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Review

Dementia Risk After Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) is a condition that occurs as a result of uncontrolled pressure applied to the brain in situations such as falls, accidents, and sports, disrupting an individual's daily life. The severity of problems experienced varies depending on the levels of damage (mild, moderate, severe). Following the primary and secondary injury processes, the brain's recovery reactions can lead to cognitive impairments in the long term. The idea that the brain may not want to remember such traumas, resulting in the inability to recall certain memories for a short or long period, could lead to the conclusion that dementia is normal. However, this is not a sufficient basis. Therefore, examining scientific studies on this topic would be a more rational option. The purpose of this review is to acquire information from literature studies on the risk of TBIs causing dementia, possible mechanisms, and triggering factors.

Keywords: Alzheimer's disease, dementia, traumatic brain injury

The main causes of traumatic brain injury (TBI) include traffic accidents, falls, assaults, and sports-related injuries.[1] However, a recent study indicates that falls, particularly affecting the elderly, are the most common cause of TBI.[2]

The duration of symptoms following TBI is inversely related to socioeconomic status and directly proportional to psychiatric disorders and substance abuse.[3]

Traumatic brain injuries are classified as mild, moderate, and severe based on their severity, with the Glasgow Coma Scale used as a measure in this classification.[4,5] In this scale, patients' eye opening, motor skills, and verbal skills are tested and classified as severe (3-8), moderate (9-12), and mild (13-15).[6]

Brain injuries are divided into primary brain injury and secondary brain injury based on the timing of the injury. Primary brain injury can be defined as the damage caused by the impact that occurs at the moment the brain is injured, affecting the white matter tracts inside the brain. Additionally, in more severe cases of primary brain injury, there may be disruption of bone integrity by the striking or struck object, leading to penetration. Secondary brain injury, on the other hand, generally occurs following the primary injury, involving long-term damage to brain cells that can result in prolonged problems.[7,8]

NEUROINFLAMMATION AND CYTOKINES IN TBI

In TBI, secondary damage is a spontaneously progressing injury process activated by inflammatory mechanisms following the primary injury. Secondary damage, which can last for weeks from the moment of trauma, can lead to the progression of the inflammatory cascade and long-term damage to cognitive processes such as memory.[9] Additionally, secondary damage can harm the blood-brain barrier (BBB).[10]

Within the neuroimmune system, cytokines and chemokines play a role in the communication between glial cells, astrocytes, and neuroglial cells. In inflammatory conditions, the levels of these cytokines can exceed normal levels.[11,12] It is believed that the inflammation following TBI leads to pyroptosis, i.e.,

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inflammatory cell death, and these cell deaths play a role in the disruption of the BBB.[10]

In the event of damage to the neuron membrane after TBI, damage-associated molecular patterns are exposed.[13-15] Subsequently, as part of the immune system response, proinflammatory cytokines such as tumor necrosis factor, interleukin (IL)-6, and IL-1β are activated.[16] In this context, we can say that post-TBI neuroinflammation is the immune response initiated by the brain in response to TBI.

TRAUMATIC BRAIN INJURY AND MEMORY

Individuals who have experienced TBI go through a phase called post-traumatic amnesia after emerging from a coma, during which cognitive impairments are experienced.[17]

One of the cognitive impairments that patients commonly experience during this period is memory problems, a prevalent occurrence after TBI.[18-20] A study conducted on one hundred and forty-seven patients revealed that, four years after the accident, 67.5% of the patients most frequently complained of memory problems.[18] Research on its treatment indicates the effectiveness of internal memory methods such as cues and visual imagery, which can enhance performance in neuropsychological tests as well.[21]

EPIDEMIOLOGY OF DEMENTIA

Dementia has been a progressively increasing and potentially fatal condition in recent years. Meta-analyses on dementia prevalence indicate that it is 1.5% at the age of sixty-five and doubles every four years, reaching 30% at the age of eighty.[22-24] The risk of dementia is lower in men and individuals of Asian and African descent.[25-27] Similarly, the risk of dementia after TBI has been found to be higher in women and Caucasians.[28,29] According to the World Health Organization's 2010 census, approximately thirty-five and a half million people worldwide were identified as having dementia, and it is expected that this number will triple by 2050.[30]

Making a decision about the type of dementia can be challenging due to the similar and overlapping symptoms of different types. If we categorize dementia into several types, they include 1. Alzheimer's disease (AD), 2. Lewy body dementia, 3. Frontotemporal dementia (FTD), 4. Vascular dementia, 5. Mixed dementia.[31]

