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TITLE: Persistent Hormonal Changes in Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Ricardo Jorge, MD

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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14. ABSTRACT The proposed cross-sectional, case-controlled study will assess the association of Gulf War Illness (GWI) with dysregulation of major hormonal systems. A total of 90 Veterans (45 Veterans with GWI and 45 Veterans of comparable age, gender, and military experience who deployed but did not develop GWI) will be recruited from clinical and community sources. Endocrine disorders can be effectively treated by pharmacological interventions currently available, thus, reducing the time it would take for Veterans to access treatment. Consequently, treatment may result in a significant reduction of Veterans' symptomatic burden.					
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1. INTRODUCTION:

The proposed cross-sectional, case-controlled study will assess the association of Gulf War Illness (GWI) with dysregulation of major hormonal systems. Specifically, it will assess hormone measures (including the frequency of hormone deficiencies) between Gulf War Veterans with and without GWI and evaluate the relationship between endocrine measures and neurocognitive function. A total of 90 Veterans (45 Veterans with GWI and 45 Veterans of comparable age, gender, and military experience who deployed but did not develop GWI) will be recruited from clinical and community sources. Assessing hormonal dysregulations in the population has major therapeutic implications because endocrine disorders can be effectively treated by pharmacological interventions currently available, thus, reducing the time it would take for Veterans to access treatment. Consequently, treatment may result in a significant reduction of Veterans’ symptomatic burden and maximizing their recovery and quality of life.

2. KEYWORDS:

Endocrine measures; hormonal dysregulation; HPA axis; Gulf War Illness.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task: Data Collection	Timeline	Status
Identify, recruit, screen, and consent eligible participants	4/1/18 to 4/30/20	On Hold
Assess endocrine function at baseline and after stimulation tests	4/1/18 to 4/30/20	On Hold
Collect medical, background, neuropsychological, and psychiatric data from subjects in both groups	4/1/18 to 4/30/20	On Hold
Major Task: Analysis		
Determine dysfunction of major hormonal systems in veterans with GWI	4.30/20 to 9/30/20	80%
Explore association between endocrine dysregulation and prominent GWI factors of interest (i.e., deployment, exposures)	4/30/20 to 9/30/20	80%
Prepare publications and presentation	4/30/20 to 9/30/20	On Hold

What was accomplished under these goals?

Major Goal 2: Collect Data for Analysis

Efforts during the first quarter of the reporting year were focused on identification, recruitment, and data collection. The target enrollment across the three years is 90 participants. To date, 78 of 90 participants were enrolled, and of those, 72 complete the endocrine stimulation tests.

In March 2020, Baylor College of Medicine and Michael E. DeBakey VA Medical Center placed all non-interventional research studies on hold during the COVID-19 pandemic. The protocols remain on hold until further notice.

A risk assessment was conducted in August 2020. A detailed plan on steps to mitigate research staff and patient safety was submitted to the local Office of Research, and ACOS approved our risk assessment and safety plan in September 2020. The Office of Research leadership is systematically reopening research studies. On October 19th, a select number of studies were relaunched. The Office of Research is monitoring local case numbers and using data from the limited studies to assess the feasibility of conducting research during COVID-19.

In the meantime, our request for a non-cost extension was approved. The extension will afford us additional time to finish recruiting the last twelve patients for the study once research resumes. Further, we used the last two quarters of year 3 to perform preliminary data analysis. We were able to detect hormonal alterations in GWI veterans with the sample size we have. This means that, even if we are unable to enroll additional patients during the pandemic, we had sufficient signal. A brief summary of our findings is included in the Appendix.

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

Nothing to Report.

How were the results disseminated to communities of interest?

The preliminary findings have not been disseminated to the scientific community, yet. Results were used as preliminary data to support a Gulf War treatment grant application. The final results will be made public at the end of the non-cost extension.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will place a heavy emphasis on recruiting/enrolling the final set of patients upon reopening of research. In the meantime, we continue to review medical records and identify potential candidates. It is our goal to conclude enrollment within the next six to eight months and reserve the last quarter for data analysis and reporting.

