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Early clinical characteristics of patients with persistent post-concussion symptoms: A prospective study

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Abstract

Primary objective: To identify the early clinical features of patients with mild traumatic brain injury (mTBI) that are predictive of the presence of persistent post-concussion symptoms (PPCS).

Research design: A prospective study was conducted at a level I trauma centre.

Methods and procedures: One hundred and eighty mTBI patients participated in this study. The post-concussion symptoms (PCS) were evaluated with a PCS checklist. All patients were examined at 1, 2 and 8 weeks post-injury. The chi-square test was used to evaluate the associations of each PCS and the logistic regression was used to identify potential predictors of mTBI patients who might suffer from PPCS.

Main outcomes and results: Less than one-tenth of the mTBI patients examined complained of PPCS at 2 months after head trauma. Patients with PPCS are more likely to suffer from intracranial lesions. Moreover, clinical symptoms at 1 and 2 weeks post-injury, especially physical ones including headache, dizziness and fatigue, were reported significantly more often by patients with PPCS.

Conclusions: This study showed that early clinical symptoms and intracranial lesions may be strongly associated with the presence of PPCS. Thus, those specific characteristics may be used as early indicators of long-term difficulties.

Keywords: Persistent post-concussion symptoms, early predictors, prospective study

Introduction

In Taiwan, traumatic brain injury (TBI), a significant public health problem with an incidence of 160 000–200 000 people, produces more than 8000 deaths annually [1]. Taiwanese studies [2, 3] have reported that mild TBI (mTBI) accounts for 77–82% of TBIs, while western studies [4, 5] have reported that 90% of TBIs fall into this category. Other researchers [6–8] have concluded that patients who suffer from physical disturbances after mTBI lack productive capabilities. This eventually has a large burden on government economy.

Following mTBI, post-concussion symptoms (PCS), such as headache, dizziness, memory loss and psychomotor slowing, are the most common subjective complaints [9]. These PCS after mTBI usually subside less than 3 months post-injury. Many studies [10–14] have found a small proportion of patients who continue to have problems for several months or even a year after head trauma. In fact, these persistent PCS (PPCS) are often recognized as a potential risk factor for patients' long-term disabilities [15–17]. Identification of those patients likely to experience PPCS as early as possible so that

intervention and support can be targeted appropriately is of significant clinical importance.

Unfortunately, few studies [18–22] have directly identified early clinical characteristics and risk factors for patients who manifest PPCS, so it is difficult to provide early intervention. In addition, the previous studies had four major methodological weaknesses. First, the past studies recruited patients with mixed severity of head injuries. Even though the early prospective studies of King and colleagues [18, 19], who found emotional problems, such as anxiety and depression, at 7–10 days following head trauma, may significantly help predict patients' PCS at 3 months post-injury, their sample of TBI patients was a mixture of mild and moderate severities. This methodological problem limited the understanding of pure clinical manifestations of PPCS after mTBI, since moderate TBI patients have more cognitive and behavioural difficulties [23, 24] that are often associated with significant brain lesions, usually not seen in patients with mTBI.

Secondly, patients usually suffer from a severe fatigue after head trauma [25, 26] and thus the methods used to measure PCS and other clinical symptoms in past studies might have been too complicated and exhausting for practical use in a clinical setting, especially during the acute stage (e.g. 1 week) post-injury. King and colleagues [18, 19] used three self-reported rating scales to evaluate patients' emotional status, adjustment after trauma and PCS, plus another four neuropsychological tests to examine patients' orientation, memory and attention functions. Although this combination of neurobehavioral tests allows comprehensive exploration of patients' clinical symptoms following head injury, at least half an hour is required to complete all seven tests. Because of post-injury fatigue, it might be difficult to adhere to King's procedure to efficiently evaluate patients' PCS in an ordinary outpatient clinical setting, where clinicians may have only 3–5 minutes to understand patients' problems after mTBI and to further identify potential predictors of PPCS.

