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TITLE: Mission Connect Mild TBI Translational Research Consortium

PRINCIPAL INVESTIGATOR:
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CONTRACTING ORGANIZATION: Transitional Learning Center at Galveston
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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT
The purpose of this project is to identify the incidence of post traumatic hypopituitarism (PTH) in mild TBI and develop criteria for assessing which patients with a mild TBI are at risk for developing PTH. This study will also correlate the characteristics of the individuals with PTH by neuropsychological, neurophysiological and imaging testing as they relate to functional outcome. At 6 months post injury, patients will be screened for anterior pituitary function f the 61 mTBI subjects with IGF-1 results at the 6 month visit, the results fell below the lower threshold for 13.1% when using the Quest Diagnostics reference values. However, when the TBI threshold was used, there were 31 subjects (50.8%) that met the criteria for hypopituitarism, with this finding, similar to that found in moderate-severe TBI population.

15. SUBJECT TERMS-
Post traumatic hypopituitarism

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Introduction

This report is the final report describing Dr. Masel's participation in the Mission Connect Mild Traumatic Brain Injury (mTBI) Translational Research Consortium from August 1, 2008 through August 31, 2014. Dr. Masel served as the PI for Specific Aim 2.3, which was designed to study the diagnosis of post traumatic hypopituitarism after mTBI. The research activities of Specific Aim 2.3 have been conducted in collaboration with three other clinical projects in the Consortium: Specific Aims 2.1 (PI Levin), 2.2 (PI Papanicalaou/McCarthy), and 3.1.2-3.1.7 (PI Robertson) as the Integrated Clinical Protocol (ICP), which used a shared group of subjects. This project used only the mTBI subjects, for whom we determined the incidence of hypopituitarism following mTBI and develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening. We also determined the relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS at six months after mTBI. We also examined the incidence of single and multiple pituitary hormone deficiencies. The clinical characteristics, MRI imaging results, EEG and MEG results of the subjects who have pituitary deficiency will be compared to those with normal pituitary function in final publications describing this work. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will also be examined.

Body of report

SA #2.3: To study diagnosis of post-traumatic hypopituitarism after mTBI
SA #2.3.1: To determine the incidence of hypopituitarism following mTBI.
SA #2.3.2: To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening.

At the 6 Month Visit, mTBI subjects had blood samples drawn to examine six hormone levels that are indicative of anterior pituitary function, including somatomedin (IGF-1), thyroid stimulating hormone (TSH), thyroxine (Free T4), prolactin, and total cortisol in all subjects. Total testosterone was tested in male subjects, and 17 β-estradiols was tested in females.

As of August 1, 2015, 71 subjects completed the 6 month visit when pituitary labs were done; of these 61 had IGF-1 levels available for analysis. (See Table 1 below) To our knowledge, there is no ongoing study of this type (looking for pituitary dysfunction in mTBI), size or scope in the United States. Please see the Conclusion section for more detail. For a full discussion of subject screening and recruitment, please refer to Dr. Levin's report.

A summary of the mean, standard deviation, and ranges of the test results of pituitary function are presented in Table 1 below. The number of subjects falling outside the standard reference range results is also presented.

Table 1: Summary of Pituitary Test Results

Cortisol						Out of Range			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.1	4.4	3.4	21.8	0		0	
Male	44	10.8	4.4	2.4	20.0	1	2%	0	
All	66	10.6	4.4	2.4	21.8	1	1%	0	
Estradiols						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	21	75.0	56.6	11.8	207.4	1	5%	1	5%
IGF-1/Somatomedin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	21	167.9	64.3	62.0	267.0	refer to IGF-1 Table			
Male	40	182.8	76.9	65.0	388.0				
All	61	177.6	72.6	62.0	388.0				
Prolactin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.9	9.8	4.5	47.8	0		2	5%
Male	45	9.3	4.9	3.2	25.5	0		2	5%
All	67	9.8	6.8	3.2	47.8	0		4	5%
TSH						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.5	1.6	0.3	8.0	1	5%	1	5%
Male	46	1.6	1.2	0.5	6.2	0		3	7%
All	68	1.6	1.3	0.3	8.0	1	1%	4	6%
Thyroxine (Free T4)						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.0	0.1	0.8	1.3	0		0	
Male	46	1.0	0.1	0.8	1.3	1		0	
All	68	1.0	0.1	0.8	1.3	1		0	
Total Testosterone						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Male	42	394.0	187.1	106.0	819.0	10	24%	0	

