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TRAUMATIC BRAIN INJURY CAUSES FRONTOTEMPORAL DEMENTIA AND TDP-43 PROTEOLYSIS

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Abstract—Traumatic brain injury (TBI) is a major risk factor for dementia. Recently, TBI has also been suggested as a risk factor for frontotemporal dementia (FTD), and plasma immunoreactivity to the TAR-DNA binding protein 43 (TDP-43) has been observed in both patients with acute TBI and long-term survivors of this condition. We used a population-based study to estimate and compare the risk of FTD in individuals with and without TBI. Furthermore, we used a rat model of TBI to show that increased TDP-43 proteolysis following TBI produces FTD-like impairments, including abnormal limb-clasping, and impaired performances in the Morris water maze. We recruited 24,585 patients who received ambulatory or hospital care for TBI and 122,925 patients without TBI for this study. Each individual was investigated for 4 years to evaluate FTD development, and data were analyzed by Cox proportional hazard regression. In the TBI rat model, behavior and TDP-43 inclusions were assessed following intracranial administration of a caspase-3 inhibitor or vehicle. FTD was more likely to occur in the TBI group than in the group without TBI (adjusted hazard ratio, 4.43; 95% confidence interval, 3.85–5.10; $P < 0.001$). Rats developed behavioral impairments similar to those in patients with FTD after TBI. Further, the behavioral impairments were likely associated with TDP-43 short fragment mislocalization and accumulation. Our findings suggest that in humans, TBI is associated with a greater occurrence of FTD. Moreover, clinical FTD manifestations may be associated with TDP-43 proteolysis, since impaired behaviors in TBI rats were reminiscent of those in humans with FTD. **© 2015 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: traumatic brain injury, frontotemporal dementia, TAR-DNA binding protein 43.

INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of mortality and disability in young adults worldwide, and its incidence has risen sharply since 1990 (Maas et al., 2008). TBI can activate multiple apoptotic and inflammatory pathways; this chronic inflammatory response is known as secondary injury (Masel and DeWitt, 2010; Ramlackhansingh et al., 2011). Therefore, TBI has been implicated as a possible risk factor for several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Maas et al., 2008; Wang et al., 2012a,b). Previous studies suggested an increased risk of frontotemporal dementia (FTD) in patients with TBI (Rosso et al., 2003; Kalkonde et al., 2012); however, because of relatively small sample sizes, they could not exclude recall bias as a factor in the observed association. Therefore, how TBI contributes to FTD remains undetermined.

FTD occurs before the age of 65 years in 75–80% of patients. Frontotemporal lobar degeneration (FTLD), including atrophy of the frontal and temporal cortices, with neuronal loss, gliosis, and spongiosis of the superficial layers are pathological hallmarks of FTD (Seelaar et al., 2011; Sieben et al., 2012). Common signs and symptoms include significant changes in progressive behavioral changes, apathy, blunting of emotions, and/or selective language difficulties (Seelaar et al., 2011; Sieben et al., 2012). Molecular genetic studies confirmed that FTLD results from genetic mutation and has two major subtypes: FTLD with tau-positive inclusions (FTLD-tau) and FTLD with ubiquitin-positive and TAR-DNA binding protein 43 kDa (TDP-43)-positive inclusions (Zhang et al., 2009; Seelaar et al., 2011; Xu, 2012). TDP-43 regulates gene expression, transcription, and multiple aspects of RNA processing/functioning (Wang et al., 2012a,b). Loss of TDP-43 function causes several neurodegenerative diseases, a process called TDP-43 proteinopathy (Neumann et al., 2006). Initially, caspase-3-induced proteolytic cleavage of TDP-43 generates short

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Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; HRs, hazard ratios; SARK, sarkosyl; TBI, traumatic brain injury; TDP-43, TAR-DNA binding protein 43.

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C-terminal fragments (25- and 35-kDa), which induce neuronal toxicity and cell death, and form ubiquitin-positive cytoplasmic inclusions within cells (Zhang et al., 2009; Barmada et al., 2010; Wang et al., 2012a,b). In addition, the transgenic (Tg) mice with overexpressed TDP-43 may alter the levels of learning/memory-associated proteins and exhibit impaired learning/memory, progressive motor dysfunction, and hippocampal atrophy. Therefore, accumulation of TDP-43 fragments and activated caspase-3 may play a role in the pathogenesis of the FTD brain.

