7].

(d) High-Energy Phosphates: We found no differences between the groups in any phosphate metabolites, suggesting that mitochondrial dysfunction may not be a key factor in our reported lactate elevations in CFS.

(e) Correlations among Lactate, GSH and Clinical Variables: In exploratory correlational analyses, we found ventricular lactate and cortical GSH to correlate inversely (Fig. 3), not only with each other (r = -.545; p < .001), but also with several key indices of physical health and disability across all participants, further supporting a role for oxidative stress the pathophysiology of CFS and MDD.

CONCLUSION

Our finding of a significant 36% cortical GSH deficit in CFS has provided both mechanistic and face validity for an emerging oxidative stress model of this poorly understood illness, documenting for the first time a significant decrease in antioxidant capacity in living brain.

REFERENCES