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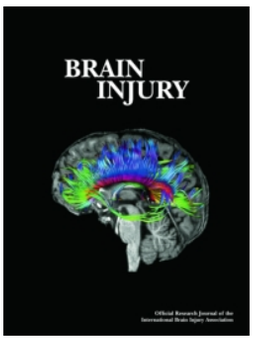

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Post-concussion symptoms three months after mild-to-moderate TBI: characteristics of sick-listed patients referred to specialized treatment and consequences of intracranial injury

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ABSTRACT

Objective: To present pre-injury, injury-related, work-related and post-injury characteristics, and to compare patients with and without traumatic intracranial abnormalities, in a treatment-seeking sample with persistent post-concussion symptoms (PPCS) after mild-to-moderate TBI.

Methods: Cross-sectional design in the context of a specialized TBI outpatient clinic. Eligible patients were aged 18–60 years, employed ≥ 50% at time of injury, and sick listed ≥ 50% at inclusion due to PPCS. Data were collected 8–12 weeks after injury through review of medical records, semi-structured interviews, questionnaires, and neuropsychological screening.

Results: The study included 116 patients, of whom 60% were women, and predominantly white-collar workers in full-time positions. Ninety-four percent had a mild TBI, and 23% had intracranial abnormalities. The full sample reported high somatic, emotional, and cognitive symptom burden, and decreased health-related quality of life. Patients with normal CT/MRI results reported higher overall symptom burden, while patients with intracranial abnormalities had worse memory function.

Conclusion: Injury severity and traumatic intracranial radiological findings should not be the sole ground for planning of rehabilitation service provision in patients with PPCS, as subjective complaints do not necessarily co-vary with these variables.

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Traumatic brain injury; concussion; persistent post-concussion symptoms; post-concussive symptoms; the rivermead post-concussion symptom questionnaire

Introduction

The estimated annual incidence rate of traumatic brain injury (TBI) in the European Union is approximately 2.5 million (1). Most injuries are classified as mild (mTBI), accounting for 70–90% of all TBIs (2). Most patients recover within the first days to weeks after a mTBI (3), but a substantial proportion of patients experience persisting symptoms. Persistent post-concussion symptoms (PPCS) usually consist of a cluster of somatic, cognitive, and emotional symptoms. The patients in this study have not been defined to necessarily have post-concussion syndrome, but to have post-concussion symptoms lasting at least 3 months.

The exact incidence of patients with PPCS is unclear due to a lack of a universally acknowledged definition and diagnostic criteria, but it is estimated to occur in approximately 5–15% of the patients after mTBI (4). However, studies have reported rates of PPCS after mTBI as high as 40–45%, depending on which criteria are applied (5–7). Our understanding of PPCS is somewhat controversial, partly because the symptoms that define it (e.g. headache, fatigue, sleep disturbances) are common in the general population (6).

PPCS comprises a combination of somatic, emotional, and cognitive symptoms typically including headache, fatigue, sleep disturbances, balance disturbances, irritability, emotional lability, and impaired concentration and memory (8–10). The duration and character of these symptoms represents a considerable burden to the patients, their families, and the healthcare system. Return to work is one of the main challenges after TBI (11), with success rates varying from 12 to 70% (12). Even patients with mTBI may struggle to reach complete return to work as long as twelve months after injury (13). Problems with reattaining pre-injury occupational status may lead to reduced social integration and quality of life (14).

Injury-related variables alone, such as loss of consciousness (LOC), post-traumatic amnesia (PTA), and neuroimaging findings, have limited value for predicting symptom burden (15,16). Several studies have also examined the differences between patients with confirmed intracranial injury seen on cerebral computer tomography (CT) or magnetic resonance imaging (MRI) (complicated mTBI) and those without (uncomplicated mTBI) (5,17). However, PPCS also frequently occurs in patients without traumatic radiological abnormalities

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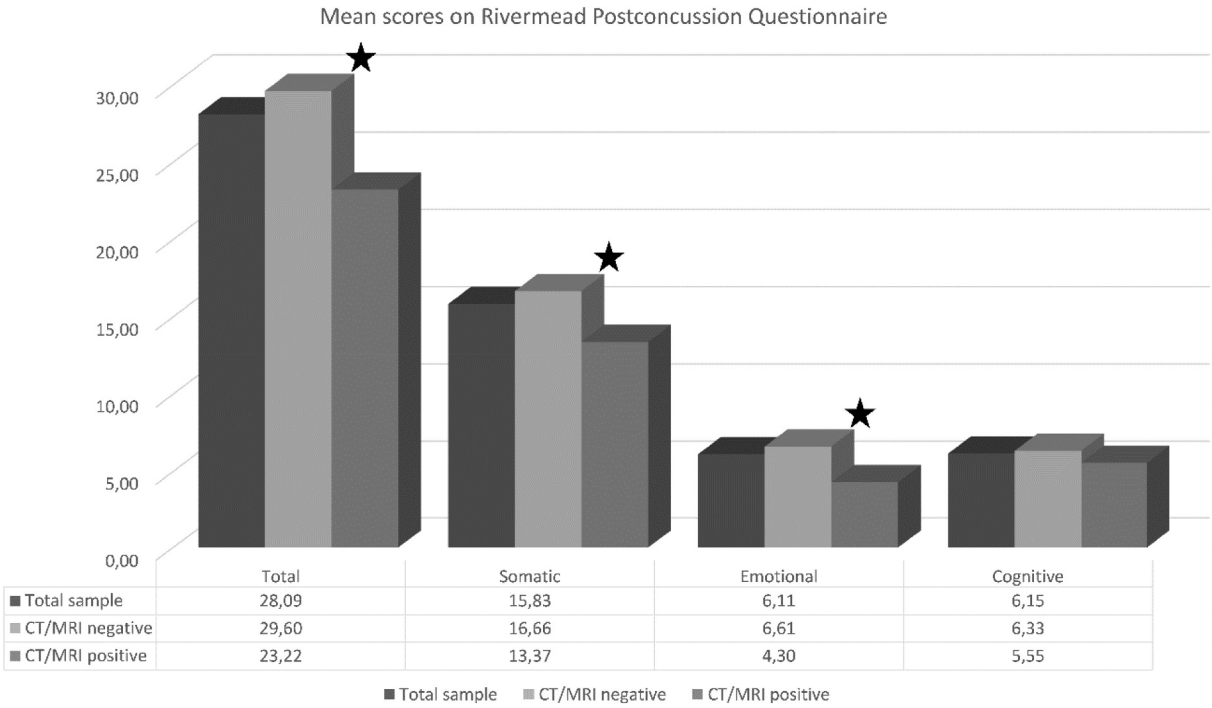