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder characterized by loss of neurons and synapses in the central nervous system, leading to cognitive decline (especially in memory), self-care deficiencies, and behavioral disturbances.[32-34] Pathologies such as senile amyloid plaques, neurofibrillary tangles (NFTs), and excessive neuronal loss develop in the brain.[35] While these pathologies can also be observed independently in normal aging, they are more specific and severe in certain regions in AD. Neurofibrillary tangles formation occurs in the neocortex, whereas senile plaques form in limbic system components such as the amygdala and hippocampus.[36-38]

Tau proteins play a crucial role in the formation of NFTs by binding to microtubules, which are essential for axonal transmission. In AD, the binding of tau protein to microtubules is hindered due to hyperphosphorylation, disrupting axonal transport. The unbound tau proteins remain within the cell, combining with filaments involved in the cell's cytoskeleton to polymerize and form NFTs.[39] Consequently, both axonal transmission and cell cytoskeletal structure are compromised. Interestingly, it has been demonstrated that tau protein alone can lead to FTD.[40]

Risk factors and symptoms of Alzheimer's disease

In addition to all of these, aging, especially beyond the age of sixty-five, is a significant risk factor, with the frequency of occurrence found to increase fivefold every year after sixty-five.[41-43] Another risk factor is genetic predisposition, with genetic studies confirming an increased risk of AD among relatives.[40,42,44] Some other risk factors include cerebrovascular diseases, obesity, smoking, frequency of physical activity, depression, and dyslipidemia.[45, 46]

Alzheimer's disease begins with the most noticeable symptom of memory impairment in its early stages, and as the disease progresses, cognitive abilities such as attention, executive functions, thinking, behavior, and speech are affected.[32,47,48] Alzheimer's disease is classified into seven stages based on clinical symptoms:

Stage 1: The patient starts to exhibit minor cognitive impairment symptoms, and this is a period when changes occur in the central nervous system.

Stage 2 (very mild cognitive impairment): The patient begins to forget the locations of items such as keys, wallet, and glasses, but other cognitive functions like

speech are not yet affected.

Stage 3 (mild cognitive impairment): Patients struggle to recall words during conversations and frequently lose their belongings. Planning and organizational skills start to decline.

Stage 4 (moderate cognitive impairment): Significant losses in short-term memory are observed, and patients may struggle to remember things they have done. Some social withdrawal may occur. This condition may arise from the concern that memory problems may create communication issues.

Stage 5 (moderately severe cognitive impairment/ early stage dementia): Patients experience confusion about time and place. They may have difficulty remembering the names of schools they graduated from and struggle with object recognition (agnosia). Learning new motor skills or performing previously known ones can be challenging (apraxia). Patients in this stage become unable to carry out routine activities such as bathing, dressing, using the toilet, and eating.

Stage 6 (severe cognitive impairment/mid-stage dementia): Difficulty in spontaneous speech, word finding, and communication skills declines. Some patients may experience urinary and fecal incontinence.

Stage 7 (very severe cognitive impairment/late-stage dementia): Patients' speech abilities are reduced, and they may experience difficulty swallowing. They require 24-hour care.[48]

Lewy Body Dementia

Lewy body dementia is the second most common type of dementia, occurring after AD.[49-52] Its key clinical features include cognitive fluctuations occurring alongside dementia, recurrent visual hallucinations, and parkinsonism.[50,53]

Frontotemporal Dementia

Frontotemporal dementia is a neurodegenerative disorder characterized by behavioral problems, executive dysfunction, and language impairments that vary depending on the stage of the disease.[54]

It is hypothesized that changes in neurotransmitters (glutamate, noradrenaline, serotonin, dopamine, and acetylcholine) play a significant role in the neuro-pathological basis and behavioral alterations in FTD.[55] Studies on the role of serotonin in FTD have observed a decrease in serotonin receptors in the temporal and frontal cortex through brain imaging and autopsy studies.[56] Additionally, a decrease in serotonin release has been identified in the raphe nucleus neurons, which control serotonin release.[57] Research on dopamine indicates that FTD patients have lower levels of the dopamine metabolite homovanillic acid in cerebrospinal fluid compared to normal individuals.[58] Furthermore, a reduction in presynaptic dopamine transporters has been detected in the putamen and caudate nucleus.[59] Studies on the glutamate neurotransmitter show a decrease in glutamate N-methyl-D-aspartic acid and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors in cortical pyramidal cells[60] and the frontal-temporal cortex.[61]

Mixed Dementia

Mixed dementia refers to the coexistence of AD and vascular dementia, although it has not been extensively studied.[62] Due to the limited comprehensive research on MD, risk factors are not well known. However, a few studies have found that it includes risk factors for both AD and vascular dementia.[62-65]

Vascular Dementia

Vascular dementia is a potentially preventable form of dementia that can develop as a secondary condition due to another disease or issue. It is the second most common type of dementia after AD.[66] Examining risk factors, research on cognitive impairment following a stroke has found that vascular dementia is the most common outcome.[67] In other words, stroke is a significant risk factor for vascular dementia.

