Risk factors and outcomes associated with post-traumatic headache after mild traumatic brain injury

Tansel Yilmaz, ¹ Gerwin Roks, ¹ Myrthe de Koning, ² Myrthe Scheenen, ² Harm van der Horn, ² Gerben Plas, ³ Gerard Hageman, ³ Guus Schoonman, ¹ Jacoba Spikman, ² Joukje van der Naalt ²

ABSTRACT

Objectives To determine the prevalence and potential risk factors of acute and chronic post-traumatic headache (PTH) in patients with mild to moderate traumatic brain injury (TBI) in a prospective longitudinal observational multicentre study. Acute PTH (aPTH) is defined by new or worsening of pre-existing headache occurring within 7 days after trauma, whereas chronic PTH (cPTH) is defined as persisting aPTH >3 months after trauma. An additional goal was to study the impact of aPTH and cPTH in terms of return to work (RTW), anxiety and depression.

Methods This was a prospective observational study conducted between January 2013 and February 2014 in three trauma centres in the Netherlands. Patients aged 16 years and older with a GCS score of 9–15 on admission to the ED, with loss of consciousness and/or amnesia were prospectively enrolled. Follow-up questionnaires were completed at 2 weeks and 3 months after injury with the Head Injury Symptom Checklist, the Hospital Anxiety and Depression Scale and RTW scale.

Results In total, 628 patients were enrolled in the study, 469 completed the 2-week questionnaire (75%) at 2 weeks and 409 (65%) at 3 months. At 2 weeks, 238 (51%) had developed aPTH and at 3 months 95 (23%) had developed cPTH. Female gender, younger age, headache immediately at the ED and CT scan abnormalities increased the risk for aPTH. Risk factors for cPTH were female gender and headache at the ED. Patients with cPTH were less likely to have returned to work than those without cPTH (35% vs 14%, P=0.001). Patients with aPTH and cPTH more often report anxiety (20% and 28%, P=0.001) and depression (19% and 28%, P=0.001) after trauma in comparison with the group without PTH (10% anxiety and 8% depression).

Conclusions PTH is an important health problem with a significant impact on long-term outcome of TBI patients. Several risk factors were identified, which can aid in early identification of subjects at risk for PTH.

INTRODUCTION

Mild traumatic brain injury (mTBI) accounts for at least 75%–90% of all TBIs worldwide.¹ ² Most patients with mTBI recover within weeks to months without specific therapy. A subgroup of patients, however, continues to experience disabling symptoms (15%–20%) in physical, behavioural and cognitive domains, which may interfere with return to work (RTW) or resumption of social activities.³ ² Headache is one of the most common reported complaints after TBI and may have profound impact on functional outcome.⁴ ⁵ In retrospective studies, the prevalence of post-traumatic headache (PTH) ranges between 30% and 90%.⁶ ⁷

PTH is classified as a secondary headache syndrome in the International Classification of Headache Disorders. This classification is primarily based on time of onset after TBI and chronicity of headache.⁸ Acute PTH (aPTH) is defined as newly developed headache or worsening of a pre-existing headache within 7 days after trauma, which is mostly self-limiting. If the headache persists for more than 3 months after injury, it is defined as chronic PTH (cPTH). Reported risk factors for both aPTH and cPTH are female gender, pre-existing migraine, history of psychiatric disorders, low socioeconomic status, low education level, medication overuse and short duration of post-traumatic amnesia (PTA).⁹ ¹⁰ ¹¹ ¹²

The aims of this study were to assess the prevalence and risk factors of aPTH and cPTH and their effect on outcome in patients with mild to moderate TBI. In addition, possible predictive factors for the transition from acute to cPTH were investigated.