Figure 1. Mean scores on RPQ and its subscales from the total sample (green) and with the sample divided into patients without intracranial abnormalities (gray) and with intracranial abnormalities (blue). Stars mark significant differences between patients without and with intracranial abnormalities.

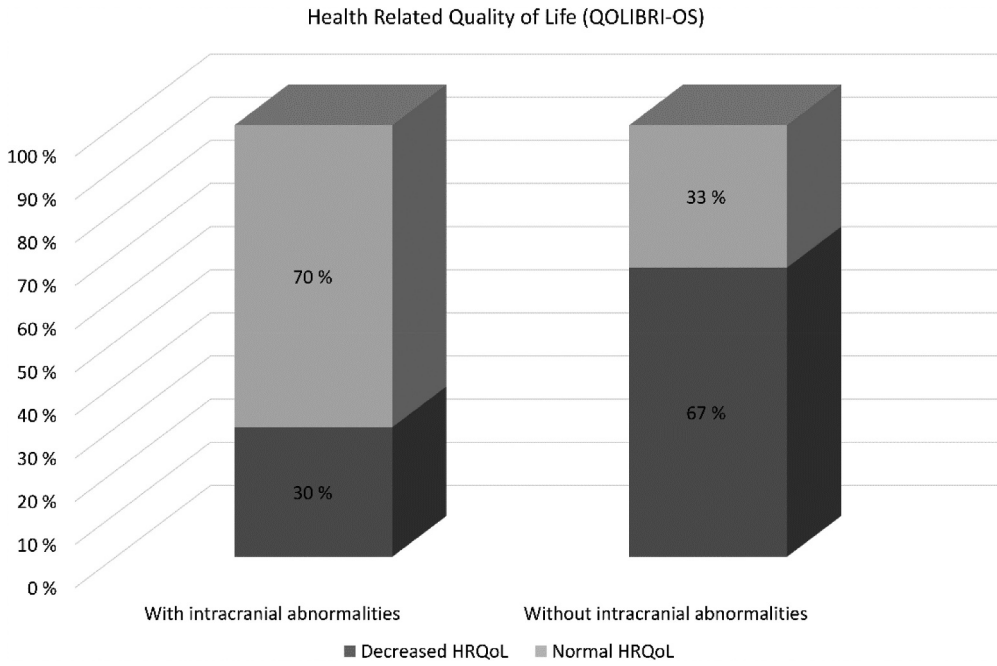

Figure 2. Health-Related Quality of Life as measured by QOLIBRI-OS, by patients with and without intracranial abnormalities.

(5,18). Some studies have shown lower levels of post-concussion symptoms in patients with uncomplicated mTBI compared to complicated mTBI and moderate TBI (5,19,20), while others have found no differences between the groups (17,21). Iverson et al. (16) found no significant difference in outcome when comparing complicated and uncomplicated mTBI, but effect sizes indicated more post-concussion and depressive symptoms in patients with uncomplicated mTBI. de Guise et al. (22) compared patients with and without radiological findings two weeks after injury and found more auditory and vestibular symptoms in the group with complicated mTBI, while the patients with uncomplicated mTBI reported more post-concussion symptoms. These findings are perplexing as it is intuitively expected that patients with more severe injuries also would report more symptoms.

Considering the complexity and lack of clear associations between injury-related variables and symptom burden (23), it is increasingly common to view PPCS from a biopsychosocial

perspective (24) where biological (i.e. brain injury), psychological (i.e. emotional state and personality), and social (i.e. participation and social support systems) factors are seen as interacting both in symptom development and maintenance (24). In this perspective, all these factors are also viewed as potential targets for intervention, as opposed to just biomedical factors.

The literature regarding predictors of PPCS is still conflicting, but in accordance with the biopsychosocial model, commonly identified prognostic factors include female gender, age, previous history of psychiatric problems, premorbid migraine/headache, previous TBIs, presence of LOC and PTA, and a higher symptom load in the acute phase (15,25–28).

Patients with PPCS represent a heterogeneous population and there is still uncertainty as to what typically characterizes these individuals. A better characterization of the population with PPCS is therefore important for several reasons. Identifying patients at risk will help medical personnel in stratification of patients to early interventions. Several larger studies provide epidemiological descriptions of patients with mild and moderate TBI. However, there is still a paucity of data specifically describing patients that do not fully recover, and subsequently are not able to return to work. As most patients recover, prospective observational studies typically end up having very limited sample sizes for studying this population. We therefore lack critical knowledge about these patients, who are the ones that are typically referred to specialist clinics for treatment and rehabilitation (29).

