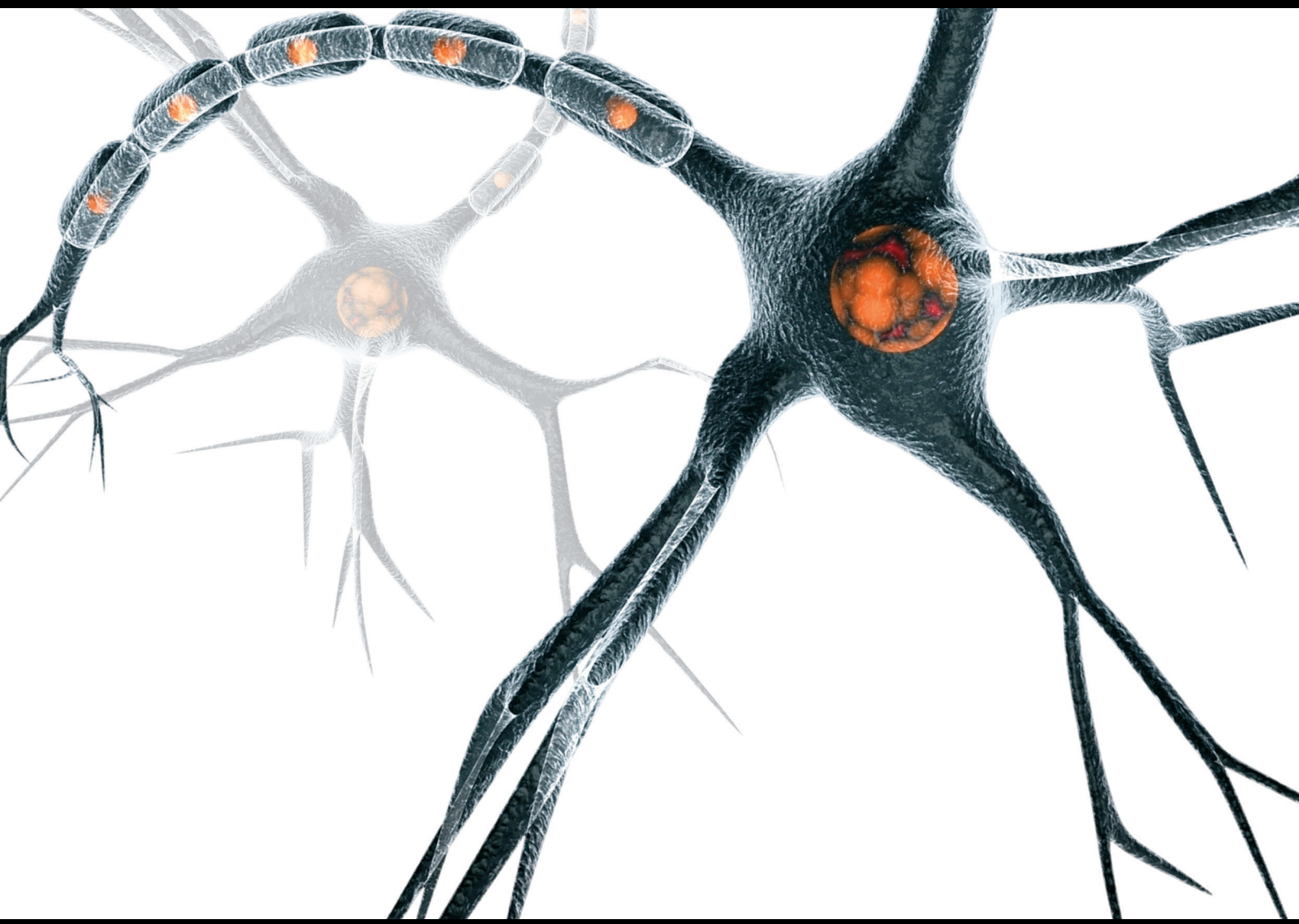
Neural Plasticity

Improving and Predicting Outcomes of Traumatic Brain Injury: Neuroplasticity, Imaging Modalities, and Perspective Therapy

Lead Guest Editor: Chih-Lung Lin
Guest Editors: Aaron S. Dumont, John H. Zhang, Mario Zuccarello, and Cheng-Sheng Chen



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Editorial

Improving and Predicting Outcomes of Traumatic Brain Injury: Neuroplasticity, Imaging Modalities, and Perspective Therapy

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Received 28 March 2017; Accepted 28 March 2017; Published 22 June 2017

Each year, a new traumatic brain injury (TBI) event occurs in an estimated 10 million people worldwide, particularly in young adults. Not only is TBI the leading cause of long-term disability and mortality worldwide, but it is also expected to become the third largest cause of global disease burden by 2020 [1, 2]. TBI is a challenging disease process, both to treat and to investigate. TBI survivors often experience substantial and lifelong cognitive, physical, and behavioral impairments that require long-term access to health care and disability services.

Over the past three decades, imaging modalities, such as positron emission tomography (PET), functional MRI (fMRI), diffusion tensor imaging (DTI), and transcranial magnetic stimulation (TMS), have played a pivotal role in predicting TBI outcome and advancing TBI treatment [3].

Burgeoning evidences for neuroplasticity have shed light on the potential therapeutic protocols focusing on synaptic proteins, new network connections, inflammatory reactions, and the recruitment of immune cells [4]. Future therapies, including gene therapies or a combination of different pharmacologic therapies and rehabilitative protocols, which may benefit victims by targeting multiple mechanisms of recovery, are of utmost interest and currently under heavy investigation by devoting neuroscientists.

The articles contained in this special issue include 4 reviews and 2 original research papers: a quantitative study focusing on predictors of recovery from TBI and a cohort study on substance related disorder after TBI.

(i) TBI survivors suffer various functional and cognitive sequelae that may impose serious medical and social problems. J. Ma et al. reviewed the complicated pathological mechanisms of diffuse axonal injury (DAI) in an attempt to facilitate more accurate diagnosis and hence improve the survival and life quality of DAI patients.

(ii) Not many studies have discussed the role of synapses after TBI. Z. Wen et al. provided a comprehensive review on the role and mechanisms of synapses in TBI and the correlation between key synaptic proteins and neuroplasticity. The article also provides insights on the role of synapses in the treatment and prognosis of TBI.

(iii) Molecular studies concerning the microglia-induced inflammation by M1 phenotype and anti-inflammation by M2 phenotype are a new strategy for treatment of TBI. In the paper titled "The

Polarization States of Microglia in TBI: A New Paradigm for Pharmacological Intervention," H. Xu et al. examined research on the polarization of microglia and their roles in the inflammation response and secondary brain injury after TBI. It is hoped that decreasing M1 phenotype and increasing M2 phenotype may shed light on the pharmacotherapy of TBI.

(iv) Studies to locate the clinical predictors of recovery from prolonged disorders of consciousness (PDC) can be arduous. In the original research presented by H. Abe et al., 14 TBI patients were investigated using diffusion tensor imaging (DTI) for long-term follow-ups of 1-2 years. The results disclosed correlation between initial severity of PDC and difference in axial diffusivity (AD) and the degree of recovery from PDC (RPDC). Microstructural white matter changes in this study implicate their possible relationship with the degree of RPDC.

(v) Efforts to correct behavioral, cognitive, mood, and executive impairment of TBI patients are costly. The article "Rehabilitation Treatment and Progress of Traumatic Brain Injury Dysfunction" by B. Dang et al. compiles the current rehabilitation treatment plans and outcomes of TBI in adults.

(vi) Whether TBI induces substance-related disorder (SRD) is currently debatable. C.-H. Wu et al. carried out a cohort study of 19 thousand TBI adults with no history of mental disorders prior to brain injury in the original paper titled "Traumatic Brain Injury and Substance Related Disorder: A 10-Year Nationwide Cohort Study in Taiwan." Results show that the overall incidence of SRD was 3.62-fold higher in the TBI group and 9.01-fold in the severe TBI group. The severity of TBI seems to have strong correlation in the subsequent risks of SRD.

Acknowledgments

We would like to thank all authors and reviewers who have contributed to this special issue. We hope this collection benefits the development and future studies in pathophysiological mechanisms, outcome predictors, and treatment strategies of TBI.

Chih-Lung Lin
Aaron S. Dumont
John H. Zhang
Mario Zuccarello
Cheng-Sheng Chen

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Hindawi
Neural Plasticity
Volume 2017, Article ID 4296075, 8 pages
https://doi.org/10.1155/2017/4296075

Review Article

Therapeutic Potentials of Synapses after Traumatic Brain Injury: A Comprehensive Review

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Received 29 November 2016; Revised 9 February 2017; Accepted 14 March 2017; Published 12 April 2017

Academic Editor: Chih-Lung Lin

Massive studies have focused on the understanding of the pathobiology of cellular and molecular changes and injury mechanisms after traumatic brain injury (TBI), but very few studies have specially discussed the role of synapses in the context of TBI. This paper specifically highlights the role and therapeutic potentials of synapses after TBI. First, we review and conclude how synapses interact with constant structural, metabolic, neuroendocrine, and inflammatory mechanisms after TBI. Second, we briefly describe several key synaptic proteins involved in neuroplasticity, which may be novel neuronal targets for specific intervention. Third, we address therapeutic interventions in association with synapses after TBI. Finally, we concisely discuss the study gaps in the synapses after TBI, in hopes that this would provide more insights for future studies. Synapses play an important role in TBI; while the understandings on the synaptic participation in the treatments and prognosis of TBI are lacking, more studies in this area are warranted.

1. Introduction

It is well established that traumatic brain injury (TBI) is closely related to the occurrences, evolvements, and prognosis of psychiatric disorders, neuronal dysfunction, and cognitive impairment [1–3]; however, the mechanisms underlying the diseases at the cellular and molecular levels such as inflammation involvement, metabolic homeostasis imbalance, and synaptic injury remain elusive. If remain untouched, it may increase the potentials for many short-term (bleeding, headaches) and long-term (cognitive impairments) symptoms [2]; therefore, the studies on the mechanisms elaborating the cellular and molecular pathology should be put on the top agenda of TBI researches.

Synapse as a basic element for brain structure has been believed to play a significant role in the disadvantageous influences following TBI; the regular fusing of the synaptic vesicle and the plasma membrane and the orderly releasing of neurotransmitters into the synaptic cleft seem to be essential to the normal neuronal interaction [4]. Although it is now widely acknowledged that synapse is important to brain development and cognitive functions [5–7], the molecular mechanisms that the synapse structure and function changes induced by TBI remain largely unclear [8–10]. Besides, the databases on synapse categories have identified 109 domains involved in synaptic functions and more than 5000 synaptic proteins [11], yet very few of the synaptic proteins have been proven to be related with the synaptic dysfunction after TBI. Comprehensive reviews on the role of synapses after TBI are significantly necessary to figure out the study status and to elucidate future studies.

TBI is a kind of disease with a lot of factors involved; the prognosis differs from one to another, and it is under the interaction of various mechanisms working unitedly or orderly, which make TBI treatment quite complicated. Therefore, we conducted this comprehensive review on the role of synapse after TBI, which mainly focused on the interactions between different functional mechanisms

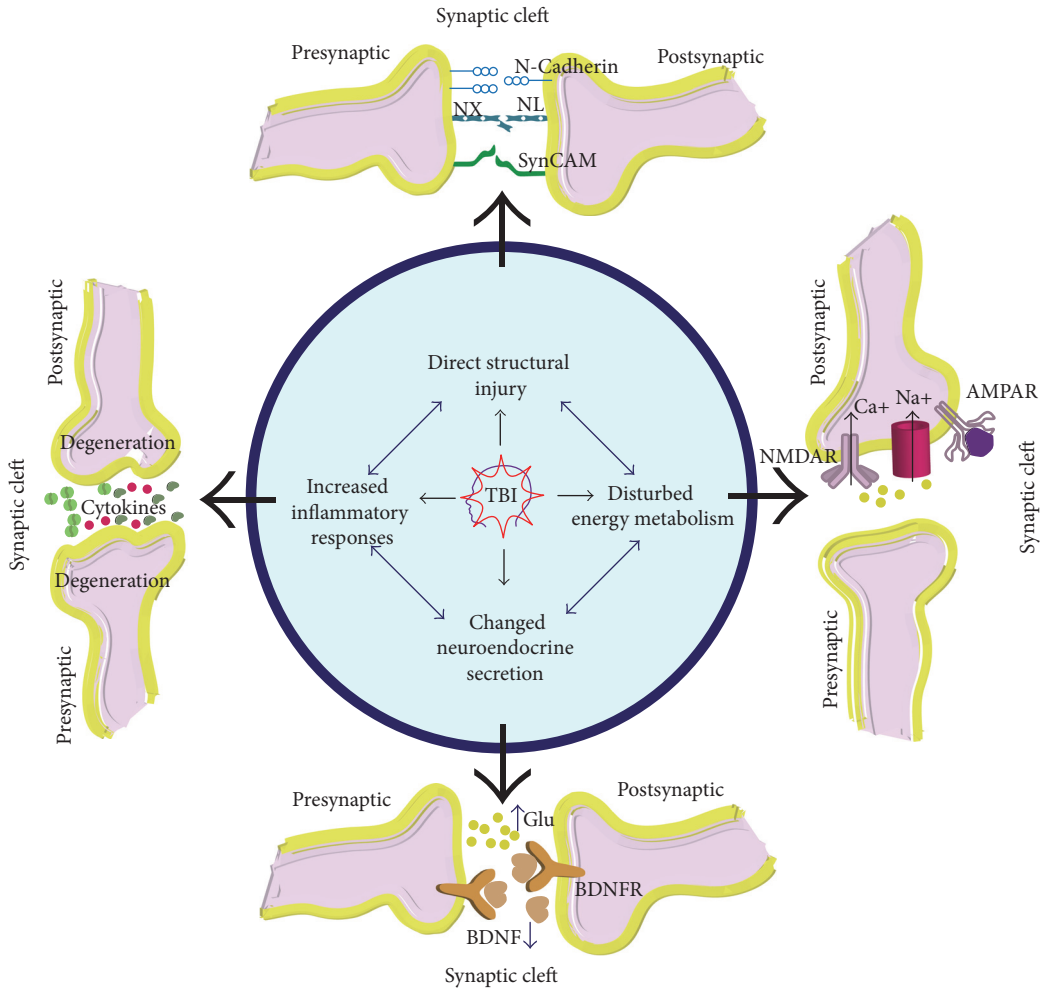

Figure 1: A brief drawing of the synaptic interaction with constant structural, metabolic, neuroendocrine, and inflammatory mechanisms after TBI; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR: N-methyl-D-aspartate receptor; Glu: glutamate.

and synapses (Figure 1), the related synaptic proteins (Figure 2), and the targeted treatments on improving the synaptic plasticity after TBI, to provide insights into future studies in this area.

2. The Interactions between Functional Mechanisms and Synapses

2.1. The Interaction between Direct Structural Injury and Synapses after TBI. It is under estimation that more than 10^{11} neurons exist in the adult human brain, and each of them is constructed with 10^4 synapses [12]. Synaptic structures have been reported to be highly vulnerable to the direct or indirect concussion attack following TBI in experimental and clinical settings [13, 14]. The focal mechanical attack resulting from the direct or contoured violence may lead to the structurally or functionally synaptic disconnection, and the structural changes of the synaptic cleft, the presynaptic and postsynaptic densities (PSDs), may cause temporary or long-term synaptic loss. This primary damages may trigger the biophysical and neurochemical change cascades and finally give rise to either synaptic repair or eternal loss.

2.2. The Interaction between Disturbed Energy Metabolism and Synapses after TBI. Membrane depolarization is initiated instantly by the damage on neuronal membranes and axons induced by TBI [15], leading to massively excitatory neurotransmitter release such as glutamate [16, 17]. The glutamate not only results in intracellular calcium accumulation but also activates the N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) [18, 19]. Additionally, mitochondrial dysfunction may occur due to the elevated calcium influx activating the intracellular proteases and finally lead to neuronal apoptosis. A huge body of energies are needed to maintain the metabolic and ionic homeostasis, and accordingly, the demand for blood glucose will increase, causing an imbalance between glucose supply and demand.

The synapses play a significant role in this process. Long-term potentiation (LTP) may be triggered by the activation of excitatory synapses, a process that requires intracellular calcium accumulation in the dendritic spine by activating NMDAR [20, 21]. The magnesium ions may block these receptor channels in a physiological situation with voltage-controlled method; however, in the stressing conditions

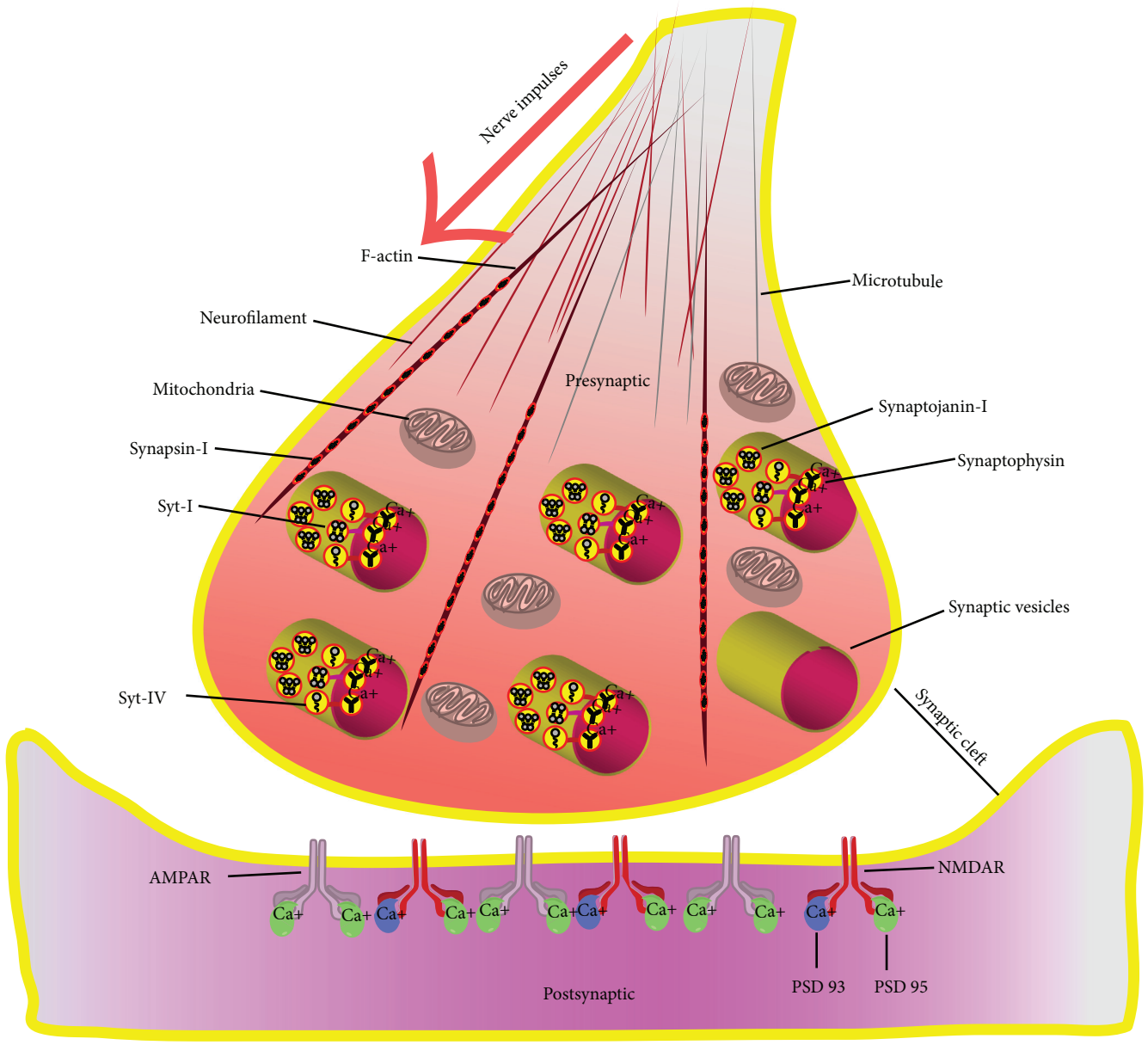

Figure 2: A brief distribution and construction of synaptic proteins. Notes: Syt-I: synaptotagmin-I; Syt-IV: synaptotagmin-IV; Syt-IV: synaptotagmin-IV; PSD-93: postsynaptic density complex protein-93; PSD-95: postsynaptic density complex protein-95.

induced by TBI, the cell depolarization largely by activating AMPAR may extrude the magnesium ions [22, 23]. Therefore, the NMDAR and AMPAR can significantly influence the LTP and eventually the energy metabolism.

