Measuring Oxidative Stress in the Brain and CFS: Therapeutic Implications

N Weiduschat[1], X Mao[1], D Vu[2], M Blate[2], G Kang[1], HS Halinder[3], AS Artis[4], S Banergee[4], G Lange[2], C Henchcliffe[3], B Natelson[2], DC Shungu[1]

[1]Departments of Radiology, Neurology and Neuroscience, Healthcare Policy and Research, Weill Cornell Medicine, New York, NY;

[2]Department of Neurology, Mount Sinai Beth Israel Medical Center, New York, NY, USA

Weill Cornell Medicine

Mount Sinai Beth Israel

ABSTRACT

OBJECTIVES

We previously reported a robust 36% deficit of occipital cortex glutathione (GSH) – the primary tissue antioxidant – in patients with ME/CFS compared to healthy comparison (HC) subjects, a finding that implicated oxidative stress in the disorder. The objectives of this study were (a) to confirm the presence of cortical GSH deficit in ME/CFS patients as measured *in vivo* with proton magnetic resonance spectroscopy (^{1}H MRS), and (b) to assess whether 4 weeks of supplementing the patients daily with the GSH synthesis precursor or prodrug, N-acetylcysteine (NAC), would spur in situ synthesis and significant elevation of cortical GSH compared to baseline.

METHODS

For this pilot clinical study, we recruited 16 medication-free patients meeting the CDC criteria for ME/CFS and 15 HC subjects. Following baseline measurement of occipital cortex GSH with ^{1}H MRS and administration of a battery of clinical assessments, both ME/CFS and HC participants received a 4-week supplement of 1800mg NAC/day. After 4 weeks, identical ^{1}H MRS scan and clinical assessments were conducted to determine the effect of NAC on cortical GSH levels and on ME/CFS symptoms as assessed with the ME/CFS Symptom Inventory.

RESULTS

At baseline, controlling for age and race, cortical GSH levels were 15% lower in ME/CFS than in HC (95%CI: -0.0005,0; p=0.04, one-tailed as the GSH deficit in ME/CFS and direction of GSH changes with NAC treatment were postulated *a priori*). Following 4 weeks of daily NAC supplementation, cortical GSH levels rose significantly relative to baseline (95%CI: 0.0001,0.0006; p=0.004, one-tailed) in ME/CFS patients to match those in HC, which did not differ compared to baseline (95%CI: -0.0002,0.0003; p=0.33, one-tailed). Lastly, NAC supplementation markedly improved symptoms in ME/CFS patients, with significant decreases in CDC ME/CFS symptom inventory total scores (95%CI: -51.5-9.6; p=0.006), case definition scores (95%CI: -28.2-2 .0; p=0.03) and "other symptoms" scores (95%CI: -24.0-7.3; p<0.001). However, GSH levels did not correlate with any clinical measure.

CONCLUSION

The results of this study have replicated our prior finding of a cortical GSH deficit in patients with ME/CFS, and provided direct evidence that NAC crosses the blood-brain barrier to spur in situ synthesis and elevation of cortical GSH in the disorder. Significantly, increasing cortical GSH levels with NAC ameliorated symptoms in ME/CFS patients. However, due to the lack of placebo control group, a strong placebo effect is likely. Future placebo-controlled, randomized clinical trials to evaluate the optimal dose, treatment duration and clinical efficacy of NAC in ME/CFS seem warranted.

REQUESTING A COPY OF PRESENTATION

A copy of the PowerPoint presentation associated with the provided ABSTRACT can be obtained for personal use, as opposed to “for wide dissemination”, because this material has not yet been published. Please email the Principal Investigated, Dr. Dikoma Shungu, at dcs7001@med.cornell.edu .

ACKNOWLEDGEMENT

- ME/CFS Patients and volunteers for participation

Funding sources:

- NINR R21 Award (Shungu)
- NIMH R01 Award (Shungu)
- CFIDS Association of America Pilot Study Awards (Shungu)
- NIMH Neurotechnology R01 (Shungu)