4. IMPACT:

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

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There were no changes in the project or its direction.

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

The greatest setback encountered during the third year of the study was COVID-19 pandemic. Non-interventional research is temporarily on hold at our facility until further notice; however, our risk assessment plan was approved in September 2020. In the meantime, we have gathered PPE and cleaning supplies to prepare for face to face visits. We have also prepared a list of potential candidates to target once research resumes. To compensate for the deficit, we have requested a non-cost extension to afford us additional time to enroll the last twelve participants into the study.

During the last quarter of year three, the research coordinator for the project, Ms. Hendrickson, left the team. A new coordinator was hired and trained by Ms. Hendrickson. Although there was overlap between coordinators, the new coordinator has only had simulated training. The team has regular team meetings, and other site personnel are readily available to guide the new coordinator once the study relaunches. We have and will continue to conduct periodic mock sessions to maintain the neuropsychological test battery administration skills until patient visits resume.

Changes that had a significant impact on expenditures

There were no significant changes affecting expenditures. The study is financially on track.

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:

Journal publications.

Nothing to Report.

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)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Ricardo Jorge, MD
Project Role:	Principal Investigator
Nearest person month worked:	2.4
Contribution to Project:	Dr. Jorge oversees all aspects of the research protocol. He makes eligibility and termination decisions and assesses participants in the study. Dr. Jorge is also responsible for evaluating adverse events and submitting safety lab orders at the screen visit.

Name:	Marco Marcelli, MD
Project Role:	Co-Investigator
Nearest person month worked:	0.6
Contribution to Project:	Dr. Marcelli oversees the dynamic tests and interprets endocrine test results. He is also responsible for submitting endocrine lab orders, evaluating adverse events, and contacting patients whose laboratory results are out of range.

Name:	Lea Steele, PhD
Project Role:	Co-Investigator
Nearest person month worked:	0.6
Contribution to Project:	Provided consultation about diagnostic algorithms and chronology of symptoms in patients with Gulf War Illness.

Name:	Audri Villalon
Project Role:	Regulatory Coordinator
Nearest person month worked:	2.5
Contribution to Project:	Ms. Villalon assists with regulatory documents and reports. She reviews invoices for accuracy and submits for processing.
Funding Source:	Unfunded

Name:	Jeanie Hendrickson
Project Role:	Research Coordinator
Nearest person month worked:	8 (originally 100% effort, reduced to 50% effort in summer)
Contribution to Project:	Ms. Hendrickson screens candidates over phone and schedules appointments. She is primarily responsible for consenting, administering neuropsychological assessments and questionnaires, and processing payments for participants. Ms. Hendrickson worked full-time until June and part-time during the summer. She has since left the project.

Name:	Mohamed Elammari
Project Role:	Research Assistant
Nearest person month worked:	5
Contribution to Project:	Mr. Elammari reviewed clinic lists and Gulf War Registry to identify participants who may be eligible for the study. He assisted with mailing recruitment letters to candidates, scheduling endocrine visit appointments, and specimen processing, as needed.

Name:	Gursimrat Bhatti
Project Role:	Research Coordinator
Nearest person month worked:	7 (currently 100% effort)
Contribution to Project:	Mr. Bhatti is the new research coordinator for this project. He will replace Ms. Jeanie Hendrickson.

Name:	Ruosha Li
Project Role:	Statistician
Nearest person month worked:	1.2 months
Contribution to Project:	Contributed to the design and organization of databases, as well as, quality monitoring.

Changes in the active other support of key personnel since the last reporting period

Ricardo Jorge, M.D.

Title: Effects of Growth Hormone Replacement Therapy in Veterans with mild TBI
Funding source: Department of Veterans Affairs Cooperative Studies Program (CSP #2018)
Role: Co-chair

Title: One-Day Life Skills Workshop for Veterans with TBI, Pain, and Psychopathology
Funding source: RR&D Merit Award

Dates: 10/01/2019 – 09/31/2023

Role: Co-I

Total direct costs:

Title: National Adaptive Trial for PTSD Related Insomnia

Funding source: Department of Veterans Affairs Cooperative Studies Program (CSP #2016)

Dates: 10/01/2019 – 09/30/2024

Role: Site PI

Total direct costs:

Marco Marcelli, M.D.

