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Review

INFLAMMATION IN TRAUMATIC BRAIN INJURY: THE RELATIONSHIP BETWEEN MICROGLIA AND NEURODEGENERATIVE DISEASES

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ABSTRACT

Traumatic brain injury (TBI) is responsible for a high prevalence of global death, disability, and morbidity, and the effects for patients and their families can be devastating, with even a mild, non-concussive injury able to have long-term effects. Microglia, the innate immune cells resident in the central nervous system (CNS), respond swiftly after TBI and are important for reparation, but also secrete pro-inflammatory cytokines, which participate in inflammation. Heightened microglial activation can result in "primed" microglia and chronic neuroinflammation, which can lead to cognitive impairment and the development of progressive neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), or chronic traumatic encephalopathy (CTE). These disorders include the abnormal accumulation of phosphorylated tau proteins and amyloid-β (Aβ) peptide deposits in the brain, with studies finding neuroinflammation and microgliosis to be linked to neuronal damage, disease worsening, and outcome. Microglial manipulation and neuroimaging are being used to define the role of microglia in these neurodegenerative diseases, develop treatments, and distinguish the correct time frame for therapeutic intervention.

Keywords: *TBI; Inflammation; Neuroinflammation; Neurodegenerative; Disease; Microglia; Immune; AD; PD; CTE*

INTRODUCTION

Traumatic brain injury (TBI) is defined by the Centers for Disease Control and Prevention as "a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury" (1). Prevalent causes of TBIs include falls, motor vehicle accidents, strikes with objects, and assault (2). TBIs can affect anyone, but a higher incidence has been reported in children, adolescents, adults over 75 years of age, and males (3). In addition, individuals who play contact sports and military service members are at higher risk due to repetitive injury over a sustained time.

TBIs are a major source of death and morbidity worldwide and can cause lifelong consequences. According to the Glasgow Coma Scale, injuries can be classified as mild, moderate, or severe, depending on the time of unconsciousness, mental state, and posttraumatic amnesia (4). The worldwide prevalence of TBI is great, considering that 2.8 million people were diagnosed in the United States alone in 2013 (2), but the true numbers are difficult to define as many mild cases go unreported.

TBI can produce neuronal, functional, and inflammatory consequences. The inflammatory response following TBI is a mix of complex, superimposed mechanisms, and age, sex, mechanism and degree of injury, secondary insults, and genetic variation are all factors that can impact that event (5)(6). Even after mild injury, TBI can cause chronic neuroinflammation and lead to neuropsychiatric and neurodegenerative pathologies months and years after the injury,

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a time of complex neuroinflammatory cascades. In addition, studies have shown that cognitive decline affects between 15 and 30% of TBI patients (7-9), and even subconcussive injury can result in long-term neurologic consequences (10).

The immune system reacts to protect the body against injury and infection, which it performs by engaging in inflammatory challenges in response to noxious stimuli. After TBI, the immune response is essential for the repair process; however, an upregulated immune response can attack healthy cells and cause damaging, chronic neuroinflammation.

The initial injury that occurred in TBI is considered the "primary injury", and the multifaceted pathophysiological reactions that follow comprise the "secondary injury", the period when neuroinflammatory processes are activated and may continue to become unresolved microglia-mediated inflammation (11). These primary and secondary TBI injuries can result in neuropathology (12). In addition, microglia-mediated inflammation can continue in this time of secondary injury long after the primary injury was incurred, contributing to chronic neuroinflammation, which has been seen in human TBI patients and animal models.

The role of post-TBI neuroinflammation in the development and progression of neurodegenerative disorders has become an interesting and promising avenue of exploration and can be useful for treatment as recent research continues to shed light on their connection. This review aims to summarize the role of microglia in TBI-induced neuroinflammation, focusing on the role they play in Alzheimer's Disease (AD), Parkinson's Disease (PD), and chronic traumatic encephalopathy (CTE), progressive neurodegenerative disorders which are being studied for this theme. AD, PD, and CTE include the following characterizations: abnormal accumulation of phosphorylated tau proteins and the formation of amyloid-β (Aβ) peptide deposits in the brain.

