New insights in post-traumatic headache with cluster headache phenotype: a cohort study

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ABSTRACT

Objectives To define the characteristics of post-traumatic headache with cluster headache phenotype (PTH-CH) and to compare these characteristics with primary CH.

Methods A retrospective study was conducted of patients seen between 2007 and 2017 in a headache centre and diagnosed with PTH-CH that developed within 7 days of head trauma. A control cohort included 553 patients with primary CH without any history of trauma who attended the headache clinic during the same period. Data including demographics, attack characteristics and response to treatments were recorded.

Results Twenty-six patients with PTH-CH were identified. Multivariate analysis revealed significant associations between PTH-CH and family history of CH (OR 3.32, 95% CI 1.31 to 8.63), chronic form (OR 3.29, 95% CI 1.70 to 6.49), parietal (OR 14.82, 95% CI 6.32 to 37.39) or temporal (OR 2.04, 95% CI 1.10 to 3.84) location of pain, and presence of prominent cranial autonomic features during attacks (miosis OR 11.24, 95% CI 3.21 to 41.34; eyelid oedema OR 5.79, 95% CI 1.33 to 4.93). Patients with PTH-CH were at a higher risk of being intractable to acute (OR 12.34, 95% CI 2.51 to 64.73) and preventive (OR 16.98, 95% CI 6.88 to 45.52) treatments and of suffering from associated chronic migraine (OR 10.35, 95% CI 3.96 to 28.82).

Conclusion This largest series of PTH-CH defines it as a unique entity with specific evolutive profile. Patients with PTH-CH are more likely to suffer from the chronic variant, have marked autonomic features, be intractable to treatment and have associated chronic migraine compared with primary CH.

INTRODUCTION

Post-traumatic headache (PTH) is defined as headache that develops within 7 days of head trauma.¹ It is difficult to determine the true prevalence of this type of headache; however, it appears to be more frequently associated with mild rather than severe head injury.² ³ Tension-type headache and migraine without aura are the usual associated phenotypes.³ Trigeminal autonomic cephalalgias (TAC) have been reported following head injury⁴ ⁵; however, only two cases fulfil the International Classification of Headache Disorders (ICHD) criteria for post-traumatic headache and cluster headache (CH), the vast majority of cases being described with a prolonged or unknown latency between CH onset and head trauma.⁶ ⁷ ⁸ ⁹

Described as one of the most painful conditions known to humans, CH is characterised by a strictly unilateral headache with associated ipsilateral cranial autonomic features.¹ It is the most frequent TAC, with an estimated lifetime prevalence of 0.12%. There have been several advances in delineating the pathophysiology of CH over the last decade. Recent functional imaging data suggest that ipsilateral hypothalamic activation with subsequent trigeminovascular and cranial autonomic activation underpins the pathogenesis of CH.¹¹ ¹² However, its relationship with head trauma remains unclear. According to Lambru and Matharu,⁶ there are three hypotheses explaining the link between head injury and CH. First, CH may occur as a direct result of head trauma; second, head trauma may only increase the risk of developing CH; and finally that the personality traits associated with CH may predispose to head trauma.

Although most PTHs resolve within 12 months of injury, approximately 18%–33% of PTHs persist, leading to loss of work capacity and significant fiscal consequences.¹³ ¹⁴ Postconcussion syndrome, with associated depression, cognitive dysfunction and insomnia, also contributes to this economic burden.¹⁵ This highlights both the clinical and medicolegal imperative to define post-traumatic headache with cluster headache phenotype (PTH-CH) accurately. Thus, this cohort study attempts to define the characteristics of PTH-CH and compare them with primary CH.

MATERIALS AND METHODS

Patients

This retrospective cohort study was conducted in a tertiary headache centre at the National Hospital for Neurology and Neurosurgery (Queen Square, London, UK) between January 2007 and May 2017. All consecutive patients with prior head trauma and diagnosed with CH according to the current International Classification of Headache Disorders - Third Edition (ICHD-3) diagnostic criteria were assessed.¹ All patients were evaluated and examined by a neurologist. After careful review of medical records, we only included patients with a latency period between head trauma and the first CH attack of 7 days at the most, thus meeting the ICHD criteria for both post-traumatic headache and CH.
A family history of CH was collected according to proxy reports from patients. To confirm a diagnosis of CH, available affected relatives were interviewed by a neurologist either over the phone or in person at the clinic. Relatives who had died or were unavailable for interview were included if they had previously been diagnosed with CH by a neurologist or had a history highly suspicious for CH.

