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14. ABSTRACT

Chronic hypopituitarism (deficient production of one or more pituitary hormones) occurs in 25-50% of cases of civilian traumatic brain injury. Although repetitive blast concussion is the signature injury of combat in Iraq and Afghanistan, the prevalence of hypopituitarism after blast-induced concussion or mild traumatic brain injury (mTBI) is undetermined. Pituitary dysfunction is associated with symptoms including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life, as well as muscular weakness, erectile dysfunction, infertility, and diminished cardiovascular function. Concentrations of 12 hormones in blood samples from Veterans of deployment to Iraq and Afghanistan who had sustained at least one blast concussion were compared with those from Veterans of deployment without blast exposure. Veterans with blast mTBI were found to have a prevalence of pituitary dysfunction of 42.9% compared to 6.7% in those not exposed. The prevalence of hypopituitarism in the general population has been estimated at 0.03%. Based on this estimation, the frequency of hypopituitarism after blast concussion is 1,430 times greater than that of the general population. The most frequent hormone deficiency disorders were growth hormone deficiency and hypogonadism, which may result in significant changes in mood, energy, body composition, muscular strength, sexual function and quality of life.

15. SUBJECT TERMS

blast, concussion, mild traumatic brain injury, pituitary, hormones, hypopituitarism, hypogonadism, growth hormone deficiency

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INTRODUCTION

Chronic hypopituitarism (deficient production of one or more anterior pituitary hormones) occurs in 25-50% of cases of civilian traumatic brain injury. However, the prevalence of posttraumatic hypopituitarism (PTHP) after blast-induced concussion or mild traumatic brain injury (mTBI) has not been determined despite the fact that repetitive blast concussion is the signature injury of combat in Iraq and Afghanistan. PTHP is associated with symptoms that overlap considerably with those of PTSD including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life. Muscular weakness, erectile dysfunction, infertility, and diminished cardiovascular function are also frequent consequences. These symptoms, if appropriately diagnosed as consequences of neuroendocrine disorders, can generally be treated successfully with hormone replacement. The objectives of this study are to measure basal hormone concentrations in blood from Veterans who sustained at least one blast-induced mTBI during deployment to Iraq or Afghanistan. The values will be compared to hormone levels in combat-zone Veterans without blast exposure to determine the frequency and nature of pituitary dysfunction resulting from blast concussions. Methods for screening for PTHP will be developed and refined. Accurate, routine diagnosis of PTHP has the potential of markedly improving the psychological health and facilitating the recovery of blast mTBI victims.

BODY

During Year 1 of the project, plasma and serum samples used for measurement of hormone concentrations were acquired from a sample repository (University of Washington Alzheimer's Disease Center Participant Registry and Sample Repository). Blood samples from healthy male civilians were culled from the repository to provide a reference sample to use in determining normal reference ranges for each hormone. Blood samples from Veterans who had sustained a blast concussion during deployment to Iraq or Afghanistan and samples from deployed Veterans without blast exposure were also withdrawn from the repository. These samples had been added to the repository as a component of another, larger study of blast concussion.

Initially, samples from 59 healthy community control participants were used to establish normal reference ranges for each of the 12 hormones and to determine criteria for classifying levels of each of the hormones in Veterans' samples as normal or abnormal. During Year 1, samples from 26 Veterans with blast mTBI and 7 deployed-control Veterans were acquired from the repository and Milestones 1-5 in the Statement of Work were completed for these samples ***(Appendix 1)***. Preliminary results based on the hormonal analysis of these samples were published (Wilkinson *et al.*, 2012). Details of inclusion/exclusion criteria and sample acquisition are described fully on p. 2 of the article, and demographic characteristics and blast exposure assessment data are described in Table 4, p. 7. ***(Appendix 2)***

Six anterior pituitary hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], growth hormone [GH], adrenocorticotropin [ACTH], thyroid-stimulating hormone [TSH] and prolactin [PRL]) were measured. In addition, concentrations of two posterior pituitary hormones (oxytocin [OT] and vasopressin [AVP], and four target-organ hormones (testosterone, insulin-like growth factor-I [IGF-I], cortisol, and thyroxine) were determined for each participant. Methods for hormone measurements and the sources of the materials used are described in Table 1, p. 3 of Wilkinson *et al.*, 2012.

Hypopituitarism was defined as a dysfunction in at least one of seven hormonal axes. (Table 2, p. 2; Wilkinson *et al.*, 2012). The specific criteria for dysfunction of each axis were derived from age-adjusted percentiles based on the lognormal distribution of concentrations for each hormone in the samples from the 59 community control participants. These criteria were modeled after those used in published studies of hypopituitarism after civilian TBI from all causes.

This initial analysis was made with a limited number of samples in relation to the target goals of the study. At the time of publication, data were available from 59 of the targeted sample of 100 healthy community control participants, 26 of the target number of 40 of Veterans with TBI and 7 of the target number of 20 deployed Veterans without blast exposure.

Eleven of the 26 Veterans with TBI were found to have one or more hormonal abnormalities consistent with hypopituitarism, whereas none of the deployment control Veterans was found to have any hormonal deficiencies (Table 1). As has been found in the majority of civilian studies of hypopituitarism after TBI, the most prevalent deficiencies in anterior pituitary function were in the GH-IGF-I axis and the gonadotropin (LH and FSH)-testosterone axis. None of the participants in either of the Veteran groups was found to have deficiencies in the pituitary-adrenal or pituitary-thyroid axis.

Single measures of GH during the daytime are of very limited utility in assessing growth hormone deficiency (GHD) because GH is secreted almost entirely during nighttime hours. For this reason, measurement of IGF-I, which is produced by the liver in response to GH, is frequently used as a surrogate for GH in diagnosing GHD. Markedly low levels IGF-I are strongly indicative of GHD. Five members of the TBI group were found with sufficiently low levels of IGF-I to meet criteria for GHD. See Table 1 below and Fig. 1, p. 4 in Wilkinson *et al.*, 2012.

The long-term sequelae of GHD in adults for health, quality of life (QoL), and morbidity are multifaceted and complex. Low GH secretion has been associated with behavioral symptoms and deficits in several cognitive domains (Popovic *et al.*, 2004; Falleti *et al.*, 2006). GHD also has significant deleterious effects on body composition and cardiovascular function. Adult GHD is associated with lipidemia, reduced lean body mass, and increased adiposity (Colao *et al.*, 2006; Colao, 2008). Poor QoL is also a prominent feature of adult GHD, especially in the areas of energy and vitality (Kelly *et al.*, 2006; Bushnik *et al.*, 2007; Svensson *et al.*, 2004). Adult GHD is also associated with reductions in muscle volume and strength, decreased physical mobility, fatigue, sleep impairment, social isolation, depression, lowered metabolic rate, low sexual drive, and reduced aerobic capacity (Rosén *et al.*, 1994; Mossberg *et al.*, 2008). However, many of the symptoms of GHD can be successfully ameliorated or reversed by growth hormone replacement therapy (Svensson *et al.*, 2004; Colao *et al.*, 2006; Falleti *et al.*, 2006; Kreitschmann-Andermahr *et al.*, 2008; Götherström *et al.*, 2009; High *et al.*, 2010; Reimunde *et al.*, 2011).

The criteria for dysfunction of the male pituitary-gonadal axis, or hypogonadism, are testosterone levels below the 5th percentile of the reference sample together with an LH or FSH level below the 10th percentile of the reference distributions as shown in Fig. p. 5 (Wilkinson *et al.*, 2012). Three of the Veterans with blast mTBI met the combined low testosterone and low LH criteria for hypogonadism. None of the deployed, non-blast-exposed Veterans were found with hormone levels indicative of pituitary-gonadal axis dysfunction.

Hypogonadism has significant deleterious consequences in addition to its adverse effects on fertility, psychosexual function, and general wellbeing. Testosterone deficiency in males is associated with decreased energy and motivation, muscle weakness, reduced lean body mass, and impaired exercise tolerance (Agha and Thompson, 2005). In addition, a recent large epidemiological study has shown that untreated hypogonadism is associated with premature mortality secondary to cardiovascular disease (Tomlinson *et al.*, 2001).

In addition, abnormalities in three other pituitary hormone levels were found among the Veterans who had sustained blast mTBI. The abnormalities were prolactin excess or deficiency (Fig. 1), vasopressin excess or deficiency (Fig. 2), and oxytocin deficiency (Fig. 3). Graphic representations of the concentrations of these hormones were not included in the published manuscript, and the data are shown and interpreted in greater detail below. None of the deployment control group was found with abnormal levels of any of these three hormones.

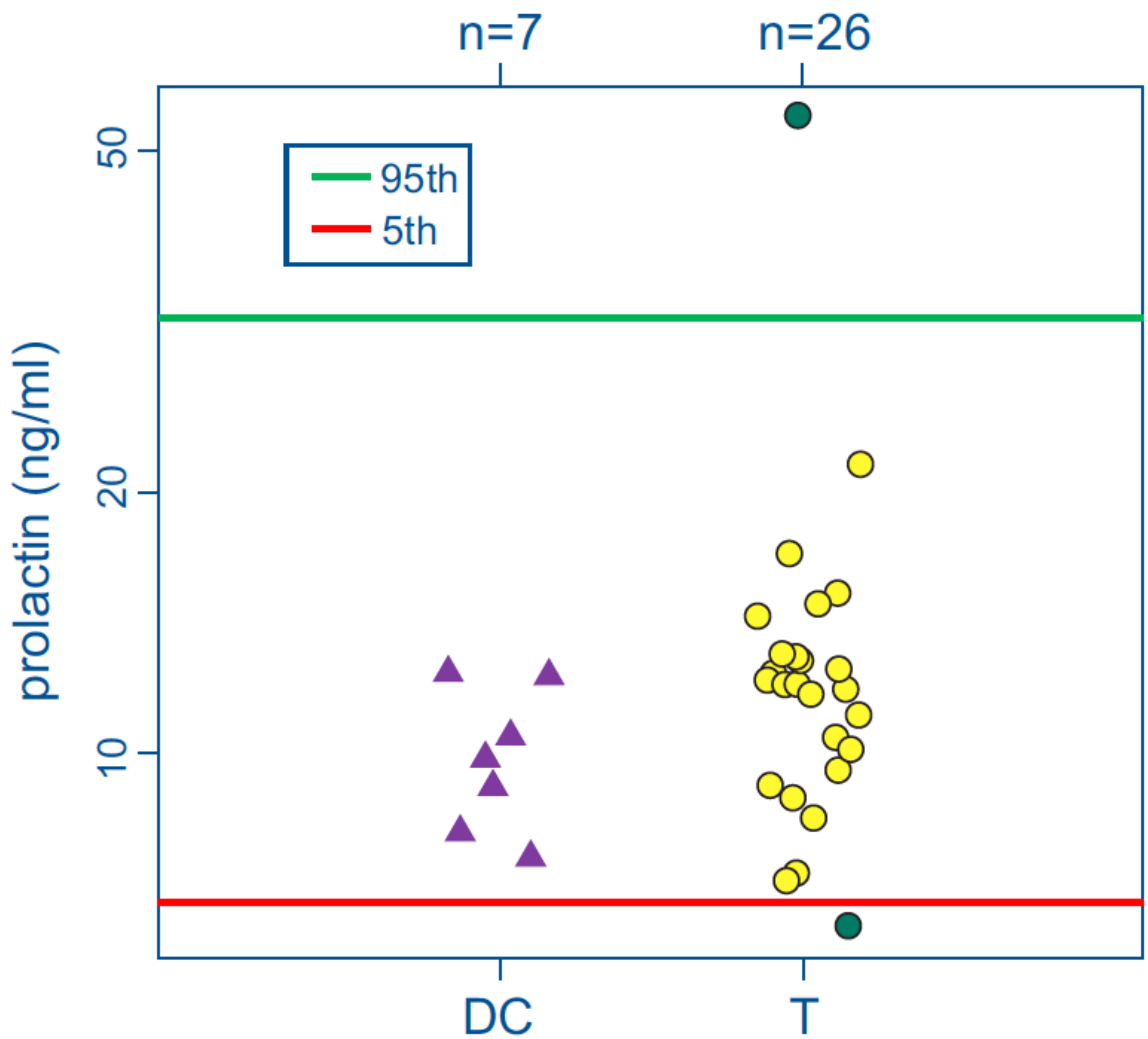

Figure 1. Data from the deployment control (DC) group are indicated on the left by purple triangles, and mTBI group data are shown by yellow circles on the right. Both hypoprolactinemia and hyperprolactinemia are associated with sexual and reproductive dysfunction including erectile dysfunction and infertility. Serum prolactin levels above the 95th percentile of the distribution of prolactin concentrations in our community control reference group were considered to be aberrant and indicative of hyperprolactinemia. Similarly, values below the 5th percentile of the distribution of prolactin concentrations in our reference sample were considered to be markers of hypoprolactinemia. None of the Veterans in the DC group were found with abnormal prolactin levels. However, one participant in the mTBI group had a prolactin value considered to abnormally low and one had an excessively high prolactin level. Data from these two Veterans are indicated by the green circles. The same two participants were also found to have probable hypogonadism as determined by our criteria based upon LH and testosterone concentration (Table 1).

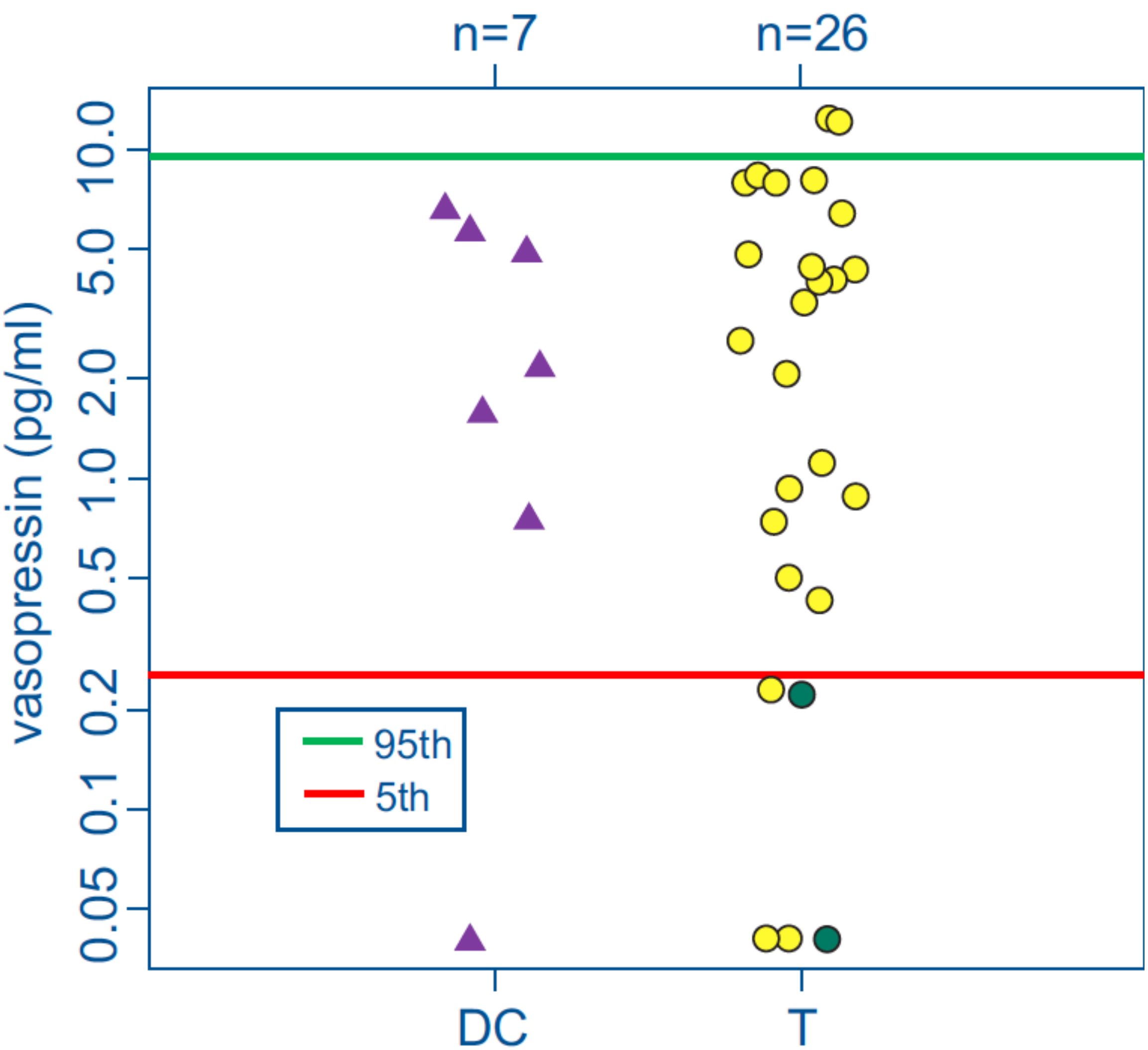

Figure 2. Similarly to the case with prolactin, both abnormally low and abnormally high levels of plasma vasopressin (antidiuretic hormone) are associated with serious medical conditions. Low levels (diabetes insipidus, DI) result in excessive thirst, excretion of large amounts of severely diluted urine, and potential dehydration. Abnormally high concentrations (syndrome of inappropriate antidiuretic hormone hypersecretion, SIADH) result in water retention and excess excretion of sodium. Elevated AVP concentrations in animals and humans have been linked to anxiety, depression, and aggression, and high plasma and/or CSF levels have been associated with personality disorder, depression, obsessive-compulsive disorder, schizophrenia, and PTSD. Data for each of the two subject groups are presented as in Figure 1. Our criterion for excessive AVP concentration was a level above the 95th percentile of our reference sample. Functional vasopressin deficiency was defined as an AVP concentration below the 5th percentile together with very dilute urine (urine specific gravity less than 1.003). Two of the mTBI group met our criterion for excessive AVP secretion, and two of the same group, indicated by the green circles, met both criteria for functional vasopressin deficiency. None of the deployment control group was found to have abnormal plasma prolactin levels.

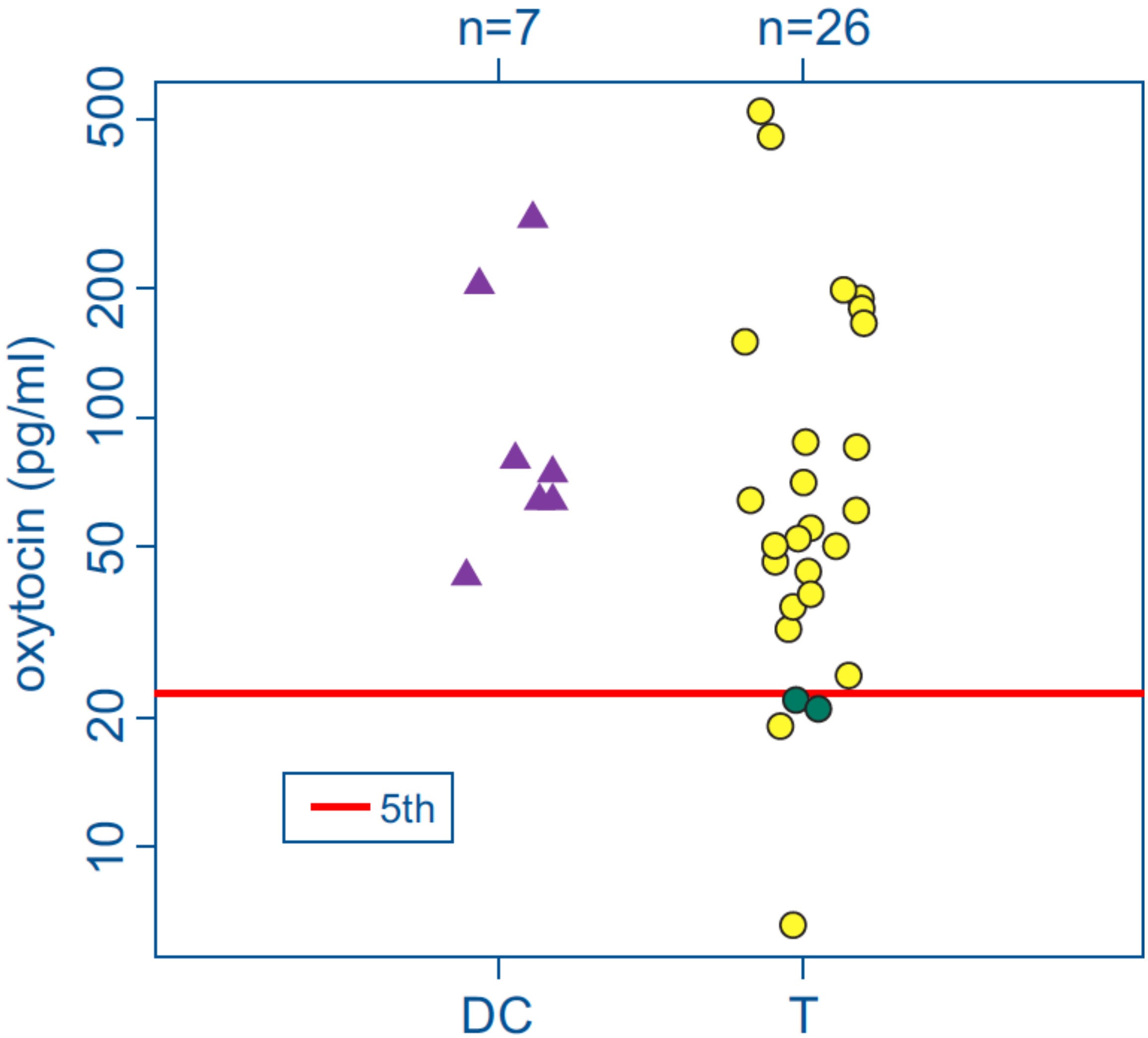

Figure 3. Oxytocin has been shown to play a role in multiple aspects of maternal, social, and romantic bonding and to have significant anxiolytic and anti-stress effects on social approach behavior and in socially challenging situations. It has also been linked to promotion of social recognition and interpretation of social signals. Extremely low concentrations of OT have been linked to mental disorders characterized by severe social disturbances such as autism. None of the Veterans in the deployment control group, but four members of the mTBI group met our sub-5th-percentile criterion for OT deficiency. The two participants whose data are marked by green circles were those who were also found to have a functional vasopressin deficiency. The occurrence of deficiencies of both of these posterior pituitary hormones in the same individuals suggest the possibility of disruption of the axons that carry these hormones through the pituitary stalk prior to release into the circulation.

