Metabolic abnormalities in the brain of subjects with Gulf War Illness

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Introduction

Some veterans who served in the Persian Gulf war have reported a variety of physical and neuropsychological symptoms, termed Gulf War Illness (GWI). These symptoms have been largely attributed to stress, since most subjects did not demonstrate abnormalities on conventional physical examinations or laboratory tests. Recently, Haley et al. (1) reported reductions of the neuronal marker N-acetylaspartate (NAA) in the basal ganglia and pons of a highly selected subset of GWI subjects, suggesting that GWI may be associated with damage to these regions.

This pilot study was performed to replicate Haley's metabolic findings in another cohort of subjects with GWI and to assess whether potential group differences may be due to structural (tissue type) differences in the basal ganglia.

Methods

We studied 11 GWI subjects (9m, 2f, age = 35.8 ± 5.1 years) who are enrolled in a VA multi-center study on GWI treatment. They met 2 of the 3 criteria for GWI. Subjects were assessed with PRIME MD for DSM IV, but not with SCID (for depression or PTSD) or CAPS (for PTSD). Eleven controls (34.4 ± 9.2 years) were healthy non-veterans without history of alcohol abuse, major depression, or PTSD. All measurements were carried out on a 1.5T Siemens (Magnetom VISION) system using a standard Siemens head coil. MRI consisted of scout, DSE (TR/TE1/TE2 = 5000/20/80), and MPRAGE (TR/TE = 9.7/4) sequences that were used for segmentation of MR images into tissue types using in-house software. Single volume PRESS spectra were obtained from the right basal ganglia and from the pons, replicating experimental conditions of Haley et al. (1). Experimental parameters: TR/TE = 1800/272 ms, 256 averages; basal ganglia spectra centered on globus pallidus: 20 x 40 x 15 mm3 along left-right x anterior-posterior x inferior-superior directions; pons 18 x 18 x 18 mm3.

Results and Discussion

All GWI subjects reported cognitive dysfunction and probably fit into Haley's Syndrome 2 category. PRIME MD showed that they had little or no alcohol or drug abuse, and no psychotic symptoms. However, 8/11 GWI subjects had PTSD symptoms, and many of them had depressive symptoms as well.

1H MRS data from the 11 subjects with Syndrome 2 are shown in the Table. In the basal ganglia (BG) of GWI, NAA/Cr was reduced 11% compared with controls ($p < 0.05$) and there was a trend to lower absolute NAA (-10%). There were no Cho or Cr group differences. NAA was also 13% lower in the pons of GWI, but this was not significant.

MRI segmentation analyses showed no significant group differences in the volumes of intracranial vault, WM, cortical and subcortical GM, sulcal and ventricular CSF, caudate, white matter signal hyperintensities, or left and right hippocampi. This lack of volumetric differences emphasizes the significance of the NAA changes in the basal ganglia.

In summary, this pilot study of a small number of subjects replicates Haley's findings of lower NAA in the right basal ganglia of GWI subjects. In addition, we found that structural differences in the size of subcortical nuclei cannot be responsible for the metabolic findings. However, our subjects (and Haley's) were not rigorously assessed for comorbid conditions such as alcoholism, depression and PTSD. It is unclear if and what kind of metabolic effects in the basal ganglia are associated with these conditions. These potential confounds and relaxation effects need to be accounted for in future work.

References

Haley RW, Marshall W, McDonald G, Daugherty M, Petty F, Fleckenstein JL. Brain Abnormalities in Gulf War Syndrome: Evaluation by 1H Magnetic Resonance Spectroscopy. Radiology 2000; 215:807-817.

1H MRS measures in the right basal ganglia (BG)

	GWI	controls	change [%]	significance p
NAA/Cr	3.62 ± 0.41	4.06 ± 0.72	-11	0.05
NAA/Cho	3.59 ± 0.92	3.90 ± 0.45	-8	0.16
Cho/Cr	1.10 ± 0.44	1.05 ± 0.22	+5	0.38
NAA [a.u.]	568 ± 160	633 ± 79	-10	0.12