Sensory hypersensitivities in those with persistent post-traumatic headache versus migraine

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Abstract

Background and Objective: Symptoms of persistent post-traumatic headache (PPTH) most often resemble those of migraine, including the presence of photo-, phono-, and cutaneous hypersensitivities. The severity of these hypersensitivity symptoms in those with PPTH compared to those with migraine has yet to be fully elucidated. The objective of this study was to compare symptoms of sensory hypersensitivities between PPTH, migraine, and healthy controls (HCs). Further defining characteristics of PPTH and its similarities to migraine might assist with developing future diagnostic criteria for PPTH and provide insights into PPTH mechanisms.

Methods: This analysis included 56 individuals with PPTH attributed to mild traumatic brain injury, 30 with migraine, and 36 HCs. To assess sensory hypersensitivities, all subjects completed the Allodynia Symptom Checklist-12, the Photosensitivity Assessment Questionnaire, and the Hyperacusis Questionnaire. Differences among groups were assessed using Fisher’s exact test, Kruskal–Wallis, or Mann–Whitney U test.

Results: PPTH and migraine groups had greater severity of cutaneous, photo-, and phono-hypersensitivity symptoms compared to HCs. There were no statistically significant differences between the PPTH and migraine groups for cutaneous allodynia (median [first quartile, third quartile]; PPTH: 4.0 [2.0, 7.0]; migraine: 5.0 [3.0, 8.0]; p = 0.54) or photosensitivity severity (PPTH: 5.0 [2.0, 7.0]; migraine: 5.0 [2.0, 6.0]; p = 0.53). Those with PPTH had higher hyperacusis scores compared to those with migraine (PPTH: 23.0 [17.0, 31.0]; migraine: 13.5 [9.0, 24.0]; p = 0.001).

Conclusion: Sensory hypersensitivity symptoms among individuals with PPTH are at least as severe as those experienced by people with migraine. Results further confirm symptom similarities between PPTH and migraine and could suggest that PPTH and migraine have a partially shared underlying pathophysiology.

Keywords

cutaneous allodynia, migraine, phonophobia, photophobia, post-traumatic headache, sensory hypersensitivity, traumatic brain injury

Introduction

Post-traumatic headache (PTH) is the most common and persistent symptom following a mild traumatic brain injury (mTBI).1 According to the International Classification of Headache Disorders, 3rd (ICHD-3) edition, PTH is defined as a secondary headache that develops within 7 days of a head trauma.2 When PTH continues for at least

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3 months, it is defined as persistent post-traumatic headache (PPTH).2

ICHD-3 diagnostic criteria for PTH do not include any specific headache characteristics or accompanying symptoms. However, it is common to describe PTH by the primary headache phenotype it most closely resembles. PPTH most commonly has a migraine phenotype, meaning that there is often presence of sensory hypersensitivities such as photosensitivity and phonosensitivity.3,4 However, the severity of sensory hypersensitivities among those with PPTH and how that severity compares to that found in people with migraine have been inadequately investigated. The objective of this study was to compare the severity of sensory hypersensitivity symptoms between a group of individuals with PPTH attributed to mTBI, a group with migraine, and healthy control (HC) subjects. Enhancing the description of PPTH symptoms might contribute to development of future versions of PPTH diagnostic criteria and could provide insights into PTH mechanisms.

Methods

Participants were enrolled into this United States Department of Defense-funded study from the Mayo Clinic in Arizona and the Phoenix Veterans Affairs Health Care System using convenience sampling. The overall goal of the research program was to identify similarities and differences in headache characteristics, other symptoms, and brain imaging findings among those with PPTH versus migraine. Other results from this research program have been previously published.5–9 The study was approved by the Mayo Clinic and the Phoenix Veterans Affairs Health Care System Institutional Review Boards and the Department of Defense Human Research Protection Office. All research subjects participated in the informed consent process and signed informed consent documents.

Adults between the ages of 18 and 65 years were eligible. Migraine and PPTH were diagnosed according to the ICHD-3 beta diagnostic criteria, the ICHD version that was extant at the time of subject enrollment.10 Those with migraine had no history of brain injury, while those with PPTH had no history of migraine preceding their brain injury. HCs had no history of migraine and no history of TBI. The Ohio State University TBI Identification Method was used to assess for a history of TBI.11 All participants with available data were included in this analysis.