Lea Steele, Ph.D.

1. Current Support: “Defining and Characterizing GWI Pathobiology Using Longitudinal Brain Imaging Biomarkers of White Matter Integrity and Hemodynamic Response”. Primary award to Boston University, PI: Kim Sullivan, PhD. Steele role: Co-I, 5% effort in Years 2-3 (Dates: 9/30/19 – 9/29/22). This study was previously listed as pending.

Ruosha Li, Ph.D.

Title: Work hour patterns and diabetes disparities

Effort: 0.6 calendar month

Supporting Agency: NIH/ NIMHD

Grant Officer: Adelaida M. Rosario (hoyosar@mail.nih.gov)

Performance Period: 09/17/2018-- 05/31/2021 (currently under no cost extension)

Funding Level:

Project Goals: This study analyzes repeated Work Hour measures collected over a period of 30 years to better understand the influence of Work Hour Patterns on Diabetes development and progression, with a particular focus on differences across racial/ethnic groups. Dr. Li provides statistical support and coauthors manuscripts.

Overlap: No overlap

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

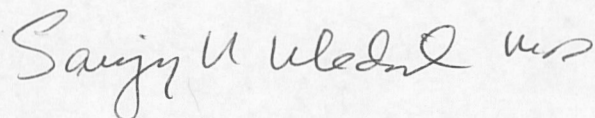
9. APPENDICES:

- Safety Monitor Reports
- Preliminary Findings

Safety Monitor Report

01/08/2020

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	October 1, 2019 – December 31, 2019



Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 3 Quarter 1 (October – December 2019)

# who completed endocrine tests:	11
# of patients with AE:	0
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None of the participants who underwent glucagon stimulation test and ACTH stimulation test between October and December 2019 experienced adverse events.

Reporting Requirements

N/A

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There were no unanticipated problems (in terms of nature, severity, or frequency) involving risks to subjects or others. There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.

Sanjay K. Uledal MD

Safety Monitor Report

04/14/2020

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	January 1, 2020 – March 31, 2020

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 4 Quarter 2 (January – March 2020)

# who completed endocrine tests:	6
# of patients with AE:	0
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None of the participants who underwent glucagon stimulation test and ACTH stimulation test between January 1 – March 31, 2020 experienced adverse events.

Reporting Requirements

N/A

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.

As a precaution during the COVID19 pandemic, all non-essential research testing was suspended until further notice.

Safety Monitor Report

07/10/2020

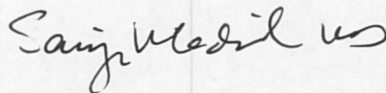
IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	April 1, 2020 – June 30, 2020

Independent Safety Monitor:

Sanjay Mediwala, MD

Board Certified Endocrinologist

Michael E. DeBakey VA Medical Center



H-41120 Summary

Year 3 Quarter 3 (April 2020 – June 2020)

# who completed endocrine tests:	0
# of patients with AE:	0
# of patients with UPIRTSO:	0

Research activities at Michael E. DeBakey VA Medical Center and Baylor College of Medicine are on hold during COVID-19 pandemic. No participants have been enrolled since March 2020.

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None

Reporting Requirements

N/A

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

None

Safety Monitor Report
09/30/2020

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	July 1, 2020 – Sept. 30, 2020

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

Sanjay Mediwala MD

H-41120 Summary

Year 3 Quarter 3 (Aug 2020 – Sept 2020)

# who completed endocrine tests:	0
# of patients with AE:	0
# of patients with UPIRTSO:	0

Research activities at Michael E. DeBakey VA Medical Center and Baylor College of Medicine are on hold during COVID-19 pandemic. No participants have been enrolled since March 2020.