Microglia activation in TBI

Immune function is greatly influenced by TBI, with an increased inflammatory response, and repetitive events can be magnifying, adding more inflammation into an already activated system (13).

Neuroinflammation occurs in the central nervous system (CNS), which comprises the brain, spinal cord, and optic nerves. Microglia, a glial component of the CNS, derive from the progenitors of mononuclear myeloid cells and respond rapidly after TBI has occurred, migrating to the source of injury within 30 minutes (14). Microglia are important for immune surveillance, mediating the innate immune capacity of the CNS with synaptic pruning, debris clearance, and tissue protection. They have a similar function to macrophages, and when activated, microglia secrete various harmful compounds to the body, including pro-inflammatory cytokines such as interleukin-6 (IL-6), and interleukin 1β (IL-1β), Tumor Necrosis Factor (TNF), and other inflammatory mediators (15). Innate immune inflammatory cytokines act on cytokine receptors and Toll-like receptors.

Microglia are ubiquitous throughout the CNS and are "quiet" in their stable microenvironment. Any detected insult or stimuli can initiate immediate response, leading to "microglial activation". Microglial "priming" occurs successively when microglia are sensitized and overly responsive to stimuli (16). After TBI, increased sensitization of microglia show raised levels of innate immune markers (17). The disruption to microglial homeostasis that occurs after a TBI can continue for months or years; this has been shown in different studies that showed increased Iba1, CD68+, MHCII, and CD68 labeled microglia after injury (18-21).

Detection of activated microglia bound to positron emission tomography (PET)-detectable ligands can indicate the level of inflammation after TBI, which was seen up to 17 years after injury and was related to impaired cognitive effects (22)(23). In a study of former professional football players who endured repetitive TBI throughout their careers, activated microglia and macrophages were shown after retirement and before the decline in cognitive processing (24). In rodent models, increased microglia labeling and white matter damage affected hippocampal-dependent learning (19).

Serum cytokines have also shown chronic hyper-activation following TBI, with elevated TNF in serum expressed post-injury, which has been linked to poor neuropsychiatric outcomes (25). The mitogen-activated protein kinase (MAPK) p38α responds to stress stimuli, controlling diverse cellular processes with unique functions (26). After diffuse TBI, p38α MAPK signaling in microglia has been seen to promote cytokine production, therefore perpetuating TBI-induced microglial activation; furthermore, microglial depletion in mice was associated with less synaptic protein loss and motor deficits, suggesting that this microglial signaling pathway may be related to the development of neuropathology post-TBI (12).

Chronic neuroinflammation after TBI should be contained if microglia response can be confined to the acute TBI stage and limited during the secondary inflammatory stage, a process that can be neuroprotective (12).

Prolonged disruption of microglial homeostasis induces neuroinflammation in the CNS and can lead to neuronal damage. However, microglial depletion has been shown to prevent detrimental gene suppression, not during the acute phase of TBI but during the dynamic inflammatory stage that follows.

Microglia are plastic, changing in appearance depending on their function (27, 28). Neurons and microglia display dynamic structural associations after TBI in a species-dependent manner (29). In a porcine TBI model, microglia were activated within 15 minutes, and reactivity was focused proximal to individual injured neurons (30). CD68+ microglial cells increased in number from the first day following injury until the 28th (31). TBI also initiates rod microglia

morphology and unique phenotype (18)(32)(33). In a study by Ziebell et al., microglia, remodeling by structural transition, were seen to become rod-shaped in the rodent cortex at one-week post-midline fluid percussion injury, retained rod morphology for no less than 4 weeks, and the formation was dependent on the presence of preserved neuronal tissue (18).

Post TBI, microglia-mediated inflammation can cause neuronal dysfunction, affecting plasticity and connectivity (23). However, a study by Witcher et al. showed that microglial depletion prevented detrimental gene suppression post-TBI, preventing TBI-associated cognitive impairments in mice (23).