Symptoms of cutaneous allodynia, the perception of pain to a normally non-painful stimulus of the skin, were assessed using the Allodynia Symptom Checklist-12 (ASC-12).12–15 The ASC-12 asks about symptoms of allodynia “during your most severe type of headache.” Answers to each of the 12 questions are scored as 0 (“does not apply to me,” “never,” or “rarely”), 1 (“less than half the time”), or 2 (“half the time or more”). A total questionnaire score of 9 or more is considered consistent with the presence of aldynia. Total scores on the ASC-12 can be further categorized as being indicative of “no” (0–2), “mild” (3–5), “moderate” (6–8), or “severe” (9 or more) aldynia. The ASC-12 has five questions that assess for mechanical static aldynia (i.e. pressure aldynia), two that assess for mechanical dynamic aldynia (i.e. brush aldynia), and five that assess for thermal aldynia (i.e. aldynia to heat and cold).15 The Photosensitivity Assessment Questionnaire (PAQ) was used to quantify photosensitivity.16 The PAQ is a 16-item questionnaire, which features 8 questions regarding photophobic or “light-avoiding” behavior and 8 questions regarding photophilic or “light-liking” behavior. For this analysis, answers to the eight questions addressing photophobia were included. The PAQ asks about photophobia symptoms without specifying a time period (e.g. answering how one feels during the prior 2 weeks or during a headache vs. when headache free). On the photophobia scale, affirmative answers are rated as a “1” and negative answers are rated as a “0,” yielding a total score between 0 and 8, with higher scores indicating greater photophobia. The Khalfa hyperacusis questionnaire was used to quantify the severity of phonosensitivity.17 This questionnaire includes 14 items, each of which is scored from 0 (”no”) to 3 (“yes, a lot”), for a total score between 0 and 42, with higher scores suggesting greater hyperacusis. The Khalfa hyperacusis questionnaire assesses for hyperacusis symptoms without specifying a time period that the respondent should consider when answering the questions.

Descriptive statistics were used to evaluate demographic data, questionnaire scores, and headache characteristics. Fisher’s exact test was used to compare categorical data measures in frequencies and percentages. In addition, Kruskal–Wallis one-way analysis of variance for three groups or the Mann–Whitney U test for two groups were used. Medians with first quartiles and third quartiles are reported for sensory hypersensitivity measures. Statistical data analyses were performed using R version 3.5.1 base.11 Statistical significance threshold was set at p < 0.05. One individual with migraine did not complete the ASC-12 and thus was excluded from the aldynia analyses.

Results

There were 122 participants, including 56 with PPTH, 30 with migraine, and 36 HCs. Demographics and headache characteristics are shown in Table 1. There were no differences among cohorts for age (median [first quartile, third quartile]: PPTH: 36.4 [31.7, 47.0] years; migraine: 40.8 [34.5, 48.6] years; HC: 37.7 [31.5, 44.6]; p = 0.32), but the migraine group had a higher proportion of women (PPTH: 34% women; migraine: 77% women; HC: 47% women; p < 0.001). On average, subjects with migraine had a higher headache frequency (20.0 [16.0, 25.0] headache days per month) than those with PPTH (15.0 [10.5, 20.0] headache days per month; p = 0.004), and more years of headache (21.4 [11.6, 31.3] years) compared to subjects...
Sixteen of the 30 participants with migraine had at least occasional auras associated with their migraine attacks. Two of 30 participants with migraine were in an episodic migraine pattern (12 and 13 days with headache per month), while 28 were in a chronic migraine pattern (reported having 15 or more headache days per month).

The mechanisms of mTBI were blast injuries ($n = 24$), falls ($n = 13$), sports injuries ($n = 9$), motor vehicle accidents ($n = 7$), and blunt force trauma ($n = 3$). Among those with PPTH, 12 had no history of TBI prior to the one that led to PPTH, 21 had one prior TBI, 6 had two prior TBIs, 2 had three prior TBIs, 4 had four prior TBIs, 2 had five prior TBIs, and 9 individuals had more than five prior TBIs. Within the PPTH subject group, 49 (88%) participants had a headache phenotype that was most similar to migraine or probable migraine, 6 participants had a headache phenotype that was most similar to tension-type headache, and 1 had a phenotype that was not classifiable.