In this analysis of the initial sample of 26 Veterans who had sustained blast concussions during deployment to Iraq or Afghanistan, five participants were found to have IGF-I concentrations consistent with GHD (Table 1). Three of the mTBI group had LH and testosterone levels indicative of hypogonadism. Of these three, two had extremely low IGF-I levels, two had aberrant prolactin concentrations, and one had an OT level below the sensitivity of the assay. In light of the fact that none of the deployment control participants (at this point, a small group of 7) were found with abnormal levels of any of the hormones measured, we feel that our data strongly suggest that blast-induced mTBI carries a high risk for chronic pituitary dysfunction.

Subj.	LH	FSH	tTest	PRL	IGF-I	AVP	OT
	mIU/ml	U/L	ng/dl	ng/ml	ng/ml	pg/ml	pg/ml
T-2	2.03	---	669	9.6	185	12.3	181
T-4	2.03	2.06	252	54.9	110	8.0	88
T-8	2.72	4.02	401	11.9	141	0.2	44
T-10	1.97	2.43	520	12.3	230	0.2	22
T-12	7.27	5.70	715	13.0	198	12.0	55
T-13	1.92	1.18	253	6.3	187	6.4	50
T-14	2.66	2.51	390	12.0	151	0.5	19
T-16	2.64	4.01	380	21.5	126	0.9	190
T-21	4.00	4.48	588	12.8	227	0.0	21
T-23	2.24	4.34	463	7.2	146	2.1	25
T-26	2.11	2.64	264	15.3	86	8.4	0

Table 1. The table shows the hormone concentrations of the 11 of 26 Veterans with blast-induced mTBI who were found to have aberrant levels (highlighted in yellow) of one or more hormones.

During Year 2, repository samples were acquired for nine additional Veterans with mTBI and eight new deployment control Veterans. Hormonal analysis of these samples revealed two additional individuals with blast mTBI who exhibited IGF-I levels suggestive of GHD and two more with LH and testosterone concentrations indicative of hypogonadism. These results confirm our early results in that 4 of 9 (44.4%) of the TBI group had abnormal hormone levels, and the most frequent anterior pituitary hormone abnormalities were again those associated with GHD and hypogonadism. In this sample, one of the eight (12.5%) members of the deployment control group was found to have serum hormone levels meeting the criteria for both hypogonadism and GHD. Overall, at the end of Year 2, 15 of 35 (42.9%) Veterans with mTBI and 1 of 15 (6.7%) deployed non-blast exposed Veterans displayed hormonal abnormalities.

Because of the study's focus on *blast* concussion in particular and in order to take a conservative approach to analysis, Veterans with *non-blast* mTBI were not excluded from the deployment control group. It is possible that the individual in the deployment control group who exhibited hormonal abnormalities had experienced an impact-related concussion that precipitated hypopituitarism. Also, it is generally considered the nature of military culture results in marked under-reporting of concussions.

The overall percentage of participants meeting criteria for GHD or hypogonadism in each of the two subject groups for all samples measured thus far are shown in Figure 4. These results confirm and support our initial conclusion that Veterans who sustain blast mTBI during deployment are at significantly greater risk for pituitary dysfunction than deployed Veterans without blast exposure and that the most prevalent hormonal abnormalities are those indicative of probable GHD and hypogonadism.

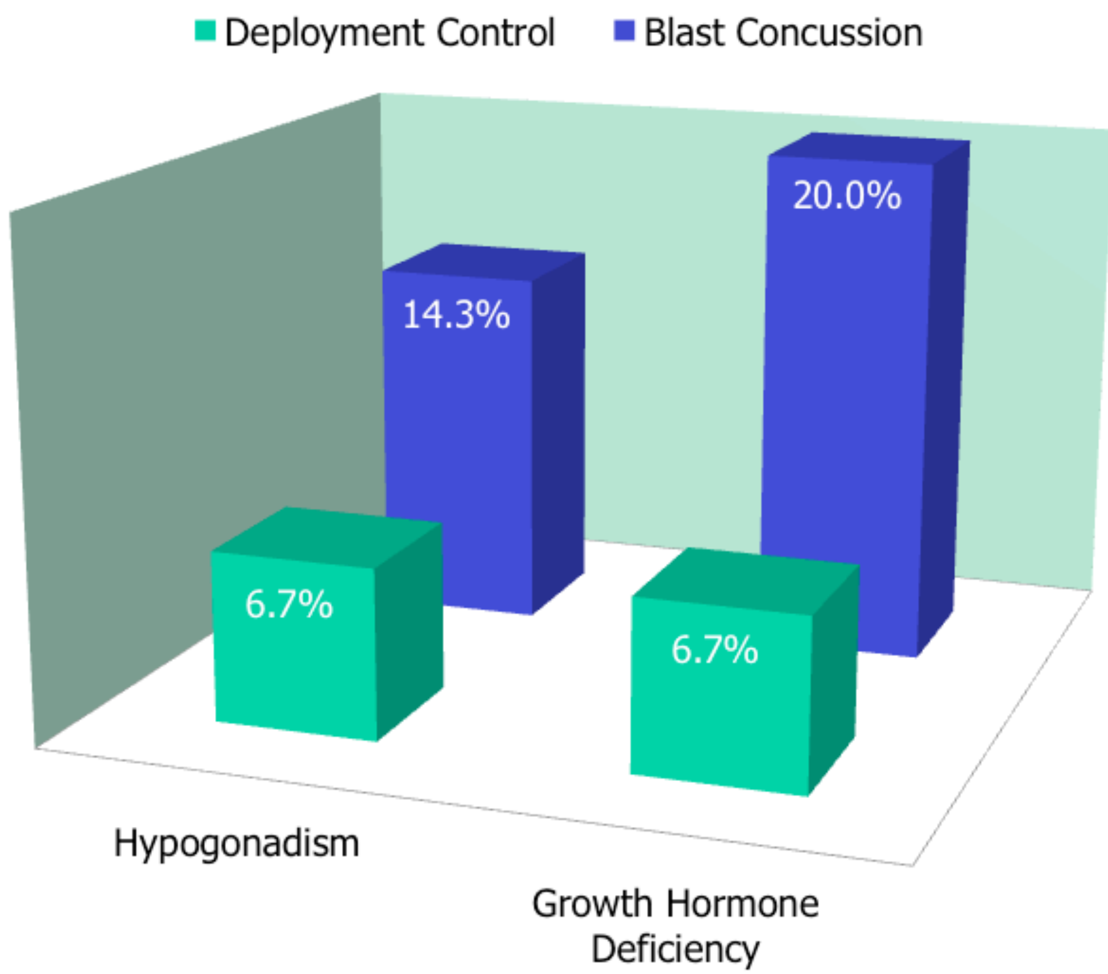

Figure 4. Results for all samples analyzed to date show that 14.3% (5/35) of mTBI subjects and 6.7% (1/15) of deployment control subjects met criteria for hypogonadism. Criteria for GHD were met by 20.0% (7/35) of mTBI subjects and 6.7% (1/15) of deployment control subjects.

Problems in Accomplishing the Tasks

A single highly significant problem was encountered in performing the tasks described in the Statement of Work and completing the study. That problem was the continuing lack of availability of a sufficient number of appropriate blood samples in the repository from which our samples were drawn. This study was dependent on the repository for samples, demographic information, and screening data. The problem stemmed from a temporary cessation of subject recruitment for the large mTBI imaging study that generated the samples in the repository. The delay was caused by the necessity for major revision of the IRB application for that study. Even after approval was obtained from both the VA Puget Sound Health Care System IRB and the University of Washington IRB for that study, recruitment has progressed extremely slowly and has twice necessitated requests for no-cost extensions.

During the final extension of this project we have succeeded in closing in on our goals for acquisition of samples to meet targets for all three participant groups. Our final sample totals are: community controls = 100/100; Veterans with blast concussion = 39/40; deployment controls = 20/20. These goals have only been reached during the past month, and the final hormone assays for all hormones in samples from all subjects are currently being carried out. Final tabulation and analysis of the data will be followed by the writing of a thorough description, analysis, and interpretation of the completed study and submission to a peer-reviewed journal.

Personnel receiving pay from the research study

Elizabeth A. Colasurdo
Steven P. Millard
Yun Xiang

KEY RESEARCH ACCOMPLISHMENTS

- Determined reference ranges for 12 pituitary and target-organ hormones in blood samples from healthy male civilians
- Used distribution statistics from above to establish criteria for defining abnormal levels of each hormone in Veteran participant groups
- Determined that 42.9% of Veterans with blast concussions for whom assays have been completed had at least one hormonal abnormality
- Found that 6.7% of deployed Veterans without a blast concussion for whom assays have been completed had one or more hormonal abnormality
- Confirmed hypothesis that blast concussion is a serious risk factor for hypopituitarism
- Determined that the most common hormonal deficits after blast mTBI were consistent with growth hormone deficiency (20.0%) and hypogonadism (14.3%)

- Referred participants identified as having probable hypopituitarism for clinical evaluation when possible
- Completed sample acquisition for all three participant groups and are currently assaying all samples for all 12 hormones

REPORTABLE OUTCOMES

Oral and Poster Presentation and Abstracts

1. "Chronic hypopituitarism after blast concussion mild traumatic brain injury in Iraq/Afghanistan combat Veterans." Charles W Wilkinson, Elaine R Peskind, Elizabeth A Colasurdo, and Jane B Shofer. Oral Presentation: 93rd Annual Meeting & Expo of The Endocrine Society, Boston Convention & Exhibition Center, Boston, MA, June 4-7, 2011.
Abstract published in *Endocrine Reviews* **32** (03_MeetingAbstracts): OR16-4, 2011. ***(Appendix 3, p.35)***
http://edrv.endojournals.org/cgi/content/meeting_abstract/32/03_MeetingAbstracts/OR16-4?sid=611ee69b-229e-4ea6-8d33-6f794557b3b7

2. "Pituitary dysfunction after traumatic brain injury (TBI): relevance for psychological health and rehabilitation." Charles W. Wilkinson. Oral Presentation, Case Conference: Butler Hospital, Warren Alpert Medical School of Brown University, Providence, RI, June 10, 2011.

3. "Pituitary dysfunction in OIF/OEF Veterans with repetitive blast mild traumatic brain injury." Charles W. Wilkinson. Oral Presentation in Symposium: Structural and Functional Neuroimaging, Pituitary Dysfunction, and Animal Modeling in Blast Concussion Mild Traumatic Brain Injury. Elaine R. Peskind, Rajendra Morey, Charles W. Wilkinson, and David G. Cook. 3rd Federal Interagency Conference on Traumatic Brain Injury, Washington Hilton, Washington, DC, June 13-15, 2011. ***(Appendix 3, p.36-37)***

4. "Blast concussion mTBI, hypopituitarism, and psychological health in OIF/OEF Veterans." Charles W. Wilkinson. Oral Presentation: Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) In Progress Review (IPR), Hilton Garden Inn, Frederick, MD, July 27, 2011.

5. "Pituitary dysfunction after blast concussion: relevance for psychological health and rehabilitation." Charles W. Wilkinson. Oral Presentation: National Intrepid Center of Excellence (NICoE) Grand Rounds, NICoE, National Naval Medical Center, Bethesda, MD, July 28, 2011.

6. "Chronic pituitary dysfunction after blast-related mild traumatic brain injury." Charles W. Wilkinson, Elaine R. Peskind, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, and

Jane B. Shofer. Poster Presentation: American College of Neuropsychopharmacology (ACNP) 50th Annual Meeting, Hilton Waikoloa Village, Waikoloa, HI, December 4-8, 2011. ***(Appendix 3, p. 38-40)***
Abstract published in *Neuropsychopharmacology* **36:**S407–S408, 2011
http://www.nature.com/npp/journal/v36/n1s/full/npp2011293a.html

7. "Chronic pituitary dysfunction associated with cognitive and neuropsychiatric deficits after blast-related concussion." Charles W. Wilkinson, Kathleen F. Pagulayan, Jane B. Shofer, and Elaine R. Peskind. Poster Presentation: 22nd Pacific Coast Brain Injury Conference, Sheraton Vancouver Wall Centre, Vancouver, BC, Canada, February 15-17, 2012. ***(Appendix 3, p. 41)***

8. "Prevalence and characteristics of chronic pituitary dysfunction after blast-related mild traumatic brain injury." Charles W. Wilkinson, Elaine R. Peskind, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, and Jane B. Shofer. Oral Presentation: Ninth World Congress on Brain Injury, Edinburgh International Conference Centre, Edinburgh, Scotland, March 21-25, 2012. ***(Appendix 3, p. 42-43)***
Abstract published in *Brain Injury* **26**:732, 2012
http://informahealthcare.com/doi/pdf/10.3109/02699052.2012.660091

9. "Chronic pituitary hormone abnormalities after blast-induced mild traumatic brain injury in combat Veterans: a psychiatric concern?" Charles W. Wilkinson. Oral Presentation, Grand Rounds: University of Washington Department of Psychiatry and Behavioral Sciences, Harborview Medical Center, Seattle, WA, April 6, 2012.

10. "Hormonal abnormalities after blast concussion in Veterans: implications for quality of life." Charles W. Wilkinson. Oral Presentation in Symposium: Overview of VA/UW Blast-related Traumatic Brain Injury Research Program. Lance Stewart, Elaine R. Peskind, Charles W. Wilkinson, and David G. Cook. VA Puget Sound Health Care System, Seattle, WA, April 9, 2012.

11. "Hormonal abnormalities after blast concussion in Veterans: implications for quality of life." Charles W. Wilkinson. Oral Presentation, Research Seminar: Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, April 9, 2012.

12. "Blast concussion is associated with high frequency of pituitary dysfunction." C. Wilkinson, K. Pagulayan, E. Colasurdo, J. Shofer, and E. Peskind. Poster Presentation: ICE/ECE 2012: 15th International Congress of Endocrinology, Fortezza da Basso, Florence, Italy, May 5-9, 2012. ***(Appendix 3, p. 44-45)***
Abstract published in *Endocrine Abstracts* **29**:P1436
http://www.endocrine-abstracts.org/ea/0029/ea0029p1436.htm

13. "Pituitary Function After Blast Concussion: Why It Happens and Why It Matters." Charles W. Wilkinson. Oral Presentation, Neuroscience Research Seminar, VA Puget Sound Health Care System, Seattle, WA, March 1, 2013.

14. "Prevalence of chronic hypopituitarism after blast concussion." Charles W. Wilkinson, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, Jane B. Shofer, and Elaine R. Peskind. Poster Presentation, Experimental Biology 2013, Boston Convention & Exhibition Center, Boston, MA, April 20-24, 2013. ***(Appendix 3, p. 46-47)***

Abstract published in *FASEB J* **27**:935.3, 2013
http://www.fasebj.org/cgi/content/meeting_abstract/27/1_MeetingAbstracts/935.3?sid=c78bc1bd-2e77-40db-b5d2-c95ae9e715ed

15. "TBI: Screening and Evaluation of Headache and Endocrine Disorders." Elaine R. Peskind and Charles W. Wilkinson. Cyber Seminar Presentation, VA HSR&D Center for Information Dissemination and Education Resources, April 25, 2013.

16. "Pituitary dysfunction after blast concussion: imaging and psychological correlates." Charles W. Wilkinson, Eric C. Petrie, Satoshi Minoshima, Donna J. Cross, Todd L. Richards, Kathleen F. Pagulayan, and Elaine R. Peskind. Poster Presentation, ENDO 2013: The Endocrine Society Annual Meeting & Expo, Moscone Center, San Francisco, CA, June 15-18, 2 013. ***(Appendix 3, p. 48)***

Abstract published in *Endocr Rev* 34: SUN-148, 2013
https://endo.confex.com/endo/2013endo/webprogram/Paper7712.html

17. "High Frequency of Pituitary Dysfunction and Associated Cognitive and Behavioral Deficits after Blast Concussion." Charles W. Wilkinson, Kathleen F. Pagulayan, Elizabeth A. Colasurdo, Jane B. Shofer, Madeleine L. Werhane, and Elaine R. Peskind. Abstract Accepted, Poster Presentation,1st PanAmerican Congress of Physiological Sciences (PanAm-2014): Physiology without borders, Rafain Palace Hotel & Convention Center, Iguassu Falls, Brazil, August 2-6, 2014. ***(Appendix 3, p. 49)***

Peer-reviewed Publication

"High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury." Charles W. Wilkinson, Kathleen F. Pagulayan, Eric C. Petrie, Cynthia L. Mayer, Elizabeth A. Colasurdo, Jane B. Shofer, Kim L. Hart, David Hoff, Matthew A. Tarabochia, and Elaine R. Peskind. *Front Neurol* **3**:11, 2012. Published online 2012 February 7. Prepublished online 2011 December 27. doi: 10.3389/fneur.2012.00011 PMCID: PMC3273706 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3273706/?tool=pubmed)

Funding Applied for and Received Based on Work Supported by this Award

VA Rehabilitation Research & Development Merit Review Award.

Application Number: 1I01RX000509-01A1.
Principal Investigator: Charles W. Wilkinson, PhD
Project Title: Pituitary dysfunction, behavioral symptoms, and quality of life after blast mTBI.
Period: April 1, 2012- March 31, 2016.
Estimated Award Total: $932,347

Research Opportunities Received Based on Experience Supported by this Award

Contact was initiated with three investigators from the Naval Medical Research Center (NMRC) in San Diego (LCDR Andrew MacGregor, PhD, MPH; Mary Clouser, MD, MPH; and Michael Galarneau, MS) to collaborate to obtain selected serum samples from the Department of Defense Serum Repository (DoDSR) maintained by the Armed Forces Health Surveillance Center (AFHSC). The DoDSR receives and stores serial serum specimens related to operational deployments worldwide which are made available to qualified DoD researchers upon acceptance of an application proposal. The AFHSC retains demographic, occupational, and medical information linked to the serum samples in the repository. The NMRC maintains the Expeditionary Medical Encounter Database (EMED), which contains clinical records completed by providers at forward-deployed medical facilities and including those of combatants with serious injuries who are subsequently evacuated to higher levels of care, as well as those with mild injury who are returned to duty. The clinical records provide details about the injury incident, such as injury mechanism, as well as the number, type, and severity of injuries, including TBI. The collaboration with NMRC investigators will involve the selection of Marines who experienced mTBI in Iraq or Afghanistan as well as deployed non-blast-exposed Marines selected on the basis of the EMED records. Matching serum samples will be requested from the DoDSR.

The hypothesis of the proposed study is that serum hormone deficiencies characteristic of hypogonadism and growth hormone deficiency (GHD) are significantly more frequent in US Marines who have sustained blast-related mild traumatic brain injury (mTBI), i.e., concussion, while deployed in Iraq, Operation Iraqi Freedom (OIF) or Afghanistan, Operation Enduring Freedom (OEF) (mTBI group) than in similarly deployed Marines not exposed to blast trauma (Non Blast Exposed (NBE) group). This hypothesis will be tested by measuring luteinizing hormone (LH), testosterone, and insulin-like growth factor-I (IGF-I) in my laboratory in predeployment and postdeployment serum samples from Marines in each of the two groups. The study will also investigate potential associations of hormonal abnormalities after blast mTBI with particular constellations of demographic, medical history, injury mechanism, and injury-specific data to determine to what extent each of these factors or combinations of factors best predict the occurrence of chronic pituitary dysfunction after blast concussion.