2.3. The Interaction between Changed Neuroendocrine Secretion and Synapses after TBI. The disturbance of the hypothalamic-pituitary-adrenal (HPA) axis has been reported in several TBI studies [24–26]. The TBI may lead to increased serum cortisol and adrenocorticotropic hormone (ACTH) level to regulate other organs in this stressing condition; on one hand, those neuroendocrine hormones may alert the body to better deal with TBI, and on the other hand, the overexpression of stress hormones can significantly facilitate the TBI. However, it should be pointed out that although HPA axis changes after TBI is well documented, the direct linkages between synaptic dysfunction and HPA after TBI remain not clear, and the direct linkage of synaptic dysfunction to post-TBI HPA dysfunction needs to be further explored in future studies.

At the same time, it should be noted that the secretions of neurotrophins in the hippocampus are reduced after TBI. Neurotrophins served as "autocrine" in regulating the brain as the target organ contain many secretory proteins including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and so on. Close relationships have been found between neurotrophins and synapse structures and functions; the neurotrophins may influence axonal and dendritic branching and remodelling [27–29], synaptogenesis in arborizing axon terminals [30],

synaptic transmission [31–33], and synapsis maturation [32, 34]. In the context of TBI, the stress hormones are excessively secreted and neurotrophin secretion decreases; accordingly, the synapses tend to be seriously damaged. How to control and adjust the neuroendocrine secretion and synapsis development after TBI is a tricking yet promising problem in the treatment of TBI.

2.4. The Interaction between Increased Inflammation Responses and Synapses after TBI. TBI-induced physiological changes may give rise to neuroinflammation and neuron death [35]. A body of proinflammatory cytokines are rapidly elevated in the acute period including IL-6, TNF-α, and so on [36]; besides, the increased cytokines levels in the brain are dramatically higher than the corresponding levels in serum [37]. Generally, the existence of proinflammatory cytokines are required for preserving synaptic strength at excitatory synapses, and it is essential to synaptic plasticity [38, 39], but excessive secretion of proinflammatory cytokines may produce detrimental effects on the synapses [40].

The TBI-induced blood-brain barrier (BBB) integrity disruption acts an important role in the neuroinflammatory response [41], which allows increased cytokine pour into the brain and ultimately activate microglia in excess. The microglia is highly alerted in the acute period after TBI [41]. The microglia offers a beneficial hand to neuronal circuit formation via phagocytosing weak synapses and regulating neurogenesis [42], but excessive microglia accumulations may cause serious impairments to the synaptic pruning and disrupt the synaptic plasticity [43, 44]. It should be emphasized that microglia might be linked to synaptic integrity in the inflammation response, yet no studies have specifically dealt with this issue in the context of TBI. The direct evidence linking microglia activation and cytokine elevation of synaptic changes after TBI is lacking, more studies on these issue are warranted.

3. The Major Synaptic Proteins Involved in TBI

Up to date, more than 5000 synaptic proteins have been identified [11], and most of them have been found in association with neurological diseases such as stroke, TBI, Alzheimer's disease, and so on. Based on literature review, we identify several key synaptic proteins and introduce them briefly (Figure 2).

A linear polymer microfilament called F-actin, which is essential for such important cellular functions as the mobility and contraction of cells during cell division [45, 46], is considered to have structural polarity which is critical to synaptotagmins [47, 48]. Synaptotagmins family is a kind of calcium-binding protein located in the synaptic vesicles, and Syt-I and Syt-IV are the most relevant in TBI. Syt-I proteolysis may hinder the synaptic vesicle from docking to the presynaptic membrane terminal [49, 50]; besides, the accumulation of deformed Syt-I may cause disadvantageous effects on presynaptic function [51], while Syt-IV increases massively after TBI and tends to reduce synaptic activity [52]. The synapsins are a family of phosphoproteins with a function of regulating the release of neurotransmitter in the presynaptic area [53]. It has been hypothesized that increased oxidative stress after TBI may lead to synapsin-I loss and further disturb the interactions between synapses [54]. Synaptophysin is a kind of calcium-binding glycoprotein acting in vesicular trafficking, docking, synaptogenesis, and synaptic plasma membrane fusing in the presynaptic. It is noteworthy that the role of synaptophysin involved in TBI remains unclear; it is found that synaptophysin levels change differently between the mild and severe TBI [55], but another study addressing these issues remains somewhat contradictory [56]. Synaptojanins act a significant role in recycling vesicles at the presynaptic area. Synaptojanin-I is predominantly distributed in nerve terminals and is extremely sensitive to calpain digestion [57]; therefore, it has been taken as a novel target for degradomic calpain [51].

4. The Treatments Targeted on Synapses after TBI

With consideration to the important role synapses played in the TBI prognosis, lots of strategies have been adopted to enhance the synaptic plasticity and promote synaptic function, and even though the treatments may largely differ, the basic principles for speeding recovery from TBI remain similar, that is, promoting synaptogenesis and synaptic terminal reconnection and then exerting the neuroprotective effects [58].

Exercises are believed to be effective in improving TBI prognosis; the underlying mechanisms include changing the brain structural integrity by enhancing neurogenesis and angiogenesis with more secretions of growth factors promoting synaptic plasticity [59–61]. Notably, aerobic exercises such as tai chi and yoga have been popularly promoted for its potential advantages in healthy and ill-attacked populations [62–67]; however, the frequency and burden of exercise after TBI differ from one to another and remain to be further elucidated [68].

Several experiments in the animal with significant synaptic function improvement should be considered. Inhibiting endocannabinoid degradation may ameliorate the neurobehavioral, neuroinflammatory, and glutamate dyshomeostasis after TBI via reducing synaptic hyperexcitability [69]. Pycnogenol, one kind of bioflavonoid with significant antioxidant and anti-inflammatory properties, provides a beneficial effect on improving CA3-CA1 synaptic function in rats after TBI [70]. Another lab study [71] indicates that tyrosine kinase EphB3 produces deleterious effects on maintaining synaptic stability and plasticity after TBI. Resveratrol, a polyphenol compound with antioxidant properties, can upregulate synaptophysin and PSD 95 and suppress neuronal autophagy [72]. Rapamycin may exert suppressing effects on the neurogenesis and synaptic reorganization shortly after TBI in the dentate gyrus and cause a neuroprotective effect [73]. Additionally, dietary omega-3 fatty acids intake can protect against the decreased synaptic plasticity and impaired learning ability after TBI [74]. Meanwhile, the low-level laser therapy after TBI seem to increase the BDNF level and promote synaptogenesis [75]. However, these data only indicate the

potential use for TBI treatments [76, 77], and more clinical evaluations are needed to assess the value of these findings.

5. Study Gaps and Future Direction

The understanding on the synaptic mechanisms involved in TBI still remains incomplete, and the interactions between synapses and the other injury mechanisms still need to be ascertained. Also, even though three-dimensional in vitro injury systems have been proposed to connect the injury degree and cell responses [78], the majority of studies are conducted in animals but not in humans, and verifying these findings in human use is a big step to move on. Particularly, the synaptic proteins in TBI are not well-studied; most studies are confined in the pathological conditions of stroke or subarachnoid hemorrhage, and more synaptic protein-related studies may facilitate the identification of new proteins and protein-targeted treatments.

Notably, the synapses seem to respond differently to the mild and severe TBI, indicating that subanalysis on the role of synapses in accordance with the degree of TBI is warranted, and based on the literature review, we found that the studies on the severe TBI were rather insufficient, regardless of molecular mechanisms or treatment options. In addition, it is important to take the dynamic characteristics of TBI into consideration; the synapses may act differently at different post-TBI periods. Besides, some studies conclude that combined therapies seem to exert synergistic effects and are more beneficial than single therapies [79, 80]; the role of synapse in this condition is not fully understood.

In conclusion, synapses play a significant part in the evolvement of TBI with a complicated link to various responsive mechanisms. With more acting mechanisms, synaptic protein treatments and synapsis-related treatments await to be elucidated, and further studies on this area are necessitated.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Zunjia Wen and Dong Li contributed equally to this work.

Acknowledgments

This work was supported by Suzhou Key Medical Center (Szzx201501), grants from the National Natural Science Foundation of China (nos. 81571115, 81422013, and 81471196), Scientific Department of Jiangsu Province (no. BL2014045), Suzhou Government (nos. SZS201413, SYS201608, and LCZX201601), and Jiangsu Province (no. 16KJB320008).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 1582182, 6 pages
https://doi.org/10.1155/2017/1582182

Review Article

Rehabilitation Treatment and Progress of Traumatic Brain Injury Dysfunction

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Received 29 November 2016; Revised 28 February 2017; Accepted 7 March 2017; Published 11 April 2017

Academic Editor: Aaron S. Dumont

Traumatic brain injury (TBI) is a major cause of chronic disability. Worldwide, it is the leading cause of disability in the under 40s. Behavioral problems, mood, cognition, particularly memory, attention, and executive function are commonly impaired by TBI. Spending to assist, TBI survivors with disabilities are estimated to be costly per year. Such impaired functional outcomes following TBI can be improved via various rehabilitative approaches. The objective of the present paper is to review the current rehabilitation treatment of traumatic brain injury in adults.

1. Introduction

Traumatic brain injury (TBI) refers to blunt, penetrating, or acceleration/deceleration force-derived craniocerebral injury, which causes symptoms such as decline in level of awareness or consciousness, memory loss or forgetfulness, other neurological or neuropsychological abnormalities, and even death. TBI is a critical public health and socioeconomic problem throughout the world. The incidence of TBI has been increasing annually. According to the World Health Organization, TBI will be a major health problem and the main reason for disability in 2020 [1]. Primary and secondary TBIs cause temporary and/or permanent dysfunction in the brain, which limits a patient's activities, affects participation in society, and lowers quality of life. This can lead to depression and other chronic diseases in TBI patients [2, 3]. This article reviews current rehabilitation treatment for TBI.

2. Hyperbaric Oxygen Therapy (HBOT) Relieves TBI

Hyperbaric oxygen therapy (HBOT) is defined as the inhalation of 100% oxygen under the pressure greater than 1 atmosphere absolute (ATA) (1 ATA = 101.3 kPa). HBOT is a current interest in the field of neurological diseases and has been proved to inhibit apoptosis, suppress inflammation, protect the integrity of blood-brain barrier, and promote angiogenesis and neurogenesis [4, 5].

The major pathogenic mechanisms of TBI include ischemia and hypoxia in brain tissues, resulting in parenchymal softening with necrosis. To date, HBOT is one of the most important clinical therapies for TBI. A study by Lin et al. [6] showed that 2.0 atmospheres absolute (ATA) oxygen in HBOT for 5 consecutive days (once per day, 1 hour per session) resulted in overexpression of the 70 kDa heat shock protein (HSP-70) and attenuated cerebral edema, oxidative damage in the hippocampus, and cognitive impairment in a rat model in a simulated high-altitude environment (9.7% oxygen concentration, 6000 meter altitude, and 0.47 ATA) for 3 consecutive days. Harch et al. [7] treated 16 TBI, post-TBI syndrome, and posttraumatic stress disorder (PTSD) patients with 40 sessions of 1.5 ATA/60 minutes of HBOT for 30 days, which greatly improved symptoms, results of neurological examinations, comprehensive IQ tests, and cognition functions. A study by Geng et al. [8] showed that HBOT may

suppress activation of inflammasome signals, thereby alleviating TBI.

In chronic brain injury, HBOT improved cerebral blood flow (CBF) and ameliorated the neuropsychological disorders [9, 10]. HBOT has also been reported to show positive effects by improving the quality of life in patients with postconcussion syndrome or mild TBI at late chronic stage [7, 11, 12]. In severe TBI, HBOT has reduced mortality and enhanced functional outcome [13–15]. These researches suggested the successful use of intensive HBO as a treatment in TBI patients.

3. Noninvasive Brain Stimulation Benefits the Treatment of TBI

To date, several technologies have been developed. The most common technologies are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Repetitive transcranial magnetic stimulation (rTMS) is a painless, noninvasive, easily operated treatment with few adverse reactions. It has specific effects in rehabilitation of TBI patients [16]. Depending on the frequency used, rTMS alters neuronal excitability by generating excitatory (>5 Hz) or inhibitory (1 Hz) activity, which can last for several hours [17, 18]. As a noninvasive brain stimulation technique, rTMS has successfully treated schizophrenia, depression, Parkinson's disease, aphasia, unilateral neglect, and cognitive impairment [19–24]. Neville et al. [25] conducted a double-blind randomized controlled trial with 36 TBI patients who were randomly and equally divided into 2 groups. TBI patients in the treatment group received 10 sessions of high-frequency rTMS (10 Hz) over the left dorsolateral prefrontal cortex (DLPFC), and TBI patients in the sham group received pseudostimulation. The patients underwent neuropsychological assessment 1 week before and then 1 week and 3 months after rTMS to evaluate direct and delayed effects. The results showed that rTMS could improve depression and cognitive function after TBI.

Dhaliwal et al. [26] and Li et al. [27] recently reported that cerebral stimulation had potential effects on TBI treatment. Although these 2 groups studied non-athletic-related injuries, they indicated the safety and potential benefits of cerebral stimulation for TBI patients. Several studies have shown that rTMS and tDCS reduce TBI-associated depression, tinnitus, neglect, memory deficits, and attention disorders [26, 27]. Middleton et al. [28] also reported that 2 TBI patients who received dual-hemisphere tDCS (1 patient had stroke and TBI) for 6 months showed significant improvement based on the upper extremity Fugl-Meyer scale. These studies demonstrate that post-TBI cerebral stimulation is safe and has potential benefits.

4. Virtual Reality Evaluates the Function and Improves the Prognosis of TBI

Computer-aided training combined with audial and visual stimulations to simulate audial, visual, and game-associated intuitive trainings that engage different components of impairment, such as memory, attention, and visual perception, greatly improves patient interest and enthusiasm in participation. Development of a computer-aided training system, especially virtual reality (VR) technology, promotes integration between computer technology and cognitive science that has incomparable advantages for assessment and training of cognitive impairment compared with cognitive training by rehabilitation therapists [29–31]. During the training process, personal, customized procedures are used to reduce the duration of the direct contact between the therapist and the patient. Studies have shown that computer-aided strategies improve patient attention, memory, and execution capabilities [32, 33]. VR training also improves patient mood through audial and visual feedback that lets patients experience emotional success and minimizes patient anxiety during treatment [34]. It also promotes persistence since patients practice until they succeed. In addition, a VR training system provides a comprehensive evaluation of patient motor function, cognitive function, daily life skills, and social skills. It directly analyzes the data and presents a written report for comparison of pre- and posttreatment conditions, which help in determining treatment goals, selecting treatment options, and evaluating training effects to achieve a perfect combination of interactive training and exercise, cognitive training, and rehabilitation assessment [35].

5. Limb or Organ Function Reconstruction following TBI

Functional electrical stimulation (FES) is a low-frequency pulse current that is used to stimulate limb or organ dysfunction. Its effects replace or correct lost function in limbs and organs. By adjusting the advanced nerve center, FES promotes functional reconstruction in patients [36]. Task-oriented functional electrical stimulation (TFES) is a combination of bilateral exercise, repetitive training, task-oriented therapy, and FES, and preliminary results have indicated positive outcomes [37–40].

Treatment outcomes of TFES are better than those of FES and conventional therapy. A possible explanation may combine the effects of FES and task-oriented therapies as well as the synergistic effect of this combination therapy. Iftime-Nielsen et al. [41] confirmed a synergistic effect between proactive attitude of patients and FES therapy. Makowski et al. [42] showed that a combination of FES therapy and conscious activity affected action stimulated by FES. Under the effect of FES, a weak and voluntary effort can produce greater reach and movement.

Calabrò et al. [43] conducted 2 different types of intensive rehabilitation training for a 34-year-old male with dysphagia after TBI, which included conventional rehabilitation training and a combination of conventional rehabilitation training and VitalStim electrical stimulation therapy for 6 weeks to access his specific swallowing function and electrophysiological parameters before and after treatment. The results showed that only VitalStim point simulation significantly improved the swallowing function of the patient. This patient could eventually and safely eat solid food after the treatment.

6. TBI Benefits from Behavioral, Emotional, and Family Therapies

TBI affects a patient's emotions, behavioral stability, and self-confidence. Primary caregivers of TBI patients experience considerable emotional stress and sense of burden. Albert et al. [44] showed that low-cost interventions relieve the burden of caregivers and improve their satisfaction. A study by Sinnakaruppan et al. [45] showed that family education programs for caregivers and TBI family members help relieve stress and strengthen coping abilities.

Common behavioral changes after TBI often include anger, depression, anxiety, and verbal or physical aggression. Emotional stability of TBI patients is necessary; otherwise, these patients cannot participate in and benefit from the rehabilitation processes. Psychotherapy (individual and group) emphasizes emotional and behavioral therapies. Studies show that training in good coping skills and anger management can reduce patient aggression. In addition, Baker et al. [46] showed that music therapy demonstrated an improvement in patient emotion and anger problems.

7. Basic Research on TBI Rehabilitation in Recent Years

In recent years, the basic research on traumatic brain injury rehabilitation increase gradually [47–51]. A recent review suggests that rat models and closed head impacts have dominated the field of behavioral testing in animal models of juvenile TBI. Both motor and cognitive functions seem to be affected [47]. A latest study revealed that long-term spatial learning-memory deficits are dependent on the severity of destruction in the white matter and hippocampus. Therapeutic strategies targeting both the white matter and hippocampus may be needed to improve the neurological functions in TBI victims [50].