Those with PPTH and those with migraine had more severe symptoms of cutaneous allodynia compared to HCs ($p < 0.001$). Median total scores were at the upper end of the mild allodynia category in both the PPTH and migraine groups.

### Table 1. Subject demographics for PPTH, migraine, and HC groups.

|                          | PPTH (n = 56) | Migraine (n = 30) | HC (n = 36) | Three-way comparison, $p$ value | PPTH versus migraine, $p$ value | PPTH versus HCs, $p$ value | Migraine versus HCs, $p$ value |
|--------------------------|--------------|-------------------|------------|-------------------------------|-------------------------------|--------------------------|-------------------------------|
| Age in years, median [1Q, 3Q] | 36.4 [31.7, 47.0] | 40.8 [34.5, 48.6] | 37.7 [31.5, 44.6] | 0.32 | 0.18 | 0.98 | 0.18 |
| Sex at birth (% female)   | 34%          | 77%               | 47%        | 0.001 | <0.001 | 0.27 | 0.02 |
| Headache days/month, median [1Q, 3Q] | 15.0 [10.5, 20.0] | 20.0 [16.0, 25.0] | NA        | NA | 0.004 | NA | NA |
| Years with headache, median [1Q, 3Q] | 8.7 [4.9, 13.2] | 21.4 [11.6, 31.3] | NA        | NA | <0.001 | NA | NA |

PPTH: persistent post-traumatic headache; HC: healthy control; 1Q: first quartile; 3Q: third quartile; NA: not applicable.

The migraine group included a larger proportion of females. Those with migraine had higher headache frequency and more years with headache compared to those with PPTH.

### Figure 1. Cutaneous allodynia, photosensitivity, and hyperacusis severity scores among those with PPTH attributed to mTBI, migraine, and HCs. Bar shows median, X shows mean. Cutaneous allodynia scores were higher in PPTH and migraine versus HCs (median [first quartile, third quartile]: PPTH: 4.0 [2.0, 7.0]; migraine: 5.0 [3.0, 8.0]; HCs: 0.0 [0.0, 0.0]; $p < 0.001$). Median scores were consistent with mild allodynia in the PPTH and migraine groups. There were no differences in scores between PPTH and migraine ($p = 0.54$). Photosensitivity scores were higher in PPTH and migraine versus HCs (PPTH: 5.0 [2.0, 7.0]; migraine: 5.00 [2.0, 6.0]; HCs: 0.0 [0.0, 1.5]; $p < 0.001$), and there was no difference between PPTH and migraine groups ($p = 0.53$). Hyperacusis scores were higher in PPTH and migraine versus HCs (PPTH: 23.0 [17.0, 31.0]; migraine: 13.5 [9.0, 24.0]; HCs: 5.0 [3.0, 7.0]; $p < 0.001$), and higher in PPTH versus migraine ($p = 0.001$). PPTH: persistent post-traumatic headache; HC: healthy control; mTBI: mild traumatic brain injury.
Among those with PPTH, 34% had no allodynia symptoms, 25% had mild allodynia, 21% had moderate allodynia, and 20% had severe allodynia. Among those with migraine, 24% had no allodynia, 28% had mild allodynia, 24% had moderate allodynia, and 24% had severe allodynia. Between those with migraine and PPTH, there were no significant differences for thermal allodynia (PPTH: 2.0 [0.5, 4.0]; migraine: 2.0 [0.0, 3.0]; \( p = 0.27 \)) or mechanical static allodynia (PPTH: 1.0 [0.0, 4.0]; migraine: 1.0 [0.0, 4.0]; \( p = 0.42 \)) (Figure 2). However, those with migraine had slightly greater symptoms of mechanical dynamic allodynia (PPTH: 0.0 [0.0, 2.0]; migraine: 2.0 [0.0, 3.0]; \( p = 0.047 \)).

There was a significant difference for median photosensitivity severity among groups (PPTH: 5.0 [2.0, 7.0]; migraine: 5.0 [2.0, 6.0]; HC: 0.0 [0.0, 1.5]; \( p < 0.001 \)), with higher scores in those with migraine and PPTH compared to HCs (Figure 1). There was no significant difference between migraine and PPTH groups (\( p = 0.53 \)).