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None

Reporting Requirements

N/A

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

None

Appendix B – Preliminary Findings

At this time, we have enrolled 78 Gulf War Veterans into the study. Of those, 72 participants completed the evaluation of the thyroid, adrenal, gonadotropic and growth hormone neuroendocrine axes. Laboratory tests included measurements of IGF-1 levels and dynamic tests for AGHD (i.e., glucagon stimulation test [GST]), as well as the following measurements of pituitary function: prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormones (bioavailable testosterone, estradiol), free thyroxine (FT4), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), cortisol, and ACTH stimulation test.

Frequency of hormonal alterations in GW Veterans: AGHD diagnosis was based upon the results of the GST corrected for body mass index (BMI) (i.e. peak GH cutoff value of 3 ng/ml for participants with BMI less than 25 and peak GH cutoff value of 1 ng/ml for participants with BMI 25 or greater). **Out of 72 GW subjects, 15 (20.8%) had abnormal GST results consistent with the presence of AGHD.** In addition, six out of 68 Veterans (8.8%) had low baseline testosterone levels (< 200 ng/dl) as measured by liquid chromatography-tandem mass spectrometry. There were no cases of adrenal insufficiency as measured by the ACTH stimulation Test or evidence of hypothalamus-pituitary-thyroid axis dysfunction in our group of Veterans. Furthermore, we did not observe cases with multiple hormonal deficiencies.

Relationship between AGHD and GWI: We have mentioned the significant symptom overlap between AGHD and GWI. Obtaining reliable estimates of the comorbidity of these 2 disorders is hindered by the lack of specificity of current GWI diagnostic criteria. Thirty years have elapsed since operations DS/DS and current evaluations. Different pathophysiological processes have developed over time obscuring the relationship between the defining symptoms and GWI and reducing the specificity of currently used criteria. In fact, establishing new diagnostic criteria for the illness is a priority for the research field. We tried to circumvent these problems by making a clinical diagnosis based on multiple information sources including medical and physical evaluation and exhaustive analysis of medical records to determine the onset of symptoms and causal mechanisms. There was a close association between AGHD and GWI. For instance, all Veterans with an AGHD diagnosis met Kansas criteria for GWI. Even if we used stricter clinical diagnostic criteria, 13 out of 14 veterans (93%) with biochemically diagnosed AGHD met diagnostic criteria for GWI. On the other hand, **13 or 31 Veterans (42%) with GWI had coexistent AGHD.**

Clinical correlates of AGHD in GW Veterans:

Demographic characteristics were similar among GW Veterans with and without AGHD. In addition, Veterans in both groups did not differ in the frequency and severity of combat exposure or in the severity of warzone experiences assessed by the Deployment Risk and Resiliency Inventory (DDRI-2) (Table 2) (29). Comparisons were based on the Wilcoxon rank-sum test or the Fisher's exact test as appropriate.

We examined the impact of AGHD in the severity of fatigue symptoms, chronic pain intensity and interference with daily activities, emotional wellbeing, severity of PTSD symptoms, sleep disturbance, and quality of life (see Table 2). Compared to the rest of GW Veterans, GH deficient patients showed increased levels of fatigue ($p < 0.04$, standardized mean difference, Cohen's $d = 0.67$), more severe chronic pain ($p < 0.02$, $d = 0.85$), greater pain interference with general activity ($p < 0.03$, $d = 0.75$), and increased severity of anxiety symptoms ($p < 0.04$, $d = 0.81$). In addition, Veterans with AGHD reported significantly diminished QoL ($p < 0.05$, $d = 0.58$). On the other hand, severity of depressive and stress symptoms, frequency of PTSD, severity of current PTSD symptoms, and PSQI total scores were not significantly different between the AGHD and the non-AGHD groups suggesting that they were not significantly

Appendix B – Preliminary Findings

associated with AGHD in this sample. However, if we examine the number of Veterans with poor sleep quality in each group (i.e., 8 out of 15 Veterans (53%) in the AGHD group and 11 of 57 Veterans (19%) in the non-AGHD group) we observe that sleep quality is significantly affected in the AGHD group ($p < 0.03$).