Studies have shown that the major cause of death after TBI is neuronal death and rupture of blood vessels. Nerve regeneration and angiogenesis play key roles in functional recovery [52–54]. Circulating endothelial progenitor cells (EPCs) are involved in angiogenesis [55, 56] and have been confirmed to reduce infarct volume, increase capillary density, and improve myocardial blood perfusion and limb ischemia in animal models [57, 58]. Erythropoietin (EPO) promotes proliferation and differentiation of red blood cells and has been used in clinical treatment of anemia, prevention of spinal cord injury [59], retinal ischemia [60],skeletal muscle ischemia [58],pulmonary hypertension [61], and myocardial ischemia-reperfusion injury [62, 63]. It is also used for prevention of TBI by enhancing antiapoptotic [59, 64], anti-inflammatory [60], and neuroprotective effects [65, 66]. Through mobilization of endothelial progenitor cells, EPO promotes angiogenesis and reduces nerve cell death, which improves functional outcomes after stroke [67–69]. Data of Wang et al. [49] showed that recombinant human EPO mobilized endothelial progenitor cells and angiogenesis to improve the functional prognosis of TBI in rats.

In summary, rehabilitation is essential after TBI treatment. Studies on the timing of corresponding rehabilitation in stroke research are common. However, the optimal window for TBI rehabilitation is rarely reported. Andelic et al. [70] divided 61 patients with severe TBI into 2 groups: the experimental group with early intervention of rehabilitation training and the control group with delayed rehabilitation training. The Glasgow Outcome Scale Extended (GOSE) and the Disability Rating Scale (DRS) were used to rate the 2 groups 12 months after training. The results demonstrated that the experimental group had significantly higher GOSE and DRS scores compared with the control group, which indicated that early intervention of rehabilitation training achieved better treatment outcomes. However, due to the complexity of TBI, an inadequate sample size, and lack of an appropriate control group, clinical rehabilitation studies have encountered significant challenges. For noninvasive brain stimulation, stimulation frequency, precise positioning, and course of treatment are closely associated with treatment efficacy. A large-scale randomized controlled trial is necessary in further studies, and additional research in this direction will extend the rehabilitation prospects of TBI.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Baoqi Dang and Wenli Chen contributed equally to this work.

Acknowledgments

This work was supported by the Suzhou Key Medical Center (Szzx201501)—grants from the National Natural Science Foundation of China (nos. 81571115, 81422013, and 81471196), Scientific Department of Jiangsu Province (no. BL2014045), Suzhou Government (nos. SZS201413, SYS201608, and LCZX201601), Jiangsu Province (no. 16KJB320008).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 9358092, 11 pages
https://doi.org/10.1155/2017/9358092

Research Article

Predictors of Recovery from Traumatic Brain Injury-Induced Prolonged Consciousness Disorder

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Received 28 October 2016; Revised 19 January 2017; Accepted 22 January 2017; Published 23 February 2017

Academic Editor: Cheng-Sheng Chen

We investigated the clinical predictors of the degree of recovery in patients with prolonged disorders of consciousness (PDC) caused by traumatic brain injury. Fourteen patients with PDC underwent two diffusion tensor imaging (DTI) studies; the first and second scans were performed at 345.6 ± 192.6 and 689.1 ± 272.2 days after the injury, respectively. In addition to the temporal changes in each of these diffusion parameters, fractional anisotropy (FA), mean diffusivity, axial diffusivity (AD), and radial diffusivity were assessed over a 1-year period. Relationship of clinical and DTI parameters with recovery from PDC (RPDC) was evaluated using Spearman's rank-correlation and stepwise multiple linear regression analysis. The mean FA and number of voxels with FA values > 0.4 (VsFA0.4) were significantly decreased at the second scan. A significant positive correlation was observed between the degree of RPDC and mean FA ($r = 0.60$) and VsFA0.4 ($r = 0.68$) as well as between the difference in VsFA0.4 ($r = 0.63$) and AD ($r = 0.54$) between the first and second scans. On multiple linear regression analysis, initial severity of PDC and the difference in AD remained significantly associated with the degree of RPDC. The microstructural white matter changes observed in this study indicate their potential relation with the degree of RPDC over the longer term.

1. Introduction

Diffuse axonal injury (DAI) is a common form of traumatic brain injury (TBI) sustained in motor vehicle collisions. The injury involves rotational forces and is characterized by extensive white matter damage [1]. The neuropathology of disorders of consciousness (coma, vegetative state, and minimally conscious state) has been extensively described at postmortem [2–4]. Diffuse disruption of subcortical white matter is the most common postmortem finding in victims of TBI associated with impaired consciousness [2]. DAI and thalamic damage were the most common postmortem structural abnormalities reported in a case series of 35 patients who remained in a vegetative state after TBI until the time of their death [3, 4]. Thus, severe TBI commonly involves multiple diffuse lesions in both white and gray matter.

Diffusion tensor imaging (DTI) has been useful in describing the microstructure changes in the chronic stage of DAI [5]. Several studies have documented posttraumatic findings of axotomy and demyelination, months to years after injury. These include findings of increased water diffusion as measured by mean diffusivity (MD) and a reduction in the directionality of diffusion as measured by fractional anisotropy (FA) on DTI [5]. These findings, in conjunction with the apparent loss of subcortical white matter volume, suggest that acute edema may be a potential early marker

of posttraumatic deterioration that ultimately impairs axonal integrity in the chronic state [5]. Few longitudinal studies have examined temporal evolution of white matter damage after DAI in humans [6–9]. However, the acute scans were collected, on average, within two months after injury; smaller time windows are necessary to obtain a more thorough understanding of the evolution of white matter damage. Further, several studies have documented correlation between decreased FA in several brain regions and unfavorable outcomes in patients with severe TBI [8, 10, 11]. A recent whole brain WM analysis of DTI parameters revealed an increase in axial diffusivity (AD) and radial diffusivity (RD) in the acute phase and a positive correlation of RD with severity of injury [5]. Longitudinal analysis showed reduction in FA and AD, but not in RD [5]. This study [5] examined the evolution of white matter integrity from acute to chronic stages of DAI due to TBI. Data from this study suggest complicated mild-to-severe TAI results in significant edema that eventually resolves leaving behind a compromised white matter microstructure. The data [5] also suggest that white matter compromise after DAI is a process involving white matter demyelination as well as axonal damage that may be present not only in the early stage but also in the chronic stage [5]. However, the mechanism that explains this finding is still unclear. DTI still appears to be capable of detecting microstructural changes after DAI.

Patients with severe PDC, such as those in a vegetative state, typically have unfavorable outcomes although gradual, subtle, and minor clinical changes are on record. In the last 2 years, our institution provided inpatient care to patients with prolonged disorders of consciousness (PDC) due to TBI. The therapeutic modalities include standard nursing care, physical therapy, and occupational therapy, as well as other alternative treatment modalities such as music therapy, aroma massage, and exposure to natural environment (i.e., feeling the sunlight, blowing wind, and exposure to seasonal temperature changes). Indeed, a few patients have shown slight positive reactions during inpatient residency at our institution.

In this study, we sought to identify potential predictors of the degree of recovery from PDC over a period of 2 years, using DTI parameters in whole brain. We examined the longitudinal alterations in anatomical connections of white matter in these patients and explored potential association of microstructural imaging biomarkers in whole brain white and gray matter with clinical markers of potential clinical relevance.

2. Methods

2.1. Patients. We retrospectively recruited 14 patients at our institution that had chronic severe PDC resulting from traffic accident-related brain injury. All patients with PDC underwent 3 T MRI studies at admission and after completion of 1 year of treatment at our institution. Mean age (±SD) of patients was 58.6 ± 19.3 years; the mean duration (±SD) from admission to study recruitment was 339.8 ± 191.7 days. The clinical characteristics of patients are presented in Table 1. The first DTI scan was performed at admission (345.6 ± 192.6 days after the initial injury); the second scan was performed approximately 1 year after admission (689.0 ± 272.2 days after the initial injury).

Furthermore, we prospectively recruited 8 healthy normal volunteers (2 males and 6 females) for comparison. The age range of the healthy participants was 32–60 (45.5 ± 9.1) years (Table 2).

2.2. Standard Protocol Approvals, Registrations, and Patient Consent. This study was conducted in compliance with the ethical principles for biomedical research on human subjects enshrined in the Declaration of Helsinki and informed consent regulations. Approval from the institutional ethics committee was obtained prior to the initiation of the study.

2.3. PDC Assessment. PDC was assessed using the Kohnan score, which measures the severity of consciousness disorder from a severe, persistent vegetative state (Appendix [12]). The Kohnan score was developed at our institution to resolve this issue. The unidimensionality and higher intra- and interrater reliability of this score have previously been reported [12]. The score is based on seven parameters, each of which is subdivided into 5 grades: extreme (10 points), severe (9 points), moderate (7 or 8 points), mild (5 points), and slight (0 points). We additionally assessed general functional recovery using the Extended Glasgow Outcome Scale (GOSE) (range 1–8; higher scores indicate superior functional outcomes). These assessments were performed at admission and at 2 years after admission.

2.4. Image Acquisition. MRI was performed using a 3.0 T Signa Excite HD scanner (General Electric, Milwaukee, WI, USA). The parameters for DTI were as follows: echo time, 59 ms; repetition time, 9,000 ms; flip angle, 90°; slice thickness, 3 mm with no gap; field of view, 28.8 × 28.8 cm; acquisition matrix, 96 × 96; image matrix, 256 × 256 with a voxel size of 1.125 × 1.125 × 3.0 mm; number of excitations, 1; and band width, 250 kHz. Images were obtained using 15-directional diffusion encoding (b value, 1,000 s/mm^2 in each direction) and one set of images with $b = 0$ s/mm^2.

A total of 46 axial sections covering the entire cerebrum were obtained. The most inferior DTI slices were positioned at the medulla oblongata during acquisition.

2.5. Image Preprocessing. All DTI data were processed using the FSL software package (the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library [13]). DTI images were skull-stripped using the Brain Extraction Tool (BET) in the FSL. The images were corrected using the Eddy Correct program of the FSL package to adjust for the effects of head movement and eddy currents. FA, MD, AD, and RD maps were generated using dtifit program in the FSL. Lastly, we calculated the mean FA, MD, AD, and RD and counted the number of voxels in which FA values were >0.4 in the whole brain (VsFA0.4) using fslstats program implemented in the FSL. We assumed that using whole brain method affected not only white matter changes but also gray

Table 1: Clinical profiles of patients with prolonged consciousness disorders due to brain injury.

	Age (y)	Gender	Diagnosis	Days until admission following injury	Days until the first scan from injury	Days until the second scan from injury	GCSE at admission	GCSE after 1 year from admission	Kohnan score at admission	Kohnan score after 1 year from admission	Degree of improvement from prolonged consciousness disorders*
1	75	Female	Right acute subdural hematoma, cerebral contusion	407	415	768	2	2	65	63	2
2	60	Male	Traumatic subarachnoid hemorrhage, pneumocephalus, diffuse axonal injury	264	266	548	3	3	34	5	29
3	68	Male	Traumatic subarachnoid hemorrhage, diffuse axonal injury, brainstem contusion	296	311	636	2	2	67	68	−1
4	68	Female	Cerebral contusion, traumatic subarachnoid hemorrhage, diffuse axonal injury, brainstem contusion	126	135	416	2	2	63	56	7
5	78	Female	Left subdural hematoma, traumatic subarachnoid hemorrhage, intracerebral hemorrhage	629	629	885	2	2	64	62	2
6	86	Male	Traumatic subarachnoid hemorrhage	155	158	591	2	2	68	64	4
7	44	Female	Traumatic subarachnoid hemorrhage, diffuse axonal injury	230	232	396	2	3	55	34	21
8	58	Male	Traumatic subarachnoid hemorrhage, left intracerebral hemorrhage	147	149	286	3	3	29	0	29
9	77	Female	Traumatic subarachnoid hemorrhage, cerebral contusion, left intracerebral hemorrhage	226	228	580	2	2	63	62	1
10	31	Male	Left intraventricular hemorrhage, left intracerebral hemorrhage, diffuse axonal injury	482	490	1173	2	2	67	64	3
11	56	Male	Cerebral contusion, intraventricular hemorrhage, brainstem contusion	350	360	779	2	2	62	52	10
12	64	Male	Traumatic subarachnoid hemorrhage, diffuse axonal injury, cerebral contusion	391	400	849	2	2	65	64	1
13	23	Female	Right acute subdural hematoma, traumatic subarachnoid hemorrhage, cerebral contusion, diffuse axonal injury	798	807	1200	2	2	67	65	2
14	33	Male	Traumatic subarachnoid hemorrhage, cerebral contusion, left cerebral hemorrhage	256	258	540	2	3	55	34	21

* is the difference in Kohnan score from admission to after 1 year.

Table 2: Each diffusion parameter of patients with prolonged consciousness disorders due to brain injury.

Number	FA at the first scan	FA at the second scan	Difference in FA from the first to the second scan	VsFA0.4 at the first scan	VsFA0.4 at the second scan	Difference in VsFA0.4 from the first to the second scan	MD [$\times 10^{-3}$ mm^2/s] at the first scan	MD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in MD [$\times 10^{-3}$ mm^2/s] from the first to the second scan	AD [$\times 10^{-3}$ mm^2/s] at the first scan	AD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in AD [$\times 10^{-3}$ mm^2/s] from the first to the second scan	RD [$\times 10^{-3}$ mm^2/s] at the first scan	RD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in RD [$\times 10^{-3}$ mm^2/s] from the first to the second scan
1	0.21	0.21	0.00	21895	23414	−1519	1.52	1.66	−0.14	1.83	2.00	−0.17	1.37	1.49	−0.12
2	0.24	0.22	0.01	47948	39756	8192	1.48	1.40	0.08	1.82	1.71	0.11	1.31	1.25	0.06
3	0.22	0.21	0.01	35733	30750	4983	1.42	1.46	−0.04	1.74	1.77	−0.03	1.26	1.30	−0.05
4	0.22	0.21	0.01	30267	26690	3577	1.36	1.41	−0.05	1.66	1.71	−0.05	1.22	1.27	−0.05
5	0.22	0.22	0.00	31767	30802	965	1.56	1.62	−0.06	1.90	1.97	−0.07	1.39	1.44	−0.05
6	0.29	0.25	0.04	77478	55501	21977	1.43	1.52	−0.09	1.84	1.89	−0.06	1.23	1.33	−0.10
7	0.24	0.22	0.02	37712	29094	8618	1.17	1.18	−0.02	1.48	1.46	0.02	1.01	1.05	−0.04
8	0.28	0.21	0.07	84429	39949	44480	1.39	1.38	0.02	1.81	1.67	0.14	1.19	1.23	−0.04
9	0.21	0.21	0.00	24037	26024	−1987	1.67	1.66	0.01	2.02	2.00	0.01	1.49	1.49	0.01
10	0.19	0.19	0.00	28011	21844	6167	1.47	1.54	−0.07	1.74	1.83	−0.09	1.33	1.39	−0.07
11	0.29	0.24	0.05	72447	40235	32212	1.39	1.30	0.09	1.80	1.62	0.18	1.18	1.14	0.05
12	0.22	0.21	0.01	37434	33854	3580	1.43	1.50	−0.07	1.74	1.80	−0.06	1.28	1.34	−0.07
13	0.22	0.20	0.03	26234	17710	8524	1.52	1.51	0.00	1.86	1.82	0.04	1.34	1.36	−0.02
14	0.26	0.25	0.00	56620	46882	9738	1.81	1.47	0.34	2.27	1.86	0.41	1.58	1.28	0.30

FA: fractional anisotropy; VsFA0.4: number of voxels with a fractional anisotropy value greater than 0.4 in the whole brain; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity.

matter and ventricles. To eliminate these effects, we chose the method of VsFA0.4 that selects only the voxel with high FA values.

2.6. Statistical Analysis. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 24.0 for Mac (IBM SPSS, Chicago, IL, USA). Comparisons over time for group Kohnan scores, GOSE, FA, VsFA0.4, MD, AD, and RD were conducted using the paired t-test or Wilcoxon rank-sum test according to the results of the Shapiro–Wilk test. The Spearman rank-correlation coefficient was used to evaluate the relationships between age, time of admission from injury, degree of recovery from PDC (as determined by change in the Kohnan score during the 2-year period after admission), and the diffusion tensor parameters. These diffusion tensor parameters used for comparisons were FA, VsFA0.4 MD, AD, and RD in the first scan and the differences in the same parameters between the first and the second scan. All univariate potential factors with a P value < 0.1 were entered into the multivariate linear regression model. In addition, variance inflation factors were computed to examine the possible collinearity problem among the predictors. Stepwise multiple regression analyses were performed to identify the variables associated with the degree of recovery from PDC. The alpha level was set to 0.05 for all statistical tests and adjusted for multiple tests (e.g., $n = 5$, $P > 0.01$, comparison of the mean FA, MD, AD, and RD) with Bonferroni correction.

3. Results

In this study, 12 patients had a GOSE score of 2 (vegetative state), and 2 patients had GOSE score of 3 (severe disorder) at admission. However, Kohnan scores at admission showed more variability (range: 29–68). These ranged from minimum consciousness disorder (<39) to complete vegetative state (>65). After 2 years, there was no significant change in GOSE scores ($P = 0.16$, Wilcoxon rank-sum test): 10 patients had a GOSE score of 2, while 4 patients had a GOSE score of 3. In contrast, a subset of PDC patients showed a significant recovery based on the Kohnan score (58.9 ± 12.3 *versus* 48.7 ± 22.7, $P < 0.01$; Wilcoxon rank-sum test) (Table 3). The mean difference in Kohnan scores at admission and at completion of 2 years was 10.14 ± 11.10.

In patients with PDC, FA, VsFA0.4, MD, AD, and RD values in the first scan were 0.24 ± 0.03, 43715.14 ± 20913.54, 1.47 ± 0.15 [$\times 10^{-3}$ mm^2/s], 1.82 ± 0.18 [$\times 10^{-3}$ mm^2/s], and 1.30 ± 0.14 [$\times 10^{-3}$ mm^2/s], respectively, whereas those in the second scan were 0.22 ± 0.02, 33036.07 ± 10413.59, 1.47 ± 0.01 [$\times 10^{-3}$ mm^2/s], 1.79 ± 0.15 [$\times 10^{-3}$ mm^2/s], and 1.31 ± 0.13 [$\times 10^{-3}$ mm^2/s], respectively (Table 3). Patients with PDC showed significant changes in FA ($P = 0.006$, paired t-test) and VsFA0.4 ($P = 0.003$, Wilcoxon rank-sum test) over time. However, there were no significant differences in MD ($P = 0.993$, paired t-test), AD ($P = 0.506$, paired t-test), and RD ($P = 0.650$, paired t-test) values between the first and second scans (Table 4). In contrast, any significant change of DTI parameters was not shown in the 8 normal healthy participants (Table 5).

No significant correlations were observed between the degree of recovery from PDC and age. Kohnan score was strongly associated ($r = -0.76$, $P = 0.002$) with the degree of recovery from PDC. Among the DTI parameters, significant correlations were observed between the degree of recovery from PDC and FA ($r = 0.60$, $P < 0.05$) and VsFA0.4 at the first scan ($r = 0.68$, $P = 0.008$); however, no significant correlation was observed between the MD, AD, and LD at the first scan (Table 6). In the longitudinal DTI parameters, no significant correlations were observed between the degree of recovery from PDC and difference in FA, MD, and RD over time (Table 6). However, a significant positive correlation was observed between the degree of recovery from PDC and time-dependent changes in AD ($r = 0.544$, $P < 0.05$) and VsFA0.4 ($r = 0.624$, $P < 0.05$) between the first and second scans (Table 6).