This study describes the characteristics (demographic, premorbid, injury-related, work-related and self-reported symptoms) of a group of patients with PPCS who are sick-listed and treatment-seeking. All patients had post-concussion symptoms 8–12 weeks after mild-to-moderate TBI and had not been able to return fully to preinjury occupational levels. The main aim of the study was to describe socio-demographics, pre-, and injury-related characteristics, and investigate differences in post-injury symptom burden between patients with and without traumatic intracranial injury.

Methods

Study design

This study presents baseline data from patients enrolled in an ongoing RCT, which examines the effect of a combined cognitive and vocational intervention in patients with mild-to-moderate TBI, who have not returned to work 8–12 weeks post-injury due to post-concussive symptoms (ClinicalTrials.gov: NCT03092713). A detailed description of the RCT study design can be found in Howe et al. (30). The Regional Committee for Medical and Health Ethics in South-Eastern Norway has approved the study (2016/2038). In the current study, we explore the characteristics of the sample *before randomization* to treatment or control group.

Study setting

Patients were referred from the neurosurgical department at Oslo University Hospital (OUH), their general practitioner, or the municipalities' emergency departments, to follow-up at a specialized TBI-outpatient clinic at the Department of Physical Medicine and Rehabilitation (PMR), OUH, between July 2017 and April 2019. OUH is the Level I trauma referral center of southeast Norway. It has a population base of approximately 2.9 million and includes the city of Oslo with 693.000 inhabitants (31), thus providing a sample that is both rural and urban, with predominantly Caucasian background. Approximately 600 patients with TBI of all severities are referred to the outpatient clinic annually.

Inclusion criteria and study participants

Patients were considered eligible if they were aged between 18 and 60 years; had sustained a mild or moderate TBI in the previous 8–12 weeks; resided in Oslo or Akershus County; worked at least 50% at time of injury; and were sick listed 50% or more due to post-concussion symptoms at time of inclusion, as assessed by the Rivermead Post-Concussion Symptoms Questionnaire (32). Severity of TBI was defined using criteria from the American Congress of Rehabilitation Medicine (ACRM) (33); Glasgow Coma Scale (GCS) 10–15 (34), LOC lasting less than 24 hours and PTA lasting less than 7 days. Five hundred and ninety-two potential study participants were identified, of whom 432 were not eligible and five were not included for other reasons. The most common reason for not being eligible was too long time since injury (n = 138), age <18 or >60 (n = 81), sick leave percentage <50% (n = 50) or not working at the time of injury (n = 41). Thirty-nine patients declined participation. Due to ethical considerations, the reason why they chose not to participate was not established. This resulted in 116 patients with mild and moderate TBI being included in the RCT, and thus in the current analysis. Patients were categorized depending on whether or not they had evidence of acute traumatic intracranial abnormalities on CT or MRI images of the head. This categorization was performed regardless of injury severity (mild/moderate) based on ACRM criteria, and we only included abnormalities that were related to the most recent trauma. According to Scandinavian guidelines, patients with mTBI and intracranial abnormalities should be considered, and treated, as having a moderate TBI (35). Exclusion criteria were a history of severe neurological or psychiatric illness, active substance abuse, or the inability to speak and read Norwegian.

Procedures

Potential participants were identified during follow-up at the outpatient clinic at OUH where a PMR physician provided them with oral and written information about the study and retrieved written consent. Alternatively, they were informed about the study, had a period of deliberation, and later consented via telephone contact. All consenting participants were invited to a baseline assessment 8–12 weeks after injury.

Measures

The assessment consisted of a clinical interview regarding preinjury, injury-, and work-related information,

questionnaires concerning post-concussion and emotional symptoms, and a neuropsychological screening.

Preinjury and work-related characteristics

Preinjury information was collected using a semi-structured interview where the following variables were recorded: age, sex, level of education, relationship status, number of children living at home, previous illnesses and TBIs, employment status and duration, type of occupation, and status of sick listing at the time of inclusion. Occupation type was divided into white collar (non-manual labor) or blue collar (manual labor). Employment status included full- or part-time position.

Injury-related measures

Results of CT/MRI caput and whether the participants had been hospitalized were retrieved from medical records. A medical doctor estimated Abbreviated Injury Scale-Head (AIS-H) (36) based on injury-related information from medical records according to the following definition: 1 – minor (no treatment needed), 2 – moderate (outpatient treatment), 3 – serious (non-ICU admission), 4 – severe (ICU observation and/or basic treatment), 5 – critical (requires intubation, mechanical ventilation, or vasopressors for blood support), 6 – unsurvivable. The remaining injury-related variables were collected from medical records and supplemented with information from the patient interview, if needed. These included mechanism of injury (falls, traffic accidents, sports, violence, or exposure to inanimate objects), level of consciousness shortly after the injury measured by GCS, duration of LOC and PTA, and whether it was a work-related injury. Information regarding alcohol and drug use at the time of injury was collected from medical records based on results of ethanol blood tests in the emergency department, physician verification following patient examination, or otherwise relied on self-reported information in the interviews.

Measures of post-injury symptoms and level of functioning

Post-concussion symptoms were measured with The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (32), where patients are asked to rate 16 post-concussion symptoms on a five-point Likert scale from 0 to 4, where 0 = "Not experienced," 1 = "No longer a problem," 2 = "Mild problem," 3 = "Moderate problem" and 4 = "Severe problem." The mean was calculated by adding all scores of 2–4 and dividing by number of items. The total mean is reported, along with the percentage of patients who scored ≥3 (indicating a moderate or severe problem) on single items.

