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TITLE: A Multidisciplinary Translational Approach to Investigate the Mechanisms, Predictors, and Prevention of Persistent Post-Traumatic Headache

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14. ABSTRACT

Annually in the US there are ≈2.8 million TBI-related ED visits, hospitalizations, and deaths and over 2 million individuals are diagnosed with mild TBI (mTBI). From 2000 to 2016, 360,000 US armed service members were diagnosed with TBIs, of which over 80% were mTBIs. Post-traumatic headache (PTH) is the most common symptom following mTBI. Although some PTHs resolve within the first few days, a large proportion of individuals with PTH do not have headache resolution during the acute phase and have PTH persistence (PPTH). Optimally, individuals who are at high risk for PPTH would be identified and treated during the acute stage of PTH, prior to and with the intent of preventing PTH persistence. This Focused Program will address this area of need by investigating mechanisms for PTH persistence, biomarkers that predict an increased risk for PPTH, and methods of preventing the development of PPTH. This Focused Program consists of six synergistic, non-interdependent, individual projects that address the overarching goal via use of PTH animal models, human investigations of individuals with PTH via in-depth phenotyping, neurophysiology testing, imaging brain structure and function, and via human and animal molecular and genetic biomarker identification. Finally, this Focused Program includes a phase II clinical trial of a CGRP receptor monoclonal antibody administered during the acute stage of PTH with the intent of preventing PTH persistence.

15. SUBJECT TERMS
post-traumatic headache, traumatic brain injury, concussion, calcitonin gene related peptide

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1. Introduction

The overarching goal of this Focused Program is to identify mechanisms and predictors for the transition from acute post-traumatic headache (PTH) to persistent PTH (PPTH) and methods to prevent this transition. This Focused Program consists of six synergistic, non-interdependent, individual projects that address this overarching goal via use of animal models of PTH due to mild traumatic brain injury (mTBI), human investigations of individuals with PTH via in-depth phenotyping, neurophysiology testing including quantitative sensory testing and visual discomfort threshold testing, magnetic resonance imaging of brain structure and function, and via human and animal molecular and genetic biomarker identification. This Focused Program also includes a phase II clinical trial of a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody administered during the acute stage of PTH with the intent of preventing PTH persistence. Advanced multivariate modeling methods with machine-learning techniques will be utilized to identify the optimal combination of data from the individual projects for predicting PTH persistence and for predicting treatment response to the CGRP receptor monoclonal antibody.

2. Keywords

Post-Traumatic Headache, Traumatic Brain Injury, Concussion, Calcitonin Gene-Related Peptide, Magnetic Resonance Imaging, Quantitative Sensory Testing, Genetics

3. Accomplishments

<u>Individual Project #1: Pre-Clinical Studies</u>

- IACUC Approval at Mayo Clinic: application approved.
- IACUC Approval at University of Arizona: application approved.
- DOD Animal Care and Use Review Office (ACURO): application submitted on 1/9/2020. Mayo Clinic ACURO approval received. University of Arizona ACURO approval pending with the most recent resubmission of documents to the DOD ACURO on 9/17/2020.

<u>Human Studies Individual Projects</u>

- Institutional Review Board (IRB) Approval at Mayo Clinic: application approved.

- IRB Approval at the Phoenix VA: application approved.
- DOD Human Research Protection Office (HRPO) Approval: application submitted on 11/16/2019. DOD HRPO split the submission into several components. Approval for Mayo Clinic projects excluding the clinical trial individual project (HRPO Log Number E00773.1a) was received on 9/2/2020. Translational Genomics Research Institute approval was obtained on 9/2/2020 (HRPO Log Number E00773.1d). DOD HRPO sent a determination on 9/11/2020 that Arizona State University protocol "comprises research not involving human subjects" (HRPO Log Number E00773.1c). DOD HRPO review of the Phoenix VA (HRPO Log Number E00773.1b) portion led to requests for clarifications that were received on 9/14/2020. A response was sent back to the DOD HRPO on 9/17/2020 and further communications from the DOD HRPO are now pending as of 9/21/2020. DOD HRPO review for the clinical trial protocol (HRPO Log Number E00773.2a) is pending as of 9/21/2020.
- IND Application Submission and Exemption: completed and exemption received
- Development of Case Report Forms: completed
- Development of Study Database: completed
- Development of Headache Diary: completed
- Establishment of Biospecimen Collection, Storage, and Transfer Procedures: completed
- First research subject (healthy control) enrolled and completed first visit research procedures at Mayo Clinic on 9/9/2020. Second research subject (healthy control) enrolled and completed first visit research procedures at Mayo Clinic on 9/11/2020. These research participants completed structured interviews, study questionnaires, quantitative sensory testing, visual discomfort threshold testing, structural and functional brain magnetic resonance imaging (MRI), and collection of blood. Additional subjects are scheduled for research visits.
- Preparation of machine learning data-analytic pipelines (individual project #6): our major efforts included working with investigators in other individual projects to understand the structure and characteristics of the data to be collected in their individual projects, and modifying/optimizing our existing machine learning pipelines to prepare for the data analysis. The specific accomplishments included:

