**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.

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Description:

The primary objective of this study is to determine if CAMS based on multiple correspondence analysis identifies symptom clusters following concussion.

Primary Hypothesis: Similar symptom clusters will be seen in migraine and concussion as revealed by CAMS.

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. Therefore, we will use this analysis to determine if similar symptom clusters of migraine-associated symptoms are seen after concussion.

**DESIGN PLAN**

We will use post-concussion symptom inventory (PCSI) collected from adolescents and young adults (ages 13 – 21) with concussion and without concussion from the Minds Matter Concussion Registry, and adolescents 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]. Fatigue was going to be included, but was removed because the headache questionnaire only asked this as a trigger, and not an associated symptom. The Likert-type PCSI scores will be collapsed into the presence (PCSI score >0) versus absence (PCSI score 0) of a symptom.

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).

Inclusion criteria: Participants must meet the following inclusion criteria. (1) ages 13 to 21 years old; (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. 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 compared:

1. Adolescents and young adults being seen for a chief complaint of headache (migraine or tension-type headache)
2. Adolescents 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

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 will be included for the concussion group. Days post-injury will be recorded for those in the concussion group. 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).

**ANALYSIS PLAN**

All analyses will be carried out through Matlab®.

MCA will be conducted on the 7 neurologic symptoms both combining the pre-injury, post-injury, and headache groups, and separating the three groups. Dimensions will be compared across groups, and the first three dimensions (based on prior work), as well as any additional dimension that appears consistent across groups will be evaluated in more depth.

A mixed effects linear regression model will be used to determine if there are differences across the following groups (pre-concussion, no concussion, and headache) in CAMS dimensions. A grouping variable will be applied to registry (Headache Program or Minds Matter Concussion Program) to account for differences in questionnaires and information collection. Demographics (age, sex, race/ethnicity) and headache severity will be considered. Headache severity will be included. Covariates will be selected if they have a significant association (defined as p-value<0.1) with either the primary predictor or the primary outcome. Covariates that will be evaluated include demographic information, headache phenotype, and headache burden metrics as detailed above. Non-significant covariates will be removed by backwards elimination. Any covariate that is significant (p<0.05) or impacts the primary predictor by >15% will remain in the final analysis.

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

**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.