Fatigue and sleep

Fatigue was measured using the Fatigue Severity Scale (FSS) (37), where patients score perceived fatigue during the last 2 weeks on 9 items with a 5 level Likert scale with higher scores indicating higher levels of fatigue. The percentage of patients reporting a score corresponding to moderate or severe fatigue are reported (i.e. ≥4) (38).

Insomnia was measured with the 7 – item Insomnia Severity Index (ISI) (39) that has a 5-point scale ranging from 0 ("none") to 4 ("very") which gives a total of 0–28 points with higher scores indicating more severe perceived insomnia. The established cut-off score is 8 points. Percentage of patients scoring above the cut-off is reported.

Emotional symptoms

Patient Health Questionnaire-9 (PHQ-9) (40) measured depressive symptoms in the sample with nine items that are scored from 0 ("not at all") to 3 ("nearly every day"). Percentage with a total score ≥10, indicating moderate to severe depressive symptoms is reported.

Generalized anxiety was measured using Generalized Anxiety Disorder-7 (GAD-7) (41) that has seven items, which are scored from 0 ("not at all") to 3 ("nearly every day"). A score ≥10 indicates moderate to severe generalized anxiety symptoms. The percentage of the sample reporting a sum of 10 or higher is reported.

The Posttraumatic Symptom Scale-10 (PTSS-10) (42) was used to measure post-traumatic symptomatology. It is a 10-item scale where the patients score on a Likert scale from 1 ("not at all/never") to 7 ("very often"). The percentage of patients reporting scores of 35 or more, corresponding to the clinical cutoff, is reported.

In this study, the internal consistency of the PHQ-9, GAD-7, and PTSS-10 was measured with Cronbach's alpha and was found to be good (Cronbach's α = 0.81, 0.88, and 0.86, respectively).

Health-related quality of life

The Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) (43) and EuroQol visual analog scale (EQ VAS) (44) were used to measure health-related quality of life (HRQoL). The QOLIBRI-OS consists of six items that are scored on a scale from 1 to 5, where 1 = "not at all satisfied", and 5 = "very satisfied." The cutoff for decreased quality of life on QOLIBRI-OS corresponds to a score below 52 (45). The mean score and proportional scoring below the cutoff is reported. With EQ VAS, the patients report their overall current health on a vertical visual analog scale from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). The overall mean score is reported as well as the percentage of the sample scoring below cutoff (i.e. <84) from a population, which is similar in age and socioeconomic status, but generally healthy (46).

Cognitive function

The Cognitive Failures Questionnaire (CFQ) (47) was used to document perceived frequency of experiencing cognitive failure. There are 25 items rated from 0 ("never") to 4 ("very often") on a Likert scale. The overall mean (SD) is reported.

In addition, the patients underwent a neuropsychological screening. An IQ estimate was derived from the following four subtests of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) (48): Matrix Reasoning, Block Design, Vocabulary, Similarities. Verbal learning and memory were measured with the California Verbal Learning Test-Second Edition (CVLT-II), including measures of total learning (trials

1–5), short- and long delay-free recall (49). Prospective memory was screened using Memory for Intentions Screening Test (MIST) (50). Processing speed and executive function were measured using the Color Word Interference Test (CWIT) and the Trail Making Test (TMT) from the Delis–Kaplan Executive Function System (D-KEFS) (51), Coding from the WAIS-IV (48) and Ruff 2 and 7 Selective Attention Test (52). Validity was assessed using the Forced Choice Recognition index from CVLT-II (49). Standardized scores are reported. The results were considered within normal range if the score was ±1 SD from the mean in the normative sample.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows v. 25 (53) or Stata v. 16 (54). Descriptive analyses were performed for preinjury-, injury-related and post-injury characteristics, reporting proportions (%), number (n), and using mean (SD) when variables were normally distributed, and otherwise median (IQR). Patients lacking cerebral neuroimaging were excluded from the analysis that compared patients with and without traumatic intracranial injuries. Two-sample t-tests were applied for normally distributed variables and Mann–Whitney U or Chi-squared test for skewed data, for continuous and categorical variables, respectively. Further, the two patient groups were entered as an explanatory variable and analyzed against the dependent variables representing symptom burden. Potentially confounding variables (status of intracranial abnormality, previous mTBI, and level of education) were chosen from the literature and explored with multiple linear regression analyses, where we tested the scores that significantly differed between the groups on t-test or Mann–Whitney U-test. The necessary assumptions, including multicollinearity, were examined before conducting the regression analyses. To check for internal validity, sensitivity analyses were performed using the models run with 1,000 bootstrap samples. Significance level was set to $p < .05$.

Results

Sociodemographic characteristics

The patients had a mean age of 42 years (SD 9.8), 60% were women, and mean years of education were 16 (SD 2.5). Sixty-six percent were married or cohabitants and 51% had one or more children living in the household (See Table 1).

The patients predominantly worked full time (89%) and had permanent positions (91%) in white-collar occupations (89%). The median duration of employment at current workplace was 4.25 years (IQR 9.25 years). At inclusion, 81% of the patients were sick listed between 80% and 100%.

Self-reported premorbid conditions

The sample reported a history of the following pre-morbid conditions: anxiety 5%, depression 15%, migraine/headache 20%, cardiovascular disease 10%, musculoskeletal disorder 15%, gastrointestinal disorder 13%, ADHD 0.9%, and dyslexia 6%. Forty-three percent reported that they had previously suffered from at least one mTBI, of which 16% reported sustaining two or more previous mTBIs.

Injury-related factors

Of the 116 included patients, 94% were classified as having a mild TBI and 6% had a moderate TBI. The median GCS score was 15 (IQR 0). The mean AIS head score was 1.8 (SD .9), approaching a moderate level of injury. Forty-six percent sustained additional injuries in other body regions than the head. The most common were injuries to the face (15%), upper limbs (13%), lower limbs (11%), or neck (11%).