Among cohorts, there was a statistically significant difference in median hyperacusis scores (PPTH: 23.0 [17.0, 31.0]; migraine: 13.5 [9.0, 24.0]; HC: 5.0 [3.0, 7.0]; \( p < 0.001 \)) (Figure 1). Those with migraine and those with PPTH had higher hyperacusis scores compared to HCs. Furthermore, those with PPTH had higher scores than those with migraine (\( p = 0.001 \)).

**Discussion**

This study demonstrates that those with PPTH attributed to mTBI have symptoms of cutaneous allodynia, photosensitivity, and hyperacusis that are similar in severity to those experienced by people with migraine. In this specific cohort of subjects, the severity of hyperacusis symptoms was greater in those with PPTH compared to migraine, although this finding would need to be confirmed in future studies. Prior literature has established that most individuals with PPTH have a migraine phenotype, indicating that they often have presence of symptoms of photo- and photosensitivity. Several studies have demonstrated that PPTH is associated with presence of cutaneous allodynia. This research adds to the existing knowledge by demonstrating that the severity of such symptoms is similar in those with PPTH compared with migraine.

It is estimated that 40–80% of people with migraine develop symptoms of cutaneous allodynia during migraine attacks. This study demonstrates that symptoms of allodynia are also reported by those with PPTH and that the severity of such symptoms is similar to that seen in individuals with migraine. Furthermore, there were no significant differences in symptoms of thermal (mediated by C nociceptive and A-delta fibers) or mechanical static allodynia (mediated by A-delta nociceptive fibers) between those with PPTH and those with migraine. Differences in mechanical dynamic allodynia were small, yet statistically significant, with the migraine group having more severe symptoms of mechanical dynamic allodynia (mediated by A-beta mechanoreceptive and capsaicin-insensitive A-beta fibers). Additional studies are needed to determine if a difference in mechanical dynamic allodynia symptoms is consistently found when comparing groups of individuals with PPTH versus migraine.

A recently published study by Ashina and colleagues that included 100 individuals with PPTH attributed to mTBI found that according to scores on the ASC-12.
54% had no cutaneous allodynia, 23% had mild allodynia, 17% had moderate allodynia, and 6% had severe allodynia.18 A study of 198 soldiers with PTH attributed to mTBI reported that 35% had allodynia.19 A larger proportion of individuals with PPTH had symptoms of allodynia in our study (66%), perhaps related to our population having more years with PPTH, a larger representation of PPTH with a migraine phenotype, and inclusion of individuals with PPTH who had experienced more than one TBI. Of note, in the Ashina study of 100 individuals with PPTH discussed just above, among the 61 with a migraine-like phenotype, 56% had symptoms of allodynia, a proportion close to the 66% found in our study.18

A recently published quantitative sensory testing study demonstrated that individuals with PPTH have abnormal cephalic and extracephalic sensory thresholds compared to HCs, with identified differences being dependent upon the PPTH phenotype (i.e. most similar to migraine vs. most similar to tension-type headache).21 Since 49 of the 56 individuals with PPTH in our study had a PPTH phenotype most closely resembling migraine, it is not feasible to perform subgroup analyses according to phenotype. Although further work is needed to determine the mechanisms for cutaneous allodynia in PPTH, it is likely that recurrent and prolonged activation of the trigeminocephalocervical system, thalamus, and brain pain matrix leads to the development of peripheral and central sensitization and the development of cutaneous allodynia in PPTH. There is also evidence for dysfunctional pain adaptation and diminished conditioned pain modulation among those with PPTH.22

Photosensitivity symptoms were of similar magnitude in those with PPTH compared to those with migraine. Photosensitivity is the most common and bothersome symptom other than headache in individuals with migraine.23,24 The most common and bothersome symptoms other than headache have not yet been established in those with PPTH. However, the presence of photosensitivity and low light-induced pain thresholds have previously been reported among those with PPTH.25 A study of 198 soldiers with PTH attributed to mTBI reported that 62.7% had photophobia.19 Continuous photophobia has been reported by 46% of 100 individuals with PPTH attributed to mTBI.18 The mechanisms for photosensitivity in migraine and PPTH have not yet been completely elucidated. In migraine, mechanisms likely involve hypersensitivity of the intrinsically photosensitive retinal ganglion cells that may project to pain processing regions of the thalamus, and hypersensitivity, structural remodeling, and altered functional connectivity of visual processing regions in the brain.26–29 Functional and structural brain imaging studies in PPTH are required to determine if there are similar findings in PPTH. Furthermore, photosensitivity is considered a relatively common symptom of mTBI, even in the absence of PTH.30 However, in a study of 447 soldiers with mTBI, those with PTH (n = 198) were more likely to have photophobia compared with soldiers who had mTBI but no PTH (62.7% vs. 49.3%, p = 0.001).19 Further research is needed to determine the extent to which photosensitivity following mTBI is due to the TBI itself versus being associated with PTH.28