A proposal submitted by the NMRC investigators and I has been approved by the AFHSC and the project will begin when the linkage between serum samples and data in the EMED is completed.

CONCLUSION

In data analyzed to date, 42.9% of participants with blast mTBI showed evidence of posttraumatic hypopituitarism as determined by basal hormone measurements. The prevalence of hypopituitarism from all causes in the general population has been estimated at 300 cases per million, or 0.03%. Based on this estimation, the prevalence of pituitary dysfunction in Veterans who sustained blast concussions while deployed in Iraq or Afghanistan is 1,430 times greater than that of the general population. These data suggest a problem of enormous significance for the health, recovery, and rehabilitation of service members and Veterans. The most frequently observed hormone deficiency disorders observed after concussion are GHD and hypogonadism. Both conditions result in significant changes in mood, energy, body composition, and QoL.

PTHP is associated with a constellation of symptoms that overlap considerably with those of PTSD, including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life. Muscular weakness, erectile dysfunction, infertility, deleterious effects on body composition, and diminished cardiovascular function are also frequent consequences. These symptoms, if they result from PTSD, are often resistant to successful treatment. However, if some or all of the symptoms are indeed of neuroendocrine origin and are appropriately diagnosed as consequences of neuroendocrine disorders, they can be treated successfully with hormone replacement. Therefore, failure to consider the diagnosis of PTHP may result in inappropriate and ineffective treatment of these symptoms.

Therefore, routine screening for pituitary dysfunction after blast concussion shows promise for: (a) identifying those individuals whose symptoms are of neuroendocrine origin; (b) directing diagnostic and therapeutic strategies that might otherwise remain unconsidered; and (c) markedly facilitating recovery and rehabilitation after blast concussion.

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Blast Concussion mTBI, Hypopituitarism, and Psychological Health in OIF/OEF Veterans
PT090753 Principal Investigator: Charles W. Wilkinson, Ph.D.
Statement of Work (SOW)

Introduction and Rationale: Chronic hypopituitarism (deficient production of one or more anterior pituitary hormones) occurs in 30-70% of cases of civilian traumatic brain injury (TBI). Although repetitive blast concussion TBI (mTBI) is the signature injury sustained by combat troops deployed to Operation Iraqi Freedom (OIF) and/or Operation Enduring Freedom in Afghanistan (OEF), the incidence of hypopituitarism resulting from this type of mTBI has not been determined. Hypopituitarism is associated with symptoms easily mistaken for those of posttraumatic stress disorder (PTSD) including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life. Muscular weakness, erectile dysfunction, infertility, and diminished cardiovascular function can also result. These symptoms, if diagnosed as consequences of hypopituitarism as opposed to being of purely neurological origin, can generally be relieved with hormone replacement. Provocative testing, often used in screening for hypopituitarism after TBI, is costly, time-consuming, and labor-intensive, but measurement of basal concentrations of pituitary hormones and their target hormones has been shown to have considerable diagnostic utility. This study is designed to establish normative values for each of 12 pituitary and target-organ hormones, to measure these hormones in banked blood samples from groups of Veterans of OIF/OEF with and without blast mTBI, to establish criteria for individual hormone deficiencies and the diagnosis of hypopituitarism, to refer Veterans provisionally identified with hypopituitarism for clinical evaluation and treatment, and to determine the frequency and specific pituitary deficits consequent to blast mTBI. Accurate, routine diagnosis of hypopituitarism has the potential of markedly improving the psychological health and facilitating the recovery of blast mTBI victims.

Specific Aim 1: Measurement of basal concentrations of anterior pituitary hormones and their target-organ hormones in serum or plasma from 100 male civilian control subjects in order to establish normative parameters for each hormone concentration.

Task 1: Obtainment of all regulatory approvals required in order to proceed with this aim: biohazard, radiation safety, local institutional review board (IRB), and Department of Defense (DOD) Human Research Protection Office (HRPO) human subjects approval. Submission of applications for biohazard, radiation safety and local IRB approval has already been completed. The IRB application is for expedited review, and approval is expected before the end of the first three months (quarter 1 [Q1]) of the study. HRPO submission will follow IRB approval immediately, and all approvals are expected to be received by the end of Q2.

Task 2: Measurement of the 12 hormones (adrenocorticotropin [ACTH], cortisol, thyroid-stimulating hormone [TSH], free thyroxine, growth hormone [GH], insulin-like growth factor I [IGF-I], luteinizing hormone [LH], follicle-stimulating hormone [FSH], total testosterone, prolactin [PRL], vasopressin, and oxytocin) in blood samples from 100 community control subjects will require:

a) selection of a commercially available hormone assay kit for each hormone and tests of the performance of the assays as carried out according to the manufacturers' protocols. Test assays will not be performed until biohazard and radiation safety approvals have been obtained. Cortisol, IGF-I, LH, and vasopressin will be measured by radioimmunoassay (RIA) techniques. All other hormones will be measured using enzyme-linked immunosorbent assay (ELISA) techniques. Performance of this sub-task will be completed during months four through six (Q2) of the study duration. This sub-task does not employ any human tissue or biological fluids or any other use of human subjects and does not require IRB approval. This is a test of assay performance only.

b) procurement of banked plasma and serum samples previously obtained from 100 selected male community control subjects between the ages of 21 and 50 with a body mass index (BMI) less than 34. All samples to be analyzed will be samples banked in a regulated repository; no direct sampling of biological fluids from human participants will be employed in this study. Banked samples will NOT be obtained prior to IRB and HRPO approvals. This subtask will require only a very short period of time and is expected to be completed by the end of the Q2.

Task 3: Performance of assays of all 12 hormones listed above on plasma or serum samples from the 100 selected male community control subjects, tabulation and statistical analysis of all assay results, and use of those analyses to determine ranges of normal concentrations of each hormone to establish diagnostic criteria for individual hormone deficiencies. ACTH, cortisol, TSH, vasopressin, and oxytocin will be measured in plasma samples. Free thyroxine, GH, IGF-I, LH,FSH, total testosterone, and PRL will be measured in serum samples. Identification of pituitary hormone deficiencies will be based upon measurement of hormone values below the normative ranges established with assays of samples from community control subjects. Performance of this task will be completed during months 7-10 of the study (Q3).

All tasks addressing Specific Aim 1 are expected to be completed by the end of Q3.

Specific Aim 2: Measurement of basal concentrations of the 12 pituitary and target-organ hormones described above in banked plasma/serum samples from 40 male Veterans of OIF/OEF exposed to blast concussion mTBI – the mTBI group – and banked samples from a second group of 20 male OIF/OEF Veterans without blast concussion mTBI or PTSD – the deployment control (DC) group. Pituitary deficiencies and occurrence of hypopituitarism in individual subjects and for each of the two subject groups will be tabulated to describe the frequency and specific pituitary deficits consequent to blast mTBI.

Task 4: Performance of assays, as described above on banked samples from 100 community control subjects, of ACTH, cortisol, TSH, free thyroxine, GH, IGF-I, LH, FSH, total testosterone, PRL, vasopressin, and oxytocin in plasma/serum samples from 40 mTBI and 20 DC subjects followed by tabulation and analysis of the data. Task 4 will be completed by the end of Q4.

Task 5: Determine the individual hormone deficiencies and the probable incidence of hypopituitarism in each Veteran and in each of the two Veteran groups (mTBI and DC) by:

a) using criteria derived from community control normative data to identify individual hormone deficiencies in each of the 60 Veteran subjects (40 mTBI and 20 DC). For each of the 12 hormones, a measured value that falls in the lowest 5 percentile of the community control group will be defined as a hormone deficiency.

b) identify the existence of probable hypopituitarism in each subject. Hypopituitarism will be defined as deficiencies indicating dysfunction in any one of the following pituitary hormone/target hormone systems: ACTH/cortisol; TSH/thyroxine; GH/IGF-I; LH/FSH/testosterone; PRL; vasopressin; and oxytocin.

c) using the data from individual subjects, determine the incidence of each specific hormone deficiency in the mTBI group and in the DC group. Based on the definition of hypopituitarism above (in the description of Task 5b) determine the incidence of hypopituitarism in each of the Veteran groups. Statistically analyze the group data to identify possible significant differences in pituitary dysfunction between the two groups.

All tasks addressing Specific Aim 2 are expected to be completed by the end of Q5.

Specific Aim 3: Refer individuals provisionally identified with pituitary deficits for more extensive diagnostic tests and treatment, use those clinical data to further refine and validate the hormonal screening criteria, and determine predictive accuracy of the final screening method.

Task 6: Veteran subjects provisionally identified with pituitary dysfunction will be referred to physicians specializing in endocrinology for further clinical evaluation, diagnosis, and treatment, and results from clinical evaluations will be used to refine the cutoff criteria provided by the hormone assays. Based on the refined criteria, group data will be re-evaluated to determine specific differences related to blast mTBI, and receiver operating characteristic (ROC) analysis will be used to assess the predictive accuracy of the hormone screening method.

All tasks addressing Specific Aim 3 are expected to be completed by the end of Q6.

Consult timeline below for graphic presentation of the sequence of tasks and their expected time of completion.

Primary Outcomes:

1. Referral for clinical evaluation and treatment of Veteran subjects provisionally identified with hypopituitarism.
2. Determination of hypothesized increased incidence of specific hormone deficiencies and diagnosis of hypopituitarism in individuals exposed to blast concussion mTBI.
3. Dissemination of findings and their significance for Veterans' physical and psychological health by publication in an appropriate scientific journal.

The principal investigator Charles Wilkinson and co-investigator Elaine Peskind will participate in all tasks. All work will be performed at:

Department of Veterans Affairs Puget Sound Health Care System (VAPS)
1660 S. Columbian Way
Seattle, WA 98108

	Q1	Q2	Q3	Q4	Q5	Q6
Specific Aim 1 — Measure basal pituitary and target hormone concentrations in plasma/serum from 100 community control subjects						
Task 1: Obtain all necessary regulatory approvals for project						
1.a: Obtain biohazard and radiation safety approval	VAPS					
1.b: Obtain IRB approval to use banked blood samples	VAPS					
1.c: Obtain DOD HRPO approval for project	DOD	DOD				
Milestone 1: All regulatory approvals obtained		VAPS				
Task 2: Select and characterize samples from 100 community controls and test assay methods						
2.a: Test performance of assays for all hormones	VAPS	VAPS				
2.b: Obtain banked samples after protocols approved		VAPS				
2.c: Sort samples; select for age 21-50, BMI < 34		VAPS				
Milestone 2: Assays validated and 100 control samples identified		VAPS				
Task 3: Perform all hormone assays on samples from 100 community controls and analyze data						
3.a: Perform 12 hormone assays on 100 control samples			VAPS			
3.b: Analyze and tabulate data			VAPS			
3.c: Use data to identify normative hormone ranges			VAPS			
Milestone 3: Assays performed and normal ranges established			VAPS			
Specific Aim 2 — Measure basal pituitary and target hormone concentrations in plasma/serum from 40 OIF/OEF Veterans exposed to blast mTBI and 20 OIF/OEF Veterans without mTBI or PTSD						
Task 4: Assay and analyze all samples from 40 mTBI-exposed and 20 deployment-control Veterans						
4.a: Perform 12 hormone assays on 60 Veteran samples				VAPS		
4.b: Tabulate and analyze data				VAPS		
Milestone 4: mTBI and DC samples assayed and analyzed				VAPS		
Task 5: Use criteria derived from normative data to identify probable hypopituitarism in each Veteran group						
5.a: Use control data to set criteria for deficiencies				VAPS	VAPS	
5.b: Identify subjects with probable hypopituitarism				VAPS	VAPS	
5.c: Ascertain hormone deficit incidence in each group				VAPS	VAPS	
Milestone 5: Screening criteria established, applied and analyzed					VAPS	
Specific Aim 3 — Refer Veterans with probable hypopituitarism for clinical evaluation and treatment and use de-identified evaluations to validate and refine the diagnostic utility of the hormone assay screening procedure						
Task 6: Carry out clinical referrals and use clinical data to assess specificity and sensitivity of screening						
6.a: Refer for clinical evaluation and treatment				VAPS	VAPS	
6.b: Use clinical outcome data to refine screening criteria					VAPS	
6.c: Re-evaluate data for group hypopituitarism incidence					VAPS	
6.c: Find predictive accuracy of method by ROC analysis					VAPS	
6.d: Write manuscript and submit for publication						VAPS
Milestone 6: Publication of final results of study						VAPS

Q1 = Quarter 1 (months 1-3) / Q2 = Quarter 2 (months 4-6) / Q3 = Quarter 3 (months 7-9)
Q4 = Quarter 4 (months 10-12) / Q5 = Quarter 5 (months 13-15) / Q6 = Quarter 6 (months 16-18)

ORIGINAL RESEARCH ARTICLE
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High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury

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Studies of traumatic brain injury from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones at least 1 year after injury, in 25–50% of cases. Most studies found the occurrence of posttraumatic hypopituitarism (PTHP) to be unrelated to injury severity. Growth hormone deficiency (GHD) and hypogonadism were reported most frequently. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of PTHP after blast-related mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized. We measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least 1 year prior to the study. The other consisted of Veterans with similar military deployment histories but without blast exposure. Eleven of 26, or 42% of participants with blast concussions were found to have abnormal hormone levels in one or more pituitary axes, a prevalence similar to that found in other forms of TBI. Five members of the mTBI group were found with markedly low age-adjusted insulin-like growth factor-I (IGF-I) levels indicative of probable GHD, and three had testosterone and gonadotropin concentrations consistent with hypogonadism. If symptoms characteristic of both PTHP and PTSD can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement. Routine screening for chronic hypopituitarism after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

Keywords: traumatic brain injury, hypopituitarism, blast, concussion, growth hormone, pituitary

INTRODUCTION

Recent studies investigating chronic pituitary dysfunction resulting from TBI have reported a prevalence of posttraumatic hypopituitarism (PTHP) ranging from 5 to 95% with a median of 35%, the variation being primarily due to differences in screening criteria (Bavisetty et al., 2008; Srinivasan et al., 2009; Berg et al., 2010; Englander et al., 2010; High et al., 2010; Kokshoorn et al., 2010, 2011; Krahulik et al., 2010; Park et al., 2010; Pavlovic et al., 2010; Reimunde et al., 2011; Schneider et al., 2011). Pituitary hormone disorders are frequently among the immediate consequences of TBI; some resolve during the following months while a smaller proportion of new dysfunctions emerge (Agha et al., 2005; Aimaretti et al., 2005; Schneider et al., 2006, 2011; Tanriverdi et al., 2006, 2008b; Klose et al., 2007; Krahulik et al., 2010). By ~6 months subsequent to TBI, the pattern of pituitary deficits is considered to be relatively permanent.

The risk factors and the mechanisms, other than immediate trauma-induced tissue damage and subsequent edema, for chronic hypothalamo-pituitary dysfunction due to TBI are unclear. Roles for polymorphisms in apolipoprotein E genotype (*APOE*), inflammatory processes – both systemic and neural, and anti-hypothalamic (AHAs) and anti-pituitary antibodies (APAs) have been proposed, and each has empirical support.

There is evidence that the apolipoprotein E (*APOE*) ε3/ε3 genotype may be associated with a reduced risk of TBI-related hypopituitarism. *APOE* ε3 is the most common of the three alleles and is found in more than half of the general population. The ε2 and ε4 alleles have been associated with altered risks for Alzheimer's disease, hyperlipoproteinemia, and atherosclerosis. Pituitary dysfunction in patients with TBI has been found to be significantly less prevalent in individuals with the *APOE* ε3/ε3 genotype (17.7%)

than in patients with other genotypes (41.9%; $p = 0.01$; Tanriverdi et al., 2008a).

Evidence for the involvement of APAs and/or AHAs in the development of chronic PTHP comes from two studies. APAs were detected in 44.8% of patients who had completed a 3-year-follow-up after TBI and in none of the healthy control subjects, and the prevalence of hypopituitarism was significantly higher in APA-positive (46.2%) than APA-negative TBI patients (12.5%; $p = 0.04$; Tanriverdi et al., 2008b). In another study of active and retired boxers, AHAs were detected in 21.3% and APAs in 22.9% of boxers, whereas no evidence of APAs or AHAs was found in control subjects (Tanriverdi et al., 2010a).

It is well established that TBI results in the acute induction of both neural and systemic inflammatory responses and consequent anti-inflammatory counter-responses (Lu et al., 2009; Ziebell and Morganti-Kossmann, 2010). In addition, animal studies provide evidence of the development of a chronic inflammatory state after TBI. Three months after moderate focal brain injury in rats, persistent major histocompatibility complex (MHC)-II up-regulation, mononuclear phagocytosis, and elevated interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) synthesis were observed in large areas of the ipsilateral hemisphere (Holmin and Mathiesen, 1999). In another study, 2 months after cortical contusion injury to the medial frontal cortex of rats, IL-1β was significantly increased in the cortex and hypothalamus compared with a sham–trauma group, and glial fibrillary acidic protein (GFAP) was elevated in the cortex, hypothalamus, and anterior pituitary of the TBI group (Kasturi and Stein, 2009).

In general, the frequency of occurrence of pituitary hormone abnormalities has not been found to be related to the severity of the trauma (Lieberman et al., 2001; Agha et al., 2004a; Aimaretti et al., 2004, 2005; Bondanelli et al., 2004; Schneider et al., 2006; Park et al., 2010; Kokshoorn et al., 2011), although there have been reports of a positive relationship (Kelly et al., 2000; Klose et al., 2007). Of the traumatic brain injuries sustained by ~1.7 million Americans annually (Faul et al., 2010), 75% are considered mild TBI (mTBI; National Center for Injury Prevention and Control, 2003).

Mild TBI is defined by the American Congress of Rehabilitation Medicine (ACRM) as a head trauma resulting in any one of the following: loss of consciousness (LOC) for 30 min or less, alteration of mental state for up to 24 h (being dazed, confused, disoriented, etc.), or loss of memory for events immediately before or after the trauma (American Congress of Rehabilitation Medicine, 1993). The terms mTBI and concussion are frequently used interchangeably (National Center for Injury Prevention and Control, 2003; Department of Veterans Affairs/Department of Defense, 2009).

Mild TBI-related chronic pituitary dysfunction has been reported in boxers and kick boxers subjected to repetitive head injuries. In a preliminary study, 45% of professional boxers were found with apparent growth hormone deficiency (GHD), but no other pituitary hormone deficiencies were observed (Kelestimur et al., 2004). In a larger study of active and retired boxers 18% had pituitary hormone deficiencies in one or more axes (Tanriverdi et al., 2008c). An investigation of pituitary dysfunction in amateur kick boxers revealed GH and/or adrenocorticotropin (ACTH) deficiencies in 27.3% of the athletes (Tanriverdi et al., 2007).

In 2010, the injuries in 80% of over 30,000 U.S. military service members medically diagnosed with TBI were classified as mTBI (Military Health System, 2011), and mTBI sustained from explosive blasts is one of the most common combat injuries resulting from deployment to Iraq or Afghanistan. About 10–20% of returnees report having experienced at least one blast concussion (Tanielian et al., 2008; Terrio et al., 2009).

The extensive documentation of the high prevalence of hypopituitarism after TBI from all causes and the absence of any published studies of the frequency of PTHP after blast-related mTBI provided the rationale for this investigation of hypopituitarism in U.S. Veterans of combat in Iraq and/or Afghanistan who have experienced at least one blast concussion.

MATERIALS AND METHODS

PARTICIPANTS AND SAMPLE ACQUISITION

The VA Puget Sound Health Care System (VAPSHCS) Institutional Review Board and the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) approved the subject protocol with a waiver of informed consent. All plasma and serum samples, demographic, and blast exposure data were obtained from an established biorepository entitled "Alzheimer's Disease Research Center (ADRC) Participant Registry and Sample Repository." All subjects whose samples were utilized had consented to have their samples and data used in future research of this type.

The mTBI Veteran participants (T group) whose samples were obtained from the repository were a convenience sample of 26 male Veterans recruited from VAPSHCS, all of whom had documented hazardous duty experience in Iraq and/or Afghanistan with the U.S. Armed Forces and had reported experiencing at least one blast exposure in the war zone that resulted in acute mTBI as defined by ACRM criteria (American Congress of Rehabilitation Medicine, 1993) except that Glasgow Coma Scale scores were not obtained in the combat setting. Samples from the repository were also collected from seven male Veterans who had been deployed to Iraq and/or Afghanistan but who had not been exposed to blast and had no history of TBI. These individuals made up the deployment control (DC) group.