The most common cause of injury was falls, followed by traffic accidents, exposure to inanimate objects, sports, and violence. Alcohol intoxication at the time of injury was found in 15% of the patients. Twenty-two percent of the patients were admitted to a hospital, with an average length of stay of 1.4 days (SD 3.8).

Evidence of intracranial traumatic abnormalities on CT/MRI caput was seen in 23% of the patients, with one-third of the abnormalities being traumatic subarachnoid hemorrhage.

Post-concussion symptoms

The overall mean score on the RPQ was 28 (SD 11), indicating moderate to severe post-concussion symptoms. Fatigue (75%), headache (64%), and noise sensitivity (54%) were most frequently reported as moderate or severe problems on the somatic subscale of RPQ (cutoff ≥3). The most frequently reported emotional symptoms (cutoff ≥3) were feeling frustrated or impatient (51%) and depressed or tearful (29%). Poor concentration (48%) and taking longer to think (42%) were the most frequently reported moderate or severe cognitive problems (cutoff ≥3).

Fatigue and sleep

Moderate or severe fatigue (38) was reported by 78% of the patients on FSS, and 71% (n = 77/108) reported any (subthreshold to severe) degree of insomnia on the ISI (39).

Emotional symptoms

Forty-three percent of the patients reported moderate-to-severe depressive symptoms on PHQ-9. Twenty percent reported moderate-to-severe anxiety symptoms on GAD-7, and 20% reported scores above the clinical cutoff value (>35) on PTSS-10.

Health-related quality of life

Results from QOLIBRI-OS (45) showed mean scores of 45.7 (SD 22) with 58% (n = 67/115) of the individual scores corresponding to decreased HRQoL (score < 52). Mean score on the EQ VAS was 54.1 (SD 18) with 97% (n = 111/114) reporting decreased HRQoL when comparing to a healthy Swedish population, in the same age range, who scored a mean of 84 (46).

Self-reported and performance-based cognitive function

The total mean on the CFQ was 39 (SD 15), which is comparable to healthy controls in other studies (60,6263). The mean IQ score for the sample was 111 (SD 14). Neuropsychological

Table 1. Demographic, preinjury and injury-related characteristics 8–12 weeks post-injury.

Variable	n	With intracranial abnormalities n(%)	Normal CT/ MRI n(%)	Total sample n (%)
Preinjury factors				
Age, mean (SD)	116	45 (9)	42 (9)	42 (9.8)
Sex, female	116	12 (43)	52 (55)	69 (56)
Education, mean (SD)	116	15 (3)	16 (2)	16 (2.5)
Married/Cohabitant	116	20 (74)	50 (57)	77 (58)
Child(ren) in household	116	14 (51)	40 (49)	59 (50)
Self-reported history of				
Anxiety	116	2 (6)	4 (4)	6 (4)
Depression	116	4 (14)	12 (14)	17 (14)
Migraine/Headache	116	7 (25)	14 (17)	23 (19)
Previous concussion	115	6 (21)	38 (47)	49 (42)
≥2 previous concussions		0 (0)	16 (19)	18 (15)
Other somatic diseases	116	17 (57)	42 (52)	57 (48)
Injury-related factors				
Cause of injury	115			
Falls		18 (59)	27 (33)	49 (42)
Traffic accidents		4 (14)	17 (20)	23 (19)
Sports		3 (10)	10 (12)	14 (11)
Violence		2 (6)	4 (4)	6 (4)
Exposure to inanemate objects		0 (0)	21 (25)	23 (19)
CT/MRI findings, traumatic		27 (100)	80 (100)	27 (22)
Injury severity by ACRM criteria	116			
Mild		21 (78)	79 (99)	109 (94)
Moderate		6 (21)	1 (1)	7 (5)
Loss of consciousness (LOC)	115			
< 30 min		15 (60)	21 (25)	37 (31)
30 min – 24 hours		3 (10)	0 (0)	3 (3)
No LOC		5 (18)	49 (61)	61 (52)
Not registered		3 (10)	10 (12)	14 (11)
Post-traumatic amnesia (PTA)	115			
<1 hour		10 (36)	23 (28)	35 (29)
1 hour – 24 hours		10 (36)	6 (7)	16 (13)
25 hours – 7 days		2 (6)	0 (0)	2 (2)
No PTA		5 (18)	39 (48)	51 (43)
Not registered		0 (0)	11 (13)	11 (9)
Injured at workplace	114	3 (10)	11 (13)	16 (13)
Under the influence of alcohol at time of injury	116	8 (29)	9 (10)	17 (14)

test measures of memory, learning, attention, mental speed, and executive functioning provided mean scores within the normal range at the group level (see Table 2). All participants scored 16/16 on the CVLT-II forced recognition test, indicating valid test results.

Comparison of patients with and without traumatic intracranial injury

There were significant differences between patients with and without traumatic intracranial injury in total scores on the RPQ ($t(105) = 2.7$, $p < .01$), PHQ-9 ($t(102) = 3.06$, $p < .01$), PTSS-10 ($U = 649$, $p = .01$), ISI ($U = 688$, $p = .04$), EQ VAS ($t(103) = -2.18$, $p = .03$) and QOLIBRI-OS ($t(100) = -3.9$, $p < .01$). The difference was consistent in the direction of patients with a negative CT/MRI reporting higher symptom burden than those with intracranial abnormalities. There were no significant differences between the groups with respect to self-reported symptoms of anxiety, fatigue, or cognitive failures.

Regarding neuropsychological functioning, patients with intracranial abnormalities performed significantly worse than those without on verbal short delay-free recall on the CVLT-II ($t(104) = 2.3$, $p = .02$). See Table 3.

