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THE NEUROPROTECTIVE ROLE OF FLAVONOIDS

Al. Caraffa*

School of Pharmacy, University of Camerino, Camerino, Italy.

Correspondence to:
Alessandro Caraffa, MD,
School of Pharmacy,
University of Camerino,
Camerino, Italy.
e-mail: alecaraffa@libero.it

ABSTRACT

Flavonoids are antioxidants found in fruits and vegetables and when taken with the diet, they reduce the risk of chronic diseases and even cancer. Flavonoids possess many healthful properties including neuroprotection through the regulation of many pro-inflammatory signaling pathways such as for p38 mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF-kB). Therefore, flavonoids inhibit pro-inflammatory cytokines, reactive oxygen species (ROS), and diverse metalloproteases (MMP)s such as MMP2, MMP3, and MMP9. Here, in this paper, we primarily studied the effect of flavonoids on central nervous system (CNS) inflammation.

KEYWORDS: *flavonoids, antioxidants, neuroprotection, inflammation, central nervous system*

INTRODUCTION

Flavonoids are a family of polyphenols found in plants such as fruits, vegetables, grains, roots, and plant beverages such as juices and teas. Flavonoids are beneficial for health as they possess anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties. They also interact with the human body by modulating cellular enzyme function.

Flavonoids have a polyphenolic structure (Fig.1) and are plant secondary metabolites, with the ability to exert effects on other living organisms besides the plant itself (1).

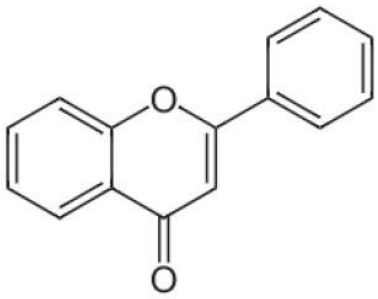

Fig. 1. *Flavonoids are plant secondary metabolites with a polyphenolic structure and exert effects on other living organisms besides the plant itself. They possess anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties and interact with the human body by modulating cellular enzyme function.*

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Many medicines and medicinal herbs utilize these secondary plant metabolites. Pharmacology utilizes flavonoids for many purposes due to their broad spectrum of therapeutic activities. Research has shown strong evidence for the preventative role of flavonoids in cardiovascular diseases and coronary heart disease (2-5), osteoporosis (6), and neurodegenerative diseases (7,8). Flavonoids are neuroprotective due to their role in regulating diverse pro-inflammatory signaling pathways including those of p38 mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF-kB).

The role of flavonoids in neuroprotection

In addition to the cardioprotective, anti-inflammatory, and chemopreventive roles played by flavonoids, they also provide neuroprotection. This is due to their modulatory actions on many signaling pathways, such as p38MAPK and NF-kB, and their ability to inhibit the production of proinflammatory cytokines, reactive oxygen species (ROS), and metalloproteases (MMP)s including MMP2, MMP3, and MMP9.

The MAPK families are involved in complex cellular programs such as proliferation, differentiation, development, transformation, and apoptosis. Flavonoids act directly on cellular signaling pathways such as phosphoinositide 3-kinase, Akt/protein kinase B, MAPK, protein kinase C, and tyrosine kinases (9). They can act on these pathways with inhibition or stimulation, which can lead to changes in phosphorylation, and thus, produce effects on cell functions. Flavonoids are also able to activate transcription factors and gene expression that are associated with the inflammatory response, apoptosis, and cell proliferation.

Flavonoids protect against inflammation by exerting effects on MAPK signaling pathways which activate transcription factors such as NF-kB. For example, myricetin, quercetin, and fisetin are dietary flavonoids commonly found in fruits, vegetables, and beverages, including mangoes, apples, berries, onions, tea, grapes, and red wine. Myricetin, quercetin, and fisetin share similar molecular structures (Fig.2) and have been seen to produce anti-inflammatory effects (10). Through suppression of phosphorylation, these flavonoids inhibit the activation of NF-kB and MAPK pathways, suppressing excessive nitric oxide (NO) production and reducing the levels proinflammatory cytokines tumor necrosis factor (TNF) and IL-6, as well as ROS (11).

