Metabolite Features of Chronic Fatigue Syndrome (CFS) Investigated by Multislice $^1$H MRSI

D. C. Shungu$^1$, X. Mao$^1$, S. Levine$^2$, P. Cheney$^3$

$^1$Department of Radiology, Columbia University, New York, NY, United States, $^2$Infectious Disease Specialist, New York, NY, United States, $^3$The Cheney Clinic, Asheville, NC, United States

**Synopsis.** This study reports the $^1$H MR spectral characteristics associated with chronic fatigue syndrome. Thirty-one subjects diagnosed with the disorder were investigated. Fifteen of 31 exhibited abnormal MRSI spectra, whereas 16 of 31 showed no significant metabolic abnormalities. Two types of distinct metabolic features were found in the 15 patients with spectroscopic abnormalities: (a) 12 of 15 patients showed increased levels of ventricular lactate, and (b) 9 of 15 patients showed increased tCho/tCr and decreased NAA/tCr ratios in the thalamic/basal ganglia area, with 6 subjects in the preceding two groups exhibiting both types of features. These results suggest that CFS might be associated with mitochondrial energy metabolism dysfunction, as well as with neuronal damage or degeneration. The different spectral patterns might also suggest a heterogeneous pathophysiology for the disorder.

**Introduction.** Chronic fatigue syndrome (CFS) is a debilitating disorder that is characterized by severe fatigue and a constellation of symptoms, including impaired concentration and short-term memory, sleep disturbances and musculoskeletal pain. Currently, the diagnosis of CFS is made only after alternative medical and psychiatric causes of the symptoms have been excluded. There are no scientifically validated tests for the illness, nor are there widely accepted cures. In this study, we report the results of a $^1$H MRSI investigation of 31 patients who presented with the symptoms of CFS. As far as we can determine, this study represents the largest MRS study of individuals with the "classical" CFS symptomatology.

**Methods.** Following a sagittal “scout” MRI scan, multislice $^1$H MRSI was performed on each patient using the method of Duyn et al., with TE/TR 280/2300 ms, FOV 240 mm, two 15-mm slices with the most inferior slice traversing the bodies of the lateral ventricle and including the upper basal ganglia and the thalami, 3.5 mm inter-slice gaps, 32x32 phase-encoding gradient steps with circular k-space sampling, and 256 time-domain sample points. Pericranial fat and tissues were suppressed using octagonally-tailored outer volume suppression pulses, and water suppression was achieved with a single CHESS pulse followed by crusher gradients. The recorded MRSI data were examined for possible metabolic abnormalities. Dysfunctional mitochondrial energy metabolism is suspected in CFS, so we looked for signs of ventricular or cerebrospinal (CSF) lactate (Lac) elevation, similar to that which we previously reported in patients with mitochondrial encephalomyopathies. There have been suggestions of basal ganglia/thalamic involvement in CFS, and, therefore, spectra from voxels within this region were also examined for possible metabolic abnormalities.

**Results.** Fifteen of 31 exhibited abnormal MRSI spectra, whereas 16 of 31 showed no significant metabolic abnormalities. Two types of distinct metabolic features were found in the 15 patients with spectroscopic abnormalities: (a) 12 of 15 patients showed increased levels of ventricular lactate (Fig 1), and (b) 9 of 15 patients showed increased tCho/tCr and decreased NAA/tCr ratios in the thalamic/basal ganglia area (Fig 2), with 6 subjects in the two groups exhibiting both increased ventricular Lac and increased thalamic/basal ganglia tCho/tCr and decreased NAA/tCr.

**Discussion.** This study has presented MR spectral patterns which are associated with patients diagnosed with CFS. Figure 1, extracted from a 7.5x7.5x15 mm$^3$ voxel within the anterior horn of the lateral ventricle, shows an unambiguously elevated Lac methyl doublet at 1.33 ppm. The detection of such a lactate elevation in 12 of 31 (38.7%) patients suggests the possibility of a mitochondrial energy metabolism dysfunction in CFS, as this is finding is akin to that which we previously reported in patients with mitochondrial encephalomyopathies. The latter disorders are characterized by a larger elevation of CSF lactate. The spectrum in Fig. 2 was obtained from the thalamic area in the patient with the most dramatic increase of tCho/tCr and decrease of NAA/tCr. This increase of tCho/tCr and decrease of NAA/tCr suggest that CFS might also be associated with neuronal damage, degeneration and/or dysfunction. This seems to substantiate an emerging theory on the pathophysiology of CFS that is supported by diverse biochemical and physiological observations. The theory posits that CFS might be caused in part by accumulation of the potent oxidant, peroxynitrite, which biochemically increases levels of nitric oxide and superoxide, which, in turn, react to produce even more peroxynitrite. The long disability of CFS may be due to this cycle, whose effects could lead to neuronal damage or degeneration. The increase of tCho/tCr and decrease of NAA/tCr would be consistent with such a disruptive process, with the increase of tCho/tCr indicating cell membrane damage and the decrease of NAA/tCr indicating neuronal loss. In addition to the above findings, the observations that 6 of 31 subjects showed both types of abnormalities (Figs. 1 & 2) and that 50% of the subjects showed no significant metabolic abnormality on the $^1$H MRSI scans suggest a complex pathophysiology, raising the question of whether the observed metabolic abnormalities might be correlated with disease severity. We are currently conducting statistical tests of the potential association between the outcome measures (metabolite levels) and CFS symptomatology, the results of which will be presented.

**References**