Additional samples from the repository which were used to establish normal hormonal reference ranges had been collected from 59 cognitively normal male community volunteers recruited from the ADRC, all of whom were medically healthy and had Mini-Mental State Examination scores of 29.4 ± 1.0 (mean ± SEM; range 27–30); Clinical Dementia Rating scores of zero; no evidence or history of cognitive or functional decline; and no history of blast exposure or head injury. These samples were used only for the establishment of normative hormone concentrations with our assay methods. Resting blood samples had been collected from all participants between 9:00 and 10:00 a.m., at least 30 min after the insertion of an intravenous catheter in an antecubital vein.

None of the Veteran or community control participants had a history of blast exposure, head injury with LOC greater than 30 min; penetrating head wound; seizure disorder; insulin-dependent diabetes; current or past DSM-IV diagnoses of schizophrenia, other psychotic disorders, bipolar disorder, or dementia; or a DSM-IV diagnosis of alcohol or other substance abuse or dependence within the previous 3 months. Participants using medications likely to affect brain function, such as opioids, benzodiazepines, or anti-depressants, were asked not to take those medications for 24 h prior to blood sampling.

BLAST EXPOSURE ASSESSMENT

Blast exposure and mTBI histories had been obtained from mTBI Veteran participants during a clinical interview in which specific inquiries were made regarding total number of blast exposures accompanied by acute symptoms of TBI and/or LOC in Iraq and/or Afghanistan and lifetime history of non-blast exposure head injuries accompanied by acute symptoms of TBI and/or LOC (e.g., sports or motor vehicle accident-related concussion).

NEUROLOGICAL ASSESSMENT

All subjects underwent a full neurological examination, including the Unified Parkinson's Disease Rating Scale (UPDRS) motor section (Martínez-Martín et al., 1994). Olfactory function was assessed using the Brief Smell Identification Test (B-SIT; Doty et al., 1996).

HORMONE MEASUREMENT

Blood samples for the measurement of plasma hormone concentrations were collected between 9:00 and 10:00 a.m. in chilled tubes containing ethylenediaminetetraacetic acid (EDTA), placed on ice, and centrifuged at 4°C prior to removal of the plasma fraction. Blood samples for measurement of serum hormones were collected in serum-separator tubes, allowed to clot at room temperature for 10 min, and centrifuged to isolate serum. Serum and plasma samples were aliquoted and stored at −70°C. Twelve pituitary or target-organ hormones were measured in these samples. The type, source, and performance characteristics of the assay kits used for the measurement of hormone concentrations in serum and plasma are shown in **Table 1**. ACTH, cortisol, thyroid-stimulating hormone (TSH), oxytocin, and vasopressin concentrations were determined in plasma; free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, insulin-like growth factor-I (IGF-I), growth hormone, and prolactin were measured in serum.

CLINICAL LAB DATA

Measurements of plasma and urine osmolality were not available but urine specific gravity was measured and used as a criterion to determine functional vasopressin insufficiency.

STATISTICAL ANALYSIS AND CRITERIA FOR PITUITARY DEFICIENCIES

The criteria for PTHP, derived using hormone measurements from the 59 community control participants are shown in **Table 2**. For each hormone, age-adjusted percentiles based on the lognormal distribution from community control participants were estimated and dysfunction in each of seven hormonal axes was defined (R Development Core Team, 2011). Hypopituitarism was defined as a dysfunction in at least one of these seven axes. These criteria were

Table 1 | Sources and characteristics of hormone assay kits.

Assay	Kit name	Manufacturer	Location
ACTH	ACTH Immunoradiometric (IRMA) Assay	Scantibodies Laboratory	Santee, CA, USA
Cortisol	GammaCoat™Cortisol ^{125}I RIA	Diasorin	Stillwater, MN, USA
FSH	DELPHIA hFSH	Perkin Elmer	Waltham, MA, USA
GH	hGH-ELISA, Ultra-Sensitive	DSL	Webster, TX, USA
IGF-I	IGF-I RIA	IBL America	Minneapolis, MN, USA
LH	ImmuChem™Coated Tube LH ^{125}I RIA	MP Biomedicals	Costa Mesa, CA, USA
Oxytocin	Oxytocin EIA Kit – Extraction-free	Peninsula Labs/Bachem	San Carlos, CA, USA
Prolactin	ImmuChem™Coated Tube Prolactin ^{125}I IRMA	MP Biomedicals	Costa Mesa, CA, USA
Testosterone	Total Testosterone	Siemens Diagnostics	Los Angeles, CA, USA
Thyroxine	Free Thyroxine (FT_4) Microplate EIA	MP Biomedicals	Costa Mesa, CA, USA
TSH	ImmuChem™Coated Tube TSH ^{125}I IRMA	MP Biomedicals	Costa Mesa, CA, USA
Vasopressin	Vasopressin Direct RIA	ALPCO	Salem, NH, USA

Hormones	Assay type	Sample type	Assay size	Sample size	Assay range	Sensitivity	Intra-assay CV	Inter-assay CV
ACTH	IRMA	Plasma	100 Tubes	200 μl	9–1693 pg/ml	<1.0 pg/ml	4.05	6.66
Cortisol	RIA	Plasma	100 Tubes	10 μl	1–60 μg/dl	0.21 μg/dl	7.03	9.20
FSH	Fluoroimmunoassay	Serum	96 Wells	25 μl	0.98–256 U/l	0.05 U/l	2.33	1.87
GH	EIA	Serum	96 Wells	100 μl	4.5–500 pg/ml	0.66 pg/ml	6.00	5.40
IGF-1	RIA	Serum	100 Tubes	100 μl	0.16–10.0 ng/ml	0.02 ng/ml	2.97	10.30
LH	RIA	Serum	100 Tubes	100 μl	2.5–200 mIU/ml	1.5 mIU/ml	5.90	7.90
Oxytocin	EIA	Plasma	96 Wells	50 μl	0–630 pg/ml	6.5 pg/ml	9.36	13.67
Prolactin	IRMA	Serum	100 Tubes	25 μl	2.5–100 ng/ml	2.5 ng/ml	5.13	8.08
Testosterone	Solid-phase RIA	Serum	100 Tubes	50 μl	20–1600 ng/dl	4 ng/dl	3.40	7.90
Thyroxine	EIA	Serum	96 Wells	50 μl	0.45–7.6 ng/dl	0.05 ng/dl	6.83	6.47
TSH	IRMA	Plasma	100 Tubes	200 μl	0.2–50 μIU/ml	0.04 μIU/ml	4.10	5.23
Vasopressin	RIA	Plasma	100 Tubes	400 μl	1.25–80 pg/ml	0.1 pg/ml	6.00	9.90

Table 2 | Screening criteria for identifying abnormal circulating hormone levels.

Axis	Criteria using lognormal distribution of community control reference sample
Adrenal insufficiency	Cortisol < 10th percentile (6.7 μg/dl), and ACTH < 10th percentile (18 pg/ml)
Thyroid deficiency	Free T-4 < 5th percentile (0.87 ng/dl), and TSH < 50th percentile (2.39 μIU/ml)
Hypogonadism	Total testosterone < 5th percentile (330 ng/dl) and either LH or FSH < 10th percentile (2.3 mIU/ml, 1.3 U/l, respectively) OR (total testosterone < 5th percentile and prolactin > 95th percentile (32 ng/ml)
Vasopressin abnormality	Vasopressin > 95th percentile (9.46 pg/ml) OR vasopressin < 5th percentile (0.27 pg/ml) and urine specific gravity < 1.003
Prolactin abnormality	Prolactin > 95th percentile (32.0 ng/ml) OR prolactin < 5th percentile (6.7 ng/ml)
GH deficiency	IGF-1 < age-adjusted 10th percentile (SDS < −1.4)
Oxytocin deficiency	Oxytocin < 5th percentile (22.7 pg/ml)
Hypopituitarism	Abnormalities in at least one of these 7 axes

modeled after those used in published studies of hypopituitarism after TBI from all causes.

RESULTS

PLASMA/SERUM HORMONE SCREENING EVALUATIONS

Eleven of 26 mTBI subjects (T), or 42%, were found to have abnormal hormone values in at least one axis. As reported in earlier studies of PTHP, deficiencies in the growth hormone-IGF-I and pituitary–gonadal axes were observed most frequently (Bavisetty et al., 2008; Dusick et al., 2008; Schneider et al., 2008; Englander et al., 2010; Kokshoorn et al., 2010; Krahulik et al., 2010; Park et al., 2010; Pavlovic et al., 2010; van der Eerden et al., 2010).

Markedly low IGF-I levels are strong indicators of adult GHD (Juul et al., 1997; Hartman et al., 2002; Hadjadj et al., 2007; Ho, 2007; Prodam et al., 2008; Tanriverdi et al., 2011; Zgaljardic et al., 2011). The red line in **Figure 1** represents the cutoff level used to define our criterion for subnormal IGF-I levels indicative of probable GHD. The cutoff level was defined to be an IGF-I concentration below the age-adjusted 10th percentile level [equivalent to an SD score (SDS) below −1.4] of the community control reference sample (**Figure 1**; **Table 2**). Five Veteran participants with mTBI (T-4, T-8, T-16, T-25, and T-28) were found to have serum IGF-I concentrations below this cutoff line. None of the Veteran participants in the DC group were found to have subnormal age-adjusted IGF-I levels (**Figure 1**).

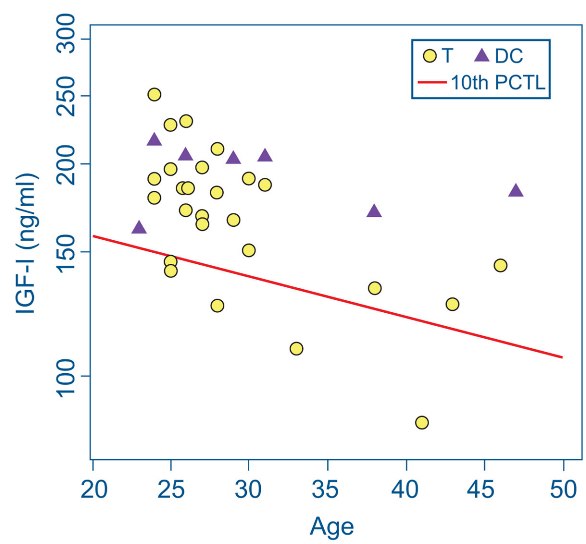

FIGURE 1 | IGF-I concentrations in serum from deployment control (DC) participants (triangles) and participants with mTBI (T, circles). The screening criterion for growth hormone deficiency was an IGF-I level below the age-adjusted 10th percentile of IGF-I concentration (diagonal red line) in the community control reference group. Serum IGF-I values of five Veterans with mTBI fell below this cutoff line. None of the DC group met this criterion.

Three participants with mTBI (T-4, T-13, and T-28) were found with abnormal hormonal profiles indicating probable hypogonadism. The criteria were a total testosterone concentration less than the 5th percentile of the reference sample together with an LH or FSH level below the 10th percentile reference level (**Figure 2**; **Table 2**). T-4 and T-28 also had the lowest two IGF-I levels among the participants (T-4: 126 ng/ml, SDS = −2.325; T-28: 86 ng/ml, SDS = −2.989). Elevated prolactin levels in conjunction with low testosterone are also indicative of hypogonadism. A serum prolactin concentration markedly higher than the 95th percentile of the reference sample was found in serum from participant T-4. A subnormal prolactin concentration (<5th percentile), also associated with sexual dysfunction, was measured in serum from T-13.

None of the Veterans in the DC group were found to have hormone levels indicative of hypogonadism. One participant in the DC group was found with a total testosterone concentration below the 5th percentile reference standard and another had an LH concentration below the 10th LH percentile, but neither exhibited the combined gonadotropin and testosterone deficiencies consistent with hypogonadism.

None of the Veteran participants in either the T or DC group exhibited abnormalities in the hypothalamic-pituitary–adrenocortical or hypothalamic-pituitary–thyroid axis (**Table 3**). The corticotrophs and thyrotrophs are located in the protected median wedge of the anterior pituitary and are anatomically less vulnerable to injury than gonadotropin- and GH-secreting cells. This differential anatomical vulnerability correlates well with the frequency of chronic hormonal abnormalities observed after TBI (Bavisetty et al., 2008; Blair, 2010; Krahulik et al., 2010).

In addition to the findings of anterior pituitary hormone abnormalities in six Veteran participants with mTBI, eight instances of anomalous posterior pituitary hormone levels were

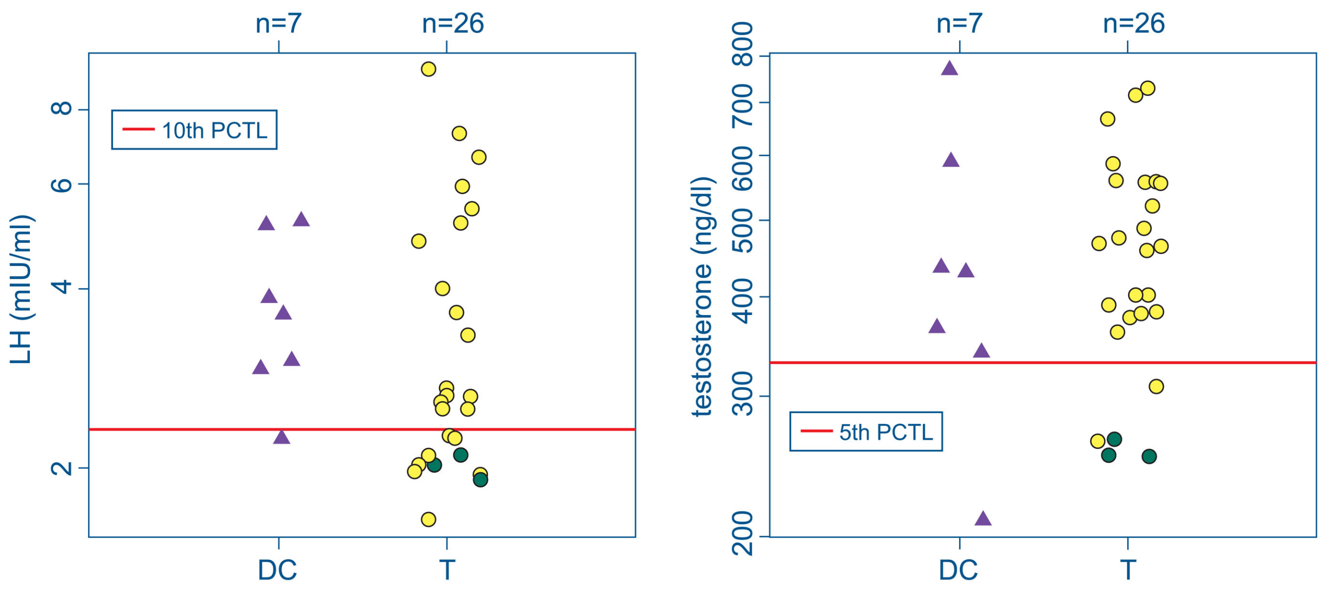

FIGURE 2 | Serum LH (left) and testosterone (right) in the deployment control (DC, triangles) and mTBI (T, circles) groups. Screening criteria for hypogonadism: LH (or FSH) levels below the 10th percentile of the control range together with testosterone below the 5th percentile (red lines). Green circles mark data from 3 T subjects falling below both cutoffs. No DC subjects met both criteria.

found in six Veterans in the mTBI group, one of whom, T-28, also had evidence of presumptive GHD and hypogonadism. The plasma oxytocin concentration was unmeasurably low in this individual (**Table 3**). None of the Veterans in the DC group were found to have abnormal posterior pituitary hormone values.

Three additional participants from the mTBI group (T-10, T-14, and T-22) also were found to have circulating oxytocin concentrations below the reference sample's 5th percentile level. Two of these participants, T-10 and T-22, also met our criteria for arginine vasopressin (AVP) deficiency: plasma vasopressin concentration below the 5th percentile of the reference level in combination with urine specific gravity less than 1.003. In addition, plasma vasopressin concentrations in participants T-2 and T-12 were abnormally elevated above the 95th percentile of the reference group.

DEMOGRAPHICS, DEPLOYMENT HISTORY, BLAST EXPOSURE, AND MEDICATION USE

After completion of hormone measurement and identification of Veterans with apparent hypopituitarism, participants in the T group were divided into two subgroups, based on the presence or absence of hormone abnormalities, for comparison of demographic, deployment history, blast exposure, and medication use data with each other and with the DC group. The three groups of Veteran participants did not differ in age, education, or body mass index at the time of enrollment, and the two mTBI subgroups did not differ significantly from one another on any of the measures of deployment history or blast exposure (**Table 4**).

CONCURRENT MEDICATIONS

Medications with potential neuroendocrine effects taken by mTBI subjects found to have indications of hypopituitarism were opiates (2/11), prazosin (2/11), selective serotonin reuptake inhibitors (SSRIs; 4/11), serotonin and norepinephrine reuptake inhibitors (SNRIs; 2/11), hypnotics (2/11), atypical antipsychotics (1/11), calcium channel blockers for migraine (1/11), benzodiazepines (1/11), and mirtazapine (1/11). Five subjects in this group were not taking any neuroactive medications. Medications with potential neuroendocrine effects taken by mTBI subjects found to have hormone levels within normal ranges were opiates (1/15), prazosin (4/15), SSRIs (3/15), SNRIs (2/15), mirtazapine (1/15), trazodone (1/15), benzodiazepines (1/15), and disulfiram (1/15). Nine subjects in this group were not taking any neuroactive medications. Medications with potential neuroendocrine effects taken by DC subjects were opiates (1/7), SSRIs (1/7), and SNRIs (1/7). Five subjects in this group were not taking any neuroactive medications.

DISCUSSION

Our findings in this preliminary study support the hypothesis that blast mTBI carries a risk of PTHP similar to that found in several previous studies of hypopituitarism in the general population after TBI from all causes. We have found that blood samples from 11 of 26, or 42% of Veterans of combat in Iraq or Afghanistan had abnormal circulating hormone concentrations consistent with PTHP. Five participants with blast mTBI exhibited evidence of anterior pituitary dysfunction, five additional subjects had anomalous posterior pituitary hormone levels, and the eleventh was found to have both anterior and posterior pituitary hormonal abnormalities. In contrast, none of the seven Veterans of deployment to Iraq and/or Afghanistan in the study who did not experience blast trauma – the DC group – were found to have evidence of pituitary dysfunction.

As Kokshoorn et al. (2010) pointed out in their review of 14 investigations of PTHP conducted between 2000 and 2009, these early studies used a broad variety of screening criteria that were sometimes described in general terms rather than with specifically

Table 3 | Plasma or serum hormone concentration for each participant.

Subject	Age	#BE	ACTH (pg/ml)	Cort (μg/dl)	LH (mIU/ml)	FSH (U/l)	tTest (ng/dl)	PRL (ng/ml)	TSH (μIU/ml)	fT-4 (ng/dl)	IGF-I (ng/ml)	GH (pg/ml)	AVP (pg/ml)	OT (pg/ml)
T-1	24	11	24	6.6	2.58	0.46	473	12.5	1.70	1.29	190	58	3.4	64
T-2	26	6	20	11.9	2.03	–	669	9.6	1.92	1.67	185	71	12.3	181
T-3	27	10	22	10.2	5.15	2.05	557	13.0	1.59	1.59	164	50	4.0	166
T-4	33	15	19	7.5	2.03	2.06	252	54.9	1.17	1.22	110	11	8.0	88
T-5	38	102	24	12.8	2.11	2.33	362	14.9	1.16	1.18	133	0	0.4	71
T-6	46	5	29	12.1	1.95	1.41	402	11.1	1.08	1.09	143	152	0.7	61
T-7	26	20	28	14.1	3.34	1.63	559	12.0	2.26	1.29	172	223	0.0	39
T-8	25	21	35	11.3	2.72	4.02	401	11.9	1.13	1.55	141	294	0.2	44
T-9	24	102	39	12.0	4.81	3.28	730	14.4	1.16	1.05	251	1288	8.0	52
T-10	26	20	30	9.6	1.97	2.43	520	12.3	2.41	1.39	230	68	0.2	22
T-11	28	9	31	10.2	1.64	2.38	382	9.2	1.30	1.22	182	0	1.1	36
T-12	27	15	27	9.9	7.27	5.70	715	13.0	1.57	1.38	198	60	12.0	55
T-13	31	7	40	7.8	1.92	1.18	253	6.3	2.24	1.14	187	0	6.4	50
T-14	30	6	36	8.8	2.66	2.51	390	12.0	3.75	1.13	151	310	0.5	19
T-15	27	11	16	7.4	2.27	3.56	377	10.1	1.40	1.14	168	42	4.4	85
T-16	28	66	25	11.7	2.64	4.01	380	21.5	0.65	1.52	126	0	0.9	190
T-17	25	18	26	11.2	9.32	3.00	465	17.1	1.26	1.25	197	0	4.8	151
T-18	24	7	30	14.2	3.65	2.21	556	12.2	1.27	1.30	179	60	4.3	32
T-19	30	1	32	18.6	5.44	3.01	457	11.7	1.55	1.13	190	66	0.0	46
T-20	28	3	17	25.0	6.65	3.91	309	10.4	0.79	1.31	210	1696	7.9	519
T-22	25	4	21	17.6	4.00	4.48	588	12.8	1.09	1.24	227	110	0.0	21
T-23	29	52	11	8.7	2.52	2.55	554	8.9	1.34	1.35	166	95	4.0	199
T-25	25	12	8	7.7	2.24	4.34	463	7.2	1.42	1.23	146	813	2.1	25
T-26	26	11	9	6.8	5.94	1.14	488	8.4	0.81	1.18	185	42	0.9	457
T-27	43	5	29	7.5	2.52	3.89	263	7.1	0.60	1.04	126	13	2.6	50
T-28	41	12	15	11.1	2.11	2.64	264	15.3	1.22	1.11	86	375	8.4	0

*Shaded values indicate hormone axis abnormalities as defined in **Table 2**. #BE, number of self-reported blast exposures meeting ACRM criteria for mTBI during military career; ACTH, adrenocorticotropin; Cort, cortisol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; tTest, total testosterone; PRL, prolactin; TSH, thyroid-stimulating hormone; fT-4, free thyroxine; IGF-I, insulin-like growth factor-I; GH, growth hormone; AVP, vasopressin; OT, oxytocin.*

defined cutoffs. We attempted to use relatively conservative and explicitly defined criteria based on the distribution of specific hormone concentrations measured in a reference population. We did not employ provocative testing but used criteria based on measurement of both pituitary hormones and their target-organ hormones when possible, e.g., a combination of measurements of total testosterone, LH, FSH, and prolactin to screen for hypogonadism.

