

## IHS Child and Adolescent Research Grants 2022

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### Hormonal effects of puberty-related alterations in pain on adolescents with migraine

#### Specific aims

- Identify pubertal-related differences in experimental pain sensitivity.
- Determine the relationship between testosterone levels and experimental pain sensitivity and migraine severity

#### Study procedures

Enrollment- 27 participants without migraine and 16 with migraine completed the study visit.

The quantitative sensory testing, survey completion, and blood draws for sex hormone analyses were well tolerated by the participants.

#### Grant submission

This study demonstrated the feasibility of recruiting adolescents with migraine, which was a critical aspect of an R01 grant submission. This grant was submitted to NIH and was recently funded (“Migraine prognosis in adolescents”, PI: Nahman-Averbuch, R01NS134986)

#### Posters and Publications

Data from this study was presented by Dr. Nahman-Averbuch in the following oral presentations:

- “The role of hormonal and psychological factors on pain”. The 20th World Congress on Pain of the International Association for the Study of Pain (IASP). Amsterdam, The Netherlands. August 2024 (Chair)
- Androgen levels and migraine severity in adolescents”. 3rd USASP meeting, Seattle, WA. April 2024.
- “Hormonal effects of puberty-related alterations in pain in adolescents with migraine”. International Headache Congress, Seoul, South Korea. September, 2023
- “Puberty, Sex Hormones, and Migraine”. American Headache Society's 65 at Annual Scientific Meeting, Austin, USA. June 2023 (invited talk).
- “The role of sex hormones in pain across the lifespan”. 2nd USASP meeting, Durham, NC. April 2023.
- Poster presentation:  
Brown J, Banerjee G, McMichael A, AuBuchon J, Buday S, Baranski T, Powers S, Genizi J, Callahan DJ, Pathak S, Epperson M, Ben Abdallah A, Haroutounian S, Nahman-Averbuch H. Sex Hormone Levels in Adolescents with and without Migraine. International Association for the Study of Pain World Congress on Pain. Amsterdam, Netherlands. August, 2024

In addition, we are in the process of preparing manuscripts

- Pubertal effects on experimental pain in adolescent girls with migraine
- Androgens and migraine in adolescents
- The role of sex hormones on experimental pain in adolescent girls with vs. without migraine

The research was presented during the 21st International Headache Congress, Seoul, Korea, September 2023.

Cristina Szperka/Amy Gelfand

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## Informing Trial Outcome Measure Selection for Children & Adolescents with New Daily Persistent Headache (NDPH): Interim Report of Findings

### Specific aims

1) To use real-world data to determine the “natural history” or, more accurately, the “natural treated history” of NDPH in children/adolescents who are being treated in a pediatric neurology clinic, in order to inform selection of feasible outcome measures for future prospective, randomized, controlled trials.

Hypothesis 1: The most appropriate trial outcome measures for children and adolescents with NDPH will be different from those outcome measures most commonly used in preventive treatment trials for children and adolescents with migraine. For example, measures such as time to first headache-free day or decrease in number of moderate/severe headache days/month may be more appropriate than number of headache days/month.

2) To use real-world data to determine the “natural treated history” of NDPH in children and adolescents who are being treated in a pediatric neurology clinic in order to help inform sensible inclusion and exclusion criteria for future prospective, randomized, controlled trials in adolescents with NDPH.

Hypothesis 2: Children and adolescents who have continuous headache (with a recalled date of onset) for 4 weeks to <3 months' duration will have a similar headache trajectory to those who have had continuous headache for  $\geq 3$  months (i.e., those who would meet current ICHD criteria for NDPH).

### Final report

New daily persistent headache (NDPH) is an under-researched primary headache disorder that often has onset in adolescence and can be difficult to treat. ICHD-3 requires continuous headache for  $\geq 3$  months to diagnose NDPH, however many pediatric headache clinicians make this diagnosis before 3 months. We hypothesized that children with continuous headache of 1 to <3mo vs.  $\geq 3$ mo duration would have similar headache trajectories. Below are the Abstracts from our now two accepted manuscripts, both published in *Cephalalgia* (second one in press 2026), based upon the retrospective chart-review study of a cohort of 5-17 year olds with NDPH or shorter duration ( $\geq 1$  month) new onset headache (NOH).

### Abstract From First Paper

Background: New daily persistent headache (NDPH) is a challenging and understudied primary headache disorder with no known effective treatment. Although the International Classification of Headache Disorders criteria require that the new onset continuous headache be present for at least three months before diagnosing NDPH, the biologic basis for when a new, continuous headache starts to behave as NDPH is unknown, and some pediatric headache experts consider that the minimum duration criterion could be shorter.