Thirdly, some researchers [20, 21] investigated the PCS at 3 months post-injury and further evaluated the utility of diagnostic criteria of post-concussion syndrome in the International Classification of Diseases (ICD-10) [27] or Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [28] without directly examining the early clinical characteristics of patients who suffered from that syndrome. For instance, even though Kashluba et al. [20] found fatiguing quickly and dizziness/vertigo were the most prominent PCS at both 1 and 3 months following mTBI, they did not specifically determine the 1-month clinical features of patients who still reported remarkable

PCS at 3 months post-injury. Finally, some studies employed cross-sectional and retrospective designs. Accordingly, although Ruff and colleagues [29, 30] identified 15–20% of mTBI patients with PPCS as the 'miserable minority' and further tried to determine whether the cause of PPCS was neurogenic or psychogenic, they were still unable to recognize appropriate post-traumatic clinical predictors for PPCS.

The present study tried to resolve these methodological drawbacks. First, mTBI patients were consecutively followed from 1 week to 2 months post-injury with a screening checklist for PCS developed in a previous study [31], in which the association between post-concussion symptoms and clinical outcomes was prospectively evaluated. This checklist, which evaluates for 16 common PCS, such as headache, dizziness, memory loss and psychomotor slowing, requires only 1–3 minutes to complete. In other words, it is not necessary to have patients undergo a more expansive test battery. This allows for less fatigue. In addition, clinicians can reduce the time required to investigate patients' PCS and still identify potential clinical predictors for PPCS.

The main purpose of this study was to investigate early clinical predictors, especially PCS (e.g. headache, dizziness and fatigue, etc.), in those patients who continued to suffer from those symptoms at 2 months post-injury with a screening instrument for PCS. Accordingly, two specific aims of this study were to examine the following hypotheses: (1) some mTBI patients would suffer from PPCS at 2 months post-injury; and (2) some clinical characteristics, such as intracranial lesions and specific PCS at 1 week post-injury, would predict whether patients would have PPCS at 2 months after mild head trauma.

Methods

Participants

This study was conducted at a level I trauma centre, as part of a prospective study [31] on the association between PCS and functional outcomes after mild head trauma. Two hundred and ten mTBI patients were followed in a neurosurgery clinic over a period of 2 years (January 2004 to January 2006). A total of 180 patients suffering from mild head trauma participated in this study after the exclusion of 30 patients, who could not be contacted in the follow-up investigations.

Unfortunately, the definition and diagnosis of mTBI are still inconclusive [32–35]. Some researchers [32, 36] have defined mTBI as a GCS of 13–15, while others [35, 37] have reported that patients who had GCS scores of 14–15 should be classified in the

'real' mTBI group. In fact, many studies [38–41] have found that the pathophysiology of mTBI patients with GCS scores of 13–15 was heterogeneous, leading to further suggestions that patients with GCS of 13 should be excluded from the mild group because of a high incidence of brain damage found on Computed Tomography (CT) scans in those patients and a clinical manifestation more similar to that of patients with moderate severity. Recently, researchers [42, 43] tended to follow this perspective and recruited patients with a GCS of 14–15 to participate in their studies. Therefore, to avoid the ambiguity associated with heterogeneity of pathophysiology, the diagnosis of mTBI in this study was made by a neurosurgeon and based on the following criteria: (a) initial Glasgow Coma Scale (GCS) score of 14–15 and (b) initial loss of consciousness of less than 30 minutes [44–47]. Patients with a history of suspected psychiatric problems, cerebrovascular insults or other major medical illnesses (e.g. brain tumors, thyroid dysfunction, etc.) were excluded. However, according to the brain CT scans reviewed by a neurosurgeon and a neuroradiologist, 19% of the mTBI patients had intracranial lesions, including brain contusions, subarachnoid haemorrhages (SAH), subdural haemorrhages (SDH) or brain swelling. The demographic data of the patients are shown in Table I. The study protocol was approved by the institutional review boards of the participating institutions and the patients gave informed consent after the study requirements were explained.

The evaluation of PCS

The present study used the Checklist of Post-Concussion Symptoms (CPCS) and only used the description of clinical symptoms in the ICD-10 diagnosis of post-concussion syndrome (code F07.2) in a previous study [31], to assess the severity of 16 commonly reported PCS, including headache, dizziness, fatigue, nausea, vomiting, poor vision, tinnitus, loss of energy, depression, irritability, insomnia, anxiety, attention deficits, memory impairments, psychomotor slowing and other disturbances.