It should be cautioned that the determinations of basal hormone concentrations, such as those made in this study, are meant to be screening tools, and are not intended to be, nor should they be interpreted to be, diagnostic in the absence of clinical assessment. Measurement of basal circulating hormone concentrations is generally considered an appropriate screening tool for provisional identification of deficient thyroid function, hypogonadism, and prolactin and oxytocin deficiencies. Diagnosis of significant abnormalities of vasopressin secretion normally require confirmation by measures of plasma and/or urine osmolality, urine specific gravity (UGS), and/or the administration of a water deprivation test. Although provocative testing is generally considered necessary for diagnosis of sAI and GHD, measurement of basal cortisol and IGF-I concentrations remain valuable screening tools to identify individuals most likely to benefit from additional testing and clinical referral. Evaluation of clinical signs and symptoms are essential for definitive diagnoses in all cases.

Previous studies have found GHD to be the most prevalent chronic endocrine consequence of TBI, and it carries with it a potentially large range of symptoms. Provocative testing is considered to be a requisite for the reliable diagnosis of GHD because serum GH concentrations measured in the morning are not valid indicators of daily secretion or somatotroph function. GH secretion occurs predominantly during sleep, and morning levels are generally very low but punctuated unpredictably by short secretory bursts (Van Cauter et al., 1992). However, GH stimulates hepatic production of IGF-I that provides a useful index of somatotroph function. IGF-I concentrations have low diagnostic sensitivity for identifying GHD but are highly specific. The presence of normal IGF-I values cannot be used to exclude GDH because it is often diagnosed in individuals with normal or even elevated IGF-I levels. However, markedly low age-adjusted levels of IGF-I are strongly indicative of GHD (Juul et al., 1997; Hadjadj et al., 2007; Ho, 2007; Prodam et al., 2008; Tanriverdi et al., 2011; Zgaljardic et al., 2011). Circulating IGF-I concentrations decline markedly with increasing age, and this decline must be taken into account when interpreting them.

Table 4 | Mean ± SEM and (range) for demographic, deployment, and blast exposure data for each group of participants.

	DC ($n = 7$)	mTBI without PTHP($n = 15$)	mTBI with PTHP($n = 11$)
A. DEMOGRAPHICS			
Age (years)	31.1 ± 3.3 (23–47)	29.7 ± 1.8 (24–46)	28.8 ± 1.5 (25–41)
Education (years)	14.0 ± 0.7 (12–17)	13.3 ± 0.4 (11–16)	13.6 ± 0.5 (12–16)
Marital status	3/7 Married, 4/7 single	7/15 Married, 4/15 single, 2/15 divorced, 2/15 unknown	7/11 Married, 1/11 single, 1/11 separated, 2/11 unknown
Body mass index (BMI)	28.5 ± 2.1 ($n = 5$)[†]	27.9 ± 1.3 ($n = 14$)[†]	29.0 ± 1.3 ($n = 10$)[†]
B. DEPLOYMENT HISTORY			
Number of deployments	1.7 ± 0.4 (1–3)	1.9 ± 0.2 (1–4)	2.1 ± 0.3 (1–3)
Time between first and second deployments (months)	14.3 ± 7.0 (3.5–27.5) ($n = 3$)	15.9 ± 3.1 (4.0–39.5) ($n = 10$)	15.4 ± 2.4 (7.5–30.0) ($n = 8$)
Time between second and third deployments (months)	6.0 ± 1.0 (5.0–7.0) ($n = 2$)	8.0 ± 2.0 (6–12) ($n = 3$)	7.6 ± 2.0 (3.0–12.5) ($n = 4$)
Time between third and forth deployments (months)		8.0 ± 0.0 ($n = 1$)	
Total deployment time (months)	13.0 ± 1.8 (7–21)	18.7 ± 2.2 (7–37)	18.2 ± 1.7 (11–27)
C. BLAST EXPOSURE			
Deployment blast exposures meeting ACRM criteria for mTBI	0	11.1 ± 3.3 (1–52)	14.6 ± 5.4 (4–66)
Blast exposures meeting ACRM criteria during military career	0.3 ± 0.3 (0–2)	24.5 ± 8.7 (1–102)	16.7 ± 5.2 (4–66)
Blast exposures with LOC	0	1.3 ± 0.3 (0–4)	0.6 ± 0.2 (0–2)
Lifetime events with LOC	0.1 ± 0.1 (0–1)	3.1 ± 0.7 (0–11)	1.3 ± 0.4 (0–3)
Time since last blast exposure (months)		45.2 ± 4.2 (14–66)	47.4 ± 4.3 (20–67)

The Veterans with blast mTBI (T group) were divided into two subgroups based upon the presence or absence of abnormal hormonal profiles suggesting PTHP. [†] *BMIs were not obtained for all participants.*

Studies using receiver operating characteristic (ROC) analysis to compare the diagnostic accuracy of IGF-I relative to diagnosis of GHD based on provocative testing of GH secretion have reported a diagnostic specificity of 100% with IGF-I SDS cutoffs of −1.3 (Corneli et al., 2007) or −1.7 (Maghnie et al., 2005).

The individuals classified here as having a high probability of GHD all had values less than −1.4 SDs below the age-adjusted means of the reference sample. The high specificity of IGF-I measurements at this level assures a very low likelihood of false positives in diagnosing GHD. However, in light of the low sensitivity of IGF-I concentrations in predicting GHD, it is probable that some Veteran participants with normal IGF-I levels may be growth hormone deficient.

The long-term sequelae of GHD in adults for health, quality of life (QoL), and morbidity are multifaceted and complex. Low GH secretion has been associated with behavioral symptoms and deficits in several cognitive domains (Popovic et al., 2004; Falleti et al., 2006; Pavlovic et al., 2010). GHD also has significant deleterious effects on body composition and cardiovascular function. Adult GHD is associated with lipidemia, reduced lean body mass, and increased adiposity. Even partial GHD in adult patients is associated with adverse lipid profiles and early atherosclerosis (Colao et al., 2006a,b; Colao, 2008). Impairment in QoL is also a prominent feature of adult GHD, especially in the areas of energy and vitality (McGauley, 1989; Kelly et al., 2006; Bushnik et al., 2007; Svensson et al., 2007; Bavisetty et al., 2008). Adult GHD is also associated with reductions in muscle volume and strength, decreased physical mobility, fatigue, sleep impairment, social isolation, depression, lowered metabolic rate, low sexual drive, and reduced aerobic capacity (Rosén et al., 1994; Mossberg et al., 2008).

Many of the symptoms of GHD can be successfully ameliorated or reversed by growth hormone replacement therapy. Five retrospective studies have shown that the risk of premature death from cardiovascular disease is elevated in patients with GHD (Svensson et al., 2004a). The increased risk factors such as adverse lipid profiles, increased blood pressure, abnormal body composition, increased body weight, increased coagulability, and increased markers of inflammation have all been shown to improve with GH replacement (Svensson et al., 2004a, 2007; Götherström et al., 2007a; Verhelst and Abs, 2009). GH replacement has been found to be effective in reversing cognitive impairments in several domains including simple motor speed, information processing speed, episodic memory, mental flexibility, verbal memory, and executive functioning in patients after TBI (High et al., 2010; Reimunde et al., 2011). GH replacement also normalizes muscle strength and increases bone mineral density (Götherström et al., 2007b, 2009), improves psychiatric functioning by ameliorating depression, intensity of interpersonal sensitivity, hostility, paranoid ideation, and anxiety (Maric et al., 2010), and improves QoL (Svensson et al., 2004b, 2007; Kreitschmann-Andermahr et al., 2008).

Three of the Veteran participants in the T group met our criteria for hypogonadism: a total testosterone concentration less than the 5th percentile of the reference sample together with an LH or FSH level below the 10th percentile reference level. In our very small sample, the occurrence of hypogonadism was found to be next highest in frequency to that of GHD, as was the case in several of the studies of PTHP after TBI from all causes in the general population (Bavisetty et al., 2008; Dusick et al., 2008; Krahulik et al., 2010; Park et al., 2010; Tanriverdi et al., 2010b).

Hypogonadism has significant deleterious consequences in addition to its adverse effects on fertility, psychosexual function, and general well being. Testosterone deficiency in males is associated with decreased energy and motivation, muscle weakness, reduced lean body mass, and impaired exercise tolerance (Agha and Thompson, 2005). In addition, a recent large epidemiological study has shown that untreated hypogonadism is associated with premature mortality secondary to cardiovascular disease (Tomlinson et al., 2001).

One mTBI participant, T-4, was found to have a highly elevated concentration of prolactin, 2.5 times higher than the next highest concentration measured in the T group and more than four times higher than the highest value in the DC group. Hyperprolactinemia has been causally linked with hypogonadism, specifically by reducing LH and FSH secretion, blocking LH stimulation of testicular testosterone secretion, and producing oligospermia by reducing FSH levels, resulting in hypoactive sexual desire and erectile dysfunction.

Prolactin is the only anterior pituitary hormone that is under predominantly inhibitory control. Its secretion is suppressed by dopamine, and in the absence of this inhibition, prolactin is released at high levels. Hyperprolactinemia frequently results from the use of antipsychotic medications that act as antagonists at dopamine D2 receptors (Holt, 2008; Inder and Castle, 2011).

Participant T-4 had been taking quetiapine, an atypical antipsychotic with fast dissociation kinetics at the D2 receptor [released from D2 within 12–24 h (Seeman, 2010)] that results only in low and transient prolactin secretion (Carboni et al., 2011). It has not generally been associated with hyperprolactinemia in clinical use (Haddad and Wieck, 2004; Byerly et al., 2007; Bushe et al., 2010) although a prevalence of 22% was found in one study (Montgomery et al., 2004). It is often referred to as a dopamine-sparing antipsychotic, and although it is much less potent in elevating prolactin levels than several other antipsychotics (e.g., haloperidol and risperidone), it may have prolactin-elevating effects in some individuals, perhaps including participant T-4.

One of the Veterans with mTBI was found to have a subnormal (less than 5th percentile) prolactin concentration. Hypoprolactinemia is rare in the general population, but it too has been associated with sexual dysfunction, primarily arteriogenic erectile dysfunction and premature ejaculation (Corona et al., 2009).

We found no evidence of dysfunction in the thyroid or adrenal axes as a result of blast mTBI. Previous studies of pituitary deficiencies after TBI from all causes have generally reported a lower prevalence of TSH and adrenocorticotropin (ACTH) deficiencies than of GH or gonadotropin deficits (Bavisetty et al., 2008; Blair, 2010; Krahulik et al., 2010). This pattern may be due in part to the location of pituitary corticotrophs and thyrotrophs in the gland's protected median wedge and their blood supply via both the long hypophysial portal vessels and the inferior hypophysial artery. GH-secreting somatotrophs, on the other hand, are anatomically more vulnerable to damage because of their location in the pituitary's exposed lateral wings and their primary dependence on vascular input from the portal system alone. Gonadotrophs are distributed throughout the anterior pituitary, and the cells in the lateral wings are relatively vulnerable.

In addition to the six participants with hormonal levels consistent with hypogonadism and/or GHD, six of the Veterans with mTBI (including one with anterior pituitary hormonal abnormalities) exhibited abnormal plasma vasopressin and/or oxytocin concentrations. Oxytocin concentrations below the 5th percentile value of the community control group were observed in four of the mTBI participants. Two of the four also exhibited indications of vasopressin deficiency as defined by vasopressin levels below the 5th percentile of the community reference group together with urine specific gravity less than 1.003. The occurrence of deficits of both vasopressin and oxytocin in two participants suggests the possibility of disruption of the pituitary stalk or hypothalamic damage in these individuals. In addition, elevated plasma vasopressin concentrations above the reference 95th percentile were measured in two subjects.

In several studies, elevated cerebrospinal fluid (CSF) or peripheral vasopressin concentrations have been associated with PTSD, depression, schizophrenia, and other psychiatric disorders, but a causal relationship has not been established (Purba et al., 1996; van Londen et al., 1997; Coccaro et al., 1998; Merali et al., 2006; de Kloet et al., 2008; Goekoop et al., 2009; Heinrichs et al., 2009). In contrast, there is evidence from both animal and human studies for the positive association of oxytocin levels with social bonding, attenuation of stress responses in socially relevant challenges, mediation of social support, and positive social interactions (Heinrichs et al., 2009; Campbell, 2010).

Our finding of a high frequency of abnormal peripheral hormone levels after blast mTBI in this preliminary study is consistent with the investigations cited above, in which the prevalence of pituitary dysfunction fell in the 30–60% range in 11 of 22 reports. However, in general, those studies focused exclusively on anterior pituitary dysfunction. Although few studies have investigated the prevalence of chronic posterior pituitary hormonal abnormalities after TBI, most (Agha et al., 2004b, 2005; Krahulik et al., 2010), but not all (Bondanelli et al., 2004), found significant evidence of damage in that lobe as well. In this study we found significant anterior pituitary dysfunction in 23.1% of Veterans with mTBI and abnormal posterior pituitary hormone levels in 23.1% of this group as well. In contrast, the prevalence of hypopituitarism in the general adult population ranges between 290 and 455 cases per million (Regal et al., 2001).

The only other ongoing study of hypopituitarism after blast mTBI of which we are aware recently reported preliminary results based on two retrospective chart reviews. Of 147 Marines with blast-related mTBI screened approximately 1 year or more after injury, 25% were found to have abnormal levels of one or more anterior pituitary hormones (Stokes and Gallagher, 2011).

The Veteran groups in this study are highly similar in demographic characteristics and share the common experience of deployment under highly stressful and dangerous conditions accentuated by extreme heat and the burden of heavy equipment even when not actively engaged in combat. Despite these commonalities, the experience of blast trauma and the combat situations in which these exposures occur have major long-term consequences well beyond those of deployment to Iraq or Afghanistan. The considerable overlap between the constellations of symptoms typical of chronic hypopituitarism and persistent post-concussive symptoms (PPCS), in addition to the similarities of both to PTSD, make accurate diagnosis of the etiology, progression, and identifiable differences between the conditions of critical importance for successful treatment, recovery, and rehabilitation (Masel, 2005).

The consequences of undiagnosed and untreated pituitary hormone deficiencies are manifold and significant and include diminished QoL, cognitive deficiencies, fatigue, sleep disturbance, sexual dysfunction, deleterious changes in metabolism and body composition, behavioral and psychiatric problems including anxiety, irritability, social isolation, depression, and increased cardiovascular mortality. PTHP, unlike PTSD and PPCS, is readily treatable if correctly diagnosed, and many of its symptoms can be reversed or ameliorated with appropriate hormone replacement therapy.

Several of the authors of previous studies of hypopituitarism after TBI have advocated routine endocrine evaluation after brain injury (Masel, 2004; Leal-Cerro et al., 2005; Schneider et al., 2005; Urban et al., 2005; Powner et al., 2006; Behan and Agha, 2007; Ho, 2007; Behan et al., 2008; Tanriverdi et al., 2008b, 2010b; Blair, 2010; Krahulik et al., 2010; Park et al., 2010). A recent review of the literature (Guerrero and Alfonso, 2010) stated that because "many of the symptoms of hypopituitarism are similar to those of TBI, it is important to make clinicians caring for combat veterans aware of its occurrence... All patients who had a TBI of any severity, should undergo baseline hormonal evaluation."

To our knowledge, this is the first published study of basal hormonal evaluation of combat Veterans with blast mTBI, and our preliminary findings of PTHP in 42% of study participants supports the advisability of routine screening for hypopituitarism after brain injury in both military and civilian populations. Routine provocative testing for sAI and for GHD, the most frequently observed chronic endocrine disorder resulting from TBI, is neither economically nor practically viable. However, measurement of basal concentrations of a panel of pituitary and target-organ hormones similar to those performed here may provide valuable preliminary indications of those individuals most likely to benefit from further clinical evaluation. Similar preliminary screening for pituitary dysfunction after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

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Chronic Hypopituitarism after Blast Concussion Mild Traumatic Brain Injury in Iraq/Afghanistan Combat Veterans

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Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, as defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 33-50% of cases (1). Its occurrence has not been found to be related to trauma severity (1,2). Hypopituitarism is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, poor concentration and memory, and decreased quality of life (1). Despite these findings, the prevalence of hypopituitarism after blast concussion mild TBI, the signature injury of combat in Iraq and Afghanistan, has not yet been investigated. Mild TBI (mTBI) is characterized by brief loss of consciousness or loss of memory for events surrounding the trauma or any alteration of mental state (disorientation, confusion). In order to determine the frequency of pituitary dysfunction after blast concussion mTBI, we are measuring pituitary and target organ hormones in blood samples from Iraq/Afghanistan Veterans with mTBI taken at least one year subsequent to their last blast exposure. Most have experienced multiple blast exposures. Criteria for identifying abnormal circulating levels of LH, FSH, total testosterone, prolactin, ACTH, cortisol, TSH, free thyroxine, GH, IGF-I, and arginine vasopressin (AVP) were derived from RIA or EIA measurement of basal morning concentrations in a large group of male non-Veteran control subjects. In general, values below the 5th percentile or above the 95th percentile were defined as abnormal. When both pituitary and target organ hormones were measured for a given axis, a specific combination of criteria signaled dysfunction of that axis. Using the criteria defined in controls, 10 of 26 Veterans with blast mTBI were found to have abnormal hormone levels in one or more pituitary axes. Seven mTBI subjects exhibited deviant plasma AVP concentrations, either above or below the 5th-95th percentile normal range. The frequency of abnormally low or abnormally elevated AVP levels has been found to be relatively high in the acute stage of non-blast TBI, but it tends to decline with time. These preliminary findings suggest that the prevalence of hypopituitarism after blast concussion mTBI is similar to that in other forms of TBI, and that recovery and rehabilitation of blast-exposed Veterans may be facilitated by comprehensive screening for pituitary dysfunction.

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Nothing to Disclose: CWW, ERP, EAC, JBS

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Federal Interagency Conference on Traumatic Brain Injury

Structural and Functional Neuroimaging, Pituitary Dysfunction, and Animal Modeling in Blast Concussion Mild Traumatic Brain Injury

Presentation Type:

Symposium

General Subject Classification:

Mild TBI and Concussion

Time / Location:

Tue, 6/14, 2:15 PM
Columbia Hall 7

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Objectives:

- To understand the state-of-the-art in neuroimaging techniques for mTBI and the results of multi-modal imaging in Veterans and Service Members with repetitive blast mTBI.
- To recognize the importance of pituitary dysfunction in head trauma and potential need for screening for and treatment of pituitary and target organ hormone abnormalities in Veterans and Service Members with mTBI to improve symptoms and quality of life.
- To recognize the need for valid animal models of blast trauma mTBI and how they may be used to elucidate pathophysiological mechanisms of as well as genetic risk factors for blast concussion mTBI.

Abstract:

Repetitive blast concussion mild traumatic brain injury (mTBI) is recognized as the "signature injury" of OIF/OEF deployment. However, controversy regarding the etiology, course, and treatment of persistent somatic, cognitive and behavioral symptoms remains. This symposium addresses whether these chronic symptoms in OIF/OEF Veterans and warriors reflect persistent structural and/or functional brain changes.