Patients with and without intracranial abnormalities were compared regarding pre-injury variables to exclude potential confounders. History of previous mTBI (X^2 (1, N = 115) = 4.3, $p = .03$) and level of education ($U = 694$, $p < .01$) were significantly different between the groups. Patients without intracranial abnormalities reported a higher percentage of previous mTBIs (48% vs. 22%) and a higher level of education (16 vs. 15 years). The groups did not differ with respect to sex, age, or previous depression, anxiety, or migraine/headache.

Status of intracranial abnormality remained the only significant explanatory variable (when running multiple linear regression analyses with status of intracranial abnormality, previous mTBI, and level of education inserted as explanatory

Table 2. Results of neuropsychological screening.

Neuropsychological tests	Standardized score Mean (SD)	Neuropsychological tests	Standardized score Mean (SD)
Psychomotor speed		**Executive functions**	
TMT[a] 1, 2 and 3	11 (3)	TMT[a] 4	10 (2)
TMT[a] 5	12 (2)	CWIT[2] 3 and 4	11 (3)
CWIT[2] 1	9 (3)		
CWIT[2] 2	10 (3)		
Coding[3]	11 (3)		
Attention and concentration		**Verbal abilities**	
Ruff 2 & 7 Total speed[4]	58 (11)	Vocabulary[3]	10 (2)
Ruff 2 & 7 Total accuracy[4]	48 (7)	Similarities[3]	12 (3)
Learning and memory		**Visuospatial abilities**	
CVLT-II[5] Total learning	60 (3)	Matrix Reasoning[3]	13 (3)
CVLT-II[5] Short delay free recall	56 (9)	Block Design[3]	11 (2)
CVLT-II[5] Long delay free recall	56 (9)		
Prospective memory		**General ability index (GAI)[3]**	111 (13)
MIST[6] Total PMT	67 (28)		

[a]Trail Making Test (TMT) from the Delis–Kaplan Executive Function System (D-KEFS), [2]Color Word Interference Test, [3]Wechler Adult Intelligence Scale 4th Edition, [4]The Ruff 2 & 7 Selective Attention Test, [5]Verbal Learning Test – II, [6]Memory for Intentions Test – Prospective Memory Test, [I]T-test.

Table 3. Multiple linear regression analyses.

Variabel	F	p	R^2	Coeff.	Beta	SE	t	P>|t|	95% CI
RPQ[1]	(3, 103) = 3.16	**0.028**	0.08						
Radiological Findings (Yes)				−7.42	−0.3	2.56	−2.90	**0.005**	−12.5, −2.35
Previous mTBI[4] (Yes)				−3.06	−0.14	2.14	−1.43	0.156	−7.29, 1.18
Years of education				−0.15	−0.3	0.45	−0.33	0.742	−1.04, 0.74
PHQ-9[2]	(3, 100) = 3.22	**0.026**	0.08						
Radiological Findings (Yes)				−3.41	−0.31	1.11	−3.06	**0.003**	−5.62, −1.2
Previous mTBI[4] (Yes)				−0.52	−0.06	0.93	−0.56	0.574	−2.37, 1.32
Years of education				−0.08	−0.04	0.2	−0.42	0.673	−0.47, 0.31
PTSS-10[3]	(3, 99) = 3.47	**0.019**	0.1						
Radiological Findings (Yes)				−7.18	−0.32	2.32	−3.10	**0.003**	−11.8, −2.58
Previous mTBI[4] (Yes)				−3.08	−0.16	1.95	−1.58	0.117	−6.95, 0.79
Years of education				−0.41	−0.1	0.41	−1.00	0.321	−1.22, 0.41
Insomnia Severity Index	(3, 95) = 1.74	0.163	0.05						
Radiological Findings (Yes)				−3.50	−0.25	1.58	−2.21	0.029	−6.65, −0.36
Previous mTBI[4] (Yes)				−0.1	−0.01	1.33	−0.07	0.942	−2.74. 2.55
Years of education				−0.25	−0.1	0.28	−0.91	0.366	−0.8, 0.3
QOLIBRI[5]	(3, 98) = 5.82	**0.001**	0.15						
Radiological Findings (Yes)				16.5	0.32	5.08	3.25	**0.002**	6.4, 26.54
Previous mTBI[4] (Yes)				−4.81	−0.1	4.16	−1.16	0.251	−13.6, 3.45
Years of education				0.91	−0.1	0.9	−1.02	0.309	−2.69, 0.86
EQ VAS[6]	(3, 101) = 1.64	0.18	0.05						
Radiological Findings (Yes)				8.27	0.2	4.4	1.86	0.066	−0.5, 17.1
Previous mTBI[4] (Yes)				−1.80	−0.05	3.73	−0.48	0.630	−9.2, 5.6
Years of education				−0.03	−0.004	0.78	−0.04	0.969	−1.6, 1.5

[1]Rivermead Post-concussion Questionnaire, [2]Patient Health Questionnaire-9, [3]Post-traumatic Symptoms Scale, [4]Mild Traumatic Brain Injury, [5]Quality of Life after Brain Injury, [6]EuroQol-5D Visual Analog Scale

variables) with respect to post-concussion symptoms (See Figure 1), depressive symptoms, post-traumatic stress symptoms, and HRQoL (QOLIBRI-OS, see Figure 2), still reflecting a significantly higher symptom burden in the group without intracranial abnormalities (see Table 4). The previous differences regarding sleep and HRQoL (EQ VAS) on the other hand, were no longer significant.