Comparison with a control cohort
In order to ascertain specific characteristics in patients with PTH-CH, a comparison with a control cohort was done. All patients who attended the headache clinic during the same period and who fulfilled the criteria for primary CH were included in our control cohort (n=631). The same evaluation and data collection conducted in the PTH-CH group were performed in the cohort. In addition, any patient with history of head trauma (n=52) or patients diagnosed with CH considered as secondary to another disorder (n=26) were excluded from the final control cohort (n=553), given the possible impact on pain pathways of those events or disorders. No difference between patients with PTH-CH and patients with primary CH was found with regard to demographic data, such as current age, sex, age of onset and follow-up duration. Therefore, this allowed further comparisons regarding clinical characteristics.

Statistics
Descriptive statistics were expressed as mean with SD. The two groups of patients were compared using a Mann-Whitney non-parametric test for continuous data and a Fisher’s exact or χ² test for categorical data. For the multivariate analysis, we adopted a three-step approach. First, we balanced our two groups of patients with PTH-CH and primary CH. Indeed, when dealing with highly imbalanced classes, classification rules tend to be overwhelmed by the majority class to the detriment of the minority class. A common statistical approach to deal with imbalanced learning is to alter the class distribution to get a more balanced sample. Second, we performed variable selection to select a subset of relevant covariates for our model construction and finally a logistic regression with the previously selected features. Note that we did not split the data into a training and a test set as done usually. Indeed, due to the highly imbalanced data set, adopting the standard holdout strategy would lead to high variance estimates of the accuracy measure. Instead, we adopted a specific holdout version adapted to imbalanced learning. More specifically, we handled missing values by imputation techniques based on random decision forests. Then we used the ROSE (Random Over Sampling Examples) algorithm to balance the data. The ROSE function creates an artificial balanced sample according to a smoothed bootstrap approach. Then, on the ROSE sample we performed variable selection to get a subset of important covariates to feed into the logistic regression. We resorted to the powerful LASSO (Least Absolute Shrinkage and Selection Operator) algorithm to select relevant explanatory variables. The LASSO performs automatic variable selection and is capable of selecting groups of correlated variables. Eventually, we performed a logistic regression with the variables selected by the LASSO. All the numerical results were performed with the R software. The randomForest, ROSE and glmnet packages were used. The threshold for statistical significance was set to p≤0.05.
RESULTS
Demographics and clinical characteristics
We identified 26 patients diagnosed with PTH-CH within the defined study period, of whom 19 (73.0%) were male (tables 1 and 2). PTH-CH was persistent in all of them. The mean age was 48.4 years (SD 11.2) and the mean age at CH onset was 31.8 years old (SD 13.5). The mean follow-up time in our headache clinic was 6.5 years (SD 13.5). Five (19.2%) patients with PTH-CH were diagnosed with ECH or probable ECH phenotype and 21 (80.7%) with CCH or probable CCH phenotype.

Of the 21 patients with CCH phenotype, 15 were chronic at onset. Of the remaining patients, six developed the ECH phenotype immediately after the injury. The mean duration of attacks was 87.3 min (SD 55) and the mean frequency was 3.3 daily (SD 1.8). At least one autonomic feature was present during the attacks in the entire case group, with restlessness during an attack reported in all but two patients. At least one migraineous feature was reported in 24 (92.3%) patients. There was a distinct circadian periodicity, with the attacks occurring predictably during the night in 24 (92.3%) patients. Regarding concomitant headaches, six (23.0%) patients suffered from episodic migraine and five (19.2%) patients from chronic migraine. Interestingly, one developed chronic migraine at the same time as PTH-CH, whereas three patients also suffered from post-traumatic headache with a chronic migraine phenotype but related to another head injury. All patients could clearly distinguish CH attacks from migraine pain. Of the 26 patients with PTH-CH, a family history of CH in at least one first-degree relative was confirmed in 15.3% of patients, consisting of 4 individuals from 3 families. Two patients were brother and sister and their mother also suffered from CH, confirmed by us at the clinic. The affected relatives of the two remaining patients with PTH-CH with probable family history had passed away and therefore were not available for interview. Nevertheless, one (the mother of the patient with PTH-CH) had previously been diagnosed with CH and the other (the uncle of the patient with PTH-CH) had a history that was highly suspicious for CH (extremely severe headaches localised behind the eye and occurring during the night).

