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Research paper

Traumatic brain injury and affective disorder: A nationwide cohort study in Taiwan, 2000–2010

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ABSTRACT

Background: Studies investigating the relationship between head injury and the subsequent onset of affective disorders often show conflicting results.
Aims: To investigate the risk of affective disorders following traumatic brain injury in a large Taiwanese cohort.
Method: This retrospective cohort study makes use of the National Health Insurance Research Database. A cohort containing 68,376 individuals who experienced traumatic brain injury (TBI) during 2000–2010 and had no prior history of mental disorders before the injury was identified. Using Cox Proportional Hazards regression, the subsequent risk of affective disorders was determined.
Results: TBI was associated with a higher risk of both bipolar disorder (Hazard Ratio [HR]=1.42, 95% Confidence Interval [CI]=[1.26, 1.59]) and major depression (HR=1.41, 95% CI=[1.28, 1.54]). More severe injury was associated with greater risk. The first year following the injury was the highest risk period for major depression, while the highest risk period for bipolar disorder was delayed until two to four years following the injury.
Limitations: Using a claims database, we were unable to assess confounding variables that were not contained in the data set.
Conclusions: The elevated risks of affective disorders after TBI speak to the psychiatric need of individuals who suffer from brain injury. Early detection and timely intervention may help prevent secondary and tertiary disability associated with head trauma.

1. Introduction

The association between traumatic brain injury (TBI) and the subsequent development of affective disorders (including major depression and bipolar disorders) has been debated. While the increased risk of major depressive disorder following TBI has gained more empirical support, results are conflicting regarding the risk of bipolar disorder subsequent to TBI (Jorge and Arciniegas, 2014). Earlier studies tended to indicate that individuals with a history of TBI do not experience an elevation in the risk of bipolar disorder (Jorge and Arciniegas, 2014; Silver et al., 2001; van Reekum et al., 2000; Wilcox and Nasrallah, 1987). However, these studies were mostly based on clinical case series gathered from a single hospital, and thus may not be representative of the overall TBI patient population. More recent studies using population based sample tended to find a mild to moderately elevated risk of bipolar disorder after head injury; the estimated incident rate ratio ranged between 1.2 and 2.0 (Mortensen et al., 2003; Orlovska et al., 2014; Tsai et al., 2014).

Psycho-social adjustment after brain injury is generally challenging. Studies have consistently supported a positive relationship between TBI and the subsequent development of major depressive disorder. The traumatic and life-threatening nature of the

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accident may proceed through an increased risk of post-traumatic stress disorder (PTSD), which has a comorbidity with major depressive disorder that can be as high as 80% (Brown et al., 2001; Oquendo et al., 2005). Furthermore, maladjustment associated with impairment of daily function and cognitive ability is quite common, with these declines in function being strongly associated with the onset of major depression (Jorge et al., 2004). In addition to maladjustment pathways, biological changes after CNS injuries may contribute to an increased risk of major depression and bipolar disorder due to the direct neuro-trauma of specific brain locations (Jorge and Arciniegas, 2014; Jorge et al., 2004), post-injury CNS inflammatory response (Cederberg and Siesjo, 2010; Diamond et al., 2009; Zhang and Popovich, 2011) and neurotransmitter dysregulation (van Reekum et al., 2000).

The relationship between TBI and the subsequent risk of developing affective disorders has rarely been investigated in large-scale population-based samples. The studies currently in the literature largely stem from Scandinavian countries (Mortensen et al., 2003; Orlovska et al., 2014) with only one study coming from a non-Western context – Taiwan (Tsai et al., 2014). However, the study from Taiwan only explored the risk of developing affective disorders in adolescents and young adults rather than exploring the risk in the population as a whole. In addition, prior studies have rarely explored whether there is a critical period for the impact of injury (i.e. brain injuries in early life may be more detrimental than injuries occurring in adulthood) or assessed the latency between brain injury and the onset of affective disorders. The current study aims to assess the risk of affective disorders following TBI in a population-based sample in Taiwan. We also examine the influence of age at the time of TBI to determine the age of greatest vulnerability to a subsequent increased risk for affective disorders secondary to TBI.