- Since neuroimaging data will be collected longitudinally, there could be potential batch effects due to variability in scanning and post-processing approaches. To address this, we developed domain adaptation (DA) methods to extract robust image features to mitigate the impact of batch effects on predictive modeling. We tested the performance of DA on two datasets collected by our Mayo Clinic collaborators in their previous project for migraine classification using structural MRI (D1: 26 chronic migraineurs and 42 controls; D2: 15 chronic migraineurs and 54 controls). D1 was used for training and D2 used for testing. We applied a range of commonly used machine learning classifiers including decision tree, SVM, random forest, ANN, logistic regression, AdaBoost, LogitBoost, GentleBoost, and RobustBoost. There appeared to be batch effects between the two datasets. Without DA, the test accuracy of D2 by using the trained model on D1 ranged from 0.57 to 0.71 depending on the specific machine learning classifier used. Using DA, the accuracy improved to 0.87. The results showed the promise of DA in mitigating batch effects of neuroimaging data. We will use this method to examine longitudinally collected neuroimaging data for this CDMRP project and to extract robust image features for prediction of PTH persistence and treatment response.
- To delineate patient heterogeneity, we previously developed a Multi-Mode Factor Mixture Model (MFMM) to identify patient subgroups based on neuroimaging data and demonstrated the effectiveness of this method in a migraine study. During the first year of this CDMRP project, we extended the previously published MFMM model to allow for hierarchical selection of informative imaging modalities and of informative features nested within each imaging modality, namely the hierFMM model. HierFMM is particularly suitable for the CDMRP project because there is patient heterogeneity in whether or not a patient will develop PTH persistence and respond to treatment. Also, the CDMRP project will collect a large number of neuroimaging and non-imaging (phenotype, neurophysiology, biomarkers). We will use the hierFMM model to select informative data modalities and features for delineating patient heterogeneity.

- Since this CDMRP project will include mouse data to compare with human data and inform predictive modeling, treatment, and mechanistic discovery, we reached out to collaborators in individual project #1 to learn specifics of the mouse data to be collected. As reference, we obtained data collected in a recent paper by our collaborators, which shared a similar structure and characteristics as the data to be collected in this CDMRP project. This included 113 mice to examine the effects of CGRP on acute PTH and PPTH resulting from mTBI. Different CGRP treatment paradigms were applied to mice across 14 days post-mTBI and the impact of treatment on periorbital and hindpaw stimulation was measured. Cortical spreading depression (CSD) images were also collected for a subset of the mice to examine the differences in neural response between the different cohorts. We performed simple statistical analysis to get familiar with the dataset, which prepared us for analyzing the data that will be collected in this CDMRP project.
- To further expand our experience with neurophysiologic datasets and familiarize ourselves with the datasets to be collected, we reached out to our collaborators working on individual project #2. As a reference, we obtained data collected by the team in a prior study, which shared a similar structure and characteristics as the data to be collected in this CDMRP project. This included 20 healthy controls, 20 individuals with chronic migraine, and 20 individuals with PTH attributed to mTBI, examining differences in responses to visual and cutaneous sensory stimuli. We familiarized ourselves with the neurophysiological testing procedures, the resulting data types, and performed simple statistical analysis on the dataset. Doing so prepares us for analyzing the data that will be collected in this CDMRP project.

Planned Activities During the Next Reporting Period

During the subsequent quarter we hope to receive the remaining DOD HRPO and ACURO approvals. Major tasks that we anticipate beginning during this next period (pending full ACURO and HRPO approvals) include:

- Characterization of the mouse PPTH model

- Further enrollment of healthy controls and individuals with PTH who will participate with:
    - Structured interviews
    - Study questionnaires
    - Quantitative sensory testing
    - Visual discomfort threshold testing
    - Brain MR imaging
    - Biospecimen collection
    - Enrollment into the clinical trial
- MR imaging data processing and quality control assurance
- Biospecimen processing and quality control assurance
- Extension of machine learning pipeline for predictive modeling

4. Impact

The short-term impact from this research includes identification of mechanism(s) underlying PTH persistence from animal and human studies, potential methods to prevent PTH persistence, identification of clinical, imaging, molecular and genetic predictors for PTH persistence, and a phase II randomized placebo-controlled clinical trial testing a CGRP monoclonal antibody for treatment of acute PTH and prevention of PTH persistence. The long-term impact from this research includes the ability to identify who is likely to develop PPTH and an individualized medicine approach of preventing PPTH by intervening with treatment early after onset of PTH in those individuals who are in need of such therapy (i.e. those likely to develop PPTH and those likely to respond to the treatment). This approach would substantially reduce the burden from PPTH amongst civilian and military populations.

