**STUDY INFORMATION**

Title: Cluster Analysis for Migraine-associated Symptoms (CAMS) in concussion: Comparing neurologic symptom clusters in migraine and concussion to define a post-concussive migraine phenotype.

Proposed authors:

Carlyn Patterson Gentile

Christina Szperka

Andrew Hershey

Geoff Aguirre

Christina Master

Description:

The primary objective of this study is to determine if CAMS based on multiple correspondence analysis can separate out concussion from migraine.

Primary Hypothesis: Symptom clusters will not be able to differentiate migraine from concussion because of a migraine endophenotype following concussion.

Background: We developed a novel analysis to determine underlying associations between migraine-associated symptoms in youth using a large single center headache registry (Patterson Gentile et al, 2023) and confirmed this result in a multicenter study (Patterson Gentile et al – in progress). Individuals with concussion can experience migraine-like symptoms. However, we observed different symptom clustering in our concussion and headache cohorts suggesting there are differences between these groups generally. We will use this analysis to determine if symptom clusters can be used to distinguish concussion from migraine and if subclusters can be identified in the concussion group. This builds upon the CAMS study where we have looked at concussion and headache individually, but have not yet combined the datasets. This pre-registration document is to update the pre-registered plan for combining headache and concussion datasets.

**DESIGN PLAN**

We will use post-concussion symptom inventory (PCSI) collected from youth and young adults with concussion and without concussion from the Minds Matter Concussion Registry, and youth and young adults from the headache program who answered similar questions about headache-associated symptoms. To match the two datasets, we will use the following:

The presence or absence of the following 7 neurologic symptoms will be used in our analysis: **nausea**, **light sensitivity**, **sound sensitivity**, **dizziness** [dizziness from the PCSI, combine room spinning and lightheadedness in the Headache questionnaire], **balance problems**, **visual problems** [visual problems from the PCSI, use combined double vision and blurry vision from the headache questionnaire], **difficulty thinking** [combine mentally foggy, slowed, different concentration, different remembering, and confused from the PCSI, use difficulty thinking from the headache questionnaire]. The Likert-type PCSI scores will be collapsed into the presence (PCSI score >0) versus absence (PCSI score 0) of a symptom.

Inclusion criteria: Participants must meet the following inclusion criteria. (1) ages 7 to 21 years old. *ADDENDUM: Changed to 13 – 18 years old because pre-injury data were not available for 12 and younger or older than 18*; (2) any sex, any race/ethnicity; (3) Adolescents and young adults with a diagnosis of migraine (any subtype) or tension-type headache who filled out the CHOP intake headache questionnaire between November 2022 and December 2023, OR who those from the Minds Matter Concussion registry with a pre-injury and post-injury adolescent post-concussion symptom inventory score collected between August 2017 and December 2020. *ADDENDUM: we changed the inclusion criteria from January 2020 to April 2024 (concussion dataset) and November 2022 to April 2024 to balance better matching the datasets by date and to maximize available records*. We will include those who are within a year of their concussion.

Exclusion criteria: For those in the headache group a headache diagnosis that is not migraine or tension-type headache; those with a history of post-traumatic headache will be excluded. For those with concussion, those out of the 1-year time window will be excluded, those with a remote history of concussion and/or history of migraine or chronic headaches will be excluded.

The following groups will be included:

1. Youth and young adults being seen for a chief complaint of headache (migraine or tension-type headache)
2. Youth and young adults with a diagnosis of concussion, within 1 year of concussion
   1. Subgrouping for those within 1 month of concussion vs. greater than 1 month
   2. Pre-injury and Post-injury scores will be used

Covariates

Participant demographics including age (in years), legal sex, race, and ethnicity will be recorded. Additional information available on race and gender identity will be reported in a table. History of migraine and chronic headaches and prior concussion number will be included for the concussion group. Days post-injury will be recorded for those in the concussion group, and split between <1 month, and >1 month. We will also look at day post-injury as a continuous variable. I will include prior history of concussion. We will correlate scores with headache severity: mild, moderate, or severe from headache questionnaire; from PCSI headache severity will be categorized as none (PCSI headache score = 0), mild (PCSI headache score 1-2), moderate (PCSI headache score 3-4), or severe (PCSI headache score 5-6).

Headache severity will be compared to results from the neurologic symptom MCA, which will be defined as none (PCSI headache score of 0), mild (PCSI score of 1 – 2 for patients from the concussion sample and mild overall headache rating or 0 – 10 headache pain severity score of 1 – 3), moderate (PCSI score of 3 – 4 for patients from the concussion sample and moderate overall headache rating or 0 – 10 headache pain severity score of 4 – 6), and severe (PCSI score of 5 – 6 for patients from the concussion sample and severe overall headache rating or 0 – 10 headache pain severity score of 7 – 10).

**ANALYSIS PLAN**

All analyses will be carried out through Matlab®.

MCA will be conducted on the 7 neurologic symptoms. To create the model, pre-injury scores will be taken from half of the participants with concussion without a history of migraine or chronic headache or a prior history of concussion, while post-injury scores will be taken from the other half. The same number will be taken from the headache registry with a diagnosis of migraine or probable migraine. *Addendum: To train the model, due to potential overlap/misclassification (eg. youth with high pre-injury PCSI may have migraine), we restricted selection of pre-injury to PCSI score <7, and to remove those who recovered from concussion we selected those with symptomatic concussion for the post-injury (PCSI 7). We also included only those who were within a month of concussion for model fitting to ensure we were capturing a more acute window of symptomatic concussion to train the model. Only those with a diagnosis of migraine (not probable migraine) will be used to train the model. Due to the increased date range used leading to an increased sample size, we will include 200 participants from each group (~20% of the smallest pre-injury group) to leave a larger pool for validating the model.*

All remaining participants will be used to validate the model with SVM classification. *Records used to validate the model were naïve to prior analysis.* Classification will be run with broad categories (pre-injury, post-injury, and migraine without history of injury), and more specific categories. The following categories will be considered, and will be included if they significantly differ in MCA dimension scores in their subgroups: pre-injury no history of concussion or migraine, pre-injury history of prior concussion, pre-injury with a history of migraine or chronic headache, pre-injury with history of migraine and concussion, post-injury history of prior concussion, post-injury with a history of migraine or chronic headache, post-injury with history of migraine and concussion, migraine, probable migraine, tension-type headache.

For the main model, the first three dimensions (based on prior work) will be included in the SVM classifier. We will also explore how classification changes between including the first dimension (accounting for the most variance) with up to dimensions accounting for 80% of the variance in the data. These dimensions will also be explored with the covariates as listed above.

Secondary analyses:

1. We will compare those within 1 month of concussion to those 1 – 12 months post-concussion.
2. We will compare within subjects pre- and post-injury CAMS scores.
3. We will develop a support vector machine classifier to determine if these symptoms can be used to differentiate post-concussive and migraine, and if some post-concussive individuals show more of a migraine cluster.
4. We will plan on looking at CAMS with visio-vestibular exam, VEP, and visually evoked effects metrics in a separate post-concussive group *if data are available*.
5. *We will look at longitudinal changes to PCSI CAMS if available.*

**REFERENCES**

Patterson Gentile, C., Aguirre, G. K., Hershey, A. D., & Szperka, C. L. (2023). Symptoms associated with headache in youth. *Cephalalgia*, *43*(7), 03331024231187162.

Patterson Gentile, C., Hershey, A. D., & Szperka, C. L. (In Progress). Cluster Analysis of Migraine-Associated Symptoms (CAMS) in Youth: multicenter validation and critical appraisable of the International Classification of Headache Disorders.