Patients and methods

Study design

A prospective longitudinal observational multicentre study was conducted between January 2013
Definition of acute or chronic post-traumatic headache

Headache was regarded as present when it was reported on the Head Injury Symptom Checklist (HISC). APTH was measured at 2 weeks and defined as persisting aPTH 3 months after trauma; if patients had not reported aPTH but only reported headache at 3 months, this was not classified as cPTH. To compare patients who had developed PTH with those who had not, patients were separated into three groups. The aPTH group were those patients who had reported aPTH but not cPTH. The cPTH group were those who reported both aPTH and cPTH. These two groups were compared with the group of patients who did not report PTH.

Questionnaires

The following questionnaires were applied at 2 weeks and 3 months, and not on their initial ED attendance.

The HISC: The HISC contains the 21 most commonly described post-traumatic complaints, including headache. The questionnaire is described in detail elsewhere (see online supplementary file). It is derived from the Rivermead Post-concussion Symptoms Questionnaire, which is the most common measure for post-traumatic complaints. For all 21 complaints, a preinjury and a current symptom level was indicated. Values range from 0 to 2 (0=never, 1=sometimes, 2=often). The total number of complaints (range 0–21) and the severity of complaints (range 0–42) can be determined. For analysis of PTH, scores for headache were dichotomised; no PTH (value=0) and in case of PTH (value=8). For analysis of PTH, scores for headache were dichotomised into ‘normal CT scan’ (category I) and ‘abnormal CT scan’ (categories II–VI).

Data assessment

Baseline data included age, gender, medical history, education level, state of employment before injury, presence of LOC, PTA, headache at the ED, trauma mechanism and duration of hospital admission. A non-contrast CT scan (Siemens Somatom 64) was performed when necessary as part of the clinical care and rated by an experienced radiologist. CT scan results were classified using the Marshall classification, comprising six categories (Box 1). For analysis, data was dichotomised as to extent patients have resumed to their work: (1) previous work or study resumed; (2) previous work or study not resumed. The following questionnaires were applied at 2 weeks and 3 months, and not on their initial ED attendance.

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resumed but with lower demands or part time; (3) previous work or study not resumed; (4) initially started working after injury but currently not working and (5) unemployed. For analysis, a dichotomy was applied: ‘RTW’ (categories 1–2) and ‘no RTW’ (categories 3–5).

### Statistical analysis

Data were analysed with the statistical package for the social sciences (IBM SPSS V.22). Parametric (Student’s t-test) or non-parametric (Mann-Whitney U test) tests were used for continuous variables; frequency analysis was performed using Pearson $\chi^2$ tests. Univariate and multiple logistic regression analysis were used to assess the possible risk factors for aPTH and cPTH. For multiple regression analysis all variables with a P value <0.20 in the univariate analyses were included in the model. The model was subsequently simplified by excluding the least significant variable until only significant variables were present in the model.

### RESULTS

After screening at the ED, 848 patients were eligible for inclusion. Of these patients, 93 (11%) declined participation and after discharge an additional 127 (15%) could not be traced, leaving 628 patients for analysis (figure 1). The response rate was 75% (n=469) at 2 weeks and 65% (n=409) at 3 months. The mean age of the total cohort was 45 years (SD ±20) with 37% women (mean age 47 years) and 63% men (mean age 44 years). The median GCS on admission was 15 (range 10–15), and 77% had transient LOC and PTA after trauma. Headache at the ED was reported by 45% of the total cohort. CT scan abnormalities were present in 15% of cases.

### Acute and chronic PTH

At 2 weeks, aPTH was reported by 238 (51%) of patients, and at 3 months, 95 (23%) experienced cPTH. Of all patients with aPTH, 40% (n=95/238) had cPTH. Patient characteristics for aPTH and cPTH patients are presented in table 1.

### Missing population

Table 2 shows comparison of responders (n=409) and non-responders (n=219) at 3 months. Non-responders were significantly younger, had fewer CT scan abnormalities, less amnesia and shorter duration of hospital admission. We also compared the initial loss to follow-up cohort (n=60) with the second loss to follow-up cohort (n=60). No significant differences were present regarding age, education, severity of injury, amnesia, duration of hospital stay and CT scan abnormalities.