Hyperacusis symptoms were more severe in those with PPTH compared to migraine in this study. Although it is quite likely that hyperacusis symptom severity in PPTH is at least similar to that found in migraine, further studies are needed to determine if in fact they are more severe in PPTH. In a prior study, continuous phonophobia has been reported by 60% of 100 individuals with PPTH attributed to mTBI.18 The mechanisms for phonosensitivity in migraine, PPTH, and other types of chronic pain are yet to be completely described. It is likely that there are peripheral and central mechanisms for phonosensitivity, perhaps with abnormal interactions between the peripheral and central components.31 Whereas one might presume that migraine-associated phonosensitivity is more reliant on central mechanisms, such as hypersensitive auditory cortex and abnormal sensory modulation in the brain stem, peripheral mechanisms might be additionally quite important in PPTH since the injury that led to PPTH (e.g. blast injuries) could also cause injury to peripheral components of the auditory system.32,33 In support of the notion that the TBI itself could lead to phonosensitivity, a study of 447 soldiers with mTBI found that 53.8% of soldiers without PTH (n = 249) had phonophobia.19 Although this was a substantial proportion of the mTBI population, those with mTBI and PTH (n = 198) were more likely to have phonophobia than those who had mTBI without PTH (68.6% vs. 53.8%, p = 0.002), suggesting contributions from both the mTBI and the PTH for determining the presence of phonophobia.

There are several limitations in this study. First, the research participants were enrolled from two medical centers. All of the migraine participants were enrolled from the Mayo Clinic, while about one-half of those with PPTH were enrolled from the Phoenix Veterans Affairs Health Care System. The patient populations (e.g. demographics, history of military service) differ between these two settings. Furthermore, those with migraine and PPTH were not matched for measures of headache severity, such as headache frequency and years with headache. Since those with PPTH had a lower headache frequency and fewer years with headache, we anticipate that the difference in headache characteristics could have skewed our results toward underestimating the severity of hypersensitivity symptoms in PPTH. Since the vast majority of those with migraine were in a chronic migraine pattern, it cannot be determined from this study if the results would be the same for episodic migraine. Differences in the proportions of women in the migraine and PPTH groups could have also impacted results. This analysis did not investigate potential impacts of headache medication on study outcomes. Future studies investigating symptoms of PTH should include larger sample sizes. If sample sizes are large enough, subgroup analyses could be performed that determine if mechanism of
head injury, headache frequency, time since injury, PPTH phenotype, and headache medication use are associated with severity of sensory hypersensitivity symptoms.

Conclusions
In conclusion, PPTH attributed to mTBI is accompanied by symptoms of sensory hypersensitivities including cutaneous allodynia, photosensitivity, and hyperacusis. Although it has been previously established that PPTH most often has a migraine phenotype, the severity of sensory hypersensitivity symptoms in those with PPTH compared to migraine had not been fully established. This study suggests that compared to individuals with migraine, individuals with PPTH have equally severe (cutaneous allodynia, photosensitivity) or more severe (hyperacusis) hypersensitivity symptoms. These results provide further evidence for phenotypic similarities between PPTH and migraine and point toward shared pathophysiological mechanisms.

Key findings
- PPTH attributed to mTBI is associated with sensory hypersensitivity symptoms, including cutaneous allodynia, photosensitivity, and hyperacusis.
- The hypersensitivity symptoms associated with PPTH are at least as severe as those associated with migraine.

Data availability
The data set supporting the conclusions of this article is available via the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Medical Research Program under award no. W81XWH-15-1-0286 and award no. W81XWH-19-1-0534. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. The US Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014, is the awarding and administering acquisition office.

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