Variables showing a significant association (P value < 0.1) were included in the Spearman correlation analysis. Thus, day of institution admission from injury, Kohnan score at the first assessment, FA at the first scan, VsFA0.4 at the first scan, difference in VsFA0.4, and MD and AD from the first to the second scan were included in the multivariate regression analysis. Stepwise multiple regression analysis revealed that the Kohnan score at the first scan (standardized $\beta = -0.723$, 95% CI: 32.7–63.0, $P < 0.0001$) and difference in AD over time (standardized $\beta = 0.337$, 95% CI: 4610.7–46541.3, $P < 0.05$) accurately predicted the degree of recovery from PDC [adjusted $R^2 = 0.841$].

4. Discussion

We explored potential clinical predictors of the degree of recovery from PDC after 2 years of admission, with a particular focus on the DTI parameters. Our results showed significantly decreased FA values and number of voxels in which FA values were >0.4 (VsFA0.4) in whole brain, but MD, AD, and RD showed no significant change. In contrast, healthy participants did not exhibit such changes. On correlation analysis, Kohnan score and FA and VsFA0.4, the difference of VsFA0.4, and AD were significantly correlated in monovariable analysis. Multiple regression analysis revealed that each Kohan score in the first assessment and the difference in AD over time have statistically significant contribution to the degree of recovery from PDC. Currently, to the best of our knowledge, there are no known predictors of long-term positive clinical response in patients with PDC. Several clinicians were forced to provide long-term care without established specific clinical goals for patients with PDC. Therefore, it is critical to develop predictors of long-term changes elicited through long-term therapeutic intervention in these patients. Our results demonstrate that microstructural white matter changes occurred in patients with PDC, which suggests that the assessment of white matter changes may help identify valid long-term outcome predictors in these patients.

DTI is based upon the diffusivity of water molecules, which varies in different tissues [14]. In white matter, it is more limited in the directions of diffusion. In healthy tracts, the anisotropy (limited directionality of diffusion) is higher

Table 3: Each diffusion parameter in normal healthy participants.

Number	Age (years)	Gender	FA at the first scan	FA at the second scan	Difference in FA from the first to the second scan	VsFA0.4 at the first scan	VsFA0.4 at the second scan	Difference in VsFA0.4 from the first to the second scan	MD [$\times 10^{-3}$ mm^2/s] at the first scan	MD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in MD [$\times 10^{-3}$ mm^2/s] from the first to the second scan	AD [$\times 10^{-3}$ mm^2/s] at the first scan	AD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in AD [$\times 10^{-3}$ mm^2/s] from the first to the second scan	RD [$\times 10^{-3}$ mm^2/s] at the first scan	RD [$\times 10^{-3}$ mm^2/s] at the second scan	Difference in RD [$\times 10^{-3}$ mm^2/s] from the first to the second scan
1	60	Female	0.26	96457	1.00	1.25	0.88	0.26	97531	1.02	1.27	0.89	0.26	96457	1.00	1.25	0.88
2	49	Female	0.26	111993	1.05	1.31	0.92	0.26	115720	1.04	1.30	0.91	0.26	111993	1.05	1.31	0.92
3	44	Female	0.26	123996	1.01	1.26	0.89	0.26	125776	1.01	1.27	0.88	0.26	123996	1.01	1.26	0.89
4	43	Female	0.27	122068	1.01	1.28	0.88	0.27	125151	1.01	1.28	0.88	0.27	122068	1.01	1.28	0.88
5	54	Female	0.27	150473	0.96	1.22	0.83	0.28	149240	0.99	1.26	0.86	0.27	150473	0.96	1.22	0.83
6	46	Female	0.26	118282	0.98	1.23	0.85	0.27	122442	0.99	1.25	0.86	0.26	118282	0.98	1.23	0.85
7	32	Male	0.26	111993	1.05	1.31	0.92	0.29	135897	0.88	1.14	0.75	0.26	111993	1.05	1.31	0.92
8	36	Male	0.28	144917	0.99	1.26	0.86	0.27	145240	0.99	1.26	0.86	0.28	144917	0.99	1.26	0.86

FA: fractional anisotropy; VsFA0.4: number of voxels with a fractional anisotropy value greater than 0.4 in the whole brain; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity.

Table 4: Comparison of diffusion tensor parameters and consciousness disorders.

Diffusion parameters	First scan		Second scan		P values
	Mean	Standard deviation	Mean	Standard deviation	
Kohnan score*	58.86	12.30	48.71	22.69	0.001
GSCE*	2.14	0.36	2.29	0.47	0.157
Fractional anisotropy	0.24	0.03	0.22	0.02	0.006
Number of voxels with a fractional anisotropy value greater than 0.4 in the whole brain*	43715.14	20913.55	33036.07	10413.59	0.003
Mean diffusivity (MD) [$\times 10^{-3}$ mm^2/s]	1.47	0.15	1.47	0.01	0.993
Axial diffusivity (AD) [$\times 10^{-3}$ mm^2/s]	1.82	0.18	1.79	0.15	0.506
Radial diffusivity (RD) [$\times 10^{-3}$ mm^2/s]	1.30	0.14	1.31	0.13	0.65

*Wilcoxon rank test.

Table 5: Comparison of diffusion tensor parameters in normal healthy participants.

Diffusion parameters	First scan		Second scan		P values
	Mean	Standard deviation	Mean	Standard deviation	
Fractional anisotropy	0.26	0.07	0.27	0.01	0.13
Number of voxels with a fractional anisotropy value greater than 0.4 in the whole brain	122522.38	17745.24	127124.63	16594.75	0.15
Mean diffusivity (MD) [$\times 10^{-3}$ mm^2/s]*	1.01	0.03	0.99	0.05	0.40
Axial diffusivity (AD) [$\times 10^{-3}$ mm^2/s]*	1.26	0.03	1.25	0.05	0.23
Radial diffusivity (RD) [$\times 10^{-3}$ mm^2/s]*	0.88	0.03	0.09	0.05	0.57

*Wilcoxon rank test.

Table 6: Correlation between the degree of recovery from prolonged consciousness disorder and each value.

Variable	Degree of recovery from PCD r (Spearman correlation coefficient)	P values
At the first scan or assessment		
Age	−0.24	0.41
Day of institution admission from injury	−0.48	0.086
Kohnan score	−0.76	0.002
Fractional anisotropy	0.60	0.023
Numbers of voxels with a fractional anisotropy value greater than 0.4	0.68	0.008
Mean diffusivity	−0.22	0.459
Axial diffusivity	−0.01	0.976
Radial diffusivity	−0.34	0.241
The difference between the first and the second scan		
Fractional anisotropy	0.38	0.177
Numbers of voxels with a fractional anisotropy value greater than 0.4	0.62	0.017
Mean diffusivity	0.48	0.086
Axial diffusivity	0.54	0.044
Radial diffusivity	0.40	0.162

than that in the gray matter. This difference allows for the calculation of fractional anisotropy (FA) values for tissue and the generation of white matter fiber maps. FA ranges from 0 to 1, where 0 represents isotropic diffusion (or lack of directional organization) and 1 represents anisotropic diffusion (or organized tissue such as white matter tracts) [15]. Studies have demonstrated the potential utility of DTI for providing quantitative assessments of microstructural damage in TBI, in which DAI is common [1–11, 14–16]. Although the specifics are still not well understood, FA is believed to be influenced by many factors, including the degree of myelination and axonal density and/or integrity [9, 17–19].

Table 7

Clinical symptoms	Grade				
	Extreme (10)	Severe (9)	Moderate (8/7)	Mild (5)	Slight (0)
Voluntary movement	(1) Absent (2) Acrocontracture (3) Pain reflex but slight trembling and rough breathing	(1) Almost absent but parts of the extremities move minutely (2) Part of the extremity flexed and part paralyzed (3) Pain reflex or no pain reflex with clearly frowning face	(1) Occasional all/partial extremity movement with no intention (2) Extremity could be paretic (3) Brushing away reaction for pain	(1) Occasional movement to meet an object (2) Capable of raising the arms upward or moving them in the intended direction, that is, face or head, imitating a posture of the tester	(1) Capable of movement with intention (2) Capable of unassisted posture change (partial change inclusive) (3) Moving wheelchair unassisted, even if awkwardly
Voluntary ingestion	Totally incapable of masticating and swallowing; on tube nutrition (gastric/nasal feeding)	(1) Almost on tube nutrition (2) Saliva swallowing or mastication is found (3) Capable of attempting slight perusal ingestion, that is, fruit juice, custard pudding, and so forth	(1) Capable of masticating; even if not, almost capable of assisted auroral ingestion by swallowing, though sometimes choking (2) Insufficient peroral ingestion requires tube nutrition	(1) Capable of unassisted ingestion by swallowing; mastication could be awkward (2) Capable of ingesting all the rice gruel served or chopped food with assistance (3) Attempting to reach mouth with a passed spoon or put the food into mouth awkwardly	Ingesting on own using spoon awkwardly
Fecal and urinary incontinence	No observed somatic movement when evacuating/urinating	Slight somatic movement when evacuating/urinating	After incontinence, a displeased look or some signal is observed, that is, frequent somatic movement	(1) Forced regular evacuating and urinating lead to the prevention of fecal and urinary incontinence (2) Communicating the fact in a certain way after incontinence	Except during the night, preevacuation and preurination communication is possible
Ophthalmography and visual recognition	(1) Eyes not opened (2) Eyes opened, no blink reflex	(1) Eyes opened, blink reflex (2) No following ocular movement and no focusing eyes on an object	(1) Looking straight toward the direction of the call (2) Following a moving object or staring at a TV, although understanding is impossible	(1) Discriminating close relatives followed by a facial expression (2) Favorite picture, among other things, induces a facial expression	(1) Capable of reading easy words (2) Capable of understanding simple numbers (3) When watching TV, response and laughter are apparent

Table 7: Continued.

Clinical symptoms	Grade				
	Extreme (10)	Severe (9)	Moderate (8/7)	Mild (5)	Slight (0)
Vocalizing and utterances	(1) No vocalizing (2) No lip movement under tracheostomy	(1) Groaning, among others, without meaningful utterances (2) Lip movement observed under tracheostomy	(1) A short utterance though not understandable (2) Occasional inarticulate vocal response to calls (3) Under tracheostomy, response to calls is through lip movement	(1) Occasional vocalizing of a meaningful word (2) Vocal response to calls (3) Imitating talking by the tester under tracheostomy	(1) Capable of vocalizing a simple word response (2) Lip movement corresponds to what is asked
Change of expression	No response to ambient sound stimulations and TV sounds, among other things	Change of expression, such as smiling, crying, and anger, is not due to ambient stimulations	Change of expression is occasionally found in response to ambient stimulations	Change of expression, such as smiling, crying, and anger, closely matches an expected response to the ambient stimulation	Change of expression, such as crying and smiling, exactly matches an expected response to the ambient stimulation

FA has been shown to decrease in patients with mild and moderate/severe brain injury [1, 4, 5, 11, 14–16, 19–28]. Perez et al. [5] reported significantly lower FA in the chronic phase of TBI as compared to that in healthy controls; in contrast, AD, MD, and RD in chronic patients were significantly higher than in healthy controls. Additionally, chronic FA showed a positive correlation with processing speed [28]. In this study, patients with chronic PDC had significantly lower FA and VsFA0.4 at 2 years as compared to those at admission. Our first scan data were collected 345.6 ± 192.6 days after injury, which corresponds to the chronic stage of white matter damage. Thus, our results suggest occurrence of microstructural change over the longer term. On univariate correlation analysis, FA and VsFA0.4 at the first scan significantly correlated with the degree of recovery of PDC, which is consistent with previous studies [5–8, 10, 11, 14, 20–29] where patients with higher FA showed good recovery. Temporal change in VsFA0.4 and AD significantly correlated with the degree of recovery from PDC. This probably indicates that minor microstructural changes correlate with the degree of recovery from PDC. Several previous studies [6, 8, 10, 11, 20, 25–29] have reported a positive association of FA with higher cognitive function and outcomes. However, in this study, higher difference of VsFA0.4, MD, and AD positively correlated with the degree of recovery from PDC. In other words, a time-dependent decrease in VsFA0.4, MD, and AD may be related to a better outcome in PDC. In this respect, our results are not inconsistent with those of several previous reports [6, 8, 10, 11, 20, 25–29], which indicated that a time-dependent decrease in FA was associated with poor outcomes as assessed by cognitive function and GOSE. These contradictory findings may reflect the difference in PDC severity between studies; most of our patients had GOSE scores of ≤3 and showed subtle and minor clinical changes. Although significant recoveries were observed based on Kohnan scores, the changes were not significant when based on GOSE scores, which suggests that improvement in our patients was lower than that reported in previous studies [6, 8, 10, 11, 20, 25–29]. Our subjects generally had more severe outcomes; all our patients had GOSE scores ≤ 3, which indicates more severe disability than that among patients in the previous studies [6, 8, 10, 11, 20, 25–29]. Thus, interstudy differences in results may reflect DAI severity. Differences with respect to time elapsed since injury may also have contributed to the divergent findings; we included patients with PDC in the extended chronic phase.

In patients with PDC, the degree of recovery was very small, as shown by the lack of change in GOSE scores. In our participants, induction of a severe inactive state due to brain injury might lead to secondary neurodegeneration that might be detected by DTI. However, the underlying mechanism behind longitudinal alterations in white matter remains unclear. In addition, this study had some limitations. The number of subjects was small, and they had various pathological states, such as contusion, subarachnoid hemorrhage, and intracranial hemorrhage. Thus, further longitudinal studies are warranted that combine DTI with volumetric measurements and other detailed analyses, such as functional connectivity analysis. The potential of DTI use as a prognostic tool needs further investigation in studies with a larger number of subjects.

In conclusion, on stepwise multiple linear regression analysis, Kohnan score and the difference in AD showed a significant association with the degree of recovery from PDC. In other words, we demonstrate evidence of temporal microstructural white matter changes in patients with PDC; DTI parameters are useful indices for assessment of white matter alterations in these patients. As a noninvasive modality, DTI provides in vivo quantitative pathophysiological information. Tracking white matter microstructural changes over time has the potential to measure neuroplasticity and repair after TBI and may eventually be utilized to monitor therapeutic responses. Further research is required to investigate the leads identified in this study.

Appendix

See Table 7.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

This study was supported by a medical research grant on traffic accidents from the General Insurance Association of Japan. This work was also supported by JSPS KAKENHI Grant no. JP16H06280, Grant-in-Aid for Scientific Research on Innovative Areas-Resource and Technical Support Platforms for Promoting Research "Advanced Bioimaging Support." The authors would like to thank the patients and normal healthy volunteers who participated in this study. The authors would also like to thank the imaging staff, particularly Tomohiro Chiba, for their skilled MRI acquisition. They also thank Enago for the English language review.

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Hindawi
Neural Plasticity
Volume 2017, Article ID 5405104, 11 pages
https://doi.org/10.1155/2017/5405104

Review Article

The Polarization States of Microglia in TBI: A New Paradigm for Pharmacological Intervention

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Received 28 October 2016; Revised 17 December 2016; Accepted 11 January 2017; Published 1 February 2017

Academic Editor: Mario Zuccarello

Traumatic brain injury (TBI) is a serious medical and social problem worldwide. Because of the complex pathophysiological mechanisms of TBI, effective pharmacotherapy is still lacking. The microglial cells are resident tissue macrophages located in the brain and have two major polarization states, M1 phenotype and M2 phenotype, when activated. The M1 phenotype is related to the release of proinflammatory cytokines and secondary brain injury, while the M2 phenotype has been proved to be responsible for the release of anti-inflammation cytokines and for central nervous system (CNS) repair. In animal models, pharmacological strategies inhibiting the M1 phenotype and promoting the M2 phenotype of microglial cells could alleviate cerebral damage and improve neurological function recovery after TBI. In this review, we aimed to summarize the current knowledge about the pathological significance of microglial M1/M2 polarization in the pathophysiology of TBI. In addition, we reviewed several drugs that have provided neuroprotective effects against brain injury following TBI by altering the polarization states of the microglia. We emphasized that future investigation of the regulation mechanisms of microglial M1/M2 polarization in TBI is anticipated, which could contribute to the development of new targets of pharmacological intervention in TBI.

1. Introduction

Traumatic brain injury is a major health problem worldwide [1, 2]. The pathophysiological mechanisms of TBI are complex and unclear, and effective pharmacotherapies for TBI patients remain lacking. Thus, further elucidation of the pathophysiological mechanisms of TBI is warranted, and it could help to develop new targets of pharmacological intervention for TBI.

Neuroinflammation, which includes activation of local microglia and recruitment of other immune cells from the blood, as well as production of inflammatory cytokines, plays an important role in the pathophysiology of TBI [3]. On the one hand, neuroinflammation is detrimental and contributes to brain injury following TBI; on the other hand, neuroinflammation is necessary for the clearance of harmful substances, such as cell debris, after TBI [4]. Therefore, elucidation of the role and the underlying molecular mechanisms of neuroinflammation in TBI pathology is extremely vital for presenting potential new therapeutic targets for TBI.

The microglial cells are the resident macrophage cells of the brain [5], and they can activate rapidly in response to pathological changes in the central nervous system (CNS) [6, 7], for example, traumatic/ischemic brain injury or subarachnoid hemorrhage (SAH). In recent years, researchers have discovered two polarization states of microglial cells when they are activated, the M1 phenotype and the M2 phenotype [8–11], exactly like macrophages in nonneuronal tissues [12]. There is a large difference between the roles of the two phenotypes of activated microglial cells: the M1 phenotype is related to the release of several proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), while the M2 phenotype has been proved to be responsible for the release of anti-inflammatory cytokines, such as

interleukin-10 (IL-10), and for neural regeneration processes, such as neurogenesis, angiogenesis, oligodendrogenesis, and remyelination [10]. Thus, how to alter the M1/M2 ratio to improve functional recovery after TBI has become a new pharmacological therapeutic direction in TBI. In this review, we aimed to summarize the current knowledge about the pathological significance of microglial M1/M2 polarization in the pathophysiology of TBI. In addition, we reviewed several drugs that have provided neuroprotective effects against brain injury following TBI by altering the polarization states of the microglia.

2. Microglial Phenotypes and Pathological Significance in TBI

In the parenchyma of the CNS, microglia constitute about 0.5% to 16.6% of all cells, especially in the white matter [13]. These microglial cells can remove cell debris and toxic substances, thus maintaining the homeostasis of the CNS. When insult occurs, the microglial cells activate rapidly, change their morphology into a motile "amoeboid" state, proliferate, and migrate into the damaged regions, and they release a variety of cytokines depending on the polarization states [14, 15]. Nowadays, there is a growing number of papers discussing the topic of phenotypes of microglia. The keyword "microglia phenotypes" return over 1,700 hits from PubMed in later 2016, and more than half of them were published in recent four years. Thus, exploring of the mechanisms for microglia/macrophage phenotype shift is becoming a meaningful topic.

