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Elevations of ventricular lactate levels occur in both chronic fatigue syndrome and fibromyalgia

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ABSTRACT

Background: Chronic fatigue syndrome (CFS) and fibromyalgia (FM) frequently have overlapping symptoms, leading to the suggestion that the same disease processes may underpin the two disorders – the unitary hypothesis. However, studies investigating the two disorders have reported substantial clinical and/or biological differences between them, suggesting distinct pathophysiological underpinnings.

Purpose: The purpose of this study was to further add to the body of evidence favoring different disease processes in CFS and FM by comparing ventricular cerebrospinal fluid lactate levels among patients with CFS alone, FM alone, overlapping CFS and FM symptoms, and healthy control subjects.

Methods: Ventricular lactate was assessed *in vivo* with proton magnetic resonance spectroscopic imaging (^{1}H MRSI) with the results normed across the two studies in which the data were collected.

Results: Mean CSF lactate levels in CFS, FM and CFS + FM did not differ among the three groups, but were all significantly higher than the mean values for control subjects.

Conclusion: While patients with CFS, FM and comorbid CFS and FM can be differentiated from healthy subjects based on measures of CFS lactate, this neuroimaging outcome measure is not a viable biomarker for differentiating CFS from FM or from patients in whom symptoms of the two disorders overlap.

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Chronic fatigue syndrome (CFS) and Fibromyalgia (FM) are medically unexplained illnesses which often co-occur [1]. Because the two illnesses can have features in common, some [2, 3] have suggested that they are essentially the same illness with FM patients reporting more problems with pain and CFS patients more problems with fatigue. We have termed this the 'single syndrome' hypothesis [1].

The existence of separate criteria for diagnosis of each of these disorders allows one to test the hypothesis that the two illnesses are the same or different. Finding similar

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biological changes in both illnesses would argue for commonality, or at least a shared pathophysiological marker, while finding differences would argue for different pathophysiological underpinnings for each illness. In a series of studies, we have looked across a number of physiological variables and have found differences between the two illnesses in sleep pattern [4], rates of sleep pathology [5], cardiovascular response to exercise [6] and in the dopaminergic response to a tryptophan probe [7]. In several studies, we have reported that cerebral lactate is elevated in CFS [8, 9]; recently we have extended that work and have found that patients with FM alone and those with CFS plus FM have elevations of ventricular lactate which differ significantly from healthy volunteers [10]. The purpose of this study was to extend that observation to include patients with CFS only in order to allow a comparison across these three diagnostic groups – CFS alone, FM alone and CFS + FM.

Methods

The subjects were patients with FM only, CFS only or CFS plus FM. FM only patients fulfilled the 1990 case definition [11] and reported over 3 months of widespread pain and had at least 11 of 18 tender points when pressed with 4 kg of force. CFS only patients fulfilled the 1994 CDC case definition [12] as modified by our Center as follows: Patients had to report having new onset of fatigue lasting at least 6 months and severe enough to produce a substantial or greater decrease in activity in either work, school, personal or social spheres where substantial was defined as a 3 on a 0 to 5 visual analog scale (1 was mild reduction and 5 very severe reduction). In addition, patients had to report having at least a substantial burden (again at least a 3 on the 0 to 5 scale) from four or more of the following symptoms: sore throat; tender glands; headache; myalgia; arthralgia; brain fog; unrefreshing sleep or syndromic worsening following minimal exertion. Patients with CFS plus FM fulfilled both case definitions while those with CFS only did not fulfill criteria for the diagnosis of FM and those with FM only did not fulfill criteria for CFS.

Patients with FM only or CFS plus FM were drawn from a population whose results have already been reported [10]. These patients had participated in a double blind, placebo controlled trial of milnacipran and, while medications from a range of class of drugs were allowed, SNRIs were not allowed (cohort 1). An additional group of patients with CFS only or CFS plus FM, taking no brain-active medications, also participated (cohort 2). In addition, subjects for both cohorts included healthy people, who were age and sex matched to the patients and did not exercise regularly.

Protocol for ventricular lactate measurements by ^{1}H MRSI

All neuroimaging studies were conducted on a research-dedicated, multinuclear General Electric 3.0 T EXCITE MR system at the Citigroup Biomedical Imaging Center of Weill Cornell Medical College.

In vivo levels of ventricular lactate were obtained in all subjects with a standard quadrature single-channel head coil using a multislice ^{1}H MRSI technique [13], as fully described previously [8, 10]. The lactate level data presented in this study are the mean values of the peak areas obtained for all voxels within the ventricular space. For normalization of levels across subjects, the lactate peak areas were expressed in institutional units (i.u.) as ratios

relative to the root-mean-square (rms) of the background noise in each spectrum – an approach that we have used previously in a number of studies [8, 14, 15].