Accordingly, a two-step recording procedure was used when checking symptoms on the CPCS. First, each symptom was checked and the negative

influence on the patient's daily life evaluated. Because one wanted to be sure that those symptoms were the actual cause of their social and occupational difficulties, patients were asked 'Did any of the following symptoms reduce your social or occupational abilities in the past week?' If patients reported any symptoms from that question, an examiner (a clinical neuropsychologist) scored '1' for each item they reported. Secondly, the sum of those checked items was recorded as the 'total PCS score' for each patient.

The selection of patients with PPCS

Unfortunately, the diagnosis and definition of PPCS remains unclear. Even though some recent studies [48, 49] have showed that the post-concussion syndrome in the ICD-10 might have a more comprehensive description of PCS and a higher sensitivity for diagnosing patients who suffered from PPCS than the post-concussional disorder in the DSM-IV, it is still an unresolved issue, as these two diagnostic systems have totally different criteria. In order to avoid this controversy of diagnosing post-concussion syndrome, this study only determined the patients had PPCS by defining patients as the 'PPCS group' when they reported any PCS on the CPCS, which contained clinical symptoms of post-concussion syndrome from the ICD-10 at 2 months post-injury. Other patients were designated as the 'Non-PPCS group'. The demographic data of this second group are also presented in Table I.

Procedures

Upon discharge from the emergency department or the hospital, patients were prospectively evaluated using the CPCS at 1 week, 2 weeks and 2 months post-injury. Because some patients' physical conditions improved significantly, it was not necessary to ask them to visit the outpatient clinic continuously. The authors conducted the post-injury evaluations of these individuals by telephone.

Data analysis

The chi-square test was used to evaluate the associations of each PCS, which is a categorical

Table I. Demographical data of mTBI patients in PPCS and Non-PPCS group.

	Number of participants	Male (%)	Age ($M \pm SD$)	Education ($M \pm SD$)	GCS ($M \pm SD$)	Intracranial lesions (%)
PPCS group	17	41	37.24 $\pm$ 14.19	13.18 $\pm$ 2.90	14.88 $\pm$ 0.33	53
Non-PPCS group	163	48	35.72 $\pm$ 16.42	12.31 $\pm$ 3.44	14.94 $\pm$ 0.26	15

mTBI: mild traumatic brain injury; PPCS: persistent post-concussion symptoms; GCS: Glasgow Coma Scale.

variable, between PPCS and Non-PPCS groups. Logistic regression was used to identify potential predictors of mTBI patients who might suffer from PPCS. Statistical significance was defined as a probability value of less than 0.05. Commercially available software (version 11.0; SPSS, Inc; Chicago, IL) was employed.

Results

The manifestation of PCS

As shown in Figure 1, various PCS appeared 1 week post-injury, including dizziness (in 67% of the patients), headache (39%), fatigue (23%), nausea (13%) and attention deficits (12%). At 2 weeks following head trauma, 44% of the patients still had those symptoms, notably dizziness (38%), headaches (16%) and fatigue (11%). In addition, more than 90% of the patients did not report any PCS at 2 months post-injury. In contrast to previous results [31], which showed that only 13% of the normal control subjects complained of headache, 8% complained of dizziness, fatigue and attention deficits and less than 5% complained of other PCS, the mTBI patients in the present study reported significantly more PCS than the normal subjects did at 1 and 2 weeks post-injury. However, the patients did not suffer from more PCS than the normal subjects did at 2 months following mild head trauma (Table II).

The manifestation of PPCS

MTBI patients who complained of any post-concussion symptoms at 2 months post-injury were defined as the 'PPCS group' and others as the 'Non-PPCS group'. Accordingly, 9% (17/180) of the patients who reported at least one post-concussion

symptom at 2 months after head trauma were then identified as the PPCS group. Headache (47%, 8/17), dizziness (47%, 8/17) and fatigue (35%, 6/17) were the most common PCS experienced by patients in the PPCS group.

The early clinical predictors of PPCS

In analysis of the early clinical predictors of PPCS, the chi-square analysis also showed that intracranial lesions ($\chi^2=9.72, p<0.01$) and headache ($\chi^2=5.02, p<0.05$) were strongly associated with PPCS manifestation, while dizziness ($\chi^2=3.76, p=0.052$) was close to the significance level. The logistic regression analysis (Table III) further uncovered a much greater incidence of intracranial lesions ($\beta=1.61, p<0.01$) in the PPCS group than in the Non-PPCS one.