A history of TBI especially repeated events, is a risk factor for the development and severity of different neurodegenerative diseases (13). Chronic neuroinflammation, and the continuous overly active state of primed microglia that follows TBI, have been implicated in AD, PD, CTE, Huntington's Disease, vascular dementia, and depression (34)(35). Microglial activation can lead to the production of Aβ, tau pathology, and neuroinflammation, along with a reduced release of neurotrophic factors, and subsequently, affect the quantity and function of neuronal cells. In addition, it appears that there is no clear initiator between microglia and the pathophysiological features such as tauopathy and Aβ deposition, and there are self-perpetuating cycles of inflammation.

Alzheimer's disease

There is evidence to suggest that the immune system affects AD, an age-dependent progressive neurodegenerative disease that affects the CNS; however, further studies are needed to expand the connection (16)(36)(37).

AD is the leading cause of neurodegenerative dementia in the elderly, contributing to 60-70% of cases (38). The clinical presentation is characterized by progressive memory decline, impaired executive function, impairment in cognitive domains, and behavioral and psychological symptoms (39). The pathophysiological features of AD include neurofibrillary tangles (NFT) of intracellular tau protein aggregates, Aβ plaques, gliosis, and neurodegeneration (40)(41)(42).

A history of TBIs has been associated with dementia and is considered a risk factor for AD (43)(44). TBIs can lead to white matter, neuronal damage, p-tau, and Aβ deposition (45). Neuroinflammation occurs in AD by gliosis, the injury response in the CNS of activation and proliferation of microglia and astrocytes (39). Chronic neuroinflammation after TBI results in primed microglia, triggering inflammatory cascades causing neuronal damage, which may contribute to the onset and progression of AD (46, 47).

Although the process is still unclear, Aβ has neurotoxic and inflammatory effects that play an important role in the progression of AD (48). Data has shown that microglial activation may follow Aβ deposition in AD (40), but Aβ deposition may also be induced by activated microglia (49-51), so the cause and effect relationship is unclear. However, there is a close association between Aβ deposition and activated microglia. Aβ adheres to microglia, promoting synthesization and secretion of inflammatory mediators and progressing the disease. At the same time, activated microglia can phagocytize and clear Aβ plaques (48).

A similar association can be made for phosphorylated tau protein accumulation, another main hallmark of AD. Primed microglia and chronic neuroinflammation can boost tau protein and lead to the formation of NFT of intracellular tau protein aggregates (16). Human extracellular tau collection may be internalized by microglia, glial cells, and neurons may spread between cells and progress the disease (52). Concurrently, activated microglia also phagocytize phosphorylated tau protein and can release beneficial neurotrophic factors and antioxidants, limiting AD progression (53). The production of Aβ, phosphorylated tau, neuroinflammation, and neuronal damage caused by microglial activation is closely affiliated with AD pathogenesis (16).

Parkinson's disease

PD is a progressive neurodegenerative disorder characterized by α-synuclein-containing Lewy bodies and the loss of dopaminergic neurons in the substantia nigra (SN). It is a prevalent movement disorder for older-aged adults, affecting 1% of those above 60 years of age (54). Clinical symptoms include resting tremors, impaired posture and balance, rigidity, and bradykinesia (55). Neuropathological features include the loss of dopaminergic neurons in the SN, intraneuronal inclusions called Lewy bodies, neuroinflammation, and gliosis (56). Dopaminergic neuron degeneration usually corresponds with the buildup of misfolded α-synuclein aggregates called Lewy bodies, which are spread throughout the SN and other brain regions (57). In addition, much evidence shows that microglial activation is a substantial pathological feature of PD and relative cognitive decline (58-64); however, microglia's exact role is still unclear.

Postmortem PD brains have shown microglial activation and neuroimaging studies during disease development, and both the innate and adaptive immune systems have been implicated in PD. In 1988, McGeer et al. described microglia activation in PD when they discovered human leukocyte antigen DR (HLA-DR) expression in the SN of human brains (58). Further research showed TNF expression in SN (65) and raised levels of pro-inflammatory cytokines in the brain and cerebrospinal fluid (CSF) (66-68). In addition, and further supporting the involvement of neuroinflammation in PD, some non-steroidal anti-inflammatory drugs (NSAIDs) have been seen to have a protective effect on the incidence of PD in epidemiological studies (69-70).

