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TITLE: Gulf War Illness as a Brain Autoimmune Disorder

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary goal of this reporting period was to complete recruitment and continue data analysis and dissemination. We have completed a total of 193 acquisitions, including 23 during this reporting period. In addition, during this reporting period we published a manuscript demonstrating a highly significant association between inflammatory markers and GWI symptoms, particularly those involving pain, fatigue, neurocognitive/mood, and respiratory domains. We have requested a second no cost extension to continue data analysis and dissemination.

15. SUBJECT TERMS

Gulf War Illness, Autoimmune, neuroimaging, genetics, biomarkers

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1. **INTRODUCTION:**

GWI has affected a large number of veterans of the 1990-1991 Persian Gulf War. GWI symptoms are characterized by chronic health problems, of unknown etiology. They resemble symptoms seen in various autoimmune disorders and are reflected in altered patterns of brain function. In this study, we comprehensively assess the association of GWI to autoimmune disorders using cutting-edge measures of brain structure and function, genetic analysis, and laboratory tests. In preliminary studies, we have discovered that GWI possesses a distinct functional brain pattern that is very close to that observed in a well-known autoimmune disorder, Sjogren's syndrome. Hence, the main goal of this proposal is to test the hypothesis that GWI is an autoimmune disorder. For that purpose, we are comparing the results of brain, genetic and laboratory tests in subjects with GWI to those obtained from subjects with known autoimmune disorders, to determine the extent to which GWI reflects autoimmune abnormalities. Altogether, our study will improve knowledge of GWI pathophysiology and ultimately inform diagnosis and potential treatment of GWI, e.g. along lines currently in use for treating autoimmune disorders.

2. **KEYWORDS:** Gulf War Illness, autoimmune, neuroimaging, genetics, biomarkers

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

The major goals of the project are to assess and compare 1) brain structure and function, 2) blood inflammatory and immune markers; 3) HLA genes; and 4) cognitive, mental health, neurological and general standardized clinical status in veterans with Gulf War Illness relative to veterans with autoimmune disorders.

- **What was accomplished under these goals?**

During this reporting period, we completed recruitment and data acquisition; over the course of the study we completed a total of 193 acquisitions. During this reporting period we also published a paper demonstrating a highly significant positive association between inflammatory markers and several GWI symptom domains.

- **What opportunities for training and professional development has the project provided?**

During this reporting period one of our graduate students submitted an abstract based on data from this study to the Society for Neuroscience Annual meeting. The abstract was accepted, providing a valuable opportunity for the student to disseminate findings at a large international conference.

- **How were the results disseminated to communities of interest?**

Findings supported by this grant were disseminated via presentation at local conferences and via publication.

James LM, Engdahl BE, Johnson RA, Georgopoulos AP. Gulf War Illness and Inflammation: Association of symptom severity with C-reactive protein. J Neurol Neuromed 2019; 4(2):15-19.

- **What do you plan to do during the next reporting period to accomplish the goals?**

We have requested a second no cost extension to continue data analysis and dissemination of study findings.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

The findings from the grant thus far have demonstrated similar brain signatures in autoimmune disorders and GWI as well as a genetic lack of protection involving immune-related genes in the development of GWI. In particular, genes that have been shown to protect against various autoimmune disorders are also protective against GWI. These findings implicate immune system functioning in the development of GWI and point to exposure to particular antigens in genetically vulnerable individuals as likely contributing to GWI. That is, GWI is thought tos stem from exposure to foreign antigens that could not be successfully eliminated due to lack of specific immunity, causing the antigens to persist. The persistent antigens are presumed to underlie the inflammation that is observed in GWI. These findings open avenues for potential treatment of GWI along the lines of immunotherapy.

- **What was the impact on other disciplines?**

The findings from this study led to investigations about immune-related genetic involvement in brain aging and, most recently, dementia. Two published papers have demonstrated that the same immune-related genes that are generally lacking in veterans with GWI and contribute to brain atrophy in GWI via inability to eradicate circulating antigens are associated with brain atrophy and neural network variability in healthy brain aging (James et al. 2018 EBioMedicine 29, 31-37; James et al., 2018 EBioMedicine 35, 288-294). Furthermore, a recent genetic epidemiology study demonstrated that the frequency of those same genes are inversely related to dementia prevalence in 14 European countries (James & Georgopoulos, J Neurol Neuromed, in press).

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Despite 25 years of research, GWI has been poorly understood and even attributed to psychological distress, hampering efforts to effectively treat affected veterans. The findings from this grant substantiate GWI as a medical condition, highlight genetic susceptibility to GWI, and offer insights regarding potential treatments. Taken together, these findings legitimize the difficulties of GWI veterans and offer hope for treatment to veterans who have suffered for decades.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to report.

- **Changes that had a significant impact on expenditures**

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- **Significant changes in use or care of human subjects.**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

Not applicable.

- **Significant changes in use of biohazards and/or select agents**

Not applicable.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**
  Journal publications.

James LM, Engdahl BE, Johnson RA, Georgopoulos AP. Gulf War Illness and Inflammation: Association of symptom severity with C-reactive protein. J Neurol Neuromed 2019; 4(2):15-19.

- **Books or other non-periodical, one-time publications.**

Nothing to report.

- **Other publications, conference papers, and presentations.**

Nothing to report.

- **Website(s) or other Internet site(s)**

http://brain.umn.edu

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

We have developed a database in order to facilitate data analysis and dissemination of research findings.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Apostolos Georgopoulos: No change
Brian Engdahl: No change
Lisa James: No change
Arthur Leuthold: No change
Adam Carpenter: No change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- **What other organizations were involved as partners?**

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.