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Mini Review

Traumatic Brain Injury May Lead to Alzheimer's Disease and Related Dementia

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Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in the US, particularly in those under age 40, and ~2% of the US population is living with a post-TBI associate syndrome and disorders, based on CDC reports. It is recently concerned that individuals living with TBI take an increased risk for developing several long-term health problems. An early study found that any history of brain injury increases the risk of developing Alzheimer's Disease (AD) and other dementia, and severe head trauma doubles the risk of developing AD dementia [1, 2]. Also, there is evidence that TBI may lower the age of onset of any dementia or AD [3], particularly in people with high rates of TBI, such as US and other veterans [4]. Today, it has been accepted that TBI may cause chronic traumatic encephalopathy (CTE), and some researchers have accepted that TBI as one of the AD risks may lead to AD development [5], but other researchers thought it is still exclusive [6]. In this review, we reviewed various pathological similarities between TBI and Alzheimer's Disease and Related Dementia (ADRD), which supports the view that TBI as one of AD risks may cause ADRD.

TBI may cause ADRD since its secondary injury mechanisms have several similarities with AD initiation. TBI results from an outward physical force that leads to immediate mechanical disturbance of brain tissue and follows by secondary injury events. Generally, secondary injuries occur in minutes to days, including oxidative stress, excitotoxin, calcium-influx, apoptosis, necrosis, hemorrhage, hypoxia, inflammation, etc. [7]. The principal pathologies seen in AD are amyloid beta (Aβ)-contained plaques and neurofibrillary tangles (NFTs) containing hyper-phosphorylated tau (p-tau) protein. In AD development, Aβ is reported to trigger NMDA-mediated Ca^{2+} influx, excitotoxicity; to exacerbate aging-related increases in oxidative stress; and to impair energy metabolism [8]; while TBI secondary injuries immediately cause excitotoxicity, Ca^{2+} influx, oxidative stress, etc. Moreover, oxidative stress alone can cause synapse disfunction and neuron death, leading to cognitive deficits [9], and oxidative stress can be seen in AD pathology via tau hyper-phosphorylation. Further, some primary kinases, including extracellular receptor kinase (ERK), calmodulin-dependent protein kinase (CaMKII), glycogen synthase kinase 3β (GSK3β) and cAMP response element-binding protein (CREB), are dynamically associated with oxidative stress-mediated abnormal hyper p-tau. It suggests that alteration of these kinases could exclusively be involved in the pathogenesis of AD. Consistently, those primary kinases have also involved in the pathogenesis of TBI [10-12], although there are differences in the pathogenesis of TBI and AD.

Epidemiological studies have shown that TBI is a risk factor for tauopathies [1, 3, 13], one of the two major pathological hallmarks of human AD. Usually, the tauopathies include tau hyperphosphorylation and aggregation. After a TBI event, p-tau and neurofibrillary tangles (NFTs) can be detected as early as 6 h [14, 15]. While others examined p-tau expression in post-mortem brains many years after a TBI [16]. It has been found that NFTs levels elevated in approximately 30% individual's post-mortem who had a surviving moderate to severe TBI, indicating the relationship between tau aggregation and a single TBI [16]. Sometimes, the pathological tau occurs in regions distant to the injury local that are synaptically connected, suggesting dissemination of tau aggregates [15]. Overall, TBI as a risk factor for tauopathies may induct both of tau hyperphosphorylation and aggregation. Most importantly, TBI has been suggested as a risk factor of AD from tauopathies by triggering disease onset and facilitating its progression, when tau deposition in areas vulnerable in aging and later mature areas in development [15].

Apolipoprotein E4 (ApoE4) is one of common genetic components between TBI and AD because it is closely related to neurogenesis-dysfunction and dementia. ApoE has three genotypes: 2, 3, and 4. Basically, ApoE4 is the most associated genetic risk factor for the development of AD and is expressed in more than half of the patients. However, it is estimated to be only 20% of the population. The presence of one or two ApoE4 alleles is increasing the AD risk by 3 or 12 folds, respectively [17], and also shifting the age of onset of dementia to a younger age [18]. Recent results suggest that ApoE4 is related to memory loss and overall cognitive dysfunction in patients with a history of mild TBI, but it does not affect people without neurotrauma [19].

Moreover, other researchers have proposed that ApoE4 alleles may be synergistic with TBI in increasing the risk for developing AD [20, 21]. Compared to other genotypes, ApoE4 is harmful in this process, as it inhibits neurite outgrowth, disturbs neuronal cytoskeleton, gathers amyloid β protein [22, 23], and markedly aggravate tau-mediated degeneration [24]. Therefore, it is another important similarity between TBI and AD, and a possible therapeutic target [25, 26].

Impaired adult hippocampal neurogenesis (AHN) were found in both TBI and AD animals [27, 28] and AD patients [29], which is one of the potential causes of dementia. AHN means that the additional new-born neurons are generated throughout life, and it is one of the unique phenomena of the adult mammalian brain and confers the plasticity of the entire hippocampus circuity. By studying the brains of AD patients, the number and maturation of these new-born neurons declined progressively with the progression of AD, which provides evidence a potentially relevant mechanism underlying memory deficits in AD [29]. Consistent with this study, our previous study also showed that TBI impaired AHN, may lead to learning and memory deficits in rats [27].

Notably, ApoE is mainly expressed in astrocytes and secreted into the intercellular space that regulates other cells. It is also present in certain type I neural stem cells and neurons. Most importantly, ApoE is known to regulate postnatal neurogenesis in the hippocampus [30], whereas ApoE4 impairs AHN following TBI [31].

However, it is unclear that what are the relationships among TBI, AHN, ApoE4, and AD onset.

Given that TBI and ADRD involve many similarities, including secondary injury, tauopathies, ApoE4 and AHN, people after TBI may lead to ADRD and have long time healthy problems, especially those who TBI will cause tauopathies appearing in AD vulnerable areas. This may also give us more chances to study AD initiation and find novel therapeutic targets.

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