2. Methods

2.1. Data sources

Taiwan introduced a single-payer National Health Insurance program on March 1, 1995 which now enrolls more than 99% of the 23 million Taiwanese people (http://w3.nhri.org.tw/nhird//date_01.html). In 1996, the National Health Research Institute in Taiwan established the National Health Insurance Research Database (NHIRD). The database includes medical claim files representative of the entire enrolled population in Taiwan. Recorded information includes patient demographic characteristics, diagnoses, medical expenditures, and prescription claims data. We used the ambulatory care claims, inpatient claims, and registry for beneficiaries data for a subset of one million beneficiaries from the NHIRD. Information that could be used to identify beneficiaries and medical care providers was scrambled by the National Health Research Institute.

2.2. Identification of the study cohort

This is a retrospective cohort study. Patients who received a diagnosis of traumatic brain injury (TBI) (ICD-9 CM codes 800-804, 850-854, ICD-8 codes A470, A490, A491, operation codes 0123, 0131, 0121, 0239, 0118 and 0139) in ambulatory visits or hospitalizations from 2000 through 2010 were included in the study cohort. The first ambulatory or hospitalization record of each TBI cohort member was defined as the index date. Those who had received a diagnosis of any mental disorder or substance use disorder (ICD-9 CM codes: 290-319 or ICD-8: A210-A219) before the index date were excluded from the TBI cohort. Overall, the cohort contained 68,376 individuals who experienced TBI during 2000–2010 and who had no prior history of mental disorders.

TBI cases were further categorized into three groups based on the severity of the injury. Severe TBI was defined as having undergone an operation in the course of inpatient treatment; moderate TBI was defined as having been hospitalized for TBI but not having undergone an operation; and mild TBI was defined as having not received any inpatient treatment for head injury.

The comparison cohort was randomly selected from the registry of beneficiaries who had no medical claims involving TBI between 1996 and 2010, or affective disorders (ICD-9 CM code 296, ICD-8 code A212) between 1996 and 1999. For each subject in the TBI cohort, four age-, sex- and index year (year of index date) matched comparison subjects were chosen for the comparison cohort. This yielded a total of 273,162 subjects in the comparison cohort.

2.3. Identification of affective disorders

Subjects who received a diagnosis of an affective disorder (ICD-9 CM code: 296*) after their index date were identified. Affective disorders were further categorized into bipolar disorder (ICD-9-CM codes: 296.0, 296.1 and 296.4–296.9, excluding 296.82) and major depressive disorder (ICD-9-CM codes: 296.2, 296.3 and 296.82). If both types of affective disorders were recorded, we assigned bipolar disorder as the key diagnosis.

2.4. Control covariates

We used urbanization index and insurance premium category as proxy measures to control for socioeconomic status. Urbanization index was categorized into three groups, high (metropolitan cities), medium (small cities and suburban areas) and low (rural areas) (Liu et al., 2006; Shen et al., 2012). Insurance premium was categorized into four groups based on enrollees' monthly insurance payment: 0, 1–36 USD, 37–650 USD, and 650 USD and over. Insurance premium is determined by monthly salary, and hence can be treated as an indicator of socioeconomic status.

The Charlson Comorbidity Index (CCI) was used to represent physical condition (Charlson et al., 1987). Any claim of COPD (Chronic Obstructive Pulmonary Disease, ICD-9-CM codes:491, 492, 496; A-code: A323, A325) was used as an indicator of smoking status and served as a proxy for lifestyle behaviors. Physical conditions and unhealthy lifestyle behaviors are associated with both TBI and mental illness and thus are potential confounders. Although CCI and COPD are not optimal indices for physical conditions or lifestyle behaviors, they can account for some of the confounding effects derived from these two variables. COPD was used as a proxy for unhealthy lifestyle behaviors because 80–90% of COPD morbidity can be attributed to cigarette smoking (US Surgeon General, 1984), and approximately 50% of all smokers will develop COPD in their lifetime (Mannino and Buist, 2007). Additionally, existing studies suggest that unhealthy lifestyle behaviors, namely smoking, heavy drinking, sedentary lifestyles, and unhealthy dietary choices tend to co-occur (Ma et al., 2000; Patino-Alonso et al., 2015). For these reasons, COPD has been used as a proxy for unhealthy lifestyles in previous investigations (Ritz et al., 2010). Since COPD was available in our dataset, we decided to adjust for it in the same manner in the present study.

2.5. Statistical analyses

Baseline characteristics were compared between patients with TBI and comparison subjects using the χ^2 test. After the proportional hazards assumption was verified, we used Cox Proportional Hazards model to assess the hazard ratio of developing an affective