Regarding the response to medical treatment, 2 (7.6%) patients were considered as intractable to acute treatment and 11 (42.3%) as intractable to preventive treatment. Three of them benefited from invasive neuromodulation, including occipital nerve stimulation, sphenopalatine ganglion stimulation and ventral tegmental region deep brain stimulation.

Head trauma and its relationship to headache
The details on head trauma are summarised in table 2. The vast majority of patients (n=23, 88.4%) sustained mild injury. Three (11.6%) traumas were considered as severe due to the duration of loss of consciousness and/or presence of anterograde amnesia. No intracranial haemorrhage was reported. There were however two skull fractures described in our cohort. The different mechanisms of head injury included road traffic accident (n=5), mechanical fall (n=4), collision with an object (n=7), assault (n=3) or direct penetration of the head by metal or glass (n=2). In addition, dental extractions (n=5) were assessed as the ICHD defines head injury as ‘penetration of the head by a foreign body’ but were not included for comparison with the control cohort, considering that they were not strictly identical to other patients with PTH-CH. Following the trauma, five patients had bruising and three had deep laceration. The first CH attacks occurred a few hours after the trauma in seven patients and immediately after it in five patients. The CH attacks were ipsilateral to the head injury in all patients in whom the trauma was clearly one-sided, except one (patient 2). Due to a wider and often bilateral injury, laterality was indeterminate in 11 patients.

Comparison with control cohort
Univariate analyses comparing the 21 patients with PTH-CH (without dental extractions) with the control cohort are presented in table 3. A family history of CH was identified in 50 (9.0%) patients according to medical records and confirmed over the phone or in person in 33 (5.9%) patients of the total control cohort. Regarding the headache diagnosis, patients with PTH-CH were more likely to be diagnosed with the CCH phenotype (80.9% vs 50.4%; p=0.006) and with associated chronic migraine (19.0% vs 7.6%; p=0.05) than the control cohort. Univariate analysis revealed statistical differences in terms of location, cranial autonomic features and response to preventive treatment. Indeed, a parietal location of referred pain, which was the most common site of injury, was more common in the PTH-CH group (38.0% vs 16.0%; p=0.008). They were at a higher risk of being intractable to preventive treatment than the control cohort (42.8% vs 16.0%; p=0.002). The results remained unchanged after including the five dental extractions cases (data not shown).

For multivariate analysis, we first approximately balanced the two classes with the ROSE algorithm and obtained a new sample generated from the first one with 270 patients with PTH-CH and 304 patients with no PTH-CH. On this balanced data set, in a binary logistic framework, the LASSO selected 33 variables over the 37 original ones. Then we fed the 33 selected variables into a logistic regression. For the sake of simplicity, we only represented the items with significant results out of the 33 variables in figure 1 (n=17 items).

We found significant positive association between PTH-CH and family history of CH (OR 3.32; 95%CI 1.31 to 8.63), CCH phenotype (OR 3.29; 95%CI 1.70 to 6.49), temporal location (OR 2.04; 95%CI 1.10 to 3.84), parietal location (OR 14.82; 95%CI 6.32 to 37.39), eye oedema during attacks (OR 5.79; 95%CI 2.57 to 13.82), miosis during attacks (OR 11.24; 95%CI 3.21 to 41.34), rhinorrhoea (OR 2.65; 95%CI 1.26 to 5.86), facial sweating (OR 2.53; 95%CI 1.33 to 4.93) and restlessness (OR 4.63; 95%CI 1.16 to 22.19). Multivariate analysis confirmed intractability to acute (OR 12.34; 95%CI 2.51 to 64.73) and preventive (OR 16.98; 95%CI 6.88 to 45.52) treatment as independent characteristics of patients with PTH-CH. Associated chronic migraine had one of the highest ORs (10.35; 95%CI 3.96 to 28.82) (table 4 and figure 1). Conversely, patients with PTH-CH were less likely to present with frontal referred pain (OR 0.09; 95%CI 0.03 to 0.19), absence of cranial autonomic features during attacks (OR 0.09; 95%CI 0.01 to 0.60), conjunctival injection (OR 0.33; 95%CI 0.12 to 0.86), lacrimation (OR 0.25; 95%CI 0.09 to 0.66) or flush (OR 0.28; 95%CI 0.12 to 0.59).