Patients with single TBI and chronic traumatic encephalopathy have TDP-43 proteinopathy (McKee et al., 2010; Yang et al., 2014). McKee et al. showed that repetitive head injury is associated with TDP-43 proteinopathy and motor neuron disease development (McKee et al., 2010). Unfortunately, motor neuron diseases often exhibit ubiquitin- and TDP-43-immunoreactive inclusion bodies, making it difficult to determine whether TDP-43 proteinopathy is caused by head injury. Yang et al. showed that protease-generated TDP-43 fragments may gain neurotoxic function and induce secondary injury, and that TDP-43 and its fragments may have biomarker utilities in TBI patients (Yang et al., 2014). However, in another study by Johnson et al. that aggregates of TDP-43 were not increased acutely or long-term following TBI (Johnson et al., 2011). These cases were highly selective and did not provide population-based information regarding TDP-43 proteinopathy. Therefore, it remains unknown whether the proteolysis of TDP-43 by caspase contributes to the generation of pathologic diversity in TDP-43 proteinopathies.

A greater incidence of dementia is correlated with TBI in younger aged patients (Wang et al., 2012a,b). Amyloid-β pathology is the main mechanism to explain why TBI induces dementia (Smith et al., 2013). If this is true, then middle-aged patients should have a higher incidence of TBI (Clark et al., 2000; Friedlander, 2003; Knoblach et al., 2004; Loane et al., 2009). It is unknown, however, whether post-injury accumulation of TDP-43 fragments is implicated in apoptosis and hence increasing the risk of developing FTD after TBI.

Here, we investigated an association between TBI and FTD and possible role of TDP-43 proteolysis following TBI. In a retrospective cohort study, we compared FTD risk in patients with TBI with the general population matched by sex and age. A rat model of TBI was used to determine whether caspase-3 treated, vehicle, or sham groups were comparable behaviorally by Beam-walking test, Rotarod performance test, and Morris water maze task and in TDP-43 measurements obtained during acute stage. Finally, function recovery and TDP-43 proteolysis were assessed across days.

EXPERIMENTAL PROCEDURES

Database and study sample

The Longitudinal Health Insurance Database (LHID2000), which is one of the subsets of the National Health Insurance Research Database (NHIRD) of Taiwan, was used to obtain data for our study (Wang et al., 2012a,b). The LHID2000, which is made up of 1,000,000 randomly sampled people who were alive in the year 2000, is representative of the original NHIRD and consists of de-identified secondary data, including all the original medical-claim data and registration files. The details of database generation, monitoring, and maintenance are published online (http://nhird.nhri.org.tw/).

This human-based study was designed as a retrospective cohort study. The study was approved by the NHRI Ethics Review Committee, Taiwan. TBI was defined based on at least two NHI outpatient records or one inpatient record obtained from the LHID 2000. Patients with a diagnosis of fracture of the skull (International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) code 800–804) and intracranial injury (ICD-9-CM code 850–854) established between January 1, 2002 and December 31, 2003 were included in our study (Wang et al., 2012a,b). Participants who had been given a diagnosis of FTD (ICD-9-CM code 331.1) before their index ambulatory care visit were excluded. In total, 24,585 patients with TBI were included in this cohort study.

A comparison cohort was prepared from the records of the remaining patients in the LHID2000. Five comparison subjects for every patient with TBI were selected randomly after matching for sex, age, and the year of index use of health care services, excluding those with a history of TBI and FTD. The sociodemographic characteristics, including sex, age, select comorbidities (diabetes, hyperlipidemia, hypertension, coronary artery disease [CAD], heart failure [HF], atrial fibrillation [AF], and stroke) were assessed in the two cohorts. Ultimately, 122,925 patients were enrolled in the comparison cohort.

Each patient was individually tracked for 4 years from their index use of health care, to identify those who subsequently suffered from FTD (ICD-9-CM code 331.1). Patients without TBI were designated as the reference group, and the unadjusted and adjusted hazard ratios (HRs) analyses were conducted by evaluating the association between TBI and dementia during the 4-year follow-up period, after adjusting for demographic characteristics and selected comorbidities.

Animals

Male Sprague–Dawley rats were purchased from Charles River Laboratories and were 3-month-old at the time of TBI. These rats were housed at the Animal Center of I-Shou University, Kaohsiung, Taiwan. The protocols, including all surgical procedures and animal usage, were conformed to the guidelines of the Taiwan Council for Animal Care and approved by the Institution Animal Care and Use Committee of E-Da hospital. Rats were assigned to receive TBI with vehicle treatment (TBI, $n = 38$), TBI with Caspase-3 treatment (TBI + confidence interval (CI), $n = 29$), or sham surgery with no treatment (Sham, $n = 30$) (Fig. 1A).

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