Aging and chronic psychological stress are the two main environmental risk factors for PD, and they are also responsible for increasing pro-inflammatory mediators within the CNS and altering microglial functions. Microglial activation and the release of pro-inflammatory cytokines, including TNF, IL-6, IL-1β, and interferon-γ (INF-γ), could

lead to neuronal loss (71) or could follow as a consequence, as the death of dopaminergic neurons can cause pro-inflammatory microglial "phagoptotic" phenotypes.

Microglia respond early to α-synuclein in neurons, correlated with MHCII expression, and contribute to PD by inflammation and phagocytosis of α-synuclein, factors associated with neurodegeneration (72). Microglia may be important for toxic α-synuclein clearance in neurons; however, microglial activation may also harm the neurons and lead to their death, which can be seen by decreased glucose metabolism in different brain regions of PD patients (73). a-synuclein aggregation causes neuronal dysfunction and death, but microgliosis can occur before neuronal death, not solely as a consequence (74). After neuron cell death, microglial activation is correlated with CD68 (75). Pro and anti-inflammatory functions of microglia can create imbalance, leading to chronic neuroinflammation that could lead to the onset and progression of PD (76).

Chronic traumatic encephalopathy

CTE is a progressive neurodegenerative disease believed to be caused by repeated episodes of mild TBI and is often found in athletes, such as boxers and football players, and military veterans who experienced combat. It is difficult to describe the prevalence of CTE, especially considering that diagnosis is made post-mortem by histopathological brain analysis. However, due to the widespread global practice and growing popularity of combat sports where concussive and subconcussive blows are common, added to the global number of military service members engaging in combat, considering that just among U.S. Military service members, approximately 430,000 TBIs were reported from 2000 to 2020 (77), it must be assumed that the incidence is extremely high. In a study of 85 post-mortem brains of athletes donated for research, 68 showed signs of CTE (78). Another recent and larger epidemiological study found that 6% of population-based brains showed CTE (79).

Clinical symptoms of CTE usually appear 8 to 10 years after repetitive mild TBI, and the patient may show aggression and irritability, impulsive behaviors, memory loss, and depression (80). As the disease progresses, dementia and parkinsonism may develop, and difficulties in speech and gait may present. It is a tauopathy characterized by hyperphosphorylated tau protein tangles, disseminated microgliosis, and astrocytosis (81). Some CTE cases, approximately 40%, showed Aβ plaques, which was age-dependent (82, 83).

Studies continue to indicate that chronic neuroinflammation can lead to CTE (6). Rodent studies of repetitive mild TBI have shown that following injury, neuroinflammation, and glial changes occur before tau protein pathology (84)(85). Neuroinflammation has been linked with higher tau pathology in CTE, contributing to its development and progression, with microglial cells playing a role (86). Microglial reactivity is a common feature of CTE, along with the accumulation of abnormal tau by astrocytes and neurons, where it is irregularly distributed within sulci (81)(87).

Repeated mild TBI can lead to chronic neuroinflammation and primed microglia, which release pro-inflammatory cytokine mediators. Studies have shown that increased density of CD68+ microglia in the brains of sports players was linked to CTE severity and that the time duration of repeated TBI was also associated with CD68 density (86). The chronic state of microglial activation may exacerbate tauopathy, initiating the formation of NFT and phosphorylated tau deposition, and tau can induce neuroinflammation in turn, as seen in rodent models, resulting in a self-perpetuating cycle of inflammation (88). However, it is still unclear which initiates the other, and further studies are needed to explore this relationship.

Future therapeutic implications

Neuroinflammation-based treatments for TBI are now being investigated, and with further clinical trials and research, targeting microglia activation could be beneficial. The first-stage inflammatory reaction following acute TBI is beneficial to help restore brain homeostasis. However, when chronically activated, primed microglia can harm the CNS, releasing pro-inflammatory molecules and causing secondary injury with neuronal damage that could lead to neurodegenerative pathologies. For this, medical management is targeted toward preventing the second-stage injury and limiting the harmful effects of primed microglia in chronic neuroinflammation.