DISCUSSION
To our knowledge, this is the largest series of PTH-CH reported to date. Here, we describe the clinical characteristics of 26 patients with PTH-CH who developed headaches within 7 days of head trauma that strictly fulfil the ICHD-3 criteria for both PTH and CH. We have kept five patients who underwent dental extractions apart, considering that these cases have a postsurgical rather than a typical post-traumatic aetiology. Univariate analysis comparing the remaining 21 patients with PTH-CH with a control cohort of 533 patients with primary CH revealed...
### Table 1: Demographics and clinical characteristics of patients with post-traumatic cluster headache

| Sex | Age of onset (years) | Current age (years) | Follow-up duration (years) | Type of CH | Other associated headache | Laterality | Average duration (min) | Average frequency (per day) | Autonomic feature | Restlessness | Migrainous symptoms | Intractable to acute treatment | Intractable to preventive treatment |
|-----|----------------------|---------------------|-----------------------------|------------|---------------------------|------------|------------------------|-----------------------------|-------------------|-------------|---------------------|-----------------------------|-------------------------------|
| 1   | M                    | 15                  | 34                          | 10         | CCH*                      | Side variable | 50                     | 3                           | C, L, R, N, E, FS, P | Yes          | N, V                 | No                          | No                           |
| 2   | M                    | 32                  | 54                          | 10         | CCH Episodic migraine     | L           | 60                     | 2                           | C, L, N, R, E, FF, P | Yes          | PT, PN, OSM, N         | No                          | No                           |
| 3   | M                    | 18                  | 38                          | 10         | ECH                       | R           | 120                    | 3                           | C, L, N, E, FS, P | Yes          | PT, PN, N, V, OSM     | No                          | No                           |
| 4   | F                    | 36                  | 54                          | 10         | CCH* Episodic migraine    | L, L        | 90                     | 3                           | N, E, P           | Yes          | PT, PN, N, V, OSM     | No                          | Yes                          |
| 5   | M                    | 33                  | 64                          | 8          | CCH*                      | R           | 90                     | 6                           | L, N, R, FS, FF, P, AF | Yes          | PT, PN, OSM           | No                          | Yes                          |
| 6   | M                    | 43                  | 57                          | 8          | CCH                       | L           | 150                    | 1                           | L, R             | Yes          | PT, PN               | No                          | No                           |
| 7   | M                    | 20                  | 34                          | 3          | CCH*                      | R           | 40                     | 5                           | C, L, N, R, E, FS, P | Yes          | –                    | No                          | No                           |
| 8   | M                    | 10                  | 55                          | 8          | PECH                      | L, L        | 180                    | 6                           | C, L, N, R, E, FS, FF, P, AF | Yes          | PT, PN, OSM           | No                          | Yes                          |
| 9   | M                    | 22                  | 38                          | 8          | CCH Chronic migraine      | L           | 50                     | 5                           | C, L, N, R, E, FS, P | Yes          | PT, PN, OSM           | No                          | No                           |
| 10  | M                    | 26                  | 52                          | 8          | CCH*                      | R           | 120                    | 2                           | C, L, N, FF, FS, P | Yes          | OSM                  | Yes                         | Yes                          |
| 11  | F                    | 45                  | 58                          | 8          | CCH Episodic migraine     | L           | 120                    | 2                           | FS, AE, P         | Yes          | PN, N, MS             | No                          | Yes                          |