5. Changes/Problems

The process of obtaining DOD HRPO and ACURO approvals has taken much longer than anticipated. The human protocol was submitted to the DOD HRPO on 11/16/2019, after obtaining Mayo Clinic and Phoenix VA IRB approvals. On 3/17/2020 we received communication from the DOD HRPO requesting a telephone meeting to discuss our HRPO application. During that discussion we were informed that our protocol

needed to be split into two separate protocols: 1) the clinical trial; 2) all individual projects excluding the clinical trial. We then submitted the two protocols for informal DOD HRPO review on 3/23/2020. On 4/3/2020 we were told by the DOD HRPO to move forward with submitting these protocols back to the Mayo Clinic IRB for approval. The protocols were submitted to the Mayo Clinic IRB on 4/14/2020. The two protocols were approved by the Mayo IRB on 5/15/2020 and then submitted to the DOD HRPO on 5/20/2020. The DOD HRPO split the submission into several components. Approval for Mayo Clinic projects excluding the clinical trial individual project (HRPO Log Number E00773.1a) was received on 9/2/2020. Translational Genomics Research Institute approval was obtained on 9/2/2020 (HRPO Log Number E00773.1d). DOD HRPO sent a determination on 9/11/2020 that Arizona State University protocol "comprises research not involving human subjects" (HRPO Log Number E00773.1c). DOD HRPO review of the Phoenix VA (HRPO Log Number E00773.1b) portion led to requests for clarifications that were received on 9/14/2020. A response was sent back to the DOD HRPO on 9/17/2020 and further communications from the DOD HRPO are now pending as of 9/21/2020. DOD HRPO review for the clinical trial protocol (HRPO Log Number E00773.2a) is pending as of 9/21/2020.

After obtaining Mayo Clinic and University of Arizona IACUC approvals, documents were submitted to the DOD ACURO on 1/9/2020. DOD ACURO approval for the Mayo Clinic pre-clinical studies was received on 3/17/20. Final DOD ACURO approvals for the University of Arizona are still pending. The most recent request for further modifications was received from the DOD ACURO on 5/9/2020. The most recent resubmission of documents from the University of Arizona to the DOD ACURO was on 9/17/2020.

6. Products

We have published several manuscripts about PTH and migraine within the last year. Some of the work was conducted during this prior year (during this grant period) while other work was a product of our prior DOD CDMRP award.

- Hanna JJ, Chong CD, Dumkrieger G, Ross K, Schwedt TJ. Sensory hypersensitivities in those with persistent post-traumatic headache versus migraine. Cephalalgia Reports 2020;3:1-7.

- Howard L, Schwedt TJ. Posttraumatic headache: recent progress. Curr Opin Neurol 2020;33:316-322.
- Kim SK, Chong CD, Dumkrieger G, Ross K, Berisha V, Schwedt TJ. Clinical correlates of insomnia in patients with persistent post-traumatic headache compared with migraine. J Headache Pain 2020;21:33.
- Schwedt TJ. Structural and functional brain alterations in post-traumatic headache attributed to mild traumatic brain injury: a narrative review. Front Neurol 2019;10:615.
- Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Static and dynamic functional connectivity differences between migraine and persistent post-traumatic headache: a resting-state magnetic resonance imaging study. Cephalalgia 2019;39:1366-1381.
- Si B., Schwedt TJ, Chong CD, Wu T, Li J. A novel hierarchically-structured factor mixture model for cluster discovery from multi-modality data. IISE Transactions 2020, in press.

Other manuscripts are currently in preparation or under review for publication.

- Pena A, Dumkrieger G, Berisha V, Ross K, Chong CD, Schwedt TJ. Headache characteristics and psychological factors associated with functional impairment in individuals with persistent post-traumatic headache. (under review)
- Chong CD, Berisha V, Ross K, Schwedt TJ. Distinguishing persistent post-traumatic headache from migraine: classification based on clinical symptoms and brain structural MRI data. (under review)
- Schwedt TJ. Posttraumatic headache due to mild traumatic brain injury: current knowledge and future directions. (under review)
- Kopruszinski C, Swiokla J, Weinstein T, Schwedt T, Dodick D, Anderson T, Navratilova E, Porreca F. CGRP monoclonal antibody prevents the loss of diffuse noxious inhibitory controls (DNIC) in a mouse model of post-traumatic headache. (under review)

Lectures about PTH that have been delivered within this reporting period:

- Schwedt TJ. Post-traumatic headache is not a primary headache with head trauma as a trigger. International Headache Congress 2019. September 2019. Dublin, Ireland.

7. Participants & Other Collaborating Organizations

Site 1: Mayo Clinic

5777 E Mayo Boulevard; Phoenix, AZ 85054.

Overall PI: Todd J. Schwedt, MD

Individual Project Leaders: David W. Dodick, MD, Catherine D. Chong, PhD, Amaal Starling, MD, Frank Porreca, PhD

Biostatistician: Jay Mandrekar, PhD

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Individual Project Leader: Trent Anderson, PhD

Site 3: Arizona State University

300 E. University Drive; Tempe, AZ 85281

Individual Project Leaders: Jing Li, PhD, Teresa Wu, PhD

Site 4: Translational Genomics Institute (TGen)

445 N Fifth St; Phoenix, AZ 85004

Individual Project Leader: Matt Huentelman, PhD

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Site 5: Phoenix Veterans Administration Health Care System

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Individual Project Leader: Katherine Ross, PhD

Co-Investigator: Scott Bingham, MD

8. Special Reporting Requirements

Not applicable

Appendices

None