Functional Correlates of Neuronal Loss in Gulf War Syndrome

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Introduction

Patients with three Haley Gulf War syndromes were previously shown to have reduced neuronal mass in the basal ganglia (BG) and pons, as determined by abnormally low N-acetyl aspartate to creatine (NAA/Cr) ratios on magnetic resonance spectroscopy (MRS) brain scans. These prior findings supported an organic basis to the symptom complexes. It remains to be determined, however, the extent to which the MRS findings in deep brain structures explain the varied symptoms of this group of Gulf War veterans. We hypothesize that if the NAA/Cr ratios are physiologically important, they should correlate with symptoms and clinical measures of brain function. To test the hypothesis, we correlated NAA/Cr ratios with factor scores for symptoms of Haley syndrome 2, results of audiovestibular tests, psychiatric evaluations, and brain dopamine turnover.

Methods

Twelve veterans with Haley syndrome 2 and 17 age-sex-education-matched controls from the same battalion were hospitalized for a week in the Parkland General Clinical Research Center, where they underwent single voxel MRS of the right and left basal ganglia and pons and a battery of clinical tests. Prior to hospitalization, the subjects completed a questionnaire covering the symptoms commonly reported by ill Gulf War veterans. These data were studied via factor analysis that permitted grouping of the patients by factor scores indicating shared symptoms. Of the three symptom complexes (syndromes) with the most strongly clustered symptoms, syndrome 2 was selected for further analysis because it was found to be the most disabling clinically and to have the most abnormal NAA/Cr ratios in both basal ganglia and pons.

In addition to symptom measures, tests of deep brain function, including indexes of brain dopamine turnover index (plasma homovanillic acid / plasma MHPG) and serotonin turnover index (plasma 5-hydroxy-indole-acetic acid / plasma 5-hydroxytryptamine) and audiovestibular tests were conducted and results scored. A psychologist administered psychometric screening tests for depression (the Hamilton Depression Scale) and for post-traumatic stress disorder (the Mississippi PTSD Scale), and a psychiatrist evaluated each subject following the Structured Clinical Interview for DSM-IV (SCID) to provide definitive measures of these conditions.

Association and significance were assessed with Spearman rank-order correlation coefficients.

Results

Declines in neuronal mass in deep brain structures, as reflected by reduced NAA/Cr ratios, correlated with symptoms of Haley syndrome 2 and neurophysiologic measures. Specifically, NAA/Cr in right BG was inversely correlated with each of the symptom scales comprising Haley syndrome 2 (ranging from the sexual impotence scale, r = -0.47, p=0.03 to the thought processing scale, r = -0.64, p=0.002). NAA/Cr in right BG was also inversely correlated with clinical depression (r = -0.53, p=0.003 for SCID; r = -0.57, p=0.005 for Hamilton depression scale) but not with serotonin turnover (r = -0.19, p=0.34).

NAA/Cr in the left BG was inversely correlated with fewer symptoms than was the right but was selectively associated with confusional symptoms (r = -0.69, p<0.001) as well as increased brain dopamine turnover (r = -0.77, p<0.0001).

NAA/Cr in the pons was inversely correlated with the vertigo symptom scale (r = -0.52, p=0.01) and with audiovestibular tests of reflexes controlled by the brain stem (sinosudal harmonic acceleration, r = -0.43, p=0.02; vestibular ratio from dynamic platform posturography, r = 0.47, p=0.01).

The NAA/Cr ratios in the three brain regions were not associated with the intensity of combat experienced or with the psychiatrist’s SCID diagnosis of PTSD, although there was a modest association of NAA/Cr in the right basal ganglia with the psychometric screening test for PTSD.

Discussion

Declines in neuronal mass in deep brain structures, as reflected by reduced NAA/Cr ratios, correlated with symptoms of Haley syndrome 2 and neurophysiologic measures. Specifically, neuronal damage in the right BG may give rise to most symptoms defining Haley syndrome 2, including depression. Neuronal damage in the left BG correlated with fewer symptoms than that in the right BG but was selectively associated with confusional symptoms and increased brain dopamine turnover. Prior rodent experiments selectively associated damage in the left BG with exaggerated brain dopamine production, and elevated brain dopamine was previously associated with thought disorders in humans. Neuronal damage in the pons was associated with symptoms of vertigo attacks and dizziness as well as with abnormalities on audiovestibular tests that assess the vestibulo-ocular reflex which traverses the brain stem and facilitates balance.

The lack of association between NAA/Cr ratios in the three brain regions and either the combat exposure scale or the psychiatrist’s SCID diagnosis of PTSD argues against a role for psychological stress in these Gulf War-associated symptom complex. The modest association of the Mississippi PTSD scale with NAA/Cr in right BG reflects the low specificity of this screening test, which can be falsely elevated by a variety of medical conditions.

By correlating evidence of neuronal dysfunction and/or damage on MRS in key areas of brain with symptoms that plausibly match the function of these anatomies, our data support an organic basis for the symptoms elicited in this group of patients. Moreover, the fact that decrements in brain regions in different brain regions appear to effect different functional abnormalities helps explain the observed differences in symptom complexes among groups of ill veterans. Finally, the fact that NAA/Cr levels correlate with symptoms and other sophisticated brain tests substantiates the utility of MRS for probing the organic basis of deep brain dysfunction.

References