A separate table for the out-of-range values for IGF-1 is provided (Table 2 below), since these results are gender and age dependent. Table 2 indicates two parameters used to determine IGF-1 deficiency. The first (labeled: Standard Values) are the age/gender specific values used by Quest Diagnostics, the outside lab that does the IGF-1 test for Memorial Hermann Hospital-Texas Medical Center. However, IGF-I is a very rough estimate of the GH status of an individual and GH provocative stimulation testing, such as with the glucagon stimulation test (GST) is the only way to make a definitive diagnosis of growth hormone deficiency. The normal ranges for IGF-I are difficult to interpret, especially in individuals with TBIs because IGF-I can be influenced by many different variables including weight, age, and hormonal status. Therefore, there are GH deficient subjects who will have IGF-I levels in the normal range. The cutoff of an IGF-I of less than 175 (labeled TBI Values) is based on our study that correlated the response of the GST with the baseline IGF-I. (Zgaljardic et al., 2011) "Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing."

Table 2: Subjects with Low IGF-1/Somatomedin Values

Standard* Reference Values				Standard Values		TBI Values**	
Age	**Female (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	128-488 ng/mL	9	1	2	22%	2	22%
25-29 years	89-397 ng/mL	3		0		2	67%
30-34 years	71-352 ng/mL	1		0		0	
35-39 years	63-330 ng/mL	0	1	0		0	
40-44 years	58-318 ng/mL	5		1	20%	5	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		20	2	3	15%	11	55%
Standard* Reference Values				**Standard Values**		**TBI Values****	
Age	**Male (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	121-423 ng/mL	19	2	1		4	21%
25-29 years	112-402 ng/mL	6	1	2	33%	3	50%
30-34 years	89-350 ng/mL	5	2	1	20%	5	100%
35-39 years	77-323 ng/mL	4	2	0		3	75%
40-44 years	70-307 ng/mL	5	0	0		4	80%
45-49 years	66-296 ng/mL	2	1	1		4	100%
		41	9	5	12%	21	51%

*reference lab values **TBI values (Zgaljardic et al., 2011)

The missing IGF-1 results shown in Table 2 are due to:

1. Incorrect IGF test entered by lab personnel (5)
2. Lab tests not done after sample was drawn (1)
3. Lab tests done but result cannot be located (4)

The lab order sheet for the 6 Month Visit was revised to increase the accuracy of test entry by the lab personnel, and was monitored very closely. The Research Team met regularly with the CRU staff to ensure that they were familiar with all aspects of the protocol To put this in perspective, the mTBI subjects got 6 lab tests for pituitary function at the 6 Month Visit. For the 71 enrolled mTBIs that completed the 6 Month Visit, this would be a total of 426 tests. The errors in this group represent 2.34% of the tests done.

There were no publications to date from this specific research effort.

Personnel receiving pay from this research effort: Brent E. Masel, M.D

Key research accomplishments

- Dr. Masel was an active participant in the Clinical Working Group as well as at the Partnering PI Quarterly meetings.

- A paper entitled: *The Effects of Growth Hormone Replacement Therapy on Cognition after Traumatic Brain Injury*, was a poster presentation at the 27th Army Science Conference in Orlando in November, 2010.

- Dr. Masel and Dr. Urban published: *Effect of Growth Hormone Replacement Therapy on Cognition after Traumatic Brain Injury*, Journal of Neurotrauma 27:1565-1585 (September 2010).

- Dr. Masel was a co-author on the following paper: *Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing*, Clinical Endocrinology (2011) 74, 365–369.

- Dr. Masel was a co-author on: *Manifesto for the Current Understanding and management of Traumatic Brain Injury-induced Hypopituitarism.* J. Endocrinol. Invest. 34:541-543, 2011.

- The following poster was presented at the annual Endocrine society meeting in Houston, June 23-26, 2011 on post traumatic hypopituitarism. This poster used data from the Mission Connect mTBI Translational Research Consortium study and acknowledged the DOD Award: *Do Patients with Mild Traumatic Brain Injury Have an Increased Risk for Hypopituitarism?* Authors: Saadia Alvi, Sara Ahmadi, Charles R Gilkison, Randall J Urban, Brent Masel.

- Dr. Masel was an author on: Masel, B. E., Bell, R. S., Brossart, S., Grill, R. J., Hayes, R. L., Levin, H. S., Rasband, M. N., Ritzel, D .V., Wade, C. E., DeWitt, D. S. (2012). Galveston Brain Injury Conference 2010: *Clinical and experimental aspects of blast injury. Journal of Neurotrauma,* 29(12), 2143-2171.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Neurology Department at the University of Texas Medical Branch, June 5, 2013 and also to the North American Brain Injury Society in New Orleans, September 18-20, 2013.