### Risk factors

Univariate analyses (table 3) identified potential risk factors for developing PTH (P≤0.05). For aPTH, these were female gender

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### Table 1 Demographics and characteristics in patients with acute and chronic PTH

<table>
<thead>
<tr>
<th>Time</th>
<th>Category</th>
<th>N (%)</th>
<th>aPTH</th>
<th>Without aPTH</th>
<th>P value (95% CI)**</th>
<th>cPTH</th>
<th>Without cPTH</th>
<th>P value (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td></td>
<td>469</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>aPTH</td>
<td>238</td>
<td>231</td>
<td>231 (49)</td>
<td>0.01 (0.03 to 0.20)</td>
<td>50</td>
<td>105 (53)</td>
<td>0.01 (0.08 to 0.30)</td>
</tr>
<tr>
<td></td>
<td>Without aPTH</td>
<td>231</td>
<td>231 (49)</td>
<td>0.005 (1.52 to 8.58)</td>
<td>46</td>
<td>48</td>
<td>0.30 (-1.95 to 7.03)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td>409</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cPTH</td>
<td>95</td>
<td>95</td>
<td>95 (23)</td>
<td>0.00 (0.08 to 0.30)</td>
<td>26</td>
<td>106 (27)</td>
<td>0.00 (0.08 to 0.30)</td>
</tr>
<tr>
<td></td>
<td>Without cPTH</td>
<td>314</td>
<td>314 (77)</td>
<td>0.00 (1.52 to 8.58)</td>
<td>46</td>
<td>48</td>
<td>0.30 (-1.95 to 7.03)</td>
<td></td>
</tr>
</tbody>
</table>

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*Most of patients included had moderate TBI.

**95% CI for the difference between aPTH versus without aPTH and cPTH versus without cPTH.

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All values are reported as number (N) and percentages (%) if not indicated otherwise. Only 17 patients had moderate TBI. Education was categorised in basic, middle and high education group.
(OR 1.6), headache at the ED (OR 2.4) and CT scan abnormalities (OR 2.7). Factors that decreased the risk for aPTH were low GCS (OR 0.8). Potential risk factors for developing cPTH after 3 months that can be determined at the ED were female gender (OR 1.6) and headache at ED (OR 1.7). Protective factors for cPTH were LOC (OR 0.4).

With multiple regression analyses, risk factors were identified that were independently associated with PTH (Table 4). For aPTH, female gender (OR 1.7), headache at ED (OR 2.1) and CT scan abnormalities (OR 3.1) were associated with a higher risk. For cPTH, female gender (OR 2.1) and headache at ED (OR 1.6) were associated with a higher risk, while LOC (OR 0.4) was associated with a lower risk of cPTH.

**Association of PTH with outcome**

Table 5 reports RTW levels, anxiety and depression for both aPTH and cPTH patients. Both groups had significantly higher scores for anxiety and depression when compared with patients without PTH. Regarding RTW, the cPTH group showed a significant lower level of work resumption compared with patients without cPTH (35% vs 14%, respectively, P=0.001).

**DISCUSSION**

In this prospective study from three trauma centres, over half of minor TBI patients developed aPTH and nearly a quarter cPTH. Our study showed that patients with PTH, both acute and chronic, more often report anxiety and depression. Patients with cPTH were also significantly less likely to RTW at 3 months.

The reported prevalence in literature for aPTH and cPTH ranges 31%–96% versus 8%–58%, respectively. An important explanation for this large variation is the variety of applied definitions for aPTH and cPTH. In the current study for example, the prevalence for cPTH based on the total patient group was 23% compared with 40% (95/238) when the calculation was based on patients that transitioned from aPTH to cPTH.