Two distinct polarization states of the activated microglial cells have been discovered, the M1 phenotype and the M2 phenotype, depending on particular microenvironments [16]. The M1 phenotype microglia are induced by proinflammatory molecules, such as lipopolysaccharide (LPS) or interferon-gamma (IFN-γ). This phenotype closely matches the classical activation stage and secretes high levels of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-1β, chemokines, and reactive oxygen species (ROS), which are essential for host defense [17]. They also secrete a low level of IL-10 [18]. The M2 phenotype microglia are subdivided into three subtypes: M2a, M2b, and M2c. Each of these subtypes has different trigger factors and phenotypic markers. The M2a subtype, which can be triggered by IL-4 and IL-13, is the first alternative activation stage of the microglia. It can act as an anti-inflammatory microglia subtype compared to M1 phenotype by competing for arginine, a nitrogen pool for the production of reactive nitrogen species during M1 phase [19]. The M2b subtype is a mixed activation state of microglia, it produces pro- and anti-inflammatory cytokines, such as TNF-α, IL-6, and IL-10, and it can be triggered by treating with LPS and IL-1β concurrently or with activated IgA complexes [19, 20]. The M2c subtype can be triggered by IL-10; it can shut down the immune response of the microglia [19], and it appears to play a role in tissue remodeling and matrix deposition [17] (Figure 1). The neuroprotective effects of M2 phenotype microglia have been well-studied, including the secretion of neurotrophic factors and anti-inflammatory cytokines and the clearance of cell debris through phagocytosis [10, 14]. Moreover, M2 microglia/macrophages have been found to play essential roles in driving oligodendrocyte differentiation toward the process of remyelination in the central nervous system, probably by contributing transforming growth factor-β (TGF-β) superfamily member activin-A to the remyelinating lesion environment [21].

Because different phenotypes of microglia appear and function in different phases, it is necessary to determine the time evolution of each subtype of microglial cells after TBI. However, this process has not yet been completely learned, and the experimental results have seemed different between in vitro and in vivo models. Several years ago in an in vitro experiment, researchers found that "acutely activated microglia" could reduce neural precursor cell survival and prevent neuronal differentiation, while "chronically activated microglia" could facilitate neural differentiation and cell survival [22]. Some experimental studies have supported that the "chronically activated microglia" seem to be M2 phenotype microglia and not M1. For example, there is an alteration in cytokine production. In a prolonged in vitro experiment, when exposed to LPS, the proinflammatory cytokines IL-1α/β, IL-6, and TNF-α secreted by microglia were strongly decreased, while the anti-inflammatory cytokine IL-10 and the immunomodulatory prostaglandin E2 (PGE2) increased greatly, indicating that the chronically activated M2 phenotype microglia might play a beneficial role in neuronal differentiation and cell survival [22]. In addition, in normal wound and spinal cord injury (SCI) healing, the M1 and M2a types seem to be the primary subtypes that start immediately after brain injury, and then they are gradually replaced by the M2b and M2c subtypes after 3 dpi (days after injury), indicating the start of the proliferation phase [23]. However, with in vivo TBI models, the findings have been different. Jin et al. [24] found that CD206(+)/CD11b(+) M2 phenotype microglia were increased at 1 week after controlled cortical impact (CCI), whereas CD86(+)/CD11b(+) M1 phenotype microglia were increased at 4 weeks. In a mouse model of TBI, transient M2 phenotype microglia were the initial phenotype of activated microglia in the acute stage of brain insult and peaked at 5 days after injury, but the M1 phenotype microglia remained elevated until at least 14 days [25]. Recently, another in vivo experiment demonstrated that the M2 phenotype microglia were upregulated transiently and then were replaced by M1 or a mixed transitional phenotype at 7 days after injury [26]. Actually, activated microglia could be observed in the injured cortex even 1 year after injury in a mouse CCI model, in association with lesion expansion and neurodegeneration [27]. The conflict of chronic microglial phenotypes between in vitro and in vivo models might be due to the complex signaling events surrounding microglial cells in vivo, and exploring the mechanisms underlying this phenomenon could help us to find new targets of pharmacological intervention in TBI. In humans, using the positron emission tomography (PET) ligand [11C](R)PK11195 (PK), researchers demonstrated that increased microglial activation could persist for 17 years after TBI [28]. Another study of human brain samples after TBI found that the reactive microglia could exist for up to 18 years after trauma [29].

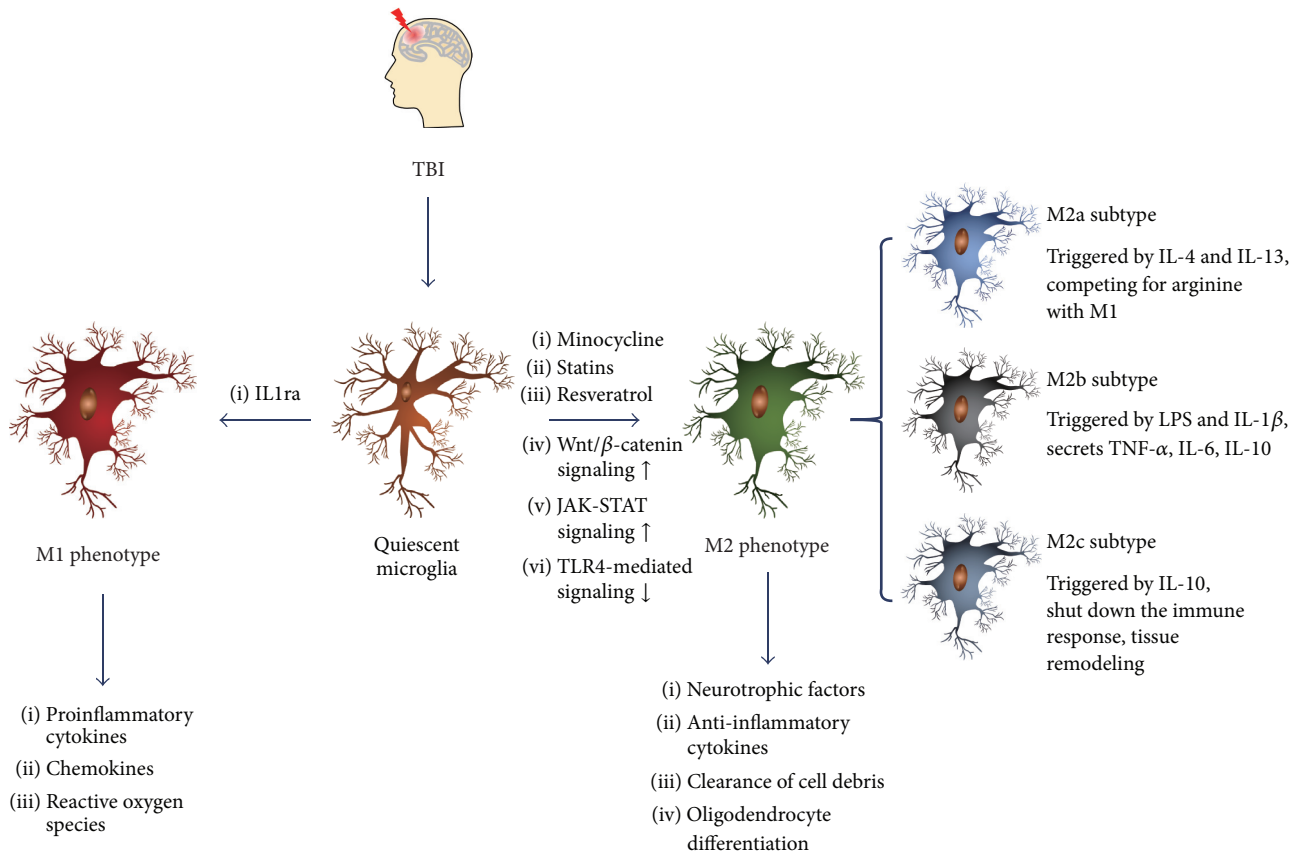

Figure 1: Two distinct polarization states of activated microglial cells and the three different subtypes of M2 phenotype microglia.

Although the phenotype of these microglia cells has not been clarified, these activated microglia indicate a chronic inflammatory response after brain injury.

In addition, it is important to know that this classification system only represents two major extreme types of activated microglia. Currently, this paradigm that simply divide the activated microglia into M1/M2 phenotypes has been challenged. Unlike the simple microenvironments in the in vitro experiments, the complex signaling events after tissue injury in vivo can lead the microglia/macrophage to a complex response or perhaps mixed phenotypes [30], which is consistent with previous studies focused on single-cell level. In mouse CCI model, microglia/macrophages could concurrently express both M1 and M2 phenotypic markers on the same cell in multiple time points [31]. This phenomenon has also been observed in other diseases such as multiple sclerosis [32] and cutaneous squamous cell carcinoma [33]. Also, the activated microglia population can change from an early "healthy" M2 phenotype into a "sick" M1 phenotype and exist for a very long time [24, 31, 34]. This point of view has changed our treatment concept of TBI and other brain insults in recent years. Therapies should no longer focus only on suppressing microglia/macrophage activation, but they should pay greater attention to the ratio of M1/M2 phenotype of microglia to decrease the harmful effects of neuroinflammation [10, 14, 35].

3. Polarization States of Microglia in TBI: Potential Therapeutic Targets for Pharmacological Intervention

So far, many anti-inflammation drugs have been discovered to manage the neuroinflammation process after TBI. Although some of these drugs have shown neuroprotective effects in animal models, none have succeeded in clinical trials, perhaps due to the strict treatment time window and the heterogeneity of subtypes of TBI. Microglial cells are the target of many anti-inflammation strategies, and their phenotypes are of great significance in TBI treatment. As mentioned above, the dominant phenotype of activated microglia could shift from acutely activated M2 to chronically activated M1 after TBI [26]. This time dependent property of microglia activation indicates that M2 phenotype microglia may have more potential in clearing cell debris in the early stage of TBI, and M1 phenotype microglia may have relationship with chronic neuroinflammation [35]. So, anti-inflammation strategies that targeted whole microglia system might not be the best answer. An increasing number of studies trying to regulate the ratio of M1 and M2 phenotype microglia have already got promising effects after brain injury, which made the polarization states of microglia a new paradigm for pharmacological intervention. Strategies inhibiting the M1 phenotype and promoting the M2 phenotype of microglial

cells could alleviate cerebral cell damage and improve neurological function recovery in variety of brain injury animal models such as CCI [18, 36] and middle cerebral artery occlusion (MCAO) [37, 38]. These efforts pay more attention on later neurogenesis, which directly leads to better long-term prognosis. Thus, developing drugs that can modulate the immune system through altering the M1/M2 ratio is a promising pharmacological intervention in TBI treatment.

However, although the phenotypes and roles of microglia have been known for several years, many drugs with the effect of inhibiting microglial activation are still regarded as having the effect of anti-inflammation and many studies that have evaluated microglia activation only using pan-microglial markers such as Iba-1 or Cd11b [3]. In fact, total microglia activation inhibition cannot represent the anti-inflammation effect, and the therapeutic purpose is far more than anti-inflammation. In this section, we review several drugs that might provide neuroprotective effects after TBI by changing microglia polarization states, and we discuss the potential mechanisms underlying them. These mechanisms include enhanced Wnt/β-catenin signaling and JAK-STAT signaling, inhibition of TLR4-mediated signaling, and p38 MAPK-dependent PPARγ activation.

3.1. Minocycline. Minocycline is a second-generation tetracycline with a variety of nonantibiotic biological effects, such as neuroprotection in experimental models of TBI, ischemia, and neurodegenerative diseases [39]. The anti-inflammation effect is the most well-known advantage of the neuroprotective effects of minocycline. A series of studies have demonstrated that minocycline can inhibit microglial activation, using pan-microglial markers in TBI, SCI, SAH, and cerebral ischemia [40–45]. Although there is a large amount of data showing this anti-inflammation effect is mostly mediated by microglia, the molecular targets still need to be discovered. One possible explanation is that minocycline may regulate microglial activation through inhibition of poly(ADP-ribose) polymerase (PARP), since minocycline contains an aromatic ring-linked carboxamide group just as other competitive PARP inhibitors [46], and PARP regulates the NF-κB driven transcription and microglia activation [47].

Despite the huge data of microglia inhibition effect, a few studies have demonstrated the function of minocycline in changing the M1/M2 ratios of microglial cells. Kobayashi and colleagues found that minocycline selectively inhibited M1 but not M2 microglia in a mouse amyotrophic lateral sclerosis (ALS) model and in primary cultured microglial cells [48]. Another study using minocycline-loaded nanoparticles in SCI drew a similar conclusion [49]. In a rat model of depression, chronic administration of minocycline decreased not only the expression of the pan-microglial marker CD11b but also the M1 proinflammatory cytokine IL-1β in sham spinal nerve ligation (SNL) animals. The expression of the M2 microglia marker MRC2 and of IL-10 and IL-1β was increased in the prefrontal cortex of olfactory bulbectomized-SNL rats, which indicated that chronic minocycline administration had an effect on altering M1/M2 microglia markers [50]. Recently, in a cerebral ischemia model, researchers discovered that treatment with minocycline could significantly decrease the levels of TNF-α and IL-1β and increase the levels of TGF-β, IL-10, and YM1 [51]. These results indicated that minocycline might also have the alternate effect of microglia/macrophage activation in TBI, and further research must be undertaken to discover it.

3.2. Etanercept. Etanercept is a biologic TNF antagonist, and it has been proved to have anti-inflammatory effects by inhibiting brain TNF-α [15]. Considering its molecular weight, it is too large to pass the blood-brain barrier (BBB); therefore, it cannot reach therapeutic concentrations in the cerebrospinal fluid in theory [52]. However, experiments have confirmed that etanercept can penetrate into contused brain tissues for unknown reasons and can play a neuroprotective role in a series of diseases, such as TBI [53, 54], SCI [55, 56], and ischemic brain injury [57, 58]. The functions of etanercept in TBI are not only to inhibit microglial activation [15] but also to reduce early overexpression of TNF-α in microglia [54] and to stimulate the newly formed neurogenesis [53]. Thus, etanercept can attenuate the effects of M1 phenotype microglia and can have neural regeneration effects, like M2 phenotype microglia [18]. These experiments showed the potential effects of etanercept in altering the M1/M2 ratio and promoting neural regeneration. Furthermore, treatment with perispinal etanercept of chronic stroke and TBI patients could produce clinical improvement, even a decade later [59]. The therapeutic efficacy of etanercept in TBI is worth studying.

3.3. Statins. Statins, known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are well known for the effects of lowering serum cholesterol level and decreasing the risk of cardiovascular events [60]. Despite their cholesterol-lowering function, the anti-inflammatory effects of statins have gained recognition in recent years. Because of their pleiotropicity, statins have been used in the management of ischemic stroke [61], neurodegenerative diseases [62, 63], and even chronic subdural hematoma [64]. In TBI management, simvastatin has the effects of attenuating microglia and astrocyte activation, decreasing proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [65], suppressing neuronal cell apoptosis [66], and inducing angiogenesis [67]. Although the microglia inhibition effects of statins have been proved, the mechanisms are still in exploration. In cultured microglia cells, rosuvastatin strongly inhibited microglia proliferation and adhesion and additionally increased the expression of several anti-inflammatory genes such as *Ccl2* and *Cxcl1*, which were implicated in microglia recruitment [68]. Another in vivo study suggests that simvastatin can exert analgesic effects by attenuating spinal microglial activation through interruption of microglial RhoA translocation and p38 MAPK activation [69].

To our knowledge, there has been no direct evidence of statins altering the M1/M2 ratio of microglia, but some studies have suggested a positive answer. In an in vitro experiment, simvastatin could play an anti-inflammation role by enhancing the switching of the M1 macrophage phenotype to the M2 macrophage phenotype [70]. Atorvastatin also has shown similar effects in myocardial infarction [71] and

might promote circulating monocyte differentiation into M2 phenotype macrophages via p38 MAPK-dependent PPARγ activation [72]. The effects of statins on microglial activation and differentiation in TBI deserve further research.

3.4. Resveratrol. Resveratrol, a stilbene formed in many edible plants as a reaction to fungal infection, has been proved effective in cancer, heart diseases, and a series of nervous system diseases in vitro and in vivo [73, 74], also including ischemic stroke [74, 75], neurodegenerative diseases [76], TBI [74, 77], and SAH [78]. There are many potential pathways for the neuroprotective effects of resveratrol, such as activation of the silent mating type information regulation 2 homolog 1 (SIRT1), AMP-activated kinase (AMPK), nuclear factor erythroid 2 (Nrf2) pathways [74], and inhibition of the NF-κB, ERK, and JNK/MAPK pathways [79, 80]. The inhibition of the microglial activation of resveratrol occurs not only in TBI models [81] but also in other in vitro and in vivo models [82–84], possibly by activating an SOCS-1-mediated signaling pathway [85], and it might be associated with neurogenesis [86]. As a natural modulator of microglial activity, resveratrol has the ability to counteract the excessive response of activated M1 microglia [87]. In a BV2 microglia cell line of hypoxia injury model, resveratrol suppressed the mRNA expression of TNF-α and promoted the mRNA expression of IL-10 [88], suggesting its ability to change microglia phenotypes. Another experiment using LPS-stimulated microglia drew the same conclusion, and the JAK-STAT signaling pathway might be involved in this process [89]. Hence, the prospective value of resveratrol in TBI is worth being studied further.

3.5. MGluR5 Agonist and Positive Allosteric Modulator. In recent years, the metabotropic glutamate receptor 5 (mGluR5) selective agonist (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) and the positive allosteric modulator (PAM) VU0360172 have attracted increasing attention in the treatment of various brain insults. Both CHPG and VU0360172 could significantly reduce the numbers of activated microglia and improve neurological function in a rat endovascular perforation model of SAH [90]. CHPG could limit neuroinflammation and improve functional recovery even a month later after TBI [91, 92], and it significantly decreased the levels of proinflammatory cytokines and increased the expression of anti-inflammatory cytokines after SO_2 treatment in BV2 microglial cells [93]. This anti-inflammatory effect might be mediated by G-protein signal transduction pathway, including activation of the phospholipase C-protein kinase C signal transduction system [94]. However, because of the weak potency and brain permeability of CHPG, researchers have found another more efficient mGluR5 PAM, VU0360172, and its ability to shift the M1/M2 microglial activation balance towards an M2 phenotype in vivo and in vitro has been shown [95]. An increasing number of studies have reported the protective effects of mGluR5 agonists and PAMs, making this young drug class a promising agent in TBI therapy.

3.6. Gp91ds-tat. Gp91ds-tat is a selective nicotinamide adenine dinucleotide phosphate oxidase (NOX-2) inhibitor. The neuroprotective effect of gp91ds-tat was first discovered in cerebrovascular dysregulation associated with increasing age [96, 97]. A more recent study showed that gp91ds-tat could significantly improve functional recovery and reduce inflammation in an SCI model, accompanied by a reduction in M1 microglia phenotype markers [98]. It seems alterations in microglia polarization and NOX activity could influence each other [98–100]. In a mouse CCI model, gp91ds-tat significantly reduced neuron damage and edema [101], and delayed gp91ds-tat treatment (24 h post injury) could alter the M1/M2 balance to the anti-inflammatory M2 phenotype, reducing oxidative damage in neurons and cognitive function deficits [26, 102]. Therefore, gp91ds-tat could have promising therapeutic effects in TBI treatment.

3.7. Rosiglitazone. As a peroxisome-proliferator-activated receptor- (PPAR-) γ agonist, rosiglitazone is not only an antidiabetic drug but also a neuroprotective agent, and it has shown various effects in treating brain ischemia [103], TBI [104], and SAH [105]. A study demonstrated rosiglitazone's ability to attenuate microglia/macrophage activation and neuronal loss after TBI [104]. In mouse models of focal cerebral ischemia and progressive Parkinson's disease, rosiglitazone showed the ability to promote microglial M2 polarization [103, 106]. Another PPAR-γ agonist pioglitazone has also been reported to decrease the M1/M2 ratio in experimental Alzheimer's disease [107], but the relationship between PPAR-γ agonists and microglia phenotype switching is still not clear. Since studies about rosiglitazone's function in microglia have been very limited, the effects of rosiglitazone in TBI still require exploration.

