**STUDY INFORMATION**

Title: A case-control study of continuous headache in youth with migraine, persistent post-traumatic headache, and new daily persistent headache.

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Description: Cross-sectional single center retrospective analysis of data from intake questionnaire collected in general neurology and headache subspeciality clinics. The main goal is to compare headache characteristics and headache-related disability of continuous headache across three diagnoses.

1. Migraine, with or without aura
2. Persistent Post-traumatic headache (PPTH)
3. New daily persistent headache (NDPH)

Hypothesis: PPTH and NDPH are not clinically distinct entities from migraine, but rather are trauma triggered migraine or sudden onset of continuous migraine without clear trigger. We predict that continuous headache categorized as migraine, PPTH, or NDPH will not differ in headache burden, headache characteristics and associated symptoms, headache triggers, or headache-related disability.

Background:

Migraine is a condition marked by paroxysmal headache attacks. The frequency of headache attacks can vary widely along a continuum with the most affected individuals reporting daily or even continuous headaches. Chronic migraine (CM) is currently defined as 15 or more headache days a month for more than 3 months (International Headache Society, 2018). While this can help identify individuals more affected by migraine, it has limitations because headache frequency and severity can wax and wane and reflects a continuum [CITE]. Further, the ICHD-3 treats continuous headaches as distinct clinical entities based on whether they gradually become more frequent and become continuous over time (migraine), start abruptly following a head injury (PPTH), or start abruptly without clear cause (NDPH). It has been hypothesized that these three diagnoses share pathophysiology given shared clinical features. NDPH may be a form of status migrainosus (Kung *et al.*, 2009; Riddle and Smith, 2019) and PPTH may be trauma-triggered migraine (Haas and Lourie, 1988). This is supported by the findings that there are few clinical differences between NDPH, CM, and PPTH. One study evaluating 1,170 children with continuous headache, 84.3% with CM and 13.2% with NDPH, found that there were no clinically significant differences in headache characteristics or headache-related disability between these two diagnoses (Reidy *et al.*, 2020). Further, participants with NDPH largely reported migrainous features at similar rates to participants with CM. Migrainous phenotype in PPTH is also high, ranging from 55 to 70% (Kuczynski *et al.*, 2013; Kamins *et al.*, 2021). If there are no differences in clinical characteristics between migraine, PPTH, and NDPH, it would support defining PPTH, NDPH under the umbrella of migraine, which would direct treatment.

We will expand upon the current literature by comparing age- and biological sex-matched groups across youth with NDPH, PPTH, and migraine with continuous headache while controlling for the duration of continuous headache (3-12 months), and the number of preventive therapies tried (2 or less). This approach will allow us to control for potential confounding variables that could impact the comparison between migraine, PPTH, and NDPH groups.

**DESIGN PLAN**

This study will include 50 age- and biological sex-matched youth ages 6 to 17 years old who filled out the Children’s Hospital of Philadelphia (CHOP) headache questionnaire. We will compare youth with continuous headache that is diagnosed as migraine, PPTH, and NDPH. Diagnosis will be defined by an algorithm applied to a patient questionnaire.

Inclusion criteria: Youth must meet the following inclusion criteria. (1) ages 6 to 17 years old at the time the questionnaire was filled out; (2) any biological sex, any race/ethnicity; (3) filled out the CHOP intake headache questionnaire between June 2017 and January 2022; (4) categorized by the diagnosis algorithm based on ICHD-3 diagnoses (publication pending) as migraine, PPTH, or NDPH; (5) report continuous headache for at least 3 months, but no more than 12 months.

Exclusion criteria: Youth will not be included if they do not meet criteria for CM, PPTH, or NDPH diagnosis. Youth who have had continuous headache for less than 3 months or greater than 12 months will not be included. Youth who have tried more than 2 prescription preventive therapies will be excluded to control for treatment prior to the start of the questionnaire.

Participants will be matched to the same biological sex, and age matched to within 120 days. Our registry has 9,363 entries. Of those, 508 report continuous headache with a duration between 3 and 12 months since onset and have tried 2 or fewer prescription preventive treatments. The diagnostic algorithm identifies 234 of those entries as migraine (44%), 89 as PPTH, and 131 as NDPH. Given that diagnosis is based on participant-reported headache features and history, the case-control selection will be blinded to clinician assigned ICD diagnosis, PPTH will be the reference group for matching because it has the fewest entries.

Participant demographics including age, biological sex, and race/ethnicity will be included as covariates. Additionally, age of headache onset, duration of severe headaches, and the presence of medication overuse headache will be considered. Premorbid diagnosis of migraine will be reported for the PPTH and NDPH groups. Finally, presentation to general neurology versus headache clinic will be considered.

We will consider (1) headache burden metrics, (1) headache characteristics, (3) treatment. See associated data dictionary for detailed information.

Headache burden metrics will include the following

1. Baseline pain severity (mild, moderate, severe scale; 0 to 10 scale)
2. Frequency of severe headache exacerbations
3. pedMIDAS (headache-related disability)

Headache characteristics will include the following

1. Pain location (side and area of the head)
2. Pain quality
3. Associated symptoms
4. Triggers
5. Aura

Treatment will include acute and preventive pharmacotherapies, and non-pharmacologic treatments including cognitive behavioral therapy, physical therapy, acupuncture, and procedural treatments including nerve block and botox.

**ANALYSIS PLAN**

All analyses will be carried out through Matlab®.

Our primary outcome will be participant-reported usual headache severity, measured on the 0-10 pain scale. Headache severity on the 0-10 pain scale will be presented as the median headache severity score with 95% confidence intervals. Headache severity as mild/moderate/severe will be graphically presented as percentages in each of the three diagnostic categories. PedMIDAS will be presented as median score with 95% confidence intervals by bootstrap analysis.

Sample size: Reidy and colleagues’ (2020) continuous headache sample, which did not identify a difference between chronic migraine and NDPH, reported a mean self-reported headache severity of 6.33/10 (SD 1.73). Based on these statistics, 40 participants per group would be needed to detect non-equivalence of +/-1 on the numeric pain scale with 80% power, and an alpha of 0.05. We will aim to age- and biological sex-match 50 participants across the three groups given that we are also pursuing multivariate analysis. This should be achievable given that PPTH, the diagnostic category with the fewest number of participants, has 89 participants, and the entire continuous headache sample has a mean age of 14.2 years (SD 2.7)

Univariate and multivariate analysis will be performed to determine if differences exist between headache diagnosis. Univariate analysis will consist of a one-way ANOVA adjusting for multiple comparisons using the Bonferroni method, or Chi squared test for categorical data to compare the three headache diagnoses across the above variables.

As a secondary analysis, multivariate multiple logistic regression analysis will be used to determine if associated symptoms, headache triggers, and headache quality and location predict headache diagnosis. Duration of symptoms at presentation, headache features, participant demographics, whether they were seen in general neurology clinic or headache clinic will also be included in the model.

Additional planned analysis

1. Multiple correspondence analysis of (1) headache triggers, (2) associated headache symptoms, (3) headache quality and location to compare the three groups and look for underlying clusters in the data
2. Comparison of number of acute treatments, IV treatments, and non-pharmacologic treatments between the NDPH, migraine, and PPTH diagnoses. Descriptive analysis will be pursued.

**REFERENCES**

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