Although headache is one of the most common reported post-traumatic complaints, its association with psychological and functional outcome is not clear. Persistent complaints after trauma contribute significantly to loss of productivity and health care-related costs although this is largely associated with severe TBI. Most patients with mild TBI resume work within 1 to 3 months after injury, with approximately 60%–70% regaining their full-time job within 6 months. However, even those who resumed their work reported complaints like headache, irritability, forgetfulness and poor concentration. In these studies, the percentage of patients with incomplete RTW seems to increase with injury severity and number of complaints. Post-traumatic complaints like fatigue, headache and poor memory have been found to be among the most frequent reported complaints even years after injury and associated with limitations in daily functioning and lower levels of life satisfaction.

In our study, 35% of patients with cPTH did not RTW 3 months after injury, which is comparable to other studies. Patients with headache were less likely to have returned to work when compared with patients without headache. Although we did not

**Table 2** Demographics and characteristics in responders and non-responders at 3 months

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>P value (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>409</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>254 (62)</td>
<td>143 (65)</td>
<td>0.43 (-0.05 to 0.11)</td>
</tr>
<tr>
<td>Female</td>
<td>155 (38)</td>
<td>76 (35)</td>
<td>0.43 (-0.05 to 0.11)</td>
</tr>
<tr>
<td>Age mean (years)</td>
<td>48</td>
<td>40</td>
<td>&lt;0.001 (-10.7 to -4.22)</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>34 (9)</td>
<td>10 (11)</td>
<td>0.52 (-0.01 to 0.07)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>0.25 (-0.17 to 0.10)</td>
</tr>
<tr>
<td>Basic</td>
<td>34 (9)</td>
<td>5 (6)</td>
<td>0.25 (0.12 to 0.06)</td>
</tr>
<tr>
<td>Middle</td>
<td>223 (56)</td>
<td>59 (65)</td>
<td>0.25 (0.60 to 0.51)</td>
</tr>
<tr>
<td>High</td>
<td>144 (36)</td>
<td>27 (30)</td>
<td>0.25 (0.41 to 0.31)</td>
</tr>
<tr>
<td>TLOC</td>
<td>320 (85)</td>
<td>163 (85)</td>
<td>0.89 (-0.03 to 0.11)</td>
</tr>
<tr>
<td>GCS at ED (median, range)*</td>
<td>15 (3–15)</td>
<td>15 (7–15)</td>
<td>0.68 (-0.14 to 0.20)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>329 (89)</td>
<td>156 (83)</td>
<td>0.05 (0.02 to 0.16)</td>
</tr>
<tr>
<td>Wounding skull/face</td>
<td>297 (74)</td>
<td>143 (68)</td>
<td>0.09 (-0.002 to 0.15)</td>
</tr>
<tr>
<td>Headache at ED</td>
<td>173 (48)</td>
<td>110 (58)</td>
<td>0.03 (-0.002 to 0.16)</td>
</tr>
<tr>
<td>CT scan abnormality</td>
<td>71 (18)</td>
<td>24 (12)</td>
<td>0.05 (0.01 to 0.12)</td>
</tr>
<tr>
<td>Injury mechanism</td>
<td>&lt;0.001 (0.11 to 0.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collision</td>
<td>108 (27)</td>
<td>44 (21)</td>
<td>&lt;0.001 (0.31 to 0.22)</td>
</tr>
<tr>
<td>Fall</td>
<td>263 (65)</td>
<td>115 (54)</td>
<td>&lt;0.001 (0.69 to 0.60)</td>
</tr>
<tr>
<td>Violence</td>
<td>15 (4)</td>
<td>41 (19)</td>
<td>&lt;0.001 (0.06 to 0.02)</td>
</tr>
<tr>
<td>Sports</td>
<td>4 (1)</td>
<td>4 (2)</td>
<td>&lt;0.001 (0.03 to 0.004)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (4)</td>
<td>10 (5)</td>
<td>&lt;0.001 (0.063 to 0.02)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>259 (64)</td>
<td>111 (51)</td>
<td>0.003 (0.05 to 0.21)</td>
</tr>
</tbody>
</table>

All values are reported as number (N) and percentages (%) if not indicated otherwise. Education was categorised in basic, middle and high education group. *Most of patients included had mild TBI, only 17 patients had moderate TBI. **95 for the difference between the responders and non-responders.