Likewise, we inserted the score for CVLT-II short delay-free recall as a dependent variable in a multiple linear regression analysis and status of intracranial abnormality, history of previous mTBI, and level of education as explanatory variables. In this case, the status of intracranial abnormality was no longer significant ($\beta = -.08$, $p = .4$).

Discussion

Here, we provide comprehensive data describing biopsychosocial characteristics in a well-defined subgroup of treatment-seeking patients with mild-to-moderate TBI who experience PPCS and have not been able to return to pre-injury work levels 8–12 weeks after injury. We also investigated whether patient characteristics differed for patients with and without traumatic intracranial injury. Patients with normal CT/MRI results reported higher overall symptom burden, while patients with intracranial abnormalities had worse memory function.

Patients in this study were predominantly female white-collar workers in full-time positions. Women are overrepresented in our sample. This is in line with other studies that also show that women tend to report more symptoms and seek healthcare services more often than men (64,65). Further, the sample was recruited from an urban population (Oslo) which is highly educated (56). Most patients were sick listed 80–100% and reported high somatic (fatigue, headache, noise sensitivity), emotional (feeling frustrated, depressed, anxious), and cognitive (poor concentration, taking longer to think) symptom burden 8–12 weeks after injury.

Patients with normal CT/MRI results reported higher levels of post-concussion symptoms, symptoms of depression and post-traumatic stress, and decreased health-related quality of life than patients with intracranial abnormalities. The fact that this absence of intracranial abnormality was associated with a higher symptom burden, and that the difference was still present when variables that systematically differed between the groups (i.e. previous mTBI and level of education) were controlled for, is somewhat paradoxical. In contrast, there was a difference in the opposite direction regarding neurocognitive function, as patients with intracranial abnormalities performed worse on a test of verbal memory compared to patients without, in univariate analysis.

Patients with normal CT/MRI results reporting more symptoms are contrary to findings in large-scale epidemiological studies (5,61). For example, Voormolen et al. (5) examined 1302 patients three months after complicated and uncomplicated mTBI and found that the presence of intracranial abnormalities on CT was a (weak) indicator for the occurrence of post-concussion symptoms. A study based on the TRACK-TBI data set (61) demonstrated the clinical relevance of early abnormal CT/MRI results after mTBI, with one or more brain contusion, or ≥4 foci of hemorrhagic axonal injury on MRI being associated with poorer 3-months outcome of global function as assessed with the Glasgow Outcome Scale – Extended. It is not completely clear why patients without intracranial abnormalities reported a higher symptom burden in the current sample, but there are a number of possible explanations. Firstly, there might be a subject expectation bias where patients with a normal CT/MRI expect a quick

Table 4. Neuropsychological screening of patients with and without intracranial abnormalities, standardized scores.

Neuropsychological test	p-value	Normal CT/MRI, median (IQR)	With intracranial abnormalities, median (IQR)	U
Psychomotor speed				
Trail making test – 1	0.92	12 (3)	12 (63)	1027
Trail making test – 2	0.45	12 (63)	12 (63)	951
Trail making test – 3	0.32	12 (3)	12 (2)	848
Trail making test – 5	0.53	13 (1)	13 (2)	820
CWIT[a] – 1	0.72	10 (63)	9 (3)	904
CWIT[a] – 2	0.77	11 (3)	11 (3)	914
WAIS-IV[2] Coding	0.45	11 (63)	11 (2)	926
Attention and concentration				
Ruff 2 & 7[3] Total speed , mean (SD)	0.24	58 (10)	55 (11)	t(96) = 1.2
Ruff 2 & 7[3] Total accuracy	0.61	49.5 (10)	49 (8)	898
Learning and memory				
CVLT – II[4] Total learning ′ mean (SD)	0.06	61 (11)	55 (14)	t (105) = 1.9
CVLT – II[4] Short Delay Free Recall	**0.04**	60 (14)	55 (19)	782
CVLT – II[4] Long Delay Free Recall	0.06	60 (14)	55 (14)	823
Prospective memory				
MIST Total PMT[5]	0.71	69 (62)	73 (32)	953
Executive functions				
Trail making test – 4	0.19	11 (3)	11 (63)	863
CWIT[a] – 3	0.01	11 (3)	12.5 (3)	631
CWIT[a] – 4	0.07	11 (63)	12 (3)	699
Verbal abilities				
WAIS-IV[2] Vocabulary	0.17	10 (3)	10 (3)	857
WAIS-IV[2] Similarities	0.60	12 (4)	11 (4)	995
Visuospatial abilities				
WAIS-IV[2] Matrix Reasoning	0.87	13 (5.5)	13 (4)	1058
WAIS-IV[2] Block Design	0.53	11 (3.5)	11 (3)	994
General Ability Index (GAI)	0.41	114 (16.5)	112 (23)	916

[a]Color Word Interference Test, [2]Wechler Adult Intelligence Scale 4th Edition, [3]The Ruff 2 & 7 Selective Attention Test, [4]Verbal Learning Test – II, [5]Memory for Intentions Test – Prospective Memory Test, [1]T-test.

recovery, while patients with intracranial abnormalities accept a protracted recuperation, both relying on what they were told by healthcare professionals in the acute phase. The expectation of a quick recovery, and the following disappointment when this does not transpire, might have rendered the patients without intracranial abnormalities more impatient and frustrated with protracted symptoms. Consequently, they might have perceived their condition as relatively worse considering this, resulting in negative symptom development, and higher self-reported symptom levels (57,66).