At 2 weeks post-injury, the chi-square analysis also revealed that headache ($\chi^2=5.57, p<0.02$), dizziness ($\chi^2=11.96, p<0.01$), fatigue ($\chi^2=11.12, p<0.01$) and poor vision ($\chi^2=5.61, p<0.02$) were strongly associated with PPCS manifestation. Moreover, the logistic regression analysis (Table III) found significantly more dizziness ($\beta=1.48, p<0.05$) in the PPCS group than in the Non-PPCS group.

Discussion

The definition of PPCS

Although many researchers [10–14] have recognized 10–15% of mTBI patients have PPCS, questions still remain about those published reports on the

Figure 1. The manifestations of post-concussion symptoms following mild traumatic brain injury within 2 months post-injury (1, 2 and 8 weeks).

Table II. The post concussion symptoms at 1 week, 2 weeks and 2 months.

	1 week (%)	2 weeks (%)	8 weeks (%)	Control* (%)
Headache	39	16	4	13
Dizziness	67	38	4	8
Anxiety	4	3	1	5
Attention deficits	12	7	1	8
Fatigue	23	11	3	8
Disgusting	13	2	1	0
Loss of energy	11	4	1	5
Depression	4	1	1	3
Memory loss	8	4	1	5
Vomiting	3	1	0	0
Poor vision	6	3	1	3
Irritability	2	3	0	5
Insomnia	4	3	1	3
Slow response	6	3	1	0
Tinnitus	3	1	1	5
Others	2	4	1	5

*Post-concussion symptoms reported by healthy control subjects ($n=40$) in a previous study [31].

epidemiology and prevalence of PPCS. For instance, Iverson and colleagues [50, 51] claimed that the estimate of PPCS is severely inflated and that the true incidence of PPCS would appear to be far less than 5% of all mTBI patients. Two main reasons accounted for that controversy. First, the diagnosis and definition of PCS remained unclear. In the last decade, the ICD-10 and the DSM-IV were two major diagnostic systems for PCS. However, the criteria for the duration of PCS in these two systems are inconsistent. According to the ICD-10 description, PCS occurs after trauma and presents no later than 4 weeks post-injury, while according to the DSM-IV, symptoms must have continued for at least 3 months post-injury. Some researchers tried to solve this diagnostic confusion by comparing the clinical utility and reliability of these two systems. Boake et al. [48] compared diagnoses of PCS by the ICD-10 and the DSM-IV and found that agreement between these two diagnoses was slight ($\kappa=0.13$) because few patients met the cognitive deficits and clinical significant criteria of the DSM-IV. Recently, McCrea [49] also suggested that the diagnosis of PCS according to the DSM-IV might be too restrictive. This study, mainly based on the symptom descriptions of ICD-10 criteria, recognized that 9% of mTBI patients manifested post-concussion symptoms at 2 months post-injury.

Secondly, whether PCS are specific to mTBI or simply a non-specific symptom cluster is also an unsolved problem. Some researchers do not recognize PCS as a specific symptom cluster. Iverson and colleagues [52, 53] investigated the prevalence of PCS-like symptoms in samples of healthy individuals and patients with depression, respectively. They found that 36–76% of both healthy subjects and depressive patients experienced PCS-like symptoms over a period of 2 weeks and that those symptoms showed a high correlation with self-reported symptoms of depression. Others [31] discovered that some specific PCS, such as headache and dizziness, presented significantly more in mTBI patients than in a healthy control group. Even though this study did not directly compare the PCS reported by mTBI

patients and healthy subjects, the prevalence of PCS in these patients at 1 and 2 weeks post-injury was 78% and 44%, respectively, which was still significantly higher than the prevalence of PCS reported by healthy participants in the previous investigation.