3.8. Azithromycin. Many macrolide antibiotics might have neuroprotective effects. Among them, azithromycin is an extraordinary drug with the effect of reducing infarct volume, decreasing brain edema, and increasing neurological deficit scores in acute ischemic damage [108]. Additionally, azithromycin had the effect of altering the macrophage phenotype from proinflammatory M1 to alternatively activated M2 cells [109, 110], probably by inhibition of TLR4-mediated signaling [111] or activation of activator protein-1 and impairment of lysosomal functions [112]. This effect was observed not only in chronic obstructive pulmonary disease [110] but also in ischemic brain injury [113] and spinal cord injury [114] at a dose of approximately 150 mg/kg. Whether it will be effective in altering microglia phenotypes in TBI treatment remains to be determined.

3.9. Alpha-7 Nicotinic Acetylcholine Receptor Agonists. TBI-induced deficits in alpha-7 nicotinic acetylcholine receptor (nAchR) expression were found to play a role in cognitive impairment as early as 2003 [115]. In recent years, nAchR has been receiving attention again. α-7 nAchR agonist, PNU-282987, could attenuate early brain injury in SAH rats [116] and could reduce peripheral inflammation and BBB disruption in TBI mice [117]. Another α-7 nAchR agonist, PHA568487, could attenuate neuroinflammation, oxidative stress, and brain injury in stroke and bone fracture

mice, probably by decreasing the number of M1 phenotype microglia/macrophages and by increasing M2 phenotype microglia/macrophages [118, 119]. Future experiments are needed to determinate whether such drugs also have the same effects in TBI.

3.10. Interleukin-1 Receptor Antagonist. Interleukin-1 receptor antagonist (IL1ra) is a competitive antagonist of the interleukin-1 type-1 receptor (IL-1R). Researchers identified the effects of IL1ra in improving recovery and delayed cytokine induction in ischemic brain injury and TBI a dozen years ago [120, 121]. Several experiments on IL-1β antibody in TBI have shown similar conclusions [122, 123]. In 2014, a phase II, randomized, controlled trial of recombinant human IL1ra in severe TBI reported promising data using this agent in the modification of neuroinflammatory response [124]. Recently, using Partial Least Squares Discriminant Analysis, researchers have found a "counterintuitive" effect of rhIL1ra on microglia, namely, that rhIL1ra treatment could increase microglial activation following severe TBI and could bias the microglial responses to the M1 phenotype but not the M2 phenotype following human TBI [125]. This result has caused us to rethink the theory of dividing cytokines into "pro-" and "anti-" inflammatory subtypes simplistically in brain insults such as TBI.

3.11. Cell Therapy. Cell therapy has been proved to be effective in many kinds of brain injury, including TBI [126]. Nowadays researchers have found that the neuroprotective mechanism of cell therapy is limited to not only neuronal replacement, but also immunomodulation. Mosher et al. showed that transplanted neural progenitor cells (NPCs) could secrete a variety of signaling proteins which have the capacity to modulate microglia functions and activity [127]. Liu et al. described that NPCs and microglia could be significantly affected by each other's presence in an allogeneic coculture model, and NPCs might have the ability of regulating the phagocytic activity of microglia [128]. These results have led to several recent studies about cell therapy's effect in mediating the microglial/macrophage phenotypes after TBI. For example, intravenous delivery of multipotent adult progenitor cells (MAPC) and intracerebral injection of human neural stem cells (NSCs) after experimental TBI can both demonstrate a decrease in M1/M2 ratio [129, 130]. Thus, modulation of M1/M2 ratio through cell therapy could be one of the therapeutic methods after TBI.

4. Conclusion

So far, there is still no management providing a strong benefit in TBI, so it is important to find therapeutic drugs with promising new mechanisms after brain damage. The neuroinflammation process, which could serve a dual function, is of great importance after TBI. Different phenotypes of activated microglial cells could play different roles in the neuroinflammation process, so finding new drugs that can alter the M1/M2 ratio of activated microglial cells could be a promising approach to decrease neuroinflammation damage and to improve outcomes. In this review, we summarized the current knowledge about the pathological significance of microglial M1/M2 polarization in the pathophysiology of TBI, and we listed several drugs with neuroprotective effects against TBI by altering the polarization states of microglial cells.

However, some limitations in the current research should be noticed. First, the methods for evaluating the effects of drugs on microglial cells must keep up with the pace; simply inhibiting the activation of microglial cells cannot replace anti-inflammation and neuroprotection. Second, the appearing time periods of the subtypes of microglial cells and the changes in the microenvironment surrounding these cells after TBI must be more deeply explored to discover the best therapeutic time window for the aforementioned drugs. Third, most of the current experiments in pharmacological intervention have focused on the phenomenon of microglial phenotype changes, while studies of mechanisms have been fewer. Future investigations should focus on the regulation mechanisms of microglial M1/M2 polarization and develop new targets of pharmacological intervention in TBI, thus providing new hope for TBI management.

Competing Interests

The authors have no conflict of interests to disclose.

Authors' Contributions

Hangzhe Xu and Zhijiang Wang contributed equally to this work.

Acknowledgments

The present study was supported by Key Program of Administration of Traditional Chinese Medicine, Zhejiang Province (no. 2014ZZ006).

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Hindawi Publishing Corporation
Neural Plasticity
Volume 2016, Article ID 9746313, 7 pages
http://dx.doi.org/10.1155/2016/9746313

Review Article

Progress of Research on Diffuse Axonal Injury after Traumatic Brain Injury

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Received 26 August 2016; Revised 25 October 2016; Accepted 15 November 2016

Academic Editor: Chih-Lung Lin

The current work reviews the concept, pathological mechanism, and process of diagnosing of DAI. The pathological mechanism underlying DAI is complicated, including axonal breakage caused by axonal retraction balls, discontinued protein transport along the axonal axis, calcium influx, and calpain-mediated hydrolysis of structural protein, degradation of axonal cytoskeleton network, the changes of transport proteins such as amyloid precursor protein, and changes of glia cells. Based on the above pathological mechanism, the diagnosis of DAI is usually made using methods such as CT, traditional and new MRI, biochemical markers, and neuropsychological assessment. This review provides a basis in literature for further investigation and discusses the pathological mechanism. It may also facilitate improvement of the accuracy of diagnosis for DAI, which may come to play a critical role in breaking through the bottleneck of the clinical treatment of DAI and improving the survival and quality of life of patients through clear understanding of pathological mechanisms and accurate diagnosis.

1. Introduction

Diffuse axonal injury (DAI) is a brain injury characterized mainly as axonal injury of the white matter. It often follows brain trauma, which causes wide-ranging denaturation of white matter, focal hemorrhage, emergence of axonal retraction balls, and microglia clusters. DAI is often accompanied by other brain injuries, and this has caused patients severe brain damage or even placed them in a persistent vegetative state. According to reports made in recent years, the mortality rate of DAI is 42%–62% [1, 2]. DAI has been as an independent category of disease accepted by neurosurgery academic. However, there are currently no standard diagnostic criteria, and the relationship to other brain injuries needs to be investigated further in order to develop better clinical treatments for DAI. Below, the authors review the concept, pathological mechanism, and methods of clinical diagnosis of DAI.

2. Concept

DAI was formally named and accepted by the international academic community in 1982. It has gone through three conceptual stages in its history. The first period began in 1956, when Strich studied autopsies from 5 patients with severe closed brain trauma and proposed that degeneration of the diffuse white matter might be attributed to the physical damage to nerve fibers. The second period began in 1961, when this Strich studied 20 patients who had died of brain trauma. He found that the shearing force of the rotational acceleration of head movement (one of the main causes of brain injury) caused the nerve fibers to break and evoked diffuse degeneration of hemisphere and brainstem. This study provides a theoretical basis for future investigations of DAI. The third period began in the 1980s, when Adams and Gennerelli studied the mechanism of development and clinical pathology of DAI thoroughly and made prominent achievements, which were given great consideration when the international academic community selected a final name for this condition.

3. Pathological Mechanism of DAI

DAI usually presents a progressive course. It takes place after external injury involving shearing force, and it mainly

manifests in the form of focal axonal changes and axonal breakage. And it can be divided into primary and secondary axonal injury. The pathological mechanism of DAI is very complicated, but a clear understanding of the pathological mechanism is very important to diagnosis, clinical treatment, and prognosis; pathological characterization has become a hot topic in neurosurgical research.

3.1. Pathological Mechanism of Primary Axonal Injury

3.1.1. Formation of Axon Retraction Balls. The main cause of primary axonal injury was axonal breakage, retraction, and the formation of what is called axon retraction balls because of the shape of the swelling at the end of the axonal axis, which was caused by the external shear force and tension. The formation of these axon retraction balls was believed to lead to the final breakage of the axon. Currently, it is thought that the axon retraction balls cause axon breakage, so interrupting protein transport, and the individual axon retraction ball has been observed under microscopy at the end of broken axons. However, multiple recent studies have shown that the site of instant, strong shearing force or tension within the brain does not always match the site of actual injury. Animal studies have shown there to be no axon breakage immediately after brain trauma, and pathological examination suggested that the myelin of the axons had remained intact [3–6]. This has sparked debate over whether it is suitable to assess the number of injured axons by determining the total number of axon retraction balls after onset of DAI.

3.2. Pathological Mechanism of Secondary Axonal Injury

3.2.1. Calcium Ion (Ca^{2+}) Influx and Calcium-Protein-Mediated Structural Protein Hydrolysis and the Cytoskeleton Network of Degrading Axons

(1) Ca^{2+} Influx Activated the Signaling Pathway of Cysteine Protein. After external instant shear force and tension act on the brain, the permeability of the axon membrane changes, and large amounts of Ca^{2+} enter the cells. The anterograde transport of axon plasma is gradually converted to retrograde transport, so activating the cysteine protein signal pathway and caspase-3. The inherent cellular calpain inhibitor calpastatin is hydrolyzed. A relatively high level of activated calpain accumulates within the cell, and this degrades the axonal cytoskeleton network. Recent studies have shown that influx of Ca^{2+} and degradation of the axonal cytoskeleton network are progressive events, during which axons usually maintain their morphology several hours after injury [7–10].

(2) Calpain-Mediated Hydrolysis of Structural Protein. Spectrin, also called cell ghost, is a structural protein found on the inner side of the membrane. It not only supports the lipid bilayer but also maintains the shape of red blood cells. It forms a transformable network beneath the plasma side of the membrane and so maintains the biconcave disk shape of red blood cells. During the early stage of injury, calpain-mediated hydrolysis of spectrin in focal axon was observed, as indicated by single and double markers' under immunohistological examination via light microscopy and electromicroscopy. Most axons show signs of calpain-mediated hydrolysis of spectrin 1-2 h after the injury. Related pathological changes include loss of microtubules, swelling of the mitochondria, and neurofilamentous knots, which indicate that calpain-mediated hydrolysis of structural protein and degradation of the cytoskeleton play important roles in the development and progression of DAI pathology [11–13].

3.2.2. Mitochondrial Damage, Imbalance of Ion Homeostasis, Release of Proapoptotic Factors, and Activation of Caspase-Mediated Programmed Cell Death. Mitochondrial damage after onset of DAI mainly includes swelling and breakage of the mitochondrial crest and membrane. This type of focal damage of mitochondria closely related to Ca^{2+} influx. Ca^{2+} influx leads to changes in the permeability of the mitochondrial membrane and affects the opening of the switching pore in said membrane. The intake of small molecules causes the mitochondria to swell and break, which further not only disrupts the energy metabolism and ion homeostasis but also releases caspases and the activators of apoptosis, so triggering caspase-mediated progressive cell death. Caspases hydrolyze proteins severely in injured axons [14–17]. In this way, impairment of the mitochondria, imbalance in ion homeostasis, the release of proapoptotic factors, and activation of caspases are key contributors to the high mortality and poor prognosis of DAI.

3.2.3. Changes in Transport Proteins, Such as Amyloid Precursor Protein (APP). Amyloid precursor protein is a single transmembrane protein present in most cells and tissues. It has drawn a great deal of attention because it can be converted to toxic β-amyloid (Aβ) after protease hydrolysis. The use of immunohistology to assess changes in APP in axons is the gold standard of neuropathology and trauma model diagnosis of DAI [18, 19]. Once pathological changes take place, the anterograde transport of APP becomes disrupted, which causes focal aggregation of APP.

3.2.4. Changes in Glia Cells. Increasing amounts of evidence show that changes in glia cells play very important roles in the development and progression of DAI. The morphological and functional changes in astrocytes, microglia, and oligodendrocytes that take place after onset of DAI and are called "glial reaction." Glial cells become activated and involved in eliminating and engulfing particles expelled from the site of injury, extend projections to fill in cavities, form glial scars, and produce matrix metal proteins (MMPs) to reconstruct damaged extracellular matrices after the progression of DAI. Glia cells also express insulin-like growth factor-1, epithelial growth factor, and other neurotrophic growth factors in order to decrease the rate of neuronal death and neural injury after the progression of DAI [20, 21].

Astroglia (AS) is a major type of glial cells in the central nervous system (CNS) originating from neural ectoderm. The distribution of AS in the brain was regular (GFAP positive cells in hippocampus and dentate gyrus in obvious

rules). This kind of order contributes to the position of the fixed relationship and the function of stable relationship between AS and neuron. And AS may also be involved in the complex functions of the brain activity, including learning and memory. When brain was injured, it usually leads to reactive hyperplasia of AS. Recently, it showed that AS clears hemorrhage in the early damage and degeneration necrosis tissue with macrophages and thereby promotes wound repair [22, 23]. Corresponding to different neurotransmitters and neuropeptide, there are many receptors in AS, such as 5-HT and γ-GABA. In recent years we thought that it (at least under the condition of in vitro) has almost all possible neurotransmitters functional receptors [24]. After being damaged, neurons produce more neurotransmitters than normal, so the receptors on the AS can upregulate and produce more growth factors to promote repairing of injury.

Oligodendrocyte (OLG) is myelin glial cells in the central nervous system and rich in grey and white matter of brain and spinal cord. The damage of OLG has far-reaching influence to white matter. Mechanical damage, ischemia, or axonal degeneration can cause the damage and apoptosis of OLG; otherwise, there is great relevance between axonal degeneration after brain injury and the apoptosis of OLG [25]. And the Fas and p75 receptor activation may be involved in apoptosis [26].

However, glial cells become activated further, to the point of overactivation, as DAI progresses. Overactivated glial cells continuously release inflammatory factors, such as IL-1β and TNF-α, and they release oxygen free radicals and cytotoxic substances, which elicits inflammatory responses, causes oxidative stress in brain tissue, and directly or indirectly induces neuronal death. Overactivation of glia cells causes the release of chondroitin sulfate proteoglycan, prevents the glia cells from reconstructing the extracellular matrix, inhibits axon growth, and weakens the ability of glial cells to eliminate products expelled from the site or injury. In this way, overactivated glial cells promote neuronal injury.

Activation of glia cells can also promote neuron-glia and glia-glia interactions. Previous studies have demonstrated that the chemokine CXCL-12, which is released from astrocytes, promotes the release of glutamate, which further promotes the release of large amounts of TNF-α from microglia. High concentrations of TNF-α impair the ability of microglia to eliminate glutamate, and this causes excitatory toxicity and injures neurons [13]. Astrocytes also release the anti-inflammatory factor IL-10, which inhibits the release of TGF-β from microglia and promotes the maturation of oligodendrocytes [27–30].

However, it remains unclear whether the activation of glial cells promotes injury or repair. The actual roles of the activation of glial cells require further investigation.

4. Diagnosis of DAI

4.1. Imaging Examination

4.1.1. Computed Tomography (CT) and Traditional MRI Examination. CT allows rapid and reliable location of focal hemorrhages related to axonal injury, but it is difficult to find injuries other than hemorrhages, especially if they are small in size or involve needle-like bleeding.

Traditional MRI examination not only allows rapid location of hemorrhages, but it is also a sensitive and reliable way of locating nonhemorrhages. It has better resolution than CT scans and it is especially suitable for injuries to the posterior cranial fossa and deep white matter. However, it still has a high rate of false negative results for small lesions and mild DAI. Moreover, patients are often unable to complete the examination due to the long time requirements.

4.1.2. Diffusion-Weighted MRI (DWI) and Diffusion Tension Imaging (DTI). As medical science has progressed, more accurate methods of diagnosing DAI have been developed. Some of these are based on DWI and DTI. DWI involves using the anisotropy of protein to identify changes in white matter after onset of DAI. Studies have shown DWI to be an accurate method of examining nonhemorrhage injuries, especially at the sites within the cranial vault. However, this method is often not sufficiently accurate for the examination and diagnosis of injuries to the corpus callosum and grey matter. DTI, which was developed as an improved form of DWI, can be used to evaluate nerve alignment, injury context, and the microstructure of white matter effectively. It can also allow direct observation of the nerve alignment and the collection of abnormal morphology information regarding major nerve fibers. In this way, DTI can detect DAI in a highly sensitive way and allow estimation of the time elapsed from injury to examination.

4.1.3. Gradient Echo Pulse Sequence-Susceptibility Weighted Imaging (GRE-SWI). GRE-SWI can detect more minor hemorrhages and so indicate the severity of DAI more accurately than other methods can, which makes it especially suitable for early diagnosis of DAI.

GRE-SWI is different from proton density and T1 and T2 weighted imaging. This new imaging method is the use of magnetic susceptibility which is different between different organizations and imaging technology. And the key to imaging is magnetic sensitive material; in some tissues, such as venous blood, bleeding, and calcification, the magnetic susceptibility is different from that of surrounding tissues. On the one hand it can shorten $T2^*$; on the other hand, it can lead to blood vessels and surrounding tissues of different phase contrast.

Diffuse axonal injury (DAI) accounts for more than 30% of severe craniocerebral injury and is the main causes leading to a vegetative state or serious nerve dysfunction. Further clinical study found hemorrhage of DAI with worse prognosis than less bleeding. However, both CT and routine MRI are not sensitive to the smaller hemorrhage stove. GRE-SWI is very sensitive to hemoglobin metabolites, such as DNA, methemoglobin, hemoglobin, and hemosiderin. So, GRE-SWI can detect these metabolites more effectively than conventional MRI [31, 32]. So the GRE-SWI play an important role in the evaluating, treating of traumatic brain injury, and prognosis judging.

Although GRE-SWI is valuable for finding the minor hemorrhage in brain clinically, it still cannot make difference between other minor hemorrhages caused by patients related diseases, such as hypertension. And the acquisition and processing technology still needed further improvement, to improve the scanning speed, reduce artifacts, and improve the signal-to-noise ratio.

4.2. Neural Electrophysiology. Neural electrophysiology is one of noninvasive tools available for studying DAI. Animal studies have shown that rats with mild DAI have abnormal neural electrophysiology regardless of whether they have sustained any axonal injury [33]. Other studies have shown pathological changes and decreases in action potential in the axonal axis of the corpus callosum of mice with brain trauma. The action potential of both myelinated nerve fibers and unmyelinated nerve fibers in the corpus callosum has been found to decrease. Among those nerve fibers, myelinated fibers were found to recover their action potential gradually as their axons were repaired, while unmyelinated nerve fibers did not [34–38]. These findings indicated that the abnormal action potential of unmyelinated nerve fibers may play an important role in the disability associated with DAI.