Dr. Peskind (VISN-20 MIRECC) used multi-modal structural and functional neuroimaging in OIF/OEF Veterans: 35 with mTBI and 13 controls. Findings in mTBI include: 1) decreased white matter integrity in optic radiations, inferior longitudinal fasciculus, brainstem, and cerebellar peduncles by diffusion tensor imaging (DTI); 2) decreased macromolecular proton-bound fraction in white and gray matter by cross-relaxation imaging; and 3) glucose hypometabolism in posterior cingulate and biparietal lobes by FDG-PET supported by default state fMRI (all $p<0.05$, corrected). Findings in mTBI were unassociated with PTSD.

Dr. Morey (VISN-6 MIRECC) examined whole brain white matter integrity in 30 Service Members and Veterans with mTBI and 42 controls. High direction DTI revealed widely distributed disruption of white matter integrity in mTBI (corpus callosum, forceps minor and major, superior and posterior corona radiata, internal capsule, superior longitudinal fasciculus ($p<0.05$; corrected) predicted by severity of acute mTBI symptoms but not current PTSD and depression.

Dr. Wilkinson (VISN-20 GRECC). While civilian impact mTBI is associated with 30-70% incidence of hypopituitarism, blast-related pituitary dysfunction has not been investigated. Findings of screening for pituitary and target-organ hormone abnormalities in mTBI Veterans who have complementary neuroimaging data will be presented.

Dr. Cook (VISN-20 GRECC) is addressing a mouse model of repetitive mTBI to understand pathophysiologic and genetic underpinnings of blast mTBI brain changes. A novel shock-tube based on blast exposures in OIF/OEF Veterans has been constructed. The design and operational properties of the shock tube and preliminary findings from mice with repetitive mild blast exposures will be presented.

http://www.nature.com/npp/journal/v36/n1s/full/npp2011293a.html

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152. Chronic Pituitary Dysfunction after Blast-related Mild Traumatic Brain Injury

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Background: Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, as defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 25-50% of cases. Its frequency of occurrence has not been found to be related to trauma severity. The most common anterior pituitary dysfunctions reported were growth hormone deficiency (GHD) and hypogonadism. Hypopituitarism, and in particular adult GHD, is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, and decreased quality of life. Despite the high frequency of hypopituitarism after civilian TBI, the prevalence of hypopituitarism after blast-related mild TBI, the signature injury of combat in Iraq and Afghanistan, has not yet been investigated. Mild TBI (mTBI) is characterized by brief loss or alteration of consciousness. The mechanisms of injury of blast mTBI are very complex and poorly understood. Blast is propagated directly through the skull and indirectly via blood vessels, and reflections of blast waves in a closed space can redirect and magnify their effects. The pituitary is vulnerable to compression due to its confinement in the sella turcica, and the narrow pituitary stalk (2-3 mm diameter) is subject to torsional and rotational forces resulting from brain movement.

Methods: In order to determine the frequency of pituitary dysfunction after blast-related mTBI, we are measuring pituitary and target organ hormones in blood samples taken from Iraq/Afghanistan Veterans with mTBI at least one year subsequent to their last blast exposure, and from Veterans after deployment in Iraq/Afghanistan without blast exposure. Criteria for identifying abnormal circulating levels of luteinizing hormone (LH), follicle-stimulating hormone, total testosterone, prolactin, adrenocorticotropin, cortisol, thyroid-stimulating hormone, free thyroxine, growth hormone, insulin-like growth factor-I (IGF-I), oxytocin, and arginine vasopressin (AVP) were derived from determinations of normative ranges of basal morning hormone concentrations in a group of male non-Veteran control subjects. In general, hormone concentrations below the 5th percentile or above the 95th percentile were defined as abnormal. When both pituitary and target organ hormones were measured for a given axis, a specific combination of criteria defined dysfunction of that axis.

Results: Based on the normative ranges defined by hormone measurements in control subjects, 11 of 26, or 42%, of Veterans with blast mTBI were found to have abnormal hormone levels in

one or more pituitary axes. Five Veterans with mTBI were found to have probable GHD, based on age-adjusted IGF-I concentrations below the 10th percentile concentration of the reference control group. Three Veterans in the mTBI group were found to have probable hypogonadism on the basis of abnormally low testosterone and LH concentrations. Six of the mTBI group were found to have abnormal levels of the posterior pituitary hormones oxytocin and/ or AVP. None of the non-blast-exposed Veterans were found to have hormone abnormalities.

Discussion: These preliminary findings suggest that the prevalence of hypopituitarism after blast-related mTBI is similar to that in other forms of TBI. Consistent with earlier studies of TBI from all causes, GH and gonadotropin deficiencies were most frequent. Posttraumatic hypopituitarism is associated with a constellation of neuropsychiatric symptoms and diminished quality of life similar to PTSD that are largely amenable to successful treatment with hormone replacement. Routine screening for pituitary dysfunction after blast mTBI shows promise for appropriately directing diagnostic and therapeutic decisions that may otherwise remain unconsidered and for markedly facilitating recovery and rehabilitation.

Disclosure: C. Wilkinson: None. **E. Peskind:** None. **E. Colasurdo:** None. **K. Pagulayan:** None. **J. Shofer:** None.

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BACKGROUND

- Recent studies have found a prevalence of chronic hypopituitarism, defined as deficient hormone production in one or more pituitary hormonal axes, of 25-50% after traumatic brain injury (TBI).
- The pituitary is extremely vulnerable to damage as a result of TBI. It is tethered to the brain by a narrow stalk (2-3 mm in diameter) subject to torsional and rotational forces caused by brain movement and is almost completely encased in a bony pocket, the sella turcica, and vulnerable to compression by brain movement or edema.
- The most common pituitary disorders resulting from TBI are adult growth hormone deficiency (GHD) and hypogonadism.
- Chronic posttraumatic hypopituitarism (PTHP) may be reflected by a markedly different hormone profile than that seen acutely, but after 6-12 months, PTHP is generally considered permanent.
- Hypopituitarism, particularly adult GHD, is characterized by symptoms that include fatigue, sleep disorders, cognitive deficiencies, social isolation, depression, anxiety, irritability, sexual dysfunction, reduced quality of life (QoL), deleterious changes in body composition, and increased cardiovascular mortality.
- Seventy-five percent of TBI are concussions, classified as mild TBI (mTBI) and defined as head trauma resulting in any one of the following:
  - o Loss of consciousness for 30 minutes or less
  - o Alteration of mental state (feeling dazed, disoriented, confused) for up to 24 hours
  - o Loss of memory for events immediately before or after the trauma.
- US military personnel deployed to Iraq or Afghanistan experience a high frequency of blast concussions, but no studies investigating the prevalence of hypopituitarism after blast mTBI have yet been published.

METHODS

- Twelve pituitary and target-organ hormones were measured in blood samples from two groups:
  - o T group (n=26): Male Veterans of deployment to Iraq or Afghanistan with blast mTBI occurring one year or more prior to blood sampling
  - o DC group (n=7): Male Veterans with similar deployment histories but without blast exposure or history of head injury.

o Luteinizing hormone (LH)
o Follicle-stimulating hormone (FSH)
o Prolactin (PRL)
o Total testosterone (tTest)
o Thyroid-stimulating hormone (TSH)
o Free thyroxine (fT4)
o Arginine vasopressin (AVP)
o Oxytocin (OT)

- Hormone deficiencies were defined by comparison with reference ranges derived from a sample of non-Veteran community control subjects.

Table 1. Demographic and blast exposure data for the DC and T groups. Individuals in the T group are divided on the basis of post hoc identification of PTHP.

	DC (n=7)	mTBI without PTHP (n=15)	mTBI with PTHP (n=11)
A. Demographics			
Age (years)	31.1 ± 3.3 [23-47]	29.7 ± 1.8 [24-46]	28.8 ± 1.5 [25-41]
Education (years)	14.0 ± 0.7 [12-17]	13.3 ± 0.4 [11-16]	13.6 ± 0.5 [12-16]
Body mass index (BMI)	28.5 ± 2.1 [n=5]#	27.9 ± 1.3 [n=14]#	29.0 ± 1.3 [n=10]#
B. Blast exposure			
Blast exposures meeting ACRM criteria for mTBI	0	11.1 ± 3.3 [1-52]	14.6 ± 5.4 [4-66]
Blast exposures with loss of consciousness (LOC)	0	1.3 ± 0.3 [0-4]	0.6 ± 0.2 [0-2]
Lifetime events with LOC	0.1 ± 0.1 [0-1]	3.1 ± 0.7 [0-11]	1.3 ± 0.4 [0-3]
Time since last blast exposure (months)		45.2 ± 4.2 [14-66]	47.4 ± 4.3 [20-67]

BMIs not recorded for all participants

Figure 1. Concentrations of IGF-I in 26 T group participants (○) and 7 DC group participants (▲). The red line represents the age-adjusted 10th percentile of the reference group IGF-I concentration. IGF-I values below this line indicate probable GHD.

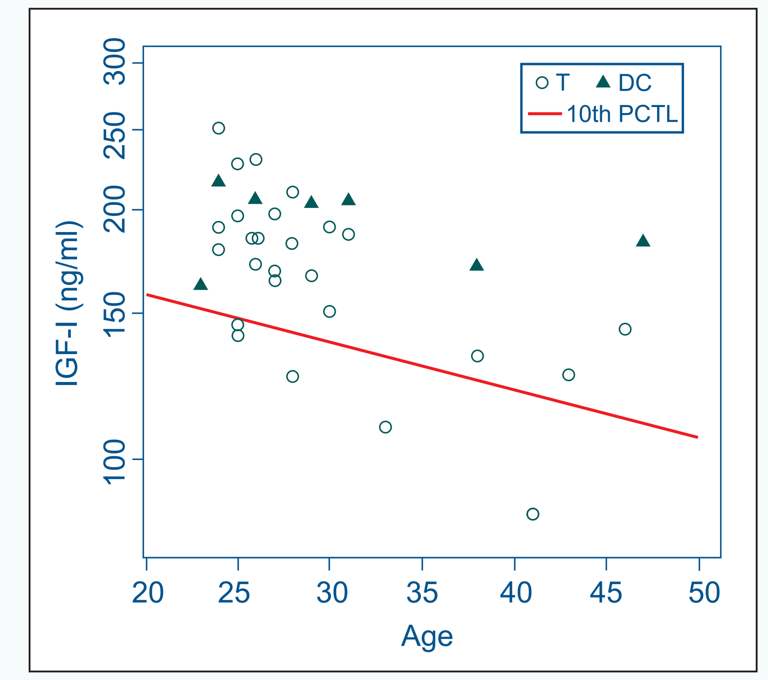
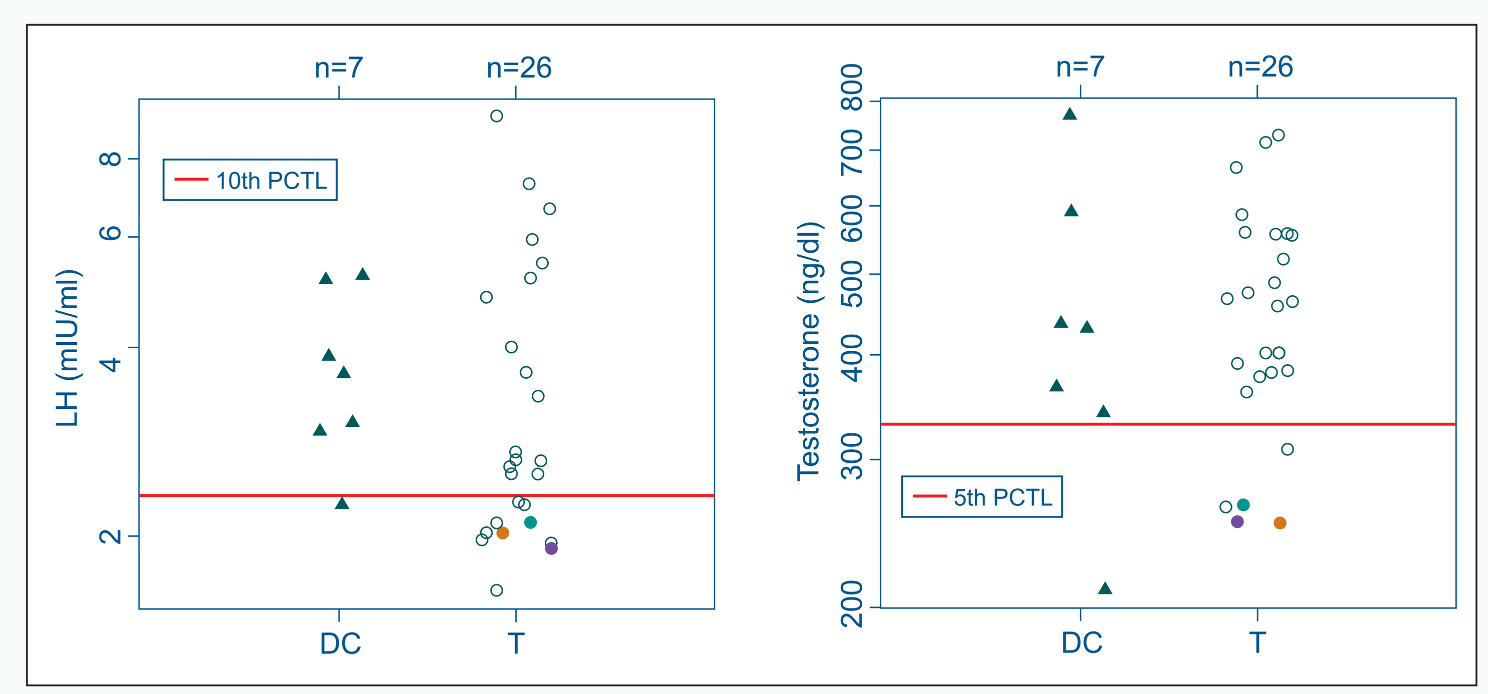


Figure 2. Concentrations of LH (left panel) and total testosterone (right panel) in T (○) and DC (▲) groups. The colored circles represent individuals who met both criteria for hypogonadism: an LH level below the 10th percentile of the reference sample and a testosterone concentration below the 5th percentile.



RESULTS

- Participants in the DC and T groups did not differ significantly in age, education, or body mass index (BMI) (Table 1). Post hoc separation of the T group into individuals with or without PTHP revealed equivalent blast exposure histories for the two sub-groups.

Growth Hormone Deficiency

- Measurement of serum concentrations of IGF-I provided provisional identification of participants with GHD.
  - o GH stimulates renal production of IGF-I, and markedly low concentrations of IGF-I are strong indicators of GHD.
  - o IGF-I concentrations decline considerably with increasing age, and screening criteria must be adjusted for age.
- Five individuals in the T group were found with IGF-I levels below the age-adjusted 10th percentile of IGF-I concentrations in the reference group that was considered indicative of probable GHD (Figure 1, Table 2).

Hypogonadism

- Our criteria for hypogonadism were a testosterone
erence range together with an LH or FSH below th
T group met these criteria for hypogonadism (Figu

Prolactin abnormalities

- Extreme PRL levels (below the 5th or above the 9
participants with probable hypogonadism (Table 2
ated with sexual dysfunction.

Posterior pituitary hormone abnormalities

- Criteria for AVP abnormalities were a concentratio
ple or levels below the 5th percentile together wit
- The criterion for OT deficiency was a concentratio
- Four participants were found with abnormal AVP le
Two of these individuals were deficient in both hor
damage or disruption of the pituitary stalk.
- Elevated AVP levels have been associated with PT
atric disorders, but a causal relationship has not b
- In contrast, there is evidence of a positive associa
cial support, and positive social interactions.

Summary of Results

- **Eleven of 26 (42%) participants with blast mTBI were**
more pituitary axes. None of the deployment control s
of any kind.

Table 2. Concentrations of 12 pituitary and target-organ
the T group. Abnormal hormone values are indicated by t
identified in the Methods section above.

Subj.	Age	ACTH pg/ml	Cort µg/dl	LH mIU/ml	FSH U/L	tTest ng/dl	PRL ng/r
T-1	24	24	6.6	2.58	0.46	473	12.
T-2	26	20	11.9	2.03	---	669	9.6
T-3	27	22	10.2	5.15	2.05	557	13.
T-4	33	19	7.5	2.03	2.06	252	54.
T-5	38	24	12.8	2.11	2.33	362	14.
T-6	46	29	12.1	1.95	1.41	402	11.
T-7	26	28	14.1	3.34	1.63	559	12.
T-8	25	35	11.3	2.72	4.02	401	11.
T-9	24	39	12.0	4.81	3.28	730	14.
T-10	26	30	9.6	1.97	2.43	520	12.
T-11	28	31	10.2	1.64	2.38	382	9.2
T-12	27	27	9.9	7.27	5.70	715	13.
T-13	31	40	7.8	1.92	1.18	253	6.3
T-14	30	36	8.8	2.66	2.51	390	12.
T-15	27	16	7.4	2.27	3.56	377	10.
T-16	28	25	11.7	2.64	4.01	380	21.
T-17	25	26	11.2	9.32	3.00	465	17.
T-18	24	30	14.2	3.65	2.21	556	12.
T-19	30	32	18.6	5.44	3.01	457	11.
T-20	28	17	25.0	6.65	3.91	309	10.
T-22	25	21	17.6	4.00	4.48	588	12.
T-23	29	11	8.7	2.52	2.55	554	8.9
T-25	25	8	7.7	2.24	4.34	463	7.2
T-26	26	9	6.8	5.94	1.14	488	8.4
T-27	43	29	7.5	2.52	3.89	263	7.1
T-28	41	15	11.1	2.11	2.64	264	15.

CONCLUSIONS

- In this preliminary study, the proportion of Veterar
similar to that in previous studies of TBI from all c
- Consistent with earlier studies, the most frequent
hypogonadism.
- PTHP has been associated with a constellation of
minished QoL similar to PTSD.
- Unlike PTSD, PTHP is readily amenable to treatm
with hormone replacement therapy.
- Therefore, routine screening for pituitary dysfuncti
propriately directing diagnostic and therapeutic de
and for markedly facilitating recovery and rehabilit

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Health Care System; the VA Northwest Network Mental Illness Research,
and Clinical Research; the University of Washington Alzheimer's Disease

(GHD), is associated with symptoms that include fatigue, anxiety, depression, irritability, sleep disturbances, sexual dysfunction, cognitive deficits, decreased quality of life, and increased cardiovascular mortality. This study investigates the prevalence of chronic PTHP after blast-related concussion.
Design: Concentrations of 12 pituitary and target-organ hormones were measured in blood samples from US military Veterans who had sustained blast concussions during deployment to Iraq and Afghanistan, and from a similar group without blast exposure, to determine the frequencies of PTHP and of specific hormonal deficits.
Results: Eleven of 26, or 42%, of subjects with blast-related concussions were found with abnormal hormone levels in one or more pituitary axes. Five individuals were found with probable GHD, and three blast-exposed participants showed evidence of hypogonadism. Veterans without blast exposure had no hormonal abnormalities.
Conclusions: There is a high prevalence of concussion-related PTHP, but consequent neuropsychiatric and behavioral symptoms are amenable to successful hormonal replacement therapy. Screening for hormone deficiencies after concussions shows promise for appropriately directing diagnostic and therapeutic decisions that may otherwise remain unconsidered.

OBJECTIVE

The Pituitary Gland & TBI

- ❖ The pituitary gland is a small gland (about the size of a garbanzo bean) located just below the base of the brain (Fig. 1A) that is often called the "master gland." The hormones it secretes control the function of the other endocrine glands (thyroid, adrenal, testes, ovaries) and directly affect many critical bodily functions.
- ❖ Recent studies have found that long-lasting pituitary hormone abnormalities (hypopituitarism) occur in 25-50% of individuals suffering traumatic brain injury (TBI).
- ❖ The frequency of hypopituitarism after TBI has not been found to be related to the severity of the trauma.