Secondly, more patients without intracranial abnormalities reported previous mTBIs, and higher levels of depressive and post-traumatic stress symptoms. Experience of previous mTBIs may modify patient expectations (67), and support misattribution of nonspecific symptoms. Studies have indeed suggested that somatization may contribute to persistent symptoms after mTBI (55,58). Consequently, the burden of symptoms may be higher due to a combination of the post-concussion symptoms and somatization (57). However, the symptom burden in this sample was still high when controlling for previous patient-reported mTBIs and it is uncertain whether, and to what extent, potential somatization might have occurred in this study.

Thirdly, patients who are admitted to the neurosurgical department at OUH and have intracranial abnormalities are generally referred to follow-up at the specialized TBI outpatient clinic, from which the study participants were recruited six to eight weeks later, regardless of symptom burden. In comparison, patients with a normal CT/MRI are commonly referred to follow-up by their GP due to experiencing PPCS and decreased functional level. Therefore, selection bias resulting from differential referral practices in patients with and without intracranial injuries cannot be ruled out. On the other hand, all patients in this study had a consultation with a PMR physician and were found to be eligible for the study, which requires confirmation of PPCS at inclusion. Thus, the study did not include patients with intracranial abnormalities that did not experience PPCS. Regarding symptom burden, the fact that we included patients from the specialized outpatient clinic 8–12 weeks post-injury may explain why the results are not in line with those found in the epidemiological CENTER-TBI and TRACK-TBI studies (5,61). In these studies, all patients were included in the acute phase (and therefore regardless of symptom burden at 8–12 weeks). The sample with TBI that is presented in this study is therefore not expected to be representative of the population with mild-to-moderate TBI in general, but rather provides important insight regarding the subgroup of patients that develop PPCS and therefore seek treatment several weeks after the injury. These are exactly the patients that will present themselves to rehabilitations centers, and the current study represents one of very few studies examining the characteristics of this specific subgroup that runs a high risk of symptom chronicity.

A history of psychiatric illness is considered a risk factor in developing PPCS after mild-to-moderate TBI (28,59,68). Iverson et al. (15) performed a systematic review regarding predictors of clinical recovery from concussion including 101 full-text articles and 13 conference abstracts. The majority of included papers found a greater risk of persistent symptoms in patients with a pre-morbid psychiatric history. However, the review also confirmed that, as with other predictors in this field, the literature is mixed. In the current sample, the self-reported history of previous depression and anxiety did not exceed the lifetime prevalence in the Norwegian population (69). However, it cannot be ruled out that the patients in the current study may have underreported their previous psychiatric history, and the lack of predictive value of pre-morbid emotional problems should be interpreted with caution.

Patients who have a potential secondary financially gain may report higher level of disability (70). The rate of potential insurance claims in this sample is unknown. However, 16 patients suffered an occupational injury, which in Norway entails a more comprehensive welfare provision. These patients did not report more symptoms than the rest of the sample. Further, all patients receive 100% compensation of salary lost due to illness the first year after injury in workers'

compensation by the Norwegian welfare system. In light of this, we do not believe this was a major factor influencing the self-reported level of symptoms.

Almost half of the patients reported having previously sustained a mTBI, of whom as many as 16% reported sustaining several mTBIs in the past. This is another claimed predictor of PPCS (71,72), and the proportion of patients reporting at least one previous TBI does seem quite high in the current sample. However, having sustained previous mTBIs was not significantly associated with reporting a higher symptom burden in this study. Interestingly, Iverson et al. (15) likewise pointed out that most studies in their systematic review did not find an association between previous concussions and worse outcome. The existing literature is still conflicting on this matter, and more knowledge is required in order to conclude.

Limitations

The inclusion criteria reflect that this study utilizes a sample recruited to an RCT examining the effect of an intervention on return to work after mild-to-moderate TBI. The inclusion criteria, including restrictions in age, work status, and the presence of PPCS 8–12 weeks post-injury, limit the generalizability of the results. However, the results do represent the working population of patients with mild-to-moderate TBI who seek treatment for PPCS, thus giving more precise information concerning the group of patients which are exactly those the rehabilitation facilities need to reach with treatment after the acute stage. Furthermore, the sample represents patients with a potential to resume their pre-injury occupation, with potential reduction of societal costs related to TBI.

Additionally, we excluded nine patients from the comparison of outcomes in patients with and without intracranial abnormalities, as they did not have CT/MRI assessment after the injury. These are presumably the patients with least severe injuries, and excluding them may have affected the results.

Beyond the data reported here, additional data regarding results of neuromuscular examination, and possible vestibular or neuro-optometric impairments would have been useful.

Lastly, the prevalence of depressive symptoms in the study was measured using PHQ-9. Some of the symptoms of PPCS and depression overlap (consequently, so do some items on RPQ and PHQ-9) to such an extent that the results concerning depressive symptoms in this patient group need to be interpreted with a fair amount of caution, as scores on PHQ-9 may have been inflated by the PPCS. An overlap between symptoms of PPCS and emotional distress may also have affected the scores of anxiety symptoms (GAD-7) and post-traumatic stress symptoms (PTSS-10). The fact that premorbid conditions were based on self-report may have resulted in some bias colored by the current situation.

Clinical implications

This study examined the characteristics of treatment-seeking patients with PPCS after mild-to-moderate TBI 8–12 weeks post-injury. The results indicate that patients with a normal CT/MRI may have a symptom burden equal to, or even superior to, that of patients with intracranial abnormalities. Medical factors such as injury severity and radiological findings should therefore not be the sole ground for prioritizing rehabilitation services. Increased knowledge regarding patient's demographic and preinjury characteristic, combined with the level of symptoms reported by patients with and without intracranial abnormalities after injury, may support healthcare workers in better understanding the subgroup with protracted recovery and help predict which patients with mild-to-moderate TBI are at risk of experiencing PPCS. This is a prerequisite for the development of efficient and individualized treatment plans.

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