| 12  | F                    | 29                  | 42                          | 7          | CCH                       | L           | 120                    | 6                           | C, L, N, R, E, P | Yes          | N, OSM                | Only 3 trials done | No                           |
| 13  | F                    | 11                  | 23                          | 5.5         | CCH                      | Side variable | 90                  | 2                           | C, L, R, E, P      | Yes          | PT, N                 | NA                          | NA                           |
| 14  | M                    | 54                  | 57                          | 5          | CCH                       | L           | 150                    | 1                           | C, FS             | No           | –                    | Yes                         | Yes                          |
| 15  | M                    | 48                  | 59                          | 5          | CCH                       | L           | 45                     | 2                           | C, L, N, R, E, FS, P | Yes          | PT, PN                | No                          | Yes                          |
| 16  | F                    | 47                  | 61                          | 4          | CCH Chronic migraine      | L, L        | 120                    | 3                           | L, N, E, FS       | Yes          | –                    | No                          | Yes                          |
| 17  | M                    | 24                  | 33                          | 2.5         | CCH Chronic migraine      | L           | 30                     | 5                           | C, L, N, R, E, FS, FF, P | Yes          | PT, PN, N, V, OSM     | No                          | Only 3 trials done |
| 18  | M                    | 45                  | 52                          | 5          | PECH Episodic migraine    | L           | 210                    | 3                           | C, R, E           | Yes          | N                    | No                          | No                           |
| 19  | M                    | 56                  | 62                          | 2          | CCH Chronic migraine      | L           | 180                    | 2                           | NA               | Yes          | PT, PN                | No                          | Yes                          |
| 20  | F                    | 51                  | 64                          | 8          | ECH                       | L           | 30                     | 2                           | C, L, N, R, E, FS, P | Yes          | –                    | Yes                         | No                           |
| 21  | M                    | 28                  | 45                          | 1          | CCH*                      | R           | 120                    | 4                           | C, L, N, R, E, FS, FF, P | Yes          | PT                    | No                          | No                           |
| 22  | M                    | 38                  | 48                          | 4.5         | CCH                       | R           | 30                     | 6                           | C, L, N, R, E, FS, P | Yes          | –                    | No                          | Yes                          |
| 23  | M                    | 26                  | 39                          | 10.5        | CCH                       | L           | 20                     | 8                           | C, L, N, R, FS, FF | Yes          | PT, PN                | No                          | Yes                          |
| 24  | M                    | 24                  | 36                          | 6.5         | CCH Chronic migraine      | R           | 60                     | 2                           | C, L, N, P, AF     | No           | PT, PN, N             | No                          | No                           |
| 25  | M                    | 33                  | 48                          | 7          | CCH                       | L           | 60                     | 4                           | C, L, N, R, E, P  | Yes          | PN, N                 | Only 3 trials done | No                           |
| 26  | F                    | 17                  | 52                          | 5          | ECH Episodic migraine     | L           | 45                     | 3                           | L, N, R           | Yes          | PT, PN, N, OSM        | Only 3 trials done | No                           |