Health related QoL was examined using the SF-36. Overall, the presence of AGHD was associated with poorer indices of: i) General Health ($p < 0.02$, $d = -0.75$); ii) Energy/Fatigue ($p < 0.001$, $d = -1.18$); iii) Physical Health Limitations ($p < 0.05$, $d = -0.62$); and iv) Social Functioning ($p < 0.05$, $d = -0.55$).

With regards to the effect of AGHD on cognition, we did not observe significant differences between the groups in most attention, executive and verbal memory measures (e.g., Continuous Performance Test, Verbal Fluency Test, Stroop Test, California Verbal Learning Test). This stems in part from the small sample size and consequent reduced power to detect significant differences as well as the lack of an homogeneously healthy non-GWI group. However, the AGHD group showed problems with motor processing and manual dexterity as evidenced by the Grooved Pegboard Test ($p < 0.007$, $d = -0.82$) and, to a lesser extent, in executive function as evidenced in the Trail Making Test ($p < 0.109$, $d = 0.37$).

Table 2. Comparison of Gulf War Veterans by AGHD status, mean (SD).

Measure	ALL N=72	AGHD N=15	No-AGHD N=57	Cohen's d
AGHD-QoL	13.4 (7.2)	16.7 (6.5)	12.6 (7.3)	0.58
DASS-21 Anxiety	9.7 (8.9)	15.3 (12.3)	8.4 (7.4)	0.81
DASS-21 Depression	11.4 (12.0)	16.0 (16.7)	10.3 (10.4)	0.48
DASS-21 Stress	13.7 (10.6)	18.4 (14.7)	12.5 (9.1)	0.57
PCL-5 Total Score	35.6 (22.8)	37.3 (28.9)	35.1 (21.2)	0.09
BMI	32.1 (6.3)	33.0 (6.7)	32.1 (6.3)	0.19
BPI Average Pain	5.1 (1.8)	6.0 (1.5)	4.9 (1.8)	0.64
BPI Interference General Activity	5.2 (2.6)	6.8 (2.1)	4.8 (2.7)	0.75
PSQI Total Score	10.6 (4.9)	11.4 (5.1)	10.4 (4.9)	0.20
DDRI-2 Combat Experiences	12.3 (12.1)	16.5 (20.1)	11.2 (9.2)	0.44
DDRI-2 Warzone Experiences	6.2 (4.5)	5.1 (5.3)	6.5 (4.3)	-0.29
DDRI-2 Chemical Exposures	16.8 (4.8)	16.9 (5.2)	16.8 (4.8)	0.00

AGHD-QoL: Quality of Life Assessment of Growth Hormone Deficiency in Adults; DASS-21: Depression, Anxiety and Stress Scale- 21 Items; PCL-5: The PTSD Checklist for DSM-5; BPI: Brief Pain Inventory; PSQI: Pittsburgh Sleep Quality Index; DDRI-2: Deployment Risk and Resiliency Inventory-2;

Relationship of AGHD with a history of TBI and neurotoxic exposure: Given that the prevalence of TBI is greater in military groups than in the civilian population, we examined the association between a lifetime history of TBI (with loss of consciousness) and AGHD. In contrast with what was observed among OIF/OEF/OND Veterans, the association with a history of TBI exposure was non-significant.

Exposure to neurotoxins has long been recognized as an important etiological factor in the pathogenesis of GWI. However, we did not observe an association between AGHD and exposure to chemical warfare, pesticides, insecticides, burning oil fumes, or prophylactic interventions such as pyridostigmine or anthrax vaccine. Global measures of chemical exposures were also not significantly different between the AGHD and the non AGHD groups (Table 2).

Summary: AGHD is relatively frequent among GW Veterans with up to 20% of them having biochemical evidence of GH deficiency. In addition, 42% of Veterans with GWI had coexistent GHD. About 10% of male GW Veterans showed decreased testosterone levels. However, there were no cases of multiple endocrine deficiencies. The presence of AGHD was associated with increased fatigue, more severe and invalidating pain, increased anxiety and poor sleep quality. More important, AGHD patients showed significant impairment in multiple domains of health related QoL.