THE LINK BETWEEN TRAUMATIC BRAIN INJURY AND DEMENTIA

Chronic traumatic encephalopathy (CTE) is a neuropathological condition that develops after head injuries. Similarities have been observed between the pathological changes observed in the brains of individuals with TBI and CTE and the pathologies associated with AD.[68]

Another piece of evidence suggesting the potential development of neurodegenerative disorders like dementia after TBI comes from studies indicating degeneration of white matter pathways (e.g., corpus callosum) and brain structures several years following moderate to severe TBI.[69-71]

Frontal and temporal brain regions, in particular, are more sensitive to trauma compared to other brain regions, and this sensitivity may be associated with

the presence of FTD.[72] In a study on TBI and dementia risk, it was found that the risk of dementia increased by 1.44 times in the 25 years following TBI.[73]

The formation of amyloid beta (Aβ) plaques is well-known in AD.[74,75] After TBI, the disruption of the BBB we mentioned may lead to the accumulation of Aβ, similar to AD, suggesting an association between AD and TBI.[76,77] It is believed that the accumulation of Aβ plaques, reaching the oligomeric form, disrupts neuronal homeostasis and increases the risk of apoptotic neuronal death.[78-80]

Following TBI, the accumulation of these Aβ plaques in the perivascular space of the brain is possible. A decrease in pH in brain plasma, i.e., metabolic acidosis, can enhance Aβ plaque accumulation.[81] Another risk factor for Aβ accumulation is ischemic damage.[80]

After TBI, blood flow in certain tissues of the brain decreases due to the impact. Subsequently, the imbalance of free radicals in tissues entering the reperfusion stage during the secondary injury process leads to oxidative stress.[82] These radicals can also be a risk factor for apoptotic neuronal death.[83-85]

The resulting oxidative stress activates the kinase protein activated by stress, leading to the stimulation of β-secretase and γ-secretase enzymes that produce the precursor of Aβ, amyloid precursor protein. In this scenario, there will be an increase in Aβ in the brain and, indirectly, neuronal deaths.

Acetylcholine is a neurotransmitter with a widespread distribution in the brain, playing a role in long-term memory and attention processes.[86-89] Acetylcholine has both nicotinic and muscarinic receptors, which play a role in memory and attention processes. A decrease in both receptor types has been found in AD patients. Additionally, a reduction in the enzyme choline acetyltransferase, which is involved in the synthesis of acetylcholine, has been observed in AD.[90]

In conclusion, TBI can lead to various problems such as attention disorders, memory impairment, depression, and cognitive decline. Dementia, which is a complex disorder that often develops as a result of the disruption of many brain activities, manifests itself through problems such as memory loss and is categorized into different types. The commonality among these types is memory issues. Typically, the brain tends to avoid remembering such traumas, and sometimes it may even erase parts of experiences as a known response. However, the memory impairments in dementia go beyond this. Neurophysiological anomalies, such as acute pathologies developing after brain injury, the immune system responding with inflammation, resulting in neuronal loss, imbalance in cell equilibrium, and disruption of neuronal transmission, are observed. As a result, the impact of damage does not diminish immediately after trauma; instead, it gradually develops and eventually leads to a state where an individual cannot perform personal tasks. The prolonged effect of damage through primary and secondary injury processes contributes to the development of dementia. The close relationship between TBI and dementia is still under investigation. According to current research, TBI is a potential risk factor for the development of dementia, affecting various neurotransmitter levels in the brain, and can lead to dementia in the short and long term through different mechanisms. This risk, exacerbated by the increased sensitivity of older individuals, can affect them more significantly. However, falls, sports injuries, and similar causes can also lead to TBI in adults and children. Although individuals aged sixty and above may experience similar cognitive problems and neuronal deaths, the affected brain regions may not lead to dementia at the same severity level. Dementia is a widespread public health concern, and further research is needed for a better understanding of its mechanisms, implementation of preventive measures, and the development of effective treatments.

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