Research advances are unveiling new findings in the study of post-TBI neuroinflammation, and new therapeutic targets are being explored. In addition, research is being done to determine the critical periods for treatment.

There is evidence showing the harmful effects of chronic neuroinflammation after TBI and the role of microglia during this secondary injury process. In some studies, microglial depletion was able to inhibit or stop this damage. Therefore, confining the microglial response to the acute, primary injury of TBI and limiting it during the neuroinflammatory secondary injury phase is a possible approach to limit neuroinflammation. This idea could be a potential therapeutic avenue for neuroprotection, although further research must be conducted (12).

Clinical trials treating TBI patients with anti-inflammatory drugs have not shown great success, and limited success has only been achieved using progesterone in younger patients (89). In addition, because of the large possible variation in outcome after TBI and the complexity of immune activation, successful treatment must be targeted to inflammatory mediators and interindividual differences such as age, genetic predisposition, and history of secondary injuries. Finally, it must be initiated at the correct time frame (89).

The manipulation of microglia activation and neuroimaging using PET and autoradiography are being used to identify the role that microglia play post-injury. In imaging, selective PET ligands for amyloid, tau, and neuroinflammation can provide insight into the post-TBI neurodegenerative process and help determine future

therapeutic approaches (6). One possible treatment approach is manipulating microglia and activating them to become a beneficial phenotype rather than a destructive one (90).

Immunotherapy needs to be focused on the right moment, targeting the moment of positive immune activity to aid reparation and debris clearance and then decreasing the negative damage of chronic inflammation afterward.

One positive achievement in treatment is aerobic exercise, which has displayed the importance of intervention timing concerning benefits in neuroinflammation and neuroprotection. Post-TBI exercise intervention has shown overall cognitive benefits in mild to moderate TBI patients, with improvements in cognitive functioning and cardiorespiratory fitness (91). In a mouse study by Piao et al., the initiation of aerobic exercise after 5 weeks after moderate TBI promoted neurogenesis, benefited cognitive recovery, and attenuated the inflammatory response. In the same study, it was also seen that earlier initiation of exercise provided different results, with no cognitive benefits and a neurotoxic pro-inflammatory response, opposing the classically held view that neuroprotection can only be achieved with early intervention (92). However, previous training before TBI was also seen to provide a beneficial preventative effect on the cerebral inflammatory response following severe TBI, an important discovery that implicates exercise induces metabolic changes that can positively alter the long-term inflammation process following TBI and limit neuronal damage (93).

The take-away message from these exercise studies, and the overall evidence so far, is that there are different time frames for intervention during the inflammatory process following TBI, and interindividual differences and TBI history are important modifying factors accounted for.

CONCLUSION

TBI is a global source of death, disability, and morbidity and can have devastating long-term consequences for patients. It provokes an initial inflammatory response which can lead to secondary injury and chronic neuroinflammation with effects on cognitive functioning and the development of neurodegenerative diseases. In addition, a history of repeated TBI, even mild, puts a person at higher risk.

Microglia respond to acute injury after TBI and are beneficial for reparation. However, the continuous state of primed microglia that follows can be destructive and cause neuronal dysfunction.

In neurodegenerative diseases such as AD, PD, and CTE, characterized by abnormal accumulation of phosphorylated tau proteins and Aβ peptide deposits in the brain, neuroinflammation and microglial activation have been implicated in neuronal damage, disease worsening, and outcome.

Genetic and pharmacological manipulations of microglia activation are now being used to unveil their significance in post-TBI inflammation, and neuroimaging studies are being used to define the role of microglia. The timing seems to be of the utmost importance in therapy, as early or late intervention has different effects on immune function, dependent on many specific patient factors.

Because of the number of people affected by TBI worldwide and the correlation between neuroinflammation and neurodegenerative disease, it is highly important to continue research in this field to develop treatment options to improve patient outcomes.

Conflict of interest

The authors declare that they have no conflict of interest.

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