- Dr. Masel authored the following book chapter relative to post traumatic hypopituitarism: Masel, B E. Neuroendocrine Dysfunction After Traumatic Brain Injury. In: Nathan D. Zasler, Douglas I. Katz, and Ross D. Zafonte, editors. Brain Injury Medicine: Principles and Practice, 2nd Edition New York: Demos Medical Publishing; 2012. pp. 887-901.

- Dr. Masel was an author on the following paper addressing the topic of post traumatic hypopituitarism as it relates to fatigue in the past year: Zgalijardic, D. J., Durham, W. J., Mossberg, K. A., Foreman, J., Joshipura, K., Masel, B. E., Sheffield-Moore, M. (2014). *Neuropsychological and physiological correlates of fatigue following traumatic brain injury*. Brain Injury, 28(4), 389-397.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Arkansas Trauma Conference, Little Rock, Arkansas May 22, 2014.

- Dr. Masel co-authored the following book chapter with a section on post traumatic hypopituitarism: Masel, B. E., & DeWitt, D. S. (2014). Traumatic brain injury disease: Long- term consequences of traumatic brain injury. In Understanding traumatic brain injury (pp. 28-53). New York NY: Oxford University Press.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the UTMB Neurology Department, Galveston, Texas September 17, 2014.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the North American Brain Injury Society meeting, San Antonio, Texas May 1, 2015.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Mission Connect Consortium Review of Science, Houston, Texas May 14, 2015.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Collegiate and Professional Sports Dieticians Association, Point Clear, Alabama, May 20, 2015.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the UTMB Neurology Department, Galveston, Texas June 17, 2015.

- Dr. Masel co-authored the following paper in the last year: Masel, B., Urban, R. *Chronic Endocrinopathies in Traumatic Brain Injury Disease* Journal of Neurotrauma 32:1–9 (2015) Mary Ann Liebert, Inc DOI: 10.1089/neu.2014.3526

Reportable outcomes

1. The analysis of pituitary hormones showed that of the subjects tested using the conservative testing values, 3 females (15%) and 5 males (15%) had low IGF-1 values indicative of Growth Hormone Deficiency. Using research-defined"TBI values" (see reference above) 11 females (55%) and 21 males (51%) had low values for IGF-1.

2. IGF-1 deficiency was the most common finding

3. Testosterone deficiency was the second most common finding

4. Similar to moderate-severe TBIs, pituitary deficiencies are surprisingly common at six months following mild TBI.

Conclusion

We discovered that post traumatic hypopituitarism is prevalent at the 6 month time point following a mTBI. A low IGF-1 (an indicator of low growth hormone levels) is the most common hormonal deficiency, with testosterone the next most common deficiency. Interestingly, these findings are surprisingly consistent with the moderate-severe TBI hypopituitarism literature, where GH deficiencies are present in approximately 15-20% of those studied, and testosterone deficiency is approximately 5-10%. Of important note, the moderate-severe TBI literature is mostly one year or more post injury, and we do not know if there would be some pituitary recovery in the population we are studying by month twelve.

We previously had run a very preliminary analysis of our data with the neuropsychological findings by Dr. Levin, and found a small relationship of pituitary dysfunction to acute symptoms as well as depressive measures. Now that enrollment and study participation is complete will run a final analysis, and identify what deficits and symptoms are specific to those with pituitary deficiencies. We anticipate producing one or more scientific publications on our results. Obviously, we will also work with other Consortium scientists to see if there is any commonality of hypopituitarism to EEG and/or imaging studies. Should there be positive findings, separate scientific publications will be produced.

It's obviously important to identify abnormalities. The more important question, however, will be whether or not treatment of the abnormalities can change symptoms. Based upon the data obtained from ***SA 2.3*** and ***2.3.1***, we have taken the next step and obtained private funding, medications and placebo, as well as local IRB approval, and have been recruiting and enrolling for a pilot study of subjects with mild TBIs who complain of fatigue. (Subjects from the Mission Connect Consortium Study have been contacted as well.) Subjects will be screened for pituitary dysfunction. Those who have Growth Hormone deficiencies will be evaluated and will be treated with rGH. Note that the data on GH deficiencies in the Mission Connect Consortium study is based on a "screening" level (IGF-1). This new study will re-screen these individuals at least one year post injury and perform definitive (provocative) testing for GH deficiencies.