Autonomic feature: AE: auricular fullness; C: conjunctival injection; E: eyelid oedema; FE: facial flushing; FS: facial sweating; L: lacrimation; N: nasal congestion; P: ptosis; R: rhinorrhoea.

Migrainous symptoms: MS: motion sensitivity; N: nausea; OSM: osmophobia; PN: phonophobia; PT: photophobia; V: vomiting.

*Secondary chronic cluster headache phenotype (initially episodic and subsequently transformed to chronic variant).*
### Table 2  Characteristics of head trauma in patients with post-traumatic cluster headache

| Side of injury | Ipsilaterality | Time from injury to CH onset | Details of head trauma                                                                 | Associated features                                                                 |
|---------------|----------------|------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| 1             | Vertex          | Indeterminate                | 5 days Head hit by a block of concrete while standing on a riverbank for fishing.         | Loss of consciousness: 2–3 min, Amnesia: No, Skin bruise or laceration: Normal      |
| 2             | Left            | Yes                          | Immediate Cheek and occiput hit while attacked by a group, then was thrown down flight of stairs. | Loss of consciousness: 20–25 min, Amnesia: Anterograde, Skin bruise or laceration: Bruising and laceration, Neuroimaging: Left zygoma fracture |
| 3             | Left            | No                           | 24 hours Hitting the front left aspect of head while walking into a metal pole.            | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 4             | Unclear         | Indeterminate                | 24 hours Concussion to occiput and neck while playing netball.                           | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 5             | Forehead        | Indeterminate                | 7 days Banging the head on the beam of a door at home.                                  | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 6             | Left            | Yes                          | 7 days Accidental fall during water skiing, hitting on the left face.                    | Loss of consciousness: 2 min, Amnesia: --, Skin bruise or laceration: Normal         |
| 7             | Unclear         | Indeterminate                | 24 hours Unknown cause of syncope during driving, then hitting a tree with head concussion. | Loss of consciousness: 15 min, Amnesia: --, Skin bruise or laceration: Normal       |
| 8             | Left            | No                           | Few days Head was hit while serving in the army. No further details available.           | Loss of consciousness: 5 min, Amnesia: --, Skin bruise or laceration: Normal         |
| 9             | Left            | Yes                          | 24 hours Head was hit by a block of concrete while standing on a riverbank for fishing. | Loss of consciousness: 24 hours, Amnesia: Immediate, Skin bruise or laceration: Bruising and laceration, Neuroimaging: Basal skull fracture |
| 10            | Left            | Indeterminate                | 24 hours Head hit by a block of concrete while standing on a riverbank for fishing.      | Loss of consciousness: 3 min, Amnesia: --, Skin bruise or laceration: Normal          |
| 11            | Left            | Yes                          | Few days Attacked by a group, then kicked.                                              | Loss of consciousness: 7 days, Amnesia: --, Skin bruise or laceration: Normal        |
| 12            | Left            | Yes                          | Immediate Attacked in a pub with the left temple punched by a customer.                  | Loss of consciousness: 7 days, Amnesia: --, Skin bruise or laceration: Normal        |
| 13            | Unclear         | Indeterminate                | 5 hours Hitting the front left aspect of head while walking into a metal pole.            | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 14            | Left            | Yes                          | Few days A piece of glass fell on the left side of the head when dismantling a conservatory. | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Incidental aneurysm |
| 15            | Left            | Yes                          | Immediate Assaulted by a prisoner with a metal mop on the left cheek.                   | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 16            | Left            | Indeterminate                | Immediate Left side of head and neck was hit by an object falling from a building.      | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 17            | Unclear         | Indeterminate                | Few hours Involved in road traffic accident; was run over by a car while riding a motorcycle. | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 18            | Left            | Yes                          | 3 hours Involved in road traffic accident but no further details available.              | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 19            | Left            | Yes                          | Few hours Fell off the bed and hit the corner of left eye on table.                     | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 20            | Left            | Yes                          | Immediate Bashed her head against the corner of a desk.                                 | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 21            | Unclear         | Indeterminate                | Few hours Involved in road traffic accident: collision with a car while riding a motorcycle. | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 22            | Right           | Yes                          | 1 day Root canal treatment of a right upper tooth followed 7 days after by insertion of crown. | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 23            | Left            | Yes                          | 3 days Dental extraction with dislocation of the jaw.                                   | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 24            | Right           | Yes                          | 7 days Lower right dental extraction.                                                   | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 25            | Left            | Yes                          | Few days Upper left dental extraction.                                                  | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |
| 26            | Bilateral       | Indeterminate                | 24 hours Four wisdom teeth extraction.                                                  | Loss of consciousness: --, Amnesia: --, Skin bruise or laceration: Normal             |

CH, cluster headache; NA, not available.
that patients with PTH-CH were more likely to have the chronic variant of CH, parietal site of pain, prominent cranial autonomic features particularly ptosis and eyelid oedema, intractability to preventive treatments, and have chronic migraine. A multivariate logistic regression model comparing the 21 patients with PTH-CH with the 553 patients with primary CH confirmed that patients with PTH-CH were more likely to have a family history of CH, the chronic variant of CH, temporal and parietal site of pain, prominent cranial autonomic features (particularly eyelid oedema, miosis, rhinorrhoea and facial sweating), restlessness, and intractability to acute and preventive treatments, as well as associated chronic migraine. These findings suggest that PTH-CH has a distinct clinical phenotype with more severe CH phenotype that is less responsive to treatments compared with primary CH. Furthermore, it implies that PTH-CH may have an alternative pathophysiological mechanism with its own evolutive profile.