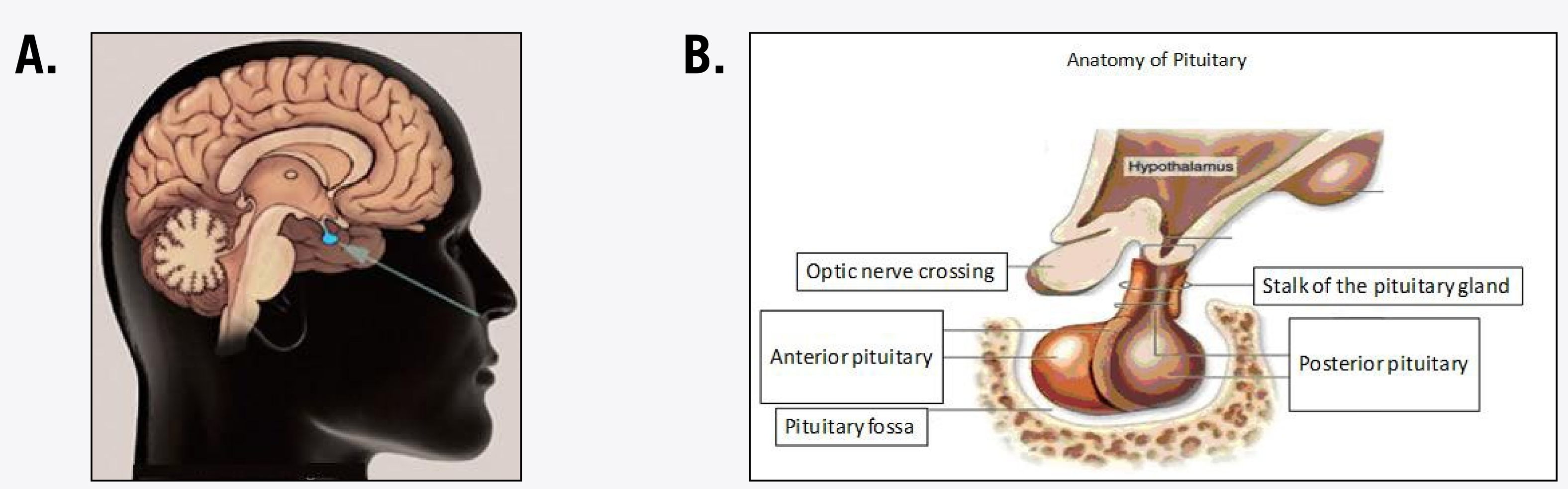

Figure 1: A. The arrow indicates the position and size of the pituitary gland in relation to the brain. **B.** Enlarged view of the pituitary gland indicating its anterior and pituitary lobes, the pituitary stalk which connects it with the hypothalamus, and the "pocket" (sella turcica) in the sphenoid bone that surrounds it and restricts its movement.

- ❖ The pituitary gland is extremely vulnerable to damage as a result of TBI because:
  - ➢ The gland is attached to the brain by a narrow stalk of tissue (2-3 mm in diameter) that carries its blood and nerve supply (Fig. 1B). This stalk is subject to torsional and rotational forces generated by brain movement.
  - ➢ In addition, the pituitary is almost completely encased in a bony pocket, the sella turcica, and is vulnerable to tissue damage from compression due to brain movement or edema.
- ❖ The most common pituitary disorders resulting from TBI are growth hormone deficiency (GHD) and sex hormone deficiencies (hypogonadism).
- ❖ Although a large number of temporary pituitary hormone abnormalities may occur immediately after the trauma, these often resolve during the succeeding weeks or months. However, new hormonal problems may emerge during the same period and they and some original deficiencies may persist.
- ❖ After 6-12 months, the remaining chronic pituitary dysfunctions are generally considered to be permanent
- ❖ Hypopituitarism, particularly GHD, is characterized by symptoms that include fatigue, sleep disorders, difficulties with learning and memory, social isolation, depression, anxiety, irritability, sexual disorders, and reduced quality of life (QoL).
- ❖ Hypopituitarism may also result in undesirable changes in body composition -- increased body fat, and decreased muscle mass and bone density -- as well as elevated blood lipid levels and increased risk of cardiovascular disease.

Mild Traumatic Brain Injury (mTBI)

Seventy-five percent of all cases of TBI are classified as mTBI, often referred to as concussion.

- ❖ mTBI is defined by the American Congress of Rehabilitation Medicine as head trauma resulting in any one of the following:
  - ➢ Loss of consciousness (LOC) for 30 minutes or less
  - ➢ Alteration of mental state (feeling dazed, disoriented, confused) for up to 24 hours
  - ➢ Loss of memory for events immediately before or after the trauma

Blast mTBI in US Military Personnel

- ❖ mTBI sustained from explosive blasts is one of the most common combat injuries resulting from deployment to Iraq or Afghanistan and is often referred to as the "signature injury" of these conflicts.
- ❖ During the first 9 months of 2011, more than 20,000 service members were *medically diagnosed* with mTBI. It is highly probable that many more blast concussions were unreported.
- ❖ However, no studies investigating the frequency of hypopituitarism after blast mTBI have been published until now: http://www.frontiersin.org/neurotrauma/abstract/19980

concentration in healthy non-Veteran men.

- ➢ Male Veterans of deployment to Iraq or Afghanistan with blast mTBI occurring one year or more prior to blood sampling: T group (n=26).
- ➢ Male Veterans with similar deployment experience but without blast exposure or history of head injury: DC group (n=7).

❖ Twelve hormones were measured in each sample. They are hormones produced by the pituitary gland or "target-organ hormones" produced by other endocrine glands regulated by the pituitary:

Pituitary Hormones
- ◇ Growth Hormone (GH)
- ◇ Thyroid-stimulating hormone (TSH)
- ◇ Adrenocorticotropin (ACTH)
- ◇ Luteinizing hormone (LH)
- ◇ Follicle-stimulating hormone (FSH)
- ◇ Prolactin (PRL)
- ◇ Arginine vasopressin (AVP)
- ◇ Oxytocin (OT)

Target-Organ Hormones
- ◇ Insulin-like growth factor-I (IGF-I)
- ◇ Free thyroxine (fT4)
- ◇ Cortisol (Cort)
- ◇ Total testosterone (tTest)

➢ GH stimulates IGF-I synthesis by the liver; TSH stimulates thyroid gland secretion of fT4 (thyroid hormone); ACTH stimulates cortisol secretion by the adrenal gland; LH, FSH, and PRL regulate testicular testosterone secretion and spermatogenesis.

- ❖ Hormone deficiencies were defined by comparison with reference ranges calculated from hormone concentrations in blood samples from the healthy community control individuals.
- ❖ Hormone concentrations measured in this study are meant only to be tools for preliminary screening for pituitary abnormalities.
- ❖ These measurements by themselves are not adequate to diagnose hormonal disorders, but they can be useful in determining which patients should be followed up for clinical diagnosis by a physician.

RESULTS

- ❖ There were no significant differences in age, education or body mass index (BMI) between study participants in the DC and T groups.
- ❖ Participants in the T group without signs of PTHP were found to have similar blast exposures to those with abnormal hormone levels.

Growth Hormone Deficiency

- ❖ Blood concentrations of IGF-I, produced by the liver in response to GH, are indirect but more reliable indicators of GHD than direct measurement of GH. IGF-I levels normally decline with age, so determinations of normal ranges must be adjusted for age.
- ❖ Five individuals in the T group were found to have IGF-I levels below the age-adjusted 10th percentile (i.e., in the lowest 10%) of IGF-I concentrations in the reference community control group. These low values were considered to indicate probable GHD (Table 1).
- ❖ GHD is associated with multiple problems related to mood and behavior, impaired learning and memory, and diminished QoL. These characteristics are similar to those of PTSD.

Subj.	Age	ACTH pg/ml	Cort µg/dl	LH mIU/ml	FSH U/L	tTest ng/dl	PRL ng/ml	TSH µIU/ml	fT4 ng/dl	IGF-I ng/ml	GH pg/ml	AVP pg/ml	OT pg/ml
T-1	24	24	6.6	2.58	0.46	473	12.5	1.70	1.29	190	58	3.4	64
T-2	26	20	11.9	2.03	---	669	9.6	1.92	1.67	185	71	12.3	181
T-3	27	22	10.2	5.15	2.05	557	13.0	1.59	1.59	164	50	4.0	166
T-4	33	19	7.5	2.03	2.06	252	54.9	1.17	1.22	110	11	8.0	88
T-5	38	24	12.8	2.11	2.33	362	14.9	1.16	1.18	133	0	0.4	71
T-6	46	29	12.1	1.95	1.41	402	11.1	1.08	1.09	143	152	0.7	61
T-7	26	28	14.1	3.34	1.63	559	12.0	2.26	1.29	172	223	0.0	39
T-8	25	35	11.3	2.72	4.02	401	11.9	1.13	1.55	141	294	0.2	44
T-9	24	39	12.0	4.81	3.28	730	14.4	1.16	1.05	251	1288	8.0	52
T-10	26	30	9.6	1.97	2.43	520	12.3	2.41	1.39	230	68	0.2	22
T-11	28	31	10.2	1.64	2.38	382	9.2	1.30	1.22	182	0	1.1	36
T-12	27	27	9.9	7.27	5.70	715	13.0	1.57	1.38	198	60	12.0	55
T-13	31	40	7.8	1.92	1.18	253	6.3	2.24	1.14	187	0	6.4	50
T-14	30	36	8.8	2.66	2.51	390	12.0	3.75	1.13	151	310	0.5	19
T-15	27	16	7.4	2.27	3.56	377	10.1	1.40	1.14	168	42	4.4	85
T-16	28	25	11.7	2.64	4.01	380	21.5	0.65	1.52	126	0	0.9	190
T-17	25	26	11.2	9.32	3.00	465	17.1	1.26	1.25	197	0	4.8	151
T-18	24	30	14.2	3.65	2.21	556	12.2	1.27	1.30	179	60	4.3	32
T-19	30	32	18.6	5.44	3.01	457	11.7	1.55	1.13	190	66	0.0	46
T-20	28	17	25.0	6.65	3.91	309	10.4	0.79	1.31	210	1696	7.9	519
T-22	25	21	17.6	4.00	4.48	588	12.8	1.09	1.24	227	110	0.0	21
T-23	29	11	8.7	2.52	2.55	554	8.9	1.34	1.35	166	95	4.0	199
T-25	25	8	7.7	2.24	4.34	463	7.2	1.42	1.23	146	813	2.1	25
T-26	26	9	6.8	5.94	1.14	488	8.4	0.81	1.18	185	42	0.9	457
T-27	43	29	7.5	2.52	3.89	263	7.1	0.60	1.04	126	13	2.6	50
T-28	41	15	11.1	2.11	2.64	264	15.3	1.22	1.11	86	375	8.4	0

Table 1. Concentrations of 12 pituitary and target-organ hormones in samples from the 26 Veterans in the T group. Abnormal hormone values are indicated by the orange highlighting. Hormone abbreviations are identified in the Methods section above.

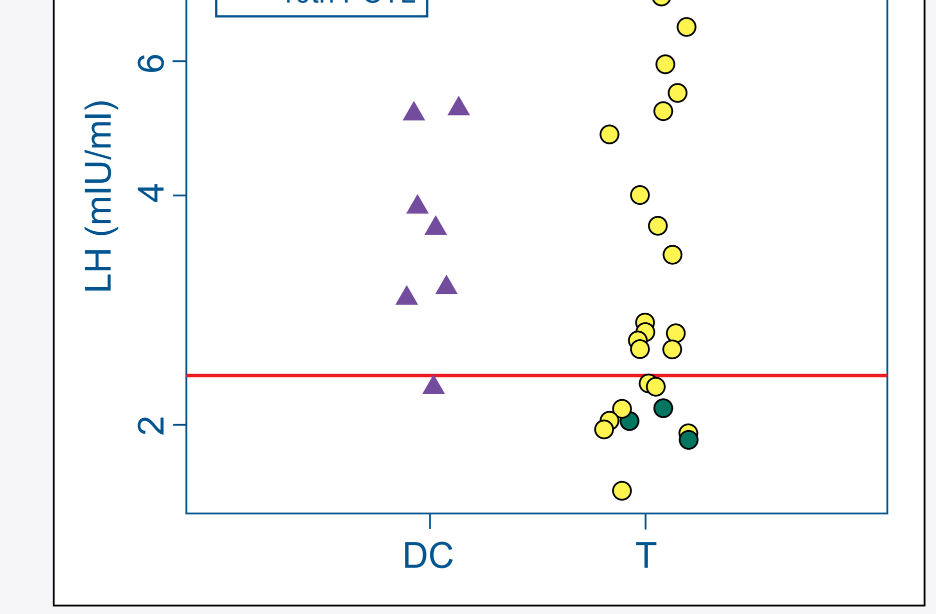

Figure 2. Concentrations of LH (left panel) and total testos
Individuals who met both criteria for hypogonadism (●): a
sample and a testosterone concentration below the 5th pe

Hypogonadism

- ❖ Our criteria for hypogonadism were a testosterone conc range together with an LH or FSH below the 10th percenti
- ❖ Three Veterans in the T group met these criteria for hyp

Prolactin Abnormalities

- ❖ Extreme PRL levels (below the 5th or above the 95th p participants with probable hypogonadism (Table 1). PRL c sexual dysfunction.

Posterior Pituitary Hormone Abnormalities

- ❖ Two hormones, AVP and OT, are secreted from the post
- ❖ Criteria for AVP abnormalities were a concentration abo levels below the 5th percentile together with a urine specit
- ❖ The criterion for OT deficiency was a concentration bel
- ❖ Four Veterans with mTBI were found to have abnormal
- ❖ Two of these individuals were deficient in both hormon or disruption of the pituitary stalk.
- ❖ Elevated AVP levels have been associated with PTSD, c disorders, but a definite causal relationship has not been e
- ❖ In contrast, there is evidence of a positive association support, and positive social interactions suggesting the pos social situations.

SUMMARY OF RESULTS

• Eleven of 26 (42%) of the Veterans with blast mTB concentrations of one or more pituitary hormones.

• None of the Veterans in the deployment control (DC abnormalities of any kind.

CONCLUSIONS

In this preliminary study, the proportion of Veterans with b in previous studies of TBI from all causes in the general po

- ❖ In agreement with earlier studies of pituitary disorc the most frequent anterior pituitary disorders found we
- ❖ Posttraumatic hypopituitarism (PTHP) has been as psychiatric, behavioral, and cognitive symptoms that s
- ❖ Unlike PTSD, PTHP is readily amenable to treatme their symptoms can be counteracted with hormone rep
- ❖ Therefore, routine screening for hypopituitarism aft directing diagnostic and therapeutic decisions that oth pituitary screening may significantly facilitate recovery individuals who have suffered TBI.

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ABSTRACTS

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Prevalence and Characteristics of Chronic Pituitary Dysfunction after Blast-related Mild Traumatic Brain Injury

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Objectives: Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 25–50% of cases. The most common pituitary disorders found were growth hormone deficiency (GHD) and hypogonadism. Hypopituitarism, and in particular adult GHD, is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, and decreased quality of life. Despite the high frequency of pituitary dysfunction after civilian TBI, the occurrence of posttraumatic hypopituitarism after blast-related mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized. The objective of this study is to evaluate the prevalence and specific nature of pituitary hormone abnormalities consequent to blast mTBI.

Methods: Concentrations of twelve pituitary and target-organ hormones were measured by radioimmunoassay or enzyme-linked immunosorbent assay of blood samples taken from two groups of US military Veterans of combat in Iraq and/or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least one year prior to entry in the study. The other group consisted of participants with similar military deployment experience but without blast exposure. Criteria for identifying abnormal circulating levels of luteinizing hormone (LH), follicle-stimulating hormone, total testosterone, prolactin, adrenocorticotropin (ACTH), cortisol, thyroid-stimulating hormone, free thyroxine, growth hormone, insulin-like growth factor-I (IGF-I), oxytocin, and arginine vasopressin (AVP) were derived from determinations of normative ranges in a group of male non-Veteran control subjects.

Results: Eleven of 26, or 42%, of participants with blast mTBI were found to have abnormal hormone levels relative to the normative ranges in one or more pituitary axes. Five members of the mTBI group were found to have probable GHD, based on their age-adjusted IGF-I concentrations. Three of the mTBI subjects were found to have abnormally low testosterone and LH concentrations consistent with hypogonadism. Six of the mTBI group were found to have abnormal levels of the posterior pituitary hormones oxytocin and/ or AVP. None of the nonblast-exposed Veterans had any abnormal hormone concentrations.
Conclusions: These preliminary findings suggest that the prevalence of hypopituitarism after blast-related mTBI is similar to that in other forms of TBI. Pituitary hormone deficiencies are associated with a constellation of neuropsychiatric symptoms and diminished quality of life similar to those of PTSD but which are amenable to successful treatment with hormone replacement. Routine screening for pituitary dysfunction after blast mTBI shows promise for appropriately directing diagnostic and therapeutic decisions that may otherwise remain unconsidered and for markedly facilitating recovery and rehabilitation.

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Blast concussion is associated with high frequency of pituitary dysfunction

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Introduction: Studies of traumatic brain injury from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones at least 1 year after injury, in 25–50% of cases. Most studies found the occurrence of posttraumatic hypopituitarism (PTHP) to be unrelated to injury severity. Growth hormone deficiency (GHD) and hypogonadism were reported most frequently. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of chronic PTHP after blast-related concussion, or mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized.

Design: We measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least 1 year prior to the study. The other consisted of Veterans with similar military deployment histories but without blast exposure.

Results: In total, 11 of 26, or 42% of participants with blast concussions were found to have abnormal hormone levels in one or more pituitary axes, a prevalence similar to that after other types of TBI. Five members of the mTBI group were found with markedly low age-adjusted IGFI levels indicative of probable GHD, and three had testosterone and gonadotropin concentrations consistent with hypogonadism. Five of the blast concussion group exhibited abnormal vasopressin and/or oxytocin levels suggestive of posterior pituitary dysfunction. Indications of dysfunction in multiple hormonal axes were observed in five Veterans with mTBI. None of the deployment control subjects exhibited any hormonal abnormalities.

Conclusion: Blast mTBI is associated with a high frequency of PTHP. If symptoms characteristic of both PTHP and PTSD can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement. Routine screening for chronic hypopituitarism after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research project.

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one or more pituitary hormones at least one year after injury, in 25-50% of cases. Most studies found the occurrence of posttraumatic hypopituitarism (PTHP) to be unrelated to injury severity. Growth hormone deficiency (GHD) and hypogonadism were reported most frequently. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of chronic PTHP after blast-related concussion, or mild traumatic brain injury (mTBI), an extremely common injury in modern military operations, has not been characterized.

DESIGN

We measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least one year prior to the study. The other consisted of Veterans with similar military deployment histories but without blast exposure.

RESULTS

Eleven of 26, or 42% of participants with blast concussions were found to have abnormal hormone levels in one or more pituitary axes, a prevalence similar to that after other types of TBI. Five members of the mTBI group were found with markedly low age-adjusted insulin-like growth factor-I (IGF-I) levels indicative of probable GHD, and three had testosterone and gonadotropin concentrations consistent with hypogonadism. Six of the blast concussion group exhibited abnormal vasopressin and/or oxytocin levels suggestive of posterior pituitary dysfunction. Indications of dysfunction in multiple hormonal axes were observed in five Veterans with mTBI. None of the deployment control subjects exhibited any hormonal abnormalities.

CONCLUSION

Blast mTBI is associated with a high frequency of PTHP. If symptoms characteristic of both PTHP and PTSD can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement. Routine screening for chronic hypopituitarism after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

Pituitary Dysfunction After Traumatic Brain Injury (TBI)

- The estimated prevalence of hypopituitarism from all causes in the general population is 300 cases per million, or 0.03%.
- However, the prevalence of hypopituitarism after TBI from all causes has been reported to be in the range of 25-50%.
- The frequency of occurrence of posttraumatic hypopituitarism (PTHP) has generally not been found to be related to trauma severity.
- The most common anterior pituitary dysfunctions found were growth hormone deficiency (GHD) and hypogonadism.
- Hypopituitarism, and in particular adult GHD, is associated with non-specific psychological and physical symptoms that can be mistaken for PTSD.
- These symptoms include fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, deleterious effects on body composition, increased risk for hypertension and cardiovascular mortality, and decreased quality of life.

Mild TBI

Mild TBI (mTBI), or concussion, is defined as traumatically induced disruption of brain function manifested by:

- Brief (< 30 min) loss of consciousness,
- Amnesia for events surrounding the trauma (< 24 hr), OR
- Altered mental state (confusion, disorientation, etc.).

Rationale

Blast-induced mTBI is one of the most common injuries seen in modern military combat operations. Despite that fact and the high frequency of hypopituitarism that has been reported after TBI from other causes , no prior studies of the prevalence of hypopituitarism after blast concussion have been published.

Potential Mechanisms of Brain Injury Due to Blast Exposure

- Blast pressure is propagated directly through the skull and indirectly through the vasculature.
- Blast may produce rapid acceleration, deceleration and rotation of the brain.

Sources of Pituitary Damage in TBI

- Torsional forces from brain movement acting on the pituitary stalk
- Compression due to the pituitary's confinement in the sella turcica
- Vascular pressure surges
- Disruption of hypothalamic function and its vascular and neural input to the pituitary

Experimental Design

- Two groups of male US Veterans of deployment to Iraq and/or Afghanistan:
  - 1. **T** group (N=26) -- diagnosed with blast-induced mTBI
  - 2. **DC** group (N=7) -- not blast-exposed and without history of head injury (deployment controls)
- Basal concentrations of 12 pituitary and target-organ hormones were assayed with commercial radioimmunoassay or enzyme-linked immunosorbent assay kits.
- Hormones measured: total testosterone (tT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), growth hormone (GH), insulin-like growth factor-I (IGF-I), adrenocorticotropin (ACTH), cortisol, thyroid-stimulating hormone (TSH), free thyroxine, vasopressin (AVP), and oxytocin (OT)
- Abnormal hormone levels were defined in relation to the distributions of hormone concentrations in a reference group of healthy community control subjects.
- Criteria for identification of abnormalities in each hormonal axis are shown in Table 1.