It is a well-accepted concept that post traumatic hypopituitarism following a <u>moderate-severe</u> TBI is fluid in the first year post injury. Some deficiencies resolve; some develop later. It is believed that around one year, however, the deficits become permanent. We have no such knowledge relative to mild TBI. By re-screening (and treating) the subjects enrolled in the Mission Connect Consortium study who are now more than one year post injury, we will see what deficiencies resolve and what new deficiencies develop and are now considered <u>permanent.</u> This will more definitively respond to ***SA #2.3.1:*** "To determine the incidence of hypopituitarism following mTBI."

As we will now know what deficiencies are permanent at one year, using our data from our 6 month screening, we will also be able more definitively achieve the goals set out in ***SA #2.3.2:*** "To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening." For example, we may be able to identify 6 month cut-offs for deficiencies that separate those whose deficiencies resolve from those who become or continue to be deficient, thus, obviating the need for further

study of some individuals beyond 6 months. Considering the very large incidence of mild TBIs, we anticipate that these results will be of great interest and benefit to the civilian and the military population.

Reference

Zgaljardic, et al. (2011) Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing, *Clinical Endocrinology* 74, 365–369

Post-traumatic Hypopituitarism after Mild TBI

W81XWH-08-2-0138 PT074693P7

PI: Brent E. Masel, MD Org: Transitional Learning Center at Galveston Award Amount: $125,000

Study Aims

- Determine incidence of hypopituitarism after mTBI
- Identify risk factors in mTBI patients for this condition
- Describe relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS

Approach

The goal of our research consortium is to improve the diagnosis and treatment of mTBI. The Integrated Clinical Protocol has 4 related studies conducted in a sample of 200 mTBI subjects and 100 subjects with orthopedic injuries, as a comparison group; however, only mTBi subjects will participate in this study.

Specific Aim 2.3 is designed to examine the incidence and effects of hypopituitarism after mTBI, which are currently unknown. In this study, the clinical characteristics, MRI imaging results, EEG and MEG results of the patients who have pituitary deficiency will be compared to those of patients with normal pituitary function. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will be examined.

Standard* Reference Values				Standard Values		TBI Values**	
Age	Female (ng/ml)	n	missing	Low	%	Low	%
18-24 years	128-488 ng/mL	9	1	2	22%	2	22%
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35-39 years	63-330 ng/mL	0	1	0		0	
40-44 years	58-318 ng/mL	5		1		5	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		20	2	3	15%	11	55%

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35-39 years	77-323 ng/mL	4	2	0		3	75%
40-44 years	70-307 ng/mL	5	0	0		4	80%
45-49 years	66-296 ng/mL	2	1	1		2	100%
		41	9	5	12%	21	51%

Accomplishment: We learned that individuals with mTBI have an unexpectedly high incidence of growth hormone and testosterone deficiencies, similar to more severe TBIs. Due to these findings, we have obtained outside funding and are enrolling patients (including those from this study in a treatment trial.

Timeline and Cost

Original Funding Period – Aug 1, 2008 – July 31, 2013
Extension Years Funding – Aug 1, 2013 – July 31, 2015
Key: blue – planned, green – actual

Activities Calendar Year	08	09	10	11	12	13	14-15
Start-up, develop protocol, plan							
IRB/HRPO Approval							
Start enrollment							
Manage subjects, collect data							
End enrollment							
Complete follow-up; analyze data							
Terminate trial							
Estimated Budget ($K)	$7	$27	$25	$25	$26	$8	$7

Updated: Aug 2015

Goals/Milestones

CY08-09 Goals – Kick-off project, develop protocol, operational planning
☑ Initial draft of Integrated Clinical Protocol, Fall 2009
☑Approvals from both IRBs and recruitment sites in Summer 2009
☑HRPO approval December 2009
CY10-11 Goals – Start enrollment, manage subjects, collect data
☑Enrollment begun February 2010
☑Transition from paper CRFs to electronic data entry, January 2011
CY12-13 Goal – Increase enrollment, collect high-quality data
☑33 subjects' pituitary lab results analyzed and included in February 2012 Quarterly Report
☑CY 13-14 Goal – Increase enrollment
CY 14-15 Goal – Complete study and analyze results

Comments/Challenges/Issues/Concerns

- Sample drawn at 6 Month Visit, so subject attrition is a concern
- 82% of subjects completing all study activities, with 68 mTBI subjects completing this study and 61 with IGF-1 results

Budget Expenditure to Date
Projected Expenditure: $125,000—Actual Expenditure: $125,000