Statistical methods

Variables were evaluated for normality of distribution. Since values of ventricular lactate had been acquired using two different neuroimaging methods [$n = 40$ and $N = 34$ respectively; total = 74 subjects], values from each cohort were converted to *z*-scores and combined into a single dependent variable of standardized values [16]. Since there were no male controls, male patients ($N = 13$) were excluded from the analysis (Data from these men did not exhibit significantly different ventricular lactate scores from the women patient participants, when controlling for age and BMI ($p > .05$). In a general linear model (GLM), the 'patient status' variable was used as a categorical variable [healthy volunteers ($n = 29$), CFS alone ($n = 17$), FM alone ($n = 7$), CFS + FM combined ($n = 21$)] and covariates included age and body mass index (BMI). When results of this analysis were significant, post-hoc GLMs were computed to allow paired comparisons to be made using the same covariates.

To evaluate the effects of BMI across diagnostic groups, the group × BMI interaction was examined in a factorial design with *z*-score ventricular lactate as the dependent variable and age as a covariate. To correct for the three potential post-hoc comparison (CFS versus HV, FM versus HV and CFS + FM versus HV), significance was set at $p \leq .016$, two-tailed. Data are presented as means with standard errors in parentheses.

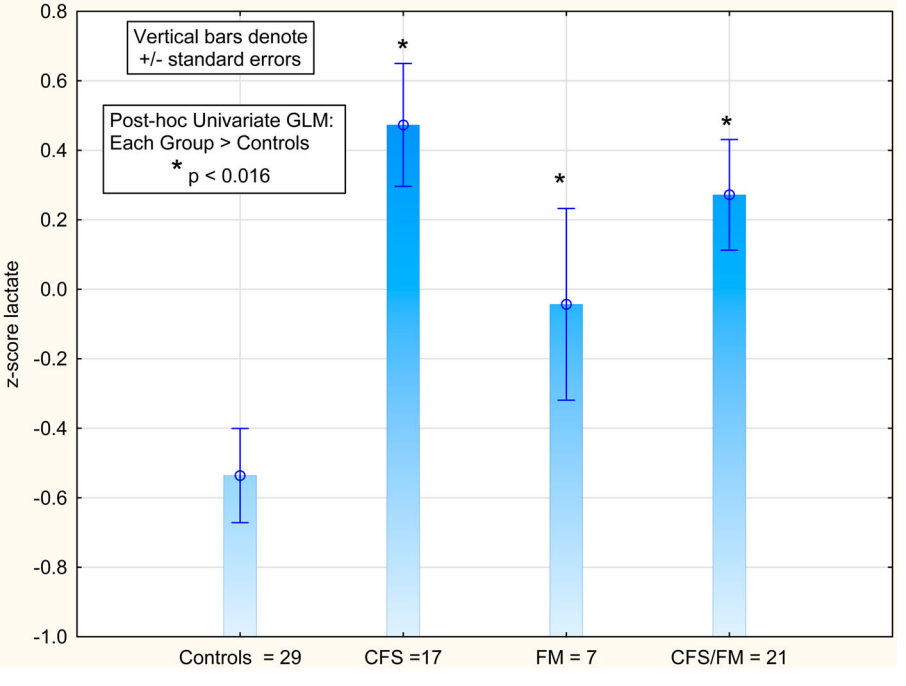

Figure 1. Mean and standard errors for *z*-score converted ventricular lactate values for controls, patients with CFS alone, FM alone and CFS plus FM. Asterisks indicate ($p < .016$) significant differences of patient groups from healthy controls.