Axis	Definition Using Control Population and Lognormal Distribution
1. Adrenal insufficiency	Cortisol < 10th percentile (6.7 ug/dl), and ACTH < 10th percentile (17.7 pg/ml)
2. Thyroid deficiency	Free T4 < 5th percentile (0.87), and TSH < 50th percentile (2.39)
3. Hypogonadism	Total testosterone < 5th percentile (330) and either LH or FSH < 10th percentile (2.3, 1.3, respectively) OR (total testosterone < 5th percentile and prolactin > 95th percentile (32.0)
4. Vasopressin abnormality	Vasopressin > 95th percentile (9.46) OR vasopressin < 5th percentile (0.27) and urine specific gravity ≤ 1.003
5. Prolactin abnormality	Prolactin > 95th percentile (32.0) or prolactin < 5th percentile (6.7)
6. GH deficiency	Age-adjusted IGF-1 < 10th percentile
7. Oxytocin deficiency	Oxytocin < 5th percentile
Hypopituitarism	Dysfunction in at least one of axes 1-7.

Table 1. Operational definitions of dysfunctions of pituitary hormone axes based on comparisons with log-normal concentration distributions in age-matched healthy community control subjects.

Results

- Five individuals in the T group, but none in the DC group, were found with markedly low IGF-I levels strongly suggestive of GHD (Fig. 1).
- Three of the T group participants had LH and testosterone concentrations meeting the criteria for hypogonadism (Fig. 2).
- Prolactin
  - No prolactin abnormalities were observed in the DC group.
  - One of the T group was found with prolactin > 95th percentile of the reference control group range.
  - One of the T group was found with prolactin < 5th percentile.
  - Both of these T subjects also had sub-threshold LH and testosterone levels.
- No abnormalities in pituitary-adrenal or pituitary thyroid axes were observed in either subject group.
- Vasopressin
  - The DC group did not exhibit any abnormal AVP concentrations.
  - Two T-group subjects had AVP levels > 95th percentile of the reference range.
  - Two of the T group were found with AVP < 5th percentile and urine specific gravity < 1.003.
- Four of the T group and none of the DC group had OT levels < 5th percentile.
- Hormone concentrations of the T subjects who showed indications of hormonal abnormalities in one or more axes are shown in Table 2.

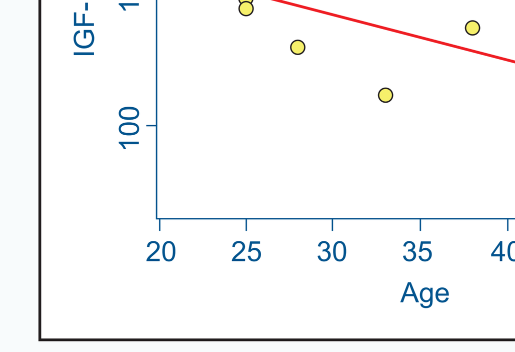

Fig. 1. The red line represents the age-adj
distribution of basal IGF-I concentrations i
control sample. IGF-I levels below that thre
indicative of probable GHD: [▲] = DC (dep
[●] = T (blast mTBI) group. Measures of IG
sensitivity for identifying GHD but are high
presence of normal or elevated IGF-I level

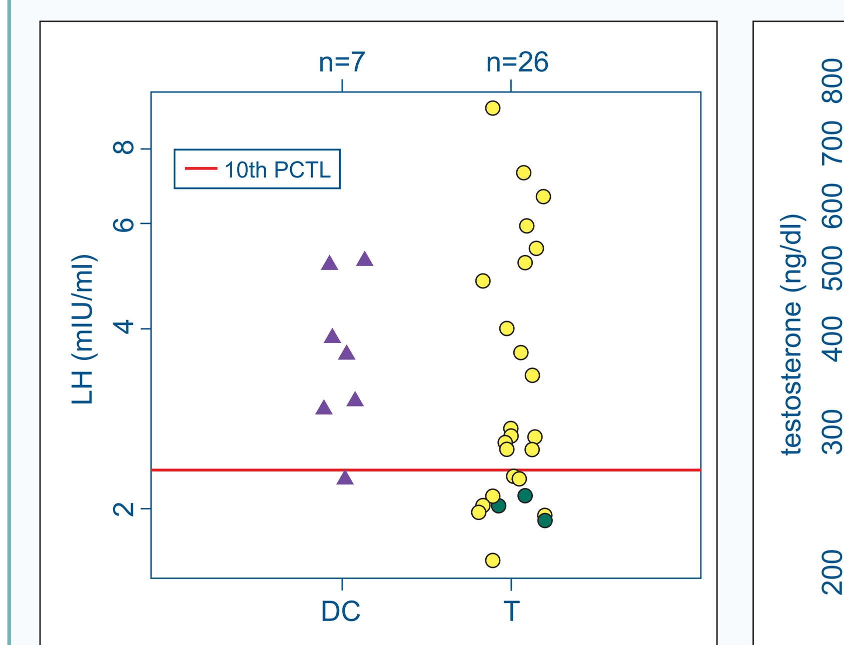

Figure 2. The dual criteria for hypogonadis
concentration below the 5th percentile of t
with an LH or FSH level below the 10th pe
distributions. Only the three subjects in the
represented by [●] met both conditions an
hypogonadal.

Subj.	LH mIU/ml	FSH U/L	tTest ng/dl	PRL ng/m
T-2	2.03	---	669	9.6
T-4	2.03	2.06	252	54.9
T-8	2.72	4.02	401	11.9
T-10	1.97	2.43	520	12.3
T-12	7.27	5.70	715	13.0
T-13	1.92	1.18	253	6.3
T-14	2.66	2.51	390	12.0
T-16	2.64	4.01	380	21.5
T-22	4.00	4.48	588	12.8
T-25	2.24	4.34	463	7.2
T-28	2.11	2.64	264	15.3

Table 2. Basal hormone concentrations of
found to have abnormal values in at least
subjects with blast mTBI exhibited dysfunc
pituitary axes, and two were deficient in bo

Summary

- Eleven of 26, or 42%, of Veterans with
  found with hormone concentrations ind
- None of the deployment control subjec
  hormone deficiencies.
- The most frequent anterior pituitary dis
  hypogonadism.
- Two T-group subjects were found to ha
  both AVP and OT suggesting disruption
  or hypothalamic damage in these indiv

Conclusions

- Blast-induced mTBI carries a high risk
- PTHP is associated with a constellation
  quality of life similar to PTSD.
- Therefore, routine screening for pituitar
  concussion shows promise for:
  - Identifying those individuals whose
    neuroendocrine origin,
  - Directing diagnostic and therapeut
    otherwise remain unconsidered, a
  - Markedly facilitating recovery and
    induced mTBI.

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Prevalence of chronic hypopituitarism after blast concussion

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Studies of traumatic brain injury (TBI) from all causes have reported a prevalence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, of 25–50%. Hypopituitarism is associated with fatigue, anxiety, depression, insomnia, cognitive dysfunction, and deleterious changes in body composition and cardiovascular function. However, the prevalence of hypopituitarism after blast concussion/mild TBI (mTBI) has not previously been investigated. We measured twelve pituitary and target organ hormones in blood samples from Veterans of deployment to Iraq or Afghanistan with mTBI and from Veterans of deployment without blast exposure. Criteria for identifying abnormal hormone levels were derived from measurement of basal hormone concentrations in male non-Veteran control subjects. Preliminary results indicate that 42% of individuals with blast mTBI exhibited abnormal hormone levels suggestive of pituitary dysfunction, with the most prevalent deficiencies being consistent with hypogonadism and growth hormone deficiency. These findings of a high frequency of hypopituitarism after blast concussion similar to that found in other forms of TBI provide support for the value of routine hormonal screening in facilitating the recovery and rehabilitation of blast-exposed Veterans. Supported by DoD PT0753 and the Dept. of Veterans Affairs.

INTRODUCTION

Pituitary Dysfunction After Traumatic Brain Injury (TBI)

- ❖ Recent studies have reported the prevalence of hypopituitarism after TBI to be in the range of 25-50%, whereas the estimated prevalence of hypopituitarism from all causes in the general population is 300 cases per million, or 0.03%.
- ❖ The most common anterior pituitary dysfunctions post-TBI are growth hormone deficiency (GHD) and hypogonadism.
- ❖ Hypopituitarism is associated with non-specific psychological and physical symptoms that overlap considerably with those of PTSD.
- ❖ These symptoms include fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, deleterious effects on body composition, increased risk for hypertension and cardiovascular mortality, and decreased quality of life.

Sources of Pituitary Damage in TBI

- ❖ Linear and rotational forces on the pituitary stalk resulting from brain movement
- ❖ Compression due to the pituitary's confinement in the sella turcica
- ❖ Vascular pressure surges
- ❖ Disruption of hypothalamic function and its vascular and neural input to the pituitary

Study Rationale

- ❖ Although blast concussion is the single most common injury seen in modern military combat operations and the frequency of hypopituitarism after other forms of TBI has been found to be high, the prevalence of hypopituitarism after blast mTBI has not been determined.

Mild TBI/Concussion

Mild TBI (mTBI), or concussion, is defined as traumatically induced disruption of brain function manifested by

- ❖ Brief (< 30 min) loss of consciousness, **OR**
- ❖ Amnesia for events surrounding the trauma, **OR**
- ❖ Altered mental state (confusion, disorientation, etc.) for up to 24 hr.

EXPERIMENTAL DESIGN

- ❖ Two groups of male US veterans of deployment to Iraq and/or Afghanistan:
- ❖ 1. **T** group -- diagnosed with blast-induced mTBI
- ❖ 2. **DC** (deployment control) group -- not blast-exposed and without history of head injury
- ❖ Basal morning concentrations of 12 pituitary and target-organ hormones were measured in serum/plasma
- ❖ Abnormal hormone levels were defined in relation to the distributions of hormone concentrations in a reference group of healthy community control subjects.

The screening criterion for growth hormone deficiency was an IGF-I level below the age-adjusted 10th perce
concentration (diagonal red line) in the community control reference group. Measures of IGF-I provide low di
for identifying GHD but are highly specific indicators. The presence of normal or elevated IGF-I levels canno
Serum IGF-I values of five Veterans with mTBI fell below this cutoff line. None of the DC group met this criter

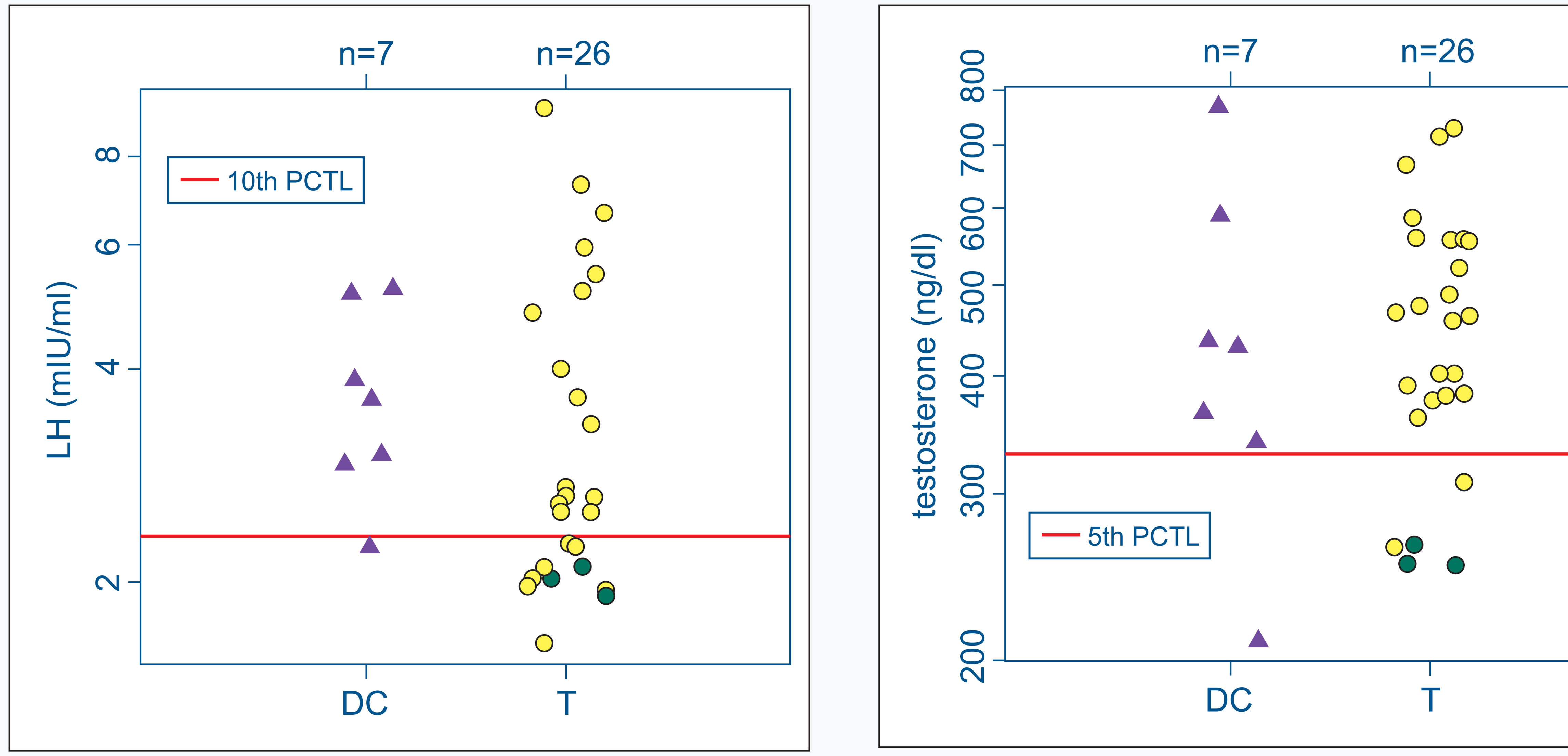

Fig. 2. Serum LH (left) and testosterone (right) in the deployment control (DC, ▲) and mTBI (T, ●) grou
for hypogonadism were a testosterone concentration below the 5th percentile of the reference group togethe
level below the 10th percentile of each of those distributions. Only the three subjects in the T group whose d
by ● met both conditions and were considered to be hypogonadal. None of the DC group met both criteria.

RESULTS

RESULTS, PART 1: First Round of Preliminary Data (Table 1)

Participants with blast mTBI (T group, N=26)

❖ Sub-threshold age-adjusted IGF-I levels indicative of GHD (Fig. 1):	N=5	(19.2
❖ LH and testosterone concentrations meeting criteria for hypogonadism (Fig. 2):	N=3	(11.5
❖ Abnormal prolactin levels: 1 > 95th and 1 < 5th percentile of reference range:	N=2	(7.7
❖ Pituitary-adrenal or pituitary-thyroid axis deficiencies:	N=0	(0.0
❖ Multiple anterior pituitary hormonal abnormalities:	N=3	(11.5
❖ Extreme vasopressin concentrations: 2 elevated; 2 low with USG < 1.003:	N=4	(15.4
❖ Oxytocin levels < 5th percentile of reference range:	N=4	(15.4
❖ Multiple anterior and/or posterior pituitary hormone deficiencies:	N=5	(19.2
❖ Abnormal basal levels in one or more pituitary hormone axes	N=11	(42.3

Deployment control participants (DC group, N=7)

❖ Abnormal basal levels in one or more pituitary hormone axes	N=0	(0.0

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Pituitary Dysfunction After Blast Concussion: Imaging and Psychological Correlates

Program: Abstracts - Orals, Featured Poster Presentations, and Posters
Session: SUN 130-162-Neuroendocrinology
Clinical

Sunday, June 16, 2013: 1:45 PM-3:45 PM

Expo Halls ABC (Moscone Center)

Poster Board SUN-148

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Studies of traumatic brain injury (TBI) from all causes have reported a prevalence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, of 25-50%. Chronic hypopituitarism is associated with a constellation of symptoms that overlaps considerably with PTSD including fatigue, anxiety, depression, sleep disorders, social isolation, aggression, sexual dysfunction, cognitive deficits, and deleterious changes in body composition and cardiovascular function. However, the prevalence of hypopituitarism after blast concussion/mild TBI (mTBI) has not previously been investigated. We measured twelve pituitary and target organ hormones in blood samples from male Veterans of deployment to Iraq or Afghanistan with mTBI (n = 36) and from male Veterans of deployment without blast exposure (n = 14). Criteria for identifying abnormal hormone levels were derived from measurement of basal hormone concentrations in healthy male non-Veteran control subjects. Subjects also underwent magnetic resonance imaging of fractional anisotropy and macromolecular proton fraction to assess brain white matter integrity; [18F]-fluorodeoxyglucose positron emission tomography imaging of cerebral glucose metabolism; structured clinical assessments of blast exposure, psychiatric diagnoses, and PTSD symptoms; neurologic evaluations; and self-report scales of postconcussive symptoms, combat exposure, depression, sleep quality, and alcohol use. Six of the initial 26 subjects with a history of blast concussion enrolled in the study were found to have hormone levels consistent with hypogonadism and/or growth hormone deficiency. Basal circulating hormone concentrations, voxelwise analyses for each of the three imaging modalities, and demographic, blast exposure, psychiatric and self-report data are presented for these six subjects and for six age-matched deployed controls. We previously found a significantly greater prevalence of anterior pituitary hormone abnormalities in the blast mTBI group than in the deployment control group and now report the imaging, neuropsychological, and behavioral characteristics of the two groups. Our findings provide support for the value of routine hormonal screening in directing diagnostic and treatment decisions that might otherwise remain unconsidered and for markedly facilitating the recovery and rehabilitation of blast-exposed Veterans.

Nothing to Disclose: CWW, ECP, SM, DJC, TLR, KFP, ERP

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Abstract ACCEPTED to be presented in a poster session during the 1st PanAmerican Congress of Physiological Sciences (PanAm-2014) Physiology without borders, to be held in the Rafain Palace Hotel & Convention Center, Iguassu Falls, Brazil, in August 2-6, 2014.

[Abstract ID: 566]

PÔSTER

HIGH FREQUENCY OF PITUITARY DYSFUNCTION AND ASSOCIATED COGNITIVE AND BEHAVIORAL DEFICITS AFTER BLAST CONCUSSION

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Abstract

Studies of traumatic brain injury from all causes have reported a prevalence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, of 25-50%.To determine if a similar frequency of hypopituitarism occurs after blast concussion, we measured 12 pituitary and target organ hormones in two groups of U.S. Veterans of combat in Iraq or Afghanistan: (1) individuals with blast-induced concussions (TBI), and (2) individuals without blast exposure. Early preliminary data indicated significant hormonal abnormalities in over 40% of the TBI group and 7% of the control group. Analyses of additional data have confirmed highly significant differences between the prevalence of pituitary dysfunction in the two groups. The most frequent abnormalities observed were those related to growth hormone deficiency and hypogonadism. Hypopituitarism was found to be associated with specific cognitive deficits and altered prevalence of fatigue, sleep disorders, and depression. Blast concussions, just as TBI induced by other mechanisms, result in a high frequency of pituitary dysfunction associated with multiple negative consequences for physical and mental health.

May 9, 2014

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Current Research Support:

PH/TBI Concept Award Wilkinson (PI) 03/15/11-06/14/14
DOD Congressionally Directed Medical Research Programs
Blast Concussion mTBI, Hypopituitarism, and Psychological Health in OIF/OEF Veterans
Role: Principal Investigator

Career Development Award Wang (PI) 12/01/11-11/30/14
DVA
Agitation, Aggression, and Adrenergic Activity in Alzheimer's Disease
Role: Mentor

RR&D Merit Review Award Wilkinson (PI) 04/01/12-03/31/16
DVA
Pituitary Dysfunction, Behavioral Symptoms, and Quality of Life after Blast mTBI
Role: Principal Investigator

Reportage of the Study in Print and Electronic Media

The abstract presented at the Experimental Biology meeting was chosen by the American Physiological Society as a "hot topic," and the society issued a press release on April 22, 2013, describing the findings presented:
http://www.the-aps.org/mm/hp/Audiences/Public-Press/For-the-Press/releases/13/13.html

The press release was posted on the University of Washington home page and, often in a slightly modified form, on several science and medicine websites and print publications.

UW Today, University of Washington home page, April 29, 2013:
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http://www.kuow.org/post/international-intervention-syria-sexual-assault-military-and-studying-hormone-levels

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