In primary CH, wide activation of ipsilateral trigeminal nociceptive pathways, involving the trigeminal-autonomic reflex, leads to central activation through the trigeminal nucleus caudalis and the superior salivatory nucleus in the brainstem. In contrast, it is suggested that PTH results from more localised changes in the trigeminal pathway due to direct damage at the site of trauma. Factors including axonal injury, reduced cerebral circulation and the inappropriate release of local

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**Table 3** Univariate analysis results of comparison between PTH-CH and primary CH (control cohort)

|                     | PTH-CH (n=21) | Control cohort (n=553) | P value |
|---------------------|---------------|------------------------|---------|
| Demographics        |               |                        |         |
| Age (years)         | 49.3±11.9     | 48.8±12.4              | 0.56    |
| Gender (male/female)| 15/6          | 379/174                | 0.77    |
| Follow-up duration (years) | 6.47±3.0    | 6.04±2.8               | 0.43    |
| Age at onset (years) | 32.9±14.4     | 31.3±13.6              | 0.56    |
| Family history of CH| 4 (19.0)      | 50 (9.0)               | 0.12    |
| Headache diagnosis  |               |                        |         |
| CH                  |               |                        |         |
| ECH and/or PECH     | 4 (19.1)      | 274 (49.5)             | 0.006   |
| CCH and/or PCCH     | 17 (80.9)     | 279 (50.4)             |         |
| Associated migraine |               |                        |         |
| Episodic migraine   | 5 (23.8)      | 99 (17.9)              | 0.49    |
| Chronic migraine    | 4 (19.0)      | 42 (7.6)               | 0.05    |
| Duration and frequency of attacks |           |                       |         |
| Usual duration (min) | 97.8±56.0   | 90.8±64.0              | 0.44    |
| Average frequency per day | 3.0±1.5      | 2.8±2.1                | 0.08    |
| Laterality          |               |                        |         |
| Strictly unilateral  | 16 (76.1)     | 444 (80.2)             | 0.64    |
| Side variable       | 5 (23.8)      | 91 (16.4)              | 0.37    |
| Bilateral           | 0             | 18 (3.2)               | 0.4     |
| Site and referred pain |           |                        |         |
| Orbital/retro-orbital | 11           | 398                    | 0.05    |
| Frontal             | 6             | 176                    | 0.75    |
| Temple              | 11            | 267                    | 0.71    |
| Parietal            | 8             | 89                     | 0.008   |
| Occiput             | 5             | 111                    | 0.67    |
| Cranial autonomic features and restlessness |           |                        |         |
| Ptosis              | 16            | 304                    | 0.05    |
| Eyelid oedema       | 12            | 192                    | 0.03    |
| Conjunctival injection | 15          | 365                    | 0.6     |
| Miosis              | 1             | 22                     | 0.85    |
| Lacrimation         | 16            | 428                    | 0.89    |
| Nasal blockage      | 14            | 320                    | 0.42    |
| Rhinorrhoea         | 13            | 330                    | 0.83    |
| Facial sweating     | 14            | 265                    | 0.09    |
| Facial flush        | 9             | 208                    | 0.63    |
| Aural fullness      | 3             | 86                     | 0.87    |
| Restlessness        | 20 (95.2)     | 428 (83.9)             | 0.06    |
| Response to medical treatment |           |                        |         |
| Acute treatment     |               |                        |         |
| Intractable         | 2             | 16                     | 0.23    |
| Indeterminate       | 4             | 130                    |         |
| Responsive          | 16            | 407                    |         |
| Preventive treatment|               |                        |         |
| Intractable         | 9             | 89                     | 0.002   |
| Indeterminate       | 8             | 210                    |         |
| Responsive          | 4             | 254                    |         |