**Methods:** In this retrospective study, we reviewed the intake questionnaires and medical records of 5–17 year-olds seen in neurology clinic for headache at the Children’s Hospital of Philadelphia. Those with a new onset continuous headache of at least one month in duration were eligible. The patient’s self-report and clinician’s description both had to indicate that the headache was new, of abrupt onset, and continuous to be included, although patients were allowed to have a prior history of infrequent headaches. We compared headache outcomes at last follow-up and at one year after continuous headache onset between those who had a continuous headache duration of 1 to <3 months (“new onset headache”, or NOH) at first visit vs. those with ≥3 months (NDPH). We used multivariate regression modeling to examine for predictors of headache outcomes.

**Results:** Of 472 patient records reviewed, 172 met the inclusion criteria for analysis. Of these, 84 had a headache duration of 1 to <3 months in duration and 88 had a duration of ≥3 months. Those with shorter duration continuous headache were younger (median (interquartile range) 13.5 (11.1–15.7) vs. 15.1 (12.3–16.5) years, and less likely to have previously received a prescription preventive for the continuous headache (n=14 (17%) vs. 26 (30%), p=0.046), but were otherwise similar to those with NDPH in terms of baseline clinical and demographic variables. Sixty-five (74%) of those with NDPH and 60 (71%) with NOH had follow-up data. At last clinic follow-up, 41/65 (63%) with NDPH and 43/60 (72%) with NOH had experienced any headache benefit (p=0.307), although 39/65 (60%) with NDPH and 29/60 (48%) with NOH still had continuous headache (p=0.191). Headache duration was not associated with outcomes in multivariate regression modeling.

**Conclusions:** Headache outcomes of children and adolescents with new onset continuous headache, whether of 1 to <3 months (NOH) or ≥3 months in duration (NDPH) are suboptimal. More research is needed to improve treatment outcomes for this patient population.

#### **Abstract from Second Paper – in press Cephalalgia**

**Background:** New daily persistent headache (NDPH) is a primary headache disorder that often presents in adolescence. Presently, there is no effective treatment for NDPH and a paucity of clinical trials exploring therapeutic options. In this study, we explored the relative benefit of currently used treatments to help inform future trials and clinical decision-making.

**Methods:** In this retrospective chart review study, patients aged 5–17 years with abrupt onset continuous headache and headache duration of at least one month (constituting NDPH or probable NDPH) were identified based on responses to a Headache Questionnaire in child neurology clinic and confirmed with chart review. We included all treatments (transitional therapy, preventive supplement, preventive medication and preventive non-medication therapy) started during continuous headache until both break in continuous headache and sustained improvement in headache were achieved. For treatments tried by at least 10 patients and for the first treatment tried in each category, we calculated proportions of any documented benefit, including “Significant” (≥30% improvement lasting ≥4 weeks) and “Some improvement” (all other improvement) and proportions of negative outcome (those with worsened headaches or side effects warranting discontinuation), as well as median time to treatment. We used multivariable regression modeling to examine for factors associated with headache outcomes. Treatments may have overlapped.

**Results:** Of the 165 patients, the largest proportion of patients experienced benefit with the first transitional therapy (62/108; 57%), which was usually intravenous medications ± oral corticosteroids. The first supplement tried, usually riboflavin ± magnesium, offered benefit in (36/118; 31%), with few negative outcomes (3/118; 3%). The first prescription preventive tried, usually amitriptyline or topiramate, offered similar benefit (37/106; 35%) as the first supplement, but with more negative outcomes (25/106; 24%). Despite being tried after oral preventives, onabotulinumtoxinA injections offered benefit to the largest proportion of patients (14/20; 70%) without negative outcomes (0%). Overall, the time to first therapy was weeks to months into continuous headache: shortest for transitional therapies (median = 49 days, interquartile range = 17–92 days), and longest for non-medication therapies (median = 144 days, interquartile range = 61–381 days). Increased time to any first treatment was associated with decreased odds of headache improvement at one-year follow-up

(odds ratio = 0.823, 95% confidence interval = 0.715–0.946,  $p = 0.006$ ).

Conclusions: Children and adolescents with new onset continuous headache experience treatment delays which are associated with worse outcomes. Clinicians should consider use of transitional therapies in combination with preventive treatments as early as possible. Prospective natural history studies and trials are needed to improve treatment outcomes for pediatric patients with NDPH.

Reference:

1. Szperka CL, Evans M, Patterson Gentile C, et al. Headache trajectories in children and adolescents with new onset continuous headache. *Cephalalgia* 2024;44:3331024241282803.

The research was presented during the 21st International Headache Congress, Seoul, Korea, September 2023.