**Table 3** Risk factors for acute and chronic PTH in univariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>aPTH OR (95% CI for OR)</th>
<th>P value</th>
<th>cPTH OR (95% CI for OR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.6 (1.1 to 2.4)</td>
<td>0.01</td>
<td>2.2 (1.4 to 3.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99 (0.97 to 0.99)</td>
<td>0.01</td>
<td>0.99 (0.98 to 1.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>0.7 (0.3, 1.3)</td>
<td>0.20</td>
<td>1.0 (0.4, 2.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Education</td>
<td>1.1 (0.8 to 1.5)</td>
<td>0.60</td>
<td>1.3 (0.9 to 1.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>TLOC</td>
<td>0.9 (0.6 to 1.7)</td>
<td>0.90</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>GCS at ED</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.04</td>
<td>1.0 (0.8 to 1.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>PTA</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.60</td>
<td>1.2 (0.5 to 2.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Wounding skull/face</td>
<td>1.4 (0.9 to 2.2)</td>
<td>0.09</td>
<td>1.3 (0.7 to 2.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Headache at ED</td>
<td>2.4 (1.6 to 3.5)</td>
<td>&lt;0.001</td>
<td>1.7 (1.0 to 2.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>CT scan abnormalities</td>
<td>2.7 (1.6 to 4.6)</td>
<td>&lt;0.001</td>
<td>1.6 (0.9 to 2.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>1.1 (0.8 to 1.6)</td>
<td>0.60</td>
<td>0.7 (0.5 to 1.2)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

aPTH, acute post-traumatic headache; cPTH, chronic PTH; PTA, post-traumatic amnesia; PTH, post-traumatic headache; TLOC, transient loss of consciousness.
assess the direct influence of headache on work resumption, this finding might provide an argument for improved clinical monitoring immediately after discharge from the ED. With an early treatment of headache and concurrent reduction of all post-traumatic complaints, earlier resumption of work and other previous activities may be facilitated.

The response rate was 75% at 2 weeks and 65% at 3 months. This study had several limitations. Follow-up was incomplete: The response rate was 75% at 2 weeks and 65% at 3 months. Because non-responders were younger with significant fewer CT scan abnormalities, less PTA and shorter duration of hospital admission suggesting less severe injury, which might have led to overestimation of the occurrence of PTH. However, since neither age nor CT findings were associated with cPTH, we believe this estimate to be realistic. We included only those patients with TBI who were seen at the ED. It has been estimated that around a quarter of patients with TBI visit the ED after their injury, patients who become unemployed after TBI showed more symptoms of anxiety and depression than those who resumed their activities after mTBI. It is unclear however whether PTH is a cause or symptom of anxiety and depression and whether RTW itself is a cause or an effect.

In the current study, the main risk factors for aPTH comprised female gender, younger age, presence of headache at the ED and CT scan abnormalities. Risk factors for developing cPTH were only female gender and presence of the headache in the ED. Female gender and CT scan abnormalities have also been identified as risk factors for PTH in previous studies. Lower educational level or psychiatric problems were not associated with a higher risk for aPTH or cPTH in contrast to other studies.

### Limitations

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CONCLUSION

PTH is a highly prevalent complaint after mild to moderate TBI, and risk factors for its development can be determined during the ED visit. A considerable proportion of patients develop aPTH and/or cPTH and this is associated with anxiety, depression and failure to RTW. It is important that increased awareness enables the identification of symptoms and risk factors for PTH to treat patients more effectively.

Correction notice This article has been corrected since it was published Online First. The name of the first author has been corrected.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Medical Ethical Committee of the UMCG.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We used all the data we have for this study.

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REFERENCES
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Emerg Med J 2017 34: 800-805 originally published online July 8, 2017
doi: 10.1136/emergmed-2015-205429

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