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**Table 4** Results of multivariate logistic regression model comparing post-traumatic headache with cluster headache phenotype (n=21) and primary cluster headache (control cohort; n=553)

| Predictive factor | OR     | 95% CI        | P value |
|-------------------|--------|---------------|---------|
| Family history of cluster headache | 3.32   | 1.31 to 8.63  | 0.012   |
| Chronic cluster headache phenotype | 3.29   | 1.70 to 6.49  | <0.001  |
| Temporal location | 2.04   | 1.10 to 3.84  | 0.024   |
| Parietal location | 14.82  | 6.32 to 37.39 | <0.001  |
| Presence of eye oedema | 5.79   | 2.57 to 13.82 | <0.001  |
| Presence of miosis | 11.24  | 3.21 to 41.34 | <0.001  |
| Presence of rhinorrhoea | 2.65   | 1.26 to 5.86  | 0.013   |
| Presence of facial sweating | 2.53   | 1.33 to 4.93  | 0.005   |
| Restlessness       | 4.63   | 1.16 to 22.19 | 0.039   |
| Associated chronic migraine | 10.35  | 3.96 to 28.82 | <0.001  |
| Intractable to acute treatment | 12.34  | 2.51 to 64.73 | 0.002   |
| Intractable to preventive treatment | 16.98  | 6.88 to 45.52 | <0.001  |

**Figure 1** Estimated OR in log-10 scale of each selected item entered into the logistic regression model with significant result (n=17). Eventually, we used the built-in ROSE.eval function in order to estimate our model accuracy. The ROSE.eval function implemented a ROSE version of holdout: the logistic regression was fitted on one sample generated by ROSE and tested on the original data set. The threshold for the logistic regression was set to 0.5. It turned out that the area under the curve was 0.874, which shows the accuracy of the estimated model. CCH, chronic cluster headache; CH, cluster headache.
neurotransmitters are likely to play a role in the initial emergence of PTH-CH. Consistent with previous reports, there was a propensity for referred pain in the parietal and temporal regions during PTH-CH attacks in our cohort. This likely reflects localised changes. Furthermore, the majority of patients with strictly unilateral headache reported pain on the side ipsilateral to the injury. Although the pain distribution may lead to attribution to some event in the past, this is consistent with previous findings and supports the hypothesis of peripheral involvement in PTH-CH pathogenesis via direct damage to local nociceptive structures.

Nevertheless, diffuse changes such as excessive neuronal depolarisation and the release of excitotoxic neurotransmitters may underpin the pathogenesis of PTH-CH. The sensitisation of central trigeminal neurons in PTH as a consequence of the initial trauma-related inflammatory process within the cranial meninges and the calvarial periosteum may also be involved. During primary CH attacks, the ipsilateral cranial autonomic features testify of cranial parasympathetic activation and sympathetic hypofunction, due to a central disinhibition of the trigeminal autonomic reflex. The more frequent eyelid oedema, miosis, rhinorrhoea and facial sweating in PTH-CH compared with primary CH in our study may reveal a marked disinhibition of pain pathways after trauma. Such long-term modulation of central pain pathways in CH following trauma would also explain the vast majority of chronic variant found in our study. Indeed, more than 80% of patients with PTH-CH suffered from the chronic variant and 15 of them developed the chronic form at onset, without any intermittent pain-free period. This further supports a continuous sensitivity to common headache triggering factors. With a chronic migraine phenotype co-occurred in 19% (4 of 21) of our cohort, exceeding the estimated 3% incidence in the general population and reaching the type co-occurred in 19% (4 of 21) of our cohort, exceeding the estimated prevalence of CH of 1.2% in the relatives, exceeding the estimated prevalence of CH of 1.2% in the first-degree relatives in patients who strictly fulfil the ICHD criteria for both PTH and CH, allowing us to consider our conclusions as strongly reliable. An association between head injury and CH has already been described in the past, but most injuries were quite remote from the first CH attack. The definition of PTH implies a close temporal relationship, established as the occurrence of headache within 7 days after head trauma. This stipulation might be somewhat arbitrary but yields a stronger evidence of causation, leading to a higher specificity of the ICHD criteria.

Indeed, a high proportion of patients with CH sustained head injury several years prior to CH onset, suggesting an association between trauma and CH, which goes beyond the rare occurrence of PTH-CH cases, thus raising the hypothesis of distinctive lifestyles in patients with CH. In conclusion, this series is the first to describe in detail the specific clinical characteristics of PTH-CH. We demonstrated that PTH-CH is more likely to present as chronic form, with marked cranial autonomic features and temporoparietal location of attacks in patients with family history of CH. They have a considerably higher risk of intractability to treatment and associated chronic migraine. This unique evolutive profile possibly reflects sensitisation of the pain neuromatrix and hypothalamus following trauma.

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