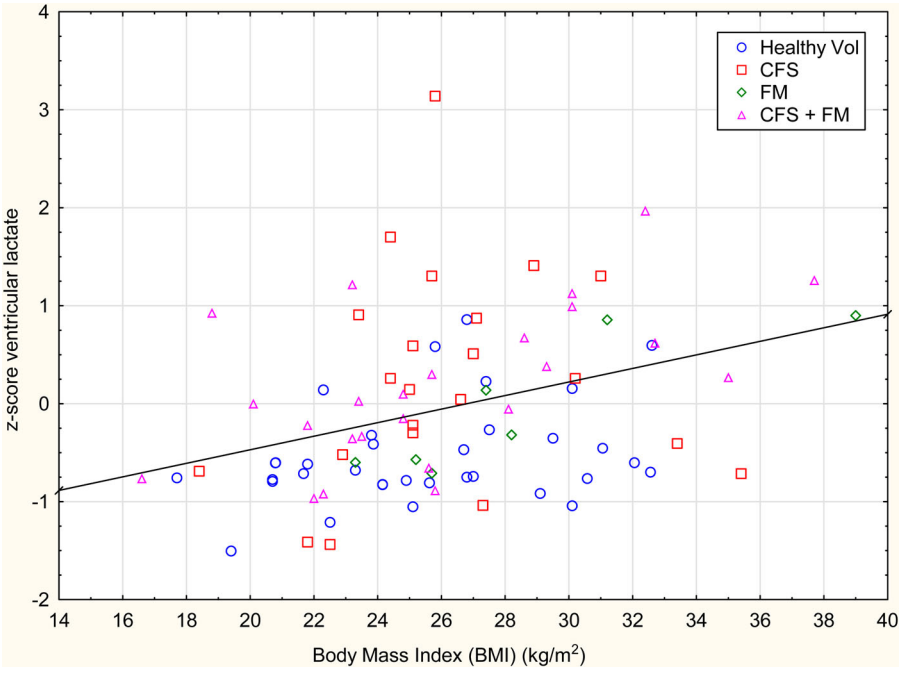

Figure 2. Relation between BMI and *z*-score converted ventricular lactate values of all study subjects combined [BMI [$F_{(1,68)} = 11.85$; $p = .001$] where an increase in BMI was associated with increased lactate, adjusted for age and diagnostic group].

Results

Variables were normally distributed. There was an overall group effect for *z*-score ventricular lactate for diagnostic group [$F_{(3,68)} = 7.59$; $p = .0002$; partial $\eta^2 = 0.25$, see Figure 1]. The model was adjusted for age [$F_{(1,68)} = 0.99$; $p = .32$] and BMI [$F_{(1,68)} = 11.85$; $p = .001$] where an increase in BMI was associated with increased lactate (Figure 2). Univariate post-hoc testing covarying for age and BMI revealed that patients with CFS alone exhibited higher levels of *z*-score ventricular lactate [$N = 17$, mean (SE) = 0.47 (0.17)] compared to healthy volunteers [$N = 29$, mean (SE) = −0.53 (0.13); $F_{(1,42)} = 18.66$; $p = .00009$]. Similar effects, adjusting for age and BMI, were observed for FM alone patients [$N = 7$, mean (SE) = −0.04 (0.16); $F_{(1,32)} = 7.08$; $p = .012$] and patients with CFS and FM [$N = 21$, mean (SE) = 0.27 (0.12); $F_{(1,46)} = 6.56$; $p = .00004$].

There were no significant differences for *z*-score converted ventricular lactate among the illness groups. Effects were unchanged by exclusion of a CFS outlier > 3 standard deviations from the mean. Although BMI directly predicted *z*-lactate (Pearson's $r = 0.37$; $N = 74$; $p = .001$; see Figure 2) the group$p \times$ BMI interaction was not significant, indicating no significant difference in the *z*-lactate increases for increases in BMI across the three diagnostic groups.

Discussion

Relative to healthy controls, ventricular lactate is elevated to the same degree for patients with CFS alone, FM alone and CFS plus FM. While elevations in this variable could be used as

biological markers of syndromes characterized by medically unexplained pain or fatigue, they cannot be used to differentiate CFS from FM. However, the existence of elevations in ventricular lactate in both illnesses suggests a problem in brain-related mitochondrial metabolism. Accumulations of ventricular lactate can be assumed to occur when aerobic metabolism is impaired. Pyruvate generated by anaerobic metabolism of glucose is not aerobically metabolized and is converted to lactate by lactate dehydrogenase [14]. Since elevations in lactate may reflect a down-stream effect of areas of anaerobic metabolism or a result of central neuro-inflammation, finding elevations do not necessarily mean that the mechanism for the lactate elevations is the same for CFS [9], where oxidative stress has been invoked, as for FM. Further research will be needed to answer this question.

Regardless, finding similar levels of ventricular lactate for CFS, CFS plus FM and FM is additional support for the single syndrome hypothesis. Although further research is needed to determine if CFS and FM are different illnesses or variants of the same pathophysiological process, ventricular lactate could certainly serve as a biological marker of underlying brain dysfunction for some patients with either or both diagnoses.

In summary, this is the first report, to our knowledge, that included, using standardized scores, three patient groups – CFS, FM and CFS plus FM – and demonstrated that each of the three groups separated from healthy volunteers but did not separate from each other. Moreover, this is the first biomarker we are aware of that identifies a biological comorbidity shared by both CFS and FM. Limitations include that all subjects in the analysis were females, but male values did not differ from females. Moreover, in order to obtain the current results, two cohorts were combined but standardized scores, which normalize both mean and variance, were used to combine the data [16]. Further studies are required to elucidate the pathophysiology of the FM-CFS spectrum.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Ms Xiangling Mao is a researcher in Radiology at Weill Cornell Medicine. She is a computer scientist with extensive experience developing computer software packages for processing, analyzing and displaying various neuroimaging data.

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