The early predictors of PPCS

This prospective study found evidence of several early clinical characteristics of mTBI patients with PPCS at 2 months post-injury, mainly the presence of intracranial lesions at both 1 and 2 weeks after head trauma and dizziness at 2 weeks post-injury. In fact, past studies have confirmed the results that intracranial lesions may be significantly associated with prolonged symptoms and poor clinical outcomes in mTBI patients. In an early study, after subdividing mTBI patients into the complicated group (with radiological evidence of focal brain lesions and depressed skull fracture) and the uncomplicated group (with normal CT scan findings), Williams et al. [38] found that the complicated group had more clinical symptoms and poorer functional outcomes than the uncomplicated one over a period of 6 months after head trauma. Recently, Borgaro et al. [54] supported this finding and provided further evidence that patients in the complicated mTBI group had more emotional and cognitive symptoms than those in the uncomplicated one. In addition to these reports regarding the negative effects of intracranial lesions on clinical outcomes, this study further identified that the presence of intracranial lesions may also be an important clinical predictor for the manifestations of PPCS.

In addition to determination of intracranial lesions, this study used a concise screening checklist for PCS to identify the early clinical symptoms of mTBI patients with PPCS. It found that over the 2 weeks post-injury, patients with PPCS reported significantly more physical symptoms, including headache, dizziness, fatigue or poor vision, than Non-PPCS patients did. Other researchers [18, 19, 55] have supported these findings. de Kruijk et al. [55] investigated the parameters at first presentation

Table III. Clinical characteristics in 1 and 2 weeks in PPCS and Non-PPCS groups.

	Headache, <i>n</i> (%)	Odds ratio	Dizziness, <i>n</i> (%)	Odds ratio	Fatigue, <i>n</i> (%)	Odds ratio	Intracranial lesions, <i>n</i> (%)	Odds ratio
<i>1 week</i>								
Non-PPCS (<i>n</i> = 163)	60 (37%)		106 (65%)		37 (23%)		26 (16%)	
PPCS (<i>n</i> = 17)	11 (65%)	2.30	15 (88%)	3.36	4 (24%)	0.02	8 (47%)	7.59**
<i>2 weeks</i>								
Non-PPCS (<i>n</i> = 163)	22 (14%)		55 (34%)		14 (9%)			
PPCS (<i>n</i> = 17)	6 (35%)	0.58	13 (77%)	5.43*	6 (35%)	2.76		

* $p < 0.05$; ** $p < 0.01$.

after mTBI that are predictive of post-traumatic complaints after 6 months. They concluded that the presence of dizziness, headache or nausea in the emergency room after mTBI is strongly associated with the severity of complaints at 6 months post-injury. Although King and colleagues [18, 19] did not specifically evaluate the early clinical symptoms of patients with PPCS, they discovered that a combined evaluation of patients' emotional disturbances, such as depression and anxiety, and the duration of post-traumatic amnesia were useful prognostic instruments for predicting PPCS at 3 months after head injury. These results provide yet another clinical screening instrument, one which both significantly reduces the burden on patients' cognitive resources required to complete it and provides evidence that the manifestations of some clinical symptoms at 1–2 weeks post-injury may predict the persistency of PCS. Specifically, this study also found that dizziness, which was the single symptom reported by patients with PPCS at 2 weeks post-injury, could predict the presence of PPCS. This result illustrates that dizziness may not only adversely influence mTBI patient's clinical outcomes, as evidenced in past studies [31, 56], but may also have a significant predictive value for manifestation of PPCS.

Limitations

The present study prospectively evaluated PCS of mTBI patients until 2 months post-injury and found that the intracranial lesions evidenced on the CT scans and dizziness at 2 weeks following TBI are early clinical predictors of PPCS. However, a few methodological weaknesses might limit the contributions of these results. First, even though this study recruited a total of 180 mTBI patients, only 17 patients (9%) were identified as having PPCS according to the criteria, which was more inclusive than the criteria of the ICD-10 or DSM-IV. This small sample size of patients with PPCS might not be representative enough to make a decisive conclusion. In addition, the intracranial lesions were not further analysed by different neuropathological conditions, since brain contusions, SAH or SDH may affect clinical outcomes in different ways. For instance, Eslinger et al. [23] found that brain contusions at frontal regions might be more highly associated with cognitive impairments, especially executive dysfunctions, than other kinds of brain lesions might.

Conclusion

This prospective study revealed that a significant number of PCS were reported by mTBI patients.

The PPCS which presented in less than one tenth of those patients were strongly related to the presence of intracranial lesions and early PCS, especially physical symptoms (e.g. dizziness and headache) at both 1 and 2 weeks post-injury. It follows that it is helpful for clinicians to monitor mTBI patients' early clinical symptoms as predictors of the persistency of PCS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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