4.3. Diagnosis Based on Biochemical Markers. Currently, commonly used biochemical markers for acute DAI diagnosis and analysis of the conditions and prognosis associated with DAI include β-APP, spectrin, and its decomposition products SBDP145 and SBDP150. Other markers include neurofilaments and the phosphorylated products of their tau subunits and hydrolyzation of myelin basic protein.

4.3.1. β-APP. The detection of β-APP is currently considered the gold standard of DAI examination in forensic and laboratory settings. It is often used for early diagnosis of DAI.

Under normal conditions, the β-APP present in axons cannot be detected using immunohistochemistry. However, after onset of DAI, the disruption of transportation through the axoplasm causes β-APP to aggregate in the axons, bringing its concentration up to detectable level. This makes it suitable for use as a marker for early diagnosis of DAI. However, detection of β-APP by immunohistochemistry after onset of DAI can cause underestimation of the scope of axonal injury. Through more in-depth studies, detection of β-APP695, an isoform of β-APP, could provide more reliable and sensitive diagnosis of DAI [39]. Attention must be paid to diseases that can cause clinically abnormal axonal metabolism, in which β-APP has been shown present via immunohistochemistry. In this way, patients' disease history must be taken into consideration, which would increase the accuracy of diagnosis via immunohistochemical examination of β-APP.

4.3.2. Spectrin-II Subunit. The spectrin-II subunit is present within the neuron body, dendrite, and axons. Along with neurofilaments and microtubule-associated proteins, it plays an important role in maintaining neuron morphology and function. The spectrin-II subunit of calpain degradation products (SBDP) detected in cerebral cortex, cortex medullary junction, corpus callosum, and cerebrospinal fluid following DAI mainly include SBDP-150 and SBDP-120. The trends in the changes of the concentrations of SBDP-150 and SBDP-120 in the cerebral cortex and corpus callosum have been shown to be similar [40], which indicate that, after onset of DAI, calpain-induced necrosis is an important pathological mechanism of DAI. However, the trends in the concentrations of SBDPs in cerebrospinal fluid are not synchronous with those of the brain, and the trends in the concentrations of degradation products from different subunits of spectrin are also different. One possible reason for this is that the proteins released from the brain parenchyma must be transported into the cerebrospinal fluid via the intercellular fluid, while proteins released from injured neurons in the subarachnoid space can be released directly into the brain [41]. In this way, the measurement of the expression of different subunits of spectrin expression could be used to assess the severity of DAI, show whether it is associated with focal or diffuse functional impairment, and provide some basis for predicting the pathological mechanism of DAI.

4.3.3. Neurofilaments. Neurofilaments are involved in the cytoskeleton and play an important role in axonal transportation. Neurofilaments are composed mainly of light chains (NF-L), medium chains (NF-M), and heavy chains (NF-H). After onset of DAI, the spatial configurations of NF-L, NF-M, and NF-H peptides were different, according to the severity of DAI. In mild and moderate DAI, three types of NF subunits presented focal disorder. In moderate DAI, compact area shows up in NF. The axons and microtubule protein decreased significantly. Phosphorylated neurofilament was hydrolyzed and finally resulted in neurofilament collapse. Because NF-H can be detected in serum after onset of DAI and increased from 6 h, peaked at 12 h and 48 h, and decreased to normal level on day 7 [42, 43]. NF-H is considered the most convenient marker of DAI diagnosis. NF-L is the most sensitive and specific marker of DAI diagnosis. NF-M must be investigated further if it can be used as a specific marker of DAI diagnosis.

4.3.4. Tau Protein. Tau is the most abundant protein in microtubule-related proteins. Tau contains a phosphoric acid group. Each molecule of tau contains 2-3 phosphoric acid groups. Overphosphorylated tau groups lose their normal transport function in axons and in turn inhibit the assembly and promote dissemble of microtubule, finally causing axonal breakage. After onset of DAI, tau was depolymerized to C-tau by calpain, which can be detected in large amounts in cerebrospinal fluid. The detection level of C-tau in the cerebrospinal fluid is negatively correlated to the severity of DAI of patients in clinical settings [44, 45]. In this way, the detection of C-tau in cerebrospinal fluid was used to quantitatively evaluate the severity of axonal injury. Investigation has shown that once the C-tau level in patients' cerebrospinal fluid reaches 2.126 mg/mL, the accuracy of prognosis of the mortality rate reaches 100% and specificity rises above 80% [46]. However, C-tau detected in serum was not found to

facilitate effective evaluation of prognosis. For this reason, the detection of C-tau levels in the cerebrospinal fluid is considered one of the most suitable biochemical markers for clinical diagnosis of DAI.

4.3.5. Myelin Basic Protein (MBP). Myelin basic protein (MBP) is the main protein in myelin in the central nervous system (CNS). It is present on the plasma side of myelin, where it keeps the protein's structure and function stable. It is specific to nerve tissue. Because of the blood-brain barrier (BBB), MBP is readily released into cerebrospinal fluid, and a very small amount of MBP is released into the blood. After onset of DAI, the CNS is damaged and the BBB can be completely destroyed. The changes in the permeability of BBB result in the increase of MBP levels in serum [47]. Determination of MBP level in serum can indicate its quantity in a timely manner, and the samples for determination are easy to collect. Scholars both within and outside of China have reported that MBP could be a suitable index of the severity of CNS injury [48]. In the same way, the determination of MBP levels in serum and cerebrospinal fluid could facilitate preliminary judgement of the severity of DAI and allow objective evaluation of the progression and prognosis of DAI. However, the sensitivity of the detection of serum MBP is not currently ideal and the use of MBP detection in clinical settings is limited.

4.3.6. Others. Other biomarkers for diagnosis of DAI include cyclooxygenase-2, aquaporin-4, inflammatory reaction factors (such as IL-1β, IL-6, and TNF), and basic fibroblast growth factor. These factors can facilitate diagnosis of continued injury, inflammatory responses, and the development and progression of DAI.

4.4. Neuropsychological Assessment. Although neuropsychological assessment as a noninvasive form of diagnosis cannot be used to quantify DAI, it can be used to indirectly show the efficacy of clinical treatment according to the differences in consciousness and cognitive disorders of patients in acute and subacute states. Studies have shown that cognitive disorder is related to the site of injury, correlated in some extent to the state of the white matter connected to specific functional areas. Increasing numbers of investigators have attempted to discern clinical efficacy directly through digitalized neuronal evaluation.

According to the different standards, a variety of partition can be made to the neuropsychological test. The most common ones are divided into a single test and battery of tests. And two common neuropsychological tests are listed as follows.

4.4.1. Halstead-Reitan Neuropsychological Battery (HRB). The test concludes infants, children, and adults, three versions. And the test is divided into part for verbal test and others for nonverbal test. The revised HRB test battery mainly surveys the following ten aspects: category test, touch operation test, music rhythm test, finger tapping test, Halstead-Wepman aphasia screening test, voice perception test, on one side of the edge test, grip strength test, the attachment test, and perceptual disorder test. Each subtest has different age norm. This set of tests use demarcation points as the norm (the critical points) to distinguish pathology. Then according to the abnormal test counting damage index damage index = abnormal test number/total number. The HRB assessment scale is listed in Table 1.

Table 1: HRB assessment scale.

Damage index	Pathologic state
0.00–0.14	normal
0.15–0.29	Borderline state
0.30–0.43	Mild brain injury
0.44–0.57	Moderate brain injury
>0.58	Severe brain injury

4.4.2. Luria-Nebraska Neuropsychological Battery, LNNB. LNNB has 1980 and 1985 two versions. The first version includes 269 projects, a total of 11 subtests. The second version added intermediate memory subtest.

There are 11 subtests that constituted the first edition of LNNB and include sports test, rhythm test, touch test, visual test, feeling type words, expressive words, writing test, reading test, math quiz, memory test, and intellectual processes test. And LNNB has three additional scales, as the disease symptoms characteristic scale (qualitative scale), the left hemisphere lateralization of scale, and right side of the scale. These scales are from the previous 11 subtests. Each project of LNNB adopted 3-level scoring mode: "0" is normal, "1" represents borderline state, and "2" indicates exception. Each subtest scores accumulation is LNNB original scores. The more scores shows the heavier damage maybe.

Additional Points

DAI occurs when external instant mechanical forces, such as shear force and tension, cause axon swelling and progress to axon breakage. The pathological mechanism of DAI is complicated: axon swelling causes the formation of axonal retraction balls, and calcium influx elicits a series of ion imbalances, impairs the mitochondria, and activates caspase-mediated programmed cell death. Calpain hydrolyzes structural proteins and degrades the cytoskeleton network. Glial cells also take part in the overall process. Pathological cascades take place after DAI. The pathological mechanism is still unclear. Due to the complicated pathological mechanisms underlying DAI, there is no uniform standard for its clinical diagnosis. Currently, most of the commonly used diagnostic standards are noninvasive methods, such as neuropsychological assessment, CT/MRI imaging, and biochemical markers. However, each individual method of diagnosing DAI has its own specific limitations. In the future, after further investigation and assessment of the pathological mechanism underlying DAI, a multimechanism form of diagnosis may be available. Ideally, this method will be more reliable and sensitive and facilitate location of the injured site

and range of DAI and realize the increase of clinical efficacy for treatment of DAI.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Junwei Ma and Kai Zhang contributed equally to this work.

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Hindawi Publishing Corporation
Neural Plasticity
Volume 2016, Article ID 8030676, 8 pages
http://dx.doi.org/10.1155/2016/8030676

Research Article

Traumatic Brain Injury and Substance Related Disorder: A 10-Year Nationwide Cohort Study in Taiwan

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Received 6 May 2016; Accepted 18 August 2016

Academic Editor: James M. Wyss

Whether traumatic brain injury (TBI) is causally related to substance related disorder (SRD) is still debatable, especially in persons with no history of mental disorders at the time of injury. This study analyzed data in the Taiwan National Health Insurance Research Database for 19,109 patients aged ≥18 years who had been diagnosed with TBI during 2000–2010. An additional 19,109 randomly selected age and gender matched patients without TBI (1 : 1 ratio) were enrolled in the control group. The relationship between TBI and SRD was estimated with Cox proportional hazard regression models. During the follow-up period, SRD developed in 340 patients in the TBI group and in 118 patients in the control group. After controlling for covariates, the overall incidence of SRD was 3.62-fold higher in the TBI group compared to the control group. Additionally, patients in the severe TBI subgroup were 9.01 times more likely to have SRD compared to controls. Notably, patients in the TBI group were prone to alcohol related disorders. The data in this study indicate that TBI is significantly associated with the subsequent risk of SRD. Physicians treating patients with TBI should be alert to this association to prevent the occurrence of adverse events.

1. Introduction

Traumatic brain injury (TBI) presents complex social problems and is a major cause of mortality and permanent disability in both developing and developed countries. In the US alone, an average of 1.4 million people experienced TBI annually. Although approximately 79% (1.1 million) of these are minor injuries that could be managed at emergency departments, approximately 17% (235,000) need to be treated in hospital, and as many as (4%) 50,000 are fatal [1, 2]. In Taiwan, the estimated annual average number of TBIs is 52,000, up to 25% of which are fatal [3]. Traumatic brain injury, also known as intracranial injury, occurs when an external force traumatically impacts the head in excess of the protective capacity of the cranium [4]. A TBI can cause chronic physical disability and neurobehavioral sequelae that produce highly disruptive cognitive and behavioural changes. Survivors often have difficulties maintaining personal relationships, and their work coping skills may be even more disabling than any residual physical disabilities [5]. Growing body of evidence also indicates that a history of TBI increases the risk of future brain injuries. Multiple brain injuries obviously have long lasting negative effects on mental health and some studies have reported a high prevalence of substance related disorder (SRD) in TBI patients [6–10]. However, an association between TBI and the subsequent development of SRD has

not been well established [10–12]. That is, whether TBI itself increases SRD risk, especially in persons with no history of mental disorders at the time of injury, is unknown. Most studies of the connection between SRD and TBI have focused almost entirely on the causal relationships between the use or abuse of drugs or alcohol and TBI. Little population-based data for this association are available, and studies of the relationship between psychological problems, substance abuse, and TBI either have been contradictory or have used very small clinical samples [9, 10].

Large-scale studies of the relationship between TBI and subsequent SRD risk are rarely performed in population-based Asian cohorts. In 2011, Ilie et al. performed a telephone survey of a cross-sectional sample of 1999 Ontario, Canada, adults aged 18–93 years. Compared to subjects without a history of TBI, those with a history of TBI had higher adjusted odds of smoking and nonmedical use of cannabis and opioids. The TBI group also had higher odds of positive results in screenings for psychological distress. However, their survey results were potentially biased because they were based on self-reported data, and the response rate for the survey was only 51%. Additionally, they could not rule out the possibility that cognitive impairments affected the responses in the TBI group [13]. Therefore, this study retrospectively analyzed data from the Taiwan National Health Insurance Research Database (NHIRD) to clarify the relationship between TBI and subsequent risk of SRD.

2. Methods

2.1. Data Sources. The NHIRD used in this population-based cohort study comprises data for 99.9% of the 23.74 million residents of Taiwan and is maintained by the national healthcare system of Taiwan [3]. This retrospective cohort study analyzed 2000–2010 data contained in the Longitudinal Health Insurance Database (LHID). This database was developed by the Taiwan National Health Insurance Program and contains data for 1 million randomly selected patients. The LHID 2010 contains original claims data for 1 million beneficiaries randomly sampled during the period from January 1 to December 31, 2010. Distributions of gender, age, and insured payroll-related amounts do not significantly differ between the LHID 2010 and the original NHIRD. The large sample size of the dataset provides an opportunity to study SRD risk in patients. Diagnoses are coded according to the International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM) code. This study was performed in accordance with the Declaration of Helsinki and was also evaluated and approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

2.2. Subject Selection. This study analyzed 19,109 patients aged 18 years or older and diagnosed with TBI (ICD-9-CM codes 800, 803-804, and 850–854; operation codes 01.23, 01.24, 01.25, 0131, 01.39, and 02.01) during 2000–2010 [3]. To ensure accurate data, the TBI group was limited to patients who had received ≥2 TBI diagnoses during ambulatory visits or ≥1 diagnoses during inpatient care. The index date was defined as the date of the first clinical visit for TBI. Those

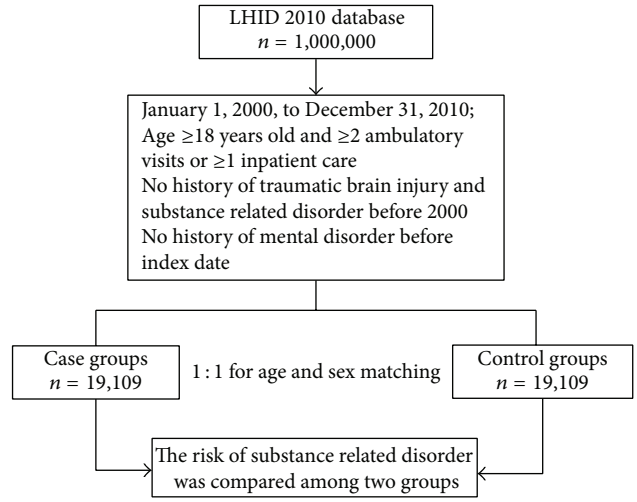

Figure 1: Flow diagram summarizing the process of enrollment. LHID: Longitudinal Health Insurance Database.

diagnosed with any mental disorder (ICD-9-CM codes 290–319) before the index date were excluded from the TBI group. The TBI group was then divided into severe, moderate, and mild TBI subgroups. A severe TBI was defined as a TBI that received surgery during the course of inpatient treatment; a moderate TBI was defined as having hospitalized for TBI but not having undergone an operation; a mild TBI was defined as any history of head injury that did not receive inpatient treatment [14].

In this study, SRD was defined as a record of an ICD-9 code for SRD (ICD-9-CM codes 291, 292, 303.0, 303.9, 304, or 305) [15] entered by a psychiatrist and either ≥2 diagnoses of SRD in ambulatory visits or ≥1 diagnosis in inpatient care. The exclusion criterion was any diagnosis of SRD on or before the index date. SRD was further categorized as alcohol abuse (ICD-9-CM codes 291, 303.0, 303.9, and 305.0) [16] or illicit drug use (ICD-9-CM codes 292 and 304, and all 305 codes except 305.0) [16, 17].

The non-TBI group was randomly selected from the registry of beneficiaries who had no TBI-related medical claims and no history of mental disorder. Each patient in the TBI group was matched with one person in the non-TBI group by age, gender, and year of TBI diagnosis (index year); thus, 19,109 patients were enrolled in the non-TBI group. A 1 : 1 ratio of TBI to non-TBI patients was maintained to enhance the power of statistical tests and to ensure a sufficient number of SRD cases for stratified analyses. A post hoc sample size calculation was performed to determine statistical power. Based on the event rate, the power for detecting a significant association between TBI and subsequent development of SRD exceeded 99% ($\alpha = 0.05$). Figure 1 shows a flowchart of the study procedure.

2.3. Outcome and Comorbidities. The outcome was the occurrence of SRD during the follow-up period. Both cohorts were followed up until December 31, 2010, or until a diagnosis of SRD.

Only a few clearly defined and modifiable risk factors have been defined for psychiatric disorders [18]. Some studies have used chronic obstructive pulmonary disease (COPD) as an indicator of smoking status and as a proxy for lifestyle-related behaviours [14, 19]. However, most studies have focused on largely unmodifiable factors such as age and gender. Potential confounders include many factors associated with both TBI and mental disorder, including common physical comorbidities such as hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–414), congestive heart failure (ICD-9-CM code 428), COPD (ICD-9-CM codes 491, 492, 494, and 496), malignancy (ICD-9-CM codes 140–208) [18], and unhealthy lifestyle behaviours [14]. The urbanization level and income-related insurance payment amounts were used to evaluate personal socioeconomic status. The urbanization level was categorized as urban, suburban, or rural [20]. The average monthly income was categorized into three groups: low (0–NT$20,000), medium (NT$20,000–40,000), or high (more than NT$40,000) [15, 21].

The Charlson Comorbidity Index (CCI) score was used to assess physical condition, that is, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild and moderate or severe liver disease, diabetes (with or without chronic complication), hemiplegia or paraplegia, renal disease, any malignancy (including lymphoma and leukemia but excluding skin malignancy), metastatic solid tumor, and AIDS/HIV. The CCI scores were then categorized into four levels: 0, 1-2, 3-4, and ≥5. Each increase in the CCI score level corresponds with a stepwise increase in cumulative mortality [22].

2.4. Statistical Analyses. Chi-square test was used to compare distributions of categorical demographics and clinical characteristics between the TBI and non-TBI groups. Student's t-test and Wilcoxon rank-sum test were used as appropriate to compare mean age and follow-up time (y) between the two cohorts. The Kaplan-Meier analysis was used to estimate the cumulative incidence of SRD, and the differences between the curves were compared by 2-tailed log-rank test. In the TBI group, survival was calculated until hospitalization, an ambulatory visit for SRD, or the end of the study period (December 31, 2010), whichever came first. Incidence rates of SRD estimated in 1000 person-years were compared between the two cohorts. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for SRD in the TBI group when the proportional hazards assumption was satisfied. Multivariable Cox models were adjusted for age, gender, income and urbanization level, CCI score, and relevant comorbidities. A 2-tailed P value of <0.05 was considered statistically significant. All data processing and statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline Characteristics of TBI and Non-TBI Groups. Table 1 compares the baseline demographic characteristics and comorbidities in the two cohorts. The mean age was 42.2 ± 17.6 years in the TBI group and 42.5 ± 17.2 years in the non-TBI group. In the TBI group, 56.98% were male. The percentages of patients with the following comorbidities were significantly higher in the TBI group compared to the non-TBI group, respectively: hypertension (36.67 versus 21.92, $P < 0.001$), diabetes mellitus (22.62 versus 12.99, $P < 0.001$), hyperlipidemia (31.06 versus 20.83, $P < 0.001$), coronary artery disease (6.69 versus 2.46, $P < 0.001$), congestive heart failure (7.04 versus 3.23, $P < 0.001$), COPD (24.41 versus 14.43, $P < 0.001$), and malignancy (8.46 versus 5.23, $P < 0.001$). The TBI group also had higher CCI scores. Moreover, patients in the TBI group were also more likely to qualify for insurance premium exemptions, less likely to pay high insurance premiums, and more likely to live in areas with low urbanization levels.

During the follow-up period, diagnoses of SRD significantly ($P < 0.001$) differed between the TBI group (1.78% (340 patients)) and the non-TBI group (0.62% (118 patients)). The TBI group also had significantly larger SRD subgroups for alcohol abuse (0.66 versus 0.13 in non-TBI, $P < 0.001$) and illicit drug abuse (0.87 versus 0.44 in non-TBI, $P < 0.001$).

3.2. Incidence and Risk of SRD. Table 2 stratifies the SRD incidence densities and HRs by gender, age, and comorbidity. During the follow-up period, 1.78% (340) patients in the TBI group and 0.62% (118) patients in the non-TBI group developed SRD. The overall SRD risk was 3.62 times greater in the TBI group compared to the non-TBI group (1.97 versus 0.41 per 1,000 person-years, resp.) after adjusting for age, gender, income, urbanization level, CCI, and related comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, COPD, and malignancy). The gender-specific analyses showed that, in both cohorts, the incidence of TBI was higher in men than in women (2.69 versus 0.57 per 1,000 person-years, resp., in the TBI group; 1.01 versus 0.19 per 1,000 person-years, resp., in the non-TBI group). Additionally, the SRD risk was significant in both men and women (adjusted HR = 3.69 versus 3.45, resp., $P < 0.001$).

The incidence of SRD was consistently higher in the TBI group at different ages, and the incidence rate consistently decreased with age. Additionally, the SRD risk decreased with age, and the age-specific risk analysis showed a significantly higher SRD risk in TBI patients aged younger than 40 years compared to those aged 40 years and older (HR = 5.03 versus 1.19; P for interaction <0.001). Regardless of comorbidities, SRD risk was higher in the TBI group than in the non-TBI group. The SRD risk contributed by TBI decreased in the presence of comorbidity (HR = 5.14 versus 2.59; P for interaction = 0.002).

Figure 2 compares the Kaplan-Meier curves for the cumulative incidence of SRD between the TBI and non-TBI groups at the 10-year follow-up. The cumulative incidence curves for SRD in the two cohorts showed a significantly higher

Table 1: Baseline characteristics of patients with and without traumatic brain injury.

Variables	Traumatic brain injury		P value
	Yes (N = 19,109)	No (N = 19,109)	
Mean age at enrollment (years, SD)	42.2 (17.6)	42.5 (17.2)	0.088
Age group, n (%)			
18–39	9567 (50.07)	9567 (50.07)	
≥40	9542 (49.53)	9542 (49.53)	1.000
Gender, n (%)			
Men	10889 (56.98)	10889 (56.98)	
Women	8220 (43.02)	8220 (43.02)	1.000
Income, n (%)			
Low (<NT$20,000)	15624 (81.76)	15484 (81.03)	
Medium (NT$20,000–40,000)	2483 (12.99)	2330 (12.19)	
High (>NT$40,000)	1002 (5.24)	1295 (6.78)	<0.001
Urbanization level, n (%)			
Urban	11230 (58.77)	11612 (60.77)	
Suburban	6303 (32.98)	6296 (32.95)	
Rural	1576 (8.25)	1201 (6.28)	<0.001
Charlson Comorbidity Index, n (%)			
0	4542 (23.77)	7752 (40.57)	
1-2	7372 (38.58)	7411 (38.78)	
3-4	3760 (19.68)	2434 (12.74)	
≥5	3435 (17.98)	1512 (7.91)	<0.001
Comorbidity, n (%)			
Hypertension	7007 (36.67)	4189 (21.92)	<0.001
Diabetes mellitus	4323 (22.62)	2482 (12.99)	<0.001
Hyperlipidemia	5936 (31.06)	3980 (20.83)	<0.001
Coronary artery disease	1279 (6.69)	471 (2.46)	<0.001
Congestive heart failure	1345 (7.04)	618 (3.23)	<0.001
Chronic obstructive pulmonary disease	4664 (24.41)	2758 (14.43)	<0.001
Malignancy	1616 (8.46)	999 (5.23)	<0.001
Newly diagnosed substance related disorders, n (%)	340 (1.78)	118 (0.62)	<0.001
Alcohol abuse	127 (0.66)	25 (0.13)	<0.001
Illicit drug use	166 (0.87)	84 (0.44)	<0.001
Combined alcohol and illicit drug use	47 (0.25)	9 (0.05)	<0.001
Mean age at diagnosis of substance related disorder (years, SD)	33.5 (11.9)	41.0 (13.3)	<0.001

SD: standard deviation.

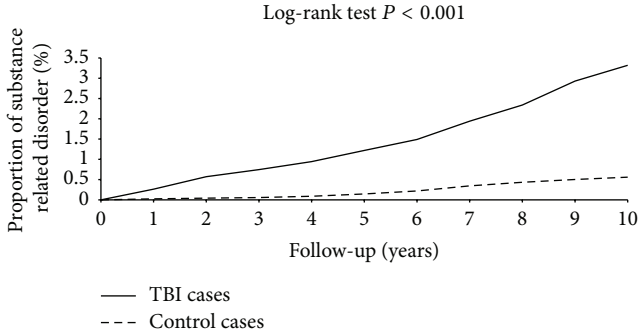

Figure 2: Cumulative incidence of substance related disorder among TBI (solid line) and control (dashed line) cases. TBI: traumatic brain injury.

incidence of SRD in the TBI group compared to the non-TBI group (log-rank test $P < 0.001$).

3.3. Predictors of SRD. The Cox regression analysis results for the TBI group revealed that the major risk factors for SRD were high CCI score (adjusted HR = 1.77; 95% CI = 1.57–2.00). Age and female gender had a protective role for SRD in these patients (Table 3).

3.4. SRD and TBI Severity. Table 4 shows that SRD risk increased with severity of TBI, particularly in those with severe TBI (adjusted HR = 9.01; 95% CI = 4.97–16.33).

Table 2: Incidence and hazard ratios of substance related disorder by demographic characteristics and comorbidity among patients with or without TBI.

Variables	Patients with TBI		Patients without TBI		Compared to non-TBI		P for interaction
	Substance related disorder	Rate	Substance related disorder	Rate	Crude HR[a] (95% CI)	Adjusted HR[a] (95% CI)	
Overall	340	1.97	118	0.41	5.71 (4.58–7.12)[c]	3.62 (2.87–4.57)[c]	
Gender							
Men	265	2.69	94	0.57	5.64 (4.40–7.23)[c]	3.69 (2.84–4.79)[c]	
Women	75	1.01	24	0.19	5.88 (3.64–9.49)[c]	3.45 (2.06–5.78)[c]	
Stratify by age							
18–39	256	2.79	65	0.45	7.20 (5.44–9.53)[c]	5.03 (3.76–6.72)[c]	<0.001
≥40	84	1.04	53	0.37	3.39 (2.39–4.81)[c]	1.91 (1.33–2.75)[c]	
Comorbidity[b]							
No	122	1.68	54	0.31	6.51 (4.69–9.04)[c]	5.14 (3.69–7.16)[c]	0.002
Yes	218	2.17	64	0.57	4.55 (3.42–6.06)[c]	2.59 (1.93–3.49)[c]	

Rate, incidence rate per 1000 person-years; 95% CI, 95% confidence interval; HR, hazard ratio; TBI, traumatic brain injury.
[a]Model adjusted for age, gender, income, urbanization level, Charlson Comorbidity Index, and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and malignancy).
[b]Patients with any examined comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and malignancy, were classified as the comorbidity group.
[c]$P < 0.001$.

Table 3: Cox regression model: significant predictors of substance related disorder after TBI.

Variables	Adjusted HR[a]	(95% CI)	P value
Charlson Comorbidity Index	1.77	(1.57–2.00)	<0.001
Age	0.54	(0.48–0.59)	<0.001
Female gender	0.38	(0.29–0.49)	<0.001

HR, hazard ratio; 95% CI, 95% confidence interval; TBI, traumatic brain injury.
[a]Model adjusted for age, gender, income, urbanization level, Charlson Comorbidity Index, and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and malignancy).
The adjusted HR and 95% CI were estimated by a stepwise Cox proportional hazards regression method.

3.5. Incidence and Risk of SRD Subtypes. Table 5 compares incidence rates and HRs for various outcomes between the TBI and non-TBI groups. After adjusting for covariates, the TBI group had a 6.22-fold higher incidence of alcohol abuse (95% CI = 3.94–9.84) and a 2.47-fold higher incidence of illicit drug use (95% CI = 1.83–3.32).

4. Discussion

To the best of our knowledge, this study is the first to perform a nationwide population-based analysis of the relationship between TBI and subsequent SRD in an Asian population. This study showed that SRD risk increases after TBI. SRD was identified in 1.78% (340) patients in the TBI group but in only 0.62% (118) patients in the non-TBI group. Overall, SRD risk was 3.62 times greater in the TBI group compared to the non-TBI group. In both genders, TBI was associated with a significantly increased risk of SRD. However, the incidence rate of post-TBI SRD decreased as age increased. Additionally, SRD risk increased with the severity of TBI. Specifically, compared to patients in the non-TBI group, SRD risk was 5.5 times higher in those with mild TBI and 6.5 times higher in those with moderate TBI. Comparisons of SRD subtypes in the TBI group further showed that alcohol abuse disorder was the leading one. Notably, patients in the TBI group were prone to suffer from alcohol abuse disorders.

Studies of the association between TBI and SRD have reported inconsistent results. A prospective survey of 939 health-maintenance organization members found that TBI survivors with no history of psychiatric disorder in the year prior to injury had an odds ratio of 4.5 for substance abuse within the 12 months after TBI. The odds ratio for substance abuse dropped to 1.4 at the third year after TBI. Prevalence rates for SRD increased from 7.3% pre-TBI to 14% at 1 year after TBI while SRD rates in matched non-TBI controls were 1.7% and 1.6% for the respective time periods [11]. Another study of 121 hospital inpatients with TBI and 133 controls by Ponsford et al. found that, in 25.4% of the TBI patients, hazardous levels of substance use were

Table 4: Incidence and hazard ratios for substance related disorder stratified by the severity of TBI.

Variables	N	Substance related disorder	Rate	Crude HR[a] (95% CI)	Adjusted HR[a] (95% CI)
Without TBI	19109	118	0.41	1.00 (reference)	1.00 (reference)
Mild TBI	5757	79	1.84	8.73 (6.25–12.19)[b]	5.50 (3.89–7.78)[b]
Moderate TBI	12786	245	1.97	9.23 (6.31–13.48)[b]	6.50 (4.41–9.58)[b]
Severe TBI	566	16	3.31	19.14 (10.75–34.05)[b]	9.01 (4.97–16.33)[b]

Rate, incidence rate per 1000 person-years; 95% CI, 95% confidence interval; HR, hazard ratio; TBI, traumatic brain injury.
[a]Model adjusted for age, gender, income, urbanization level, Charlson Comorbidity Index, and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and malignancy).
[b]$P < 0.001$.

Table 5: Incidence rates and hazard ratios of different substance related disorder risk in patients of TBI compared those without TBI.

Variables	Patients with TBI		Patients without TBI		Compared to non-TBI	
	Event	Rate	Event	Rate	Crude HR[a] (95% CI)	Adjusted HR[a] (95% CI)
Overall substance related disorder	340	1.97	118	0.41	5.71 (4.58–7.12)[b]	3.62 (2.87–4.57)[b]
Alcohol abuse	127	0.73	25	0.09	8.72 (5.60–13.58)[b]	6.22 (3.94–9.84)[b]
Illicit drug use	166	0.96	84	0.29	4.19 (3.17–5.53)[b]	2.47 (1.83–3.32)[b]
Combined alcohol and illicit drug use	47	0.27	9	0.03	8.89 (4.29–18.43)[b]	5.19 (2.43–11.10)[b]

Rate, incidence rate per 1000 person-years; 95% CI, 95% confidence interval; HR, hazard ratio; TBI, traumatic brain injury.
[a]Model adjusted for age, gender, income, urbanization level, Charlson Comorbidity Index, and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and malignancy).
[b]$P < 0.001$.

mentioned. Substance use increased and peaked by 2 years after injury. They concluded that substance use increased over time [23]. In contrast, an Australia study of sequential cohorts (aged 20–24, 40–44, and 60–64 years in wave 1) assessed TBI and SRD at baseline and 4 years later by using a survey methodology. Of the 7485 enrollees in the first wave of interviews, 89.7% were reinterviewed in the second wave of interviews. Between waves 1 and 2, 56 of the reported TBIs were mild (230.8/100000 person-years), and 44 were moderate (180.5/100000 person-years). The TBI risk was higher in males than in females and was highest in the cohort aged 20–24 years. Traffic accidents caused more moderate TBIs than mild TBIs. In wave 1 interviews, neither alcohol nor marijuana abuse is a predictor of TBI. In the second wave of interviews, TBI was not a predictor of substance related problems. However, the TBI incidence declined with age [10]. In Bombardier et al., changes in substance use from before to after TBI were investigated in 197 hospitalized adult patients. According to their data, a significant reduction in heavy drinking during the first year following TBI was reported [24].

The vast majority of TBI research has focused on the role of alcohol as a cause of TBI or risk factor for TBI rather than vice versa. However, the data analyzed in our study revealed that alcohol consumption increased after TBI and that alcohol use disorder was the most common SRD after TBI. Reports of the association between TBI and alcohol use disorder in the literature have been inconsistent. For example, a 2015 study found that a TBI group showed a higher incident rate ratio of developing alcohol use disorder (adjusted incidence rate ratio, 1.5) compared to the non-TBI group. The TBI group also had a higher risk of alcohol use disorder within 1 year after TBI [25]. In addition to these human studies, a rat model of TBI in Mayeux et al. showed that marked localized neuroinflammation at the TBI site was associated with post-TBI escalation of alcohol drinking [26]. In contrast, in Kreutzer et al., a comparison of self-reported alcohol use before and after TBI showed that, of the patients that were moderate-to-heavy drinkers before TBI, more than two-thirds of them reduced alcohol consumption, and approximately half of them quit drinking alcohol [27].

Although the exact mechanisms underlying the relationship between TBI and SRD are unclear, several possibilities could help explain the link between TBI and SRD. First, persistent inflammatory events caused by TBI in the nervous system result in gliosis, cerebral edema, and expression of proinflammatory cytokine. Notably, a large and growing body of literature indicates that the relationship between alcohol intake and inflammation is bidirectional; that is, alcohol causes inflammation of the brain, which induces an increase in alcohol consumption [28]. Therefore, TBI-related inflammatory events could induce an increase in alcohol intake. Thus, both TBI and long term alcohol intake promote neuroinflammatory events in the central nervous system. Alcohol intake after TBI was a kind of feed-forward mechanism wherein TBI-related inflammatory events promote alcohol intake, which further reinforces and amplifies inflammation in the nervous system. Second, substantial evidence indicates that another pathogenic cause of TBI is dysregulation of midbrain dopaminergic systems, which contributes to the chronic cognitive and behavioural sequelae associated with TBI [29]. Emerging evidence also indicates that TBI disrupts dopamine (DA) pathways. After electrical stimulation of the fore brain, experimental unilateral administration of controlled impacts to the parietal cortex of rats blunted striatal DA release and also decreased DA transporter [30, 31]. DA

system hypofunction is also a major cause for the development of substance and alcohol use disorders [29, 32]. Furthermore, a frontal cortex TBI can cause an organic personality disorder tending to promote substance abuse [33–35]. TBI to the frontal cortex could also increase SRD risk by introducing long term executive cognitive deficits. The frontal lobes of the brain are involved in executive functions and also have roles in predicting consequences, decision making between actions, and suppressing unacceptable psychosocial responses [36]. Losing these functions is a key element of neurobiology of substance dependence and addiction [28].

The strength of this study is the use of a large representative population-based dataset to demonstrate an association between TBI and SRD risk. The large sample size also enabled analyses stratified by the time and the severity of TBI. However, several limitations of this study are noted. First, the diagnoses of TBI and SRD were based on ICD-9-CM codes entered in patient records. Therefore, one limitation of this study is the unknown accuracy of diagnostic codes entered in the database, which depends on the performance of clinical physicians. To correct for this limitation, only TBI diagnosed by surgeons and SRD diagnosed by psychiatrists where each had at least two consensus diagnoses were included in this study. Notably, the Taiwan Bureau of National Health Insurance regularly audits medical specialists to ensure the accuracy of their insurance claim codes. Therefore, doctors and medical institutions are motivated to enter diagnostic codes accurately because they are subject to large fines for coding errors. Additionally, the NHIRD has been used for many years in various studies [26–28]. A second limitation is that the TBI population is overrepresented by (often undiagnosed) substance abusers in particular, because alcohol and other illicit drugs so often are precipitating factors in the injury. So it remains possible that a large portion of the greater diagnosis is mediated by the eventual treatment seeking of patients that were substance users/abusers before injury. Third, the NHIRD does not contain details for some data that could compromise our findings, such as family history of mental disorder, marital status, personality characteristics, Glasgow Coma Scale, mechanism of trauma, and the duration of loss of consciousness. Fourth, most Taiwanese people are of Chinese ethnicity; further studies are needed to determine whether our findings are applicable in other ethnic groups. Another issue is that, despite the high coverage rate of the National Health Insurance system and the low payments for health care in Taiwan, people with SRD may not seek medical care because they prefer to avoid embarrassment or legal issues. Finally, since statistical significance may not indicate clinical significance, further clinical trials are needed to examine the underlying mechanisms of TBI and SRD and to confirm their relationship.

5. Conclusions

In conclusion, this nationwide population-based cohort study revealed that TBI increases the risk of subsequent SRD. However, further studies are needed to collect detailed data and to explore the mechanisms underlying this association. Timely interventions may help alleviate SRD associated with brain injury.

Competing Interests

The authors have no competing interests in the publication of this study.

Authors' Contributions

Tai-Hsin Tsai and Yu-Feng Su contributed equally to the paper. Ying-Yi Lu and Chih-Lung Lin contributed equally to the paper.

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