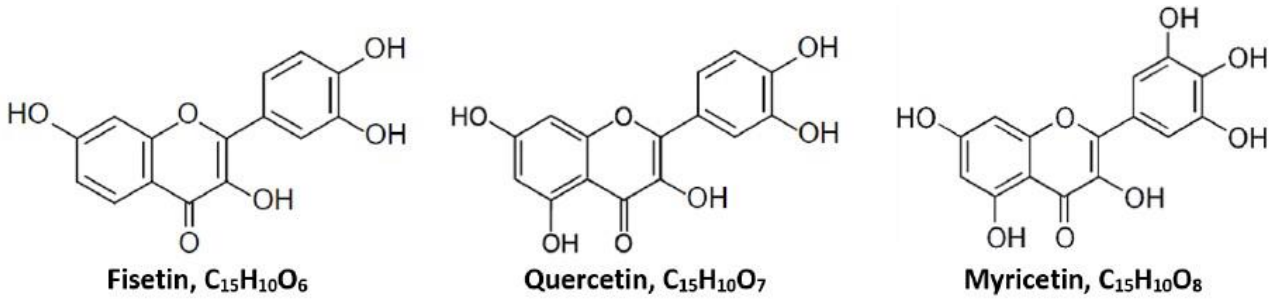

Fig. 2. *Myricetin, quercetin, and fisetin are dietary flavonoids commonly found in fruits, vegetables, and beverages such as red wine. They are members of the flavonoid class of polyphenolic compounds that share similar molecular structures to one another and have anti-inflammatory properties.*

Myricetin, which is found in many edible plants, was seen to inhibit p38MAPK activation and c-Jun N-terminal kinase (JNK), which prevented oxidative stress-induced apoptosis (12) and decreased the production of NO, iNOS, TNF, IL-6, and IL-12 in mice studies (13).

Quercetin has anti-inflammatory properties (14) that involve different cell types, with an ability to help stabilize mast cells and an immunosuppressive effect on the function of dendritic cells (15,16). Quercetin has been seen to inhibit the production of TNF and IL-1, lowering the rate of apoptotic neuronal cell death induced by microglial activation (17). Additionally, quercetin inhibits MMP-1 and down-regulates MMP-1 expression (18).

In studies, fisetin inhibited the production of proinflammatory mediators including TNF, IL-1, IL-6 by suppressing signaling pathways in macrophages (19,20). In one interesting study, it was reported that the flavonoid methoxyluteolin significantly dumped gene expression and IL-1 synthesis (21). Methoxyluteolin Inhibited Procaspase 1 Activity, and therefore, IL-1.

Matrix metalloproteinases (MMPs) are zinc-dependent enzymes and inflammatory mediators that mediate tissue remodeling in pathological and physiological processes (22). They are involved in the degradation of the extracellular matrix and tumor invasion, angiogenesis, cancer metastasis, and neuroinflammation (23). In the CNS, MMPs play a role in the formation of myelin, axonal growth, angiogenesis, and regeneration (24). The overproduction of MMPs could be

linked to neurological pathologies such as AD, PD, ischemia, and glioma (25), as some MMPs are markedly upregulated in certain disorders (26). In turn, the upregulation of MMPs contributes to the cycle of neuroinflammation by the inflammatory cascade, a series of actions that increase and perpetuate inflammation (27).

MAPK-linked MMP upregulation can be inhibited by flavonoids. In particular, long-chain fatty acids such as epigallocatechin gallate (EGCG) are MMP inhibitors and come naturally from flavonoids and green tea (28), and the flavonoids luteolin and apigenin have inhibitory activity on diverse MMPs (29).

CONCLUSIONS

Inflammatory events mostly occur in the CNS in glial cells, which produces neuroinflammation. Neuroinflammation is implicated in numerous demyelination and neurodegenerative disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and virus-associated dementia (30-34). Responding to inflammatory insults, signaling pathways activate proinflammatory transcription factors that initiate gene transcription, resulting in the production of proinflammatory cytokines and ROS.

Flavonoids provide neuroprotection by modulating different signaling pathways and inhibiting the production of inflammatory mediators including TNF, IL-1, and IL-6, ROS, and MMPs such as MMP2, 3, and 9 (29).

The precise biological activity and mechanisms by which flavonoids work is still not completely understood, but much research is being done to isolate, identify, and characterize polyphenols (35). Further understanding of their functions can lead to new therapeutic options and applications.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

IMMUNE RESPONSE IN NEUROINFLAMMATION

I. Robuffo*

CNR Sezione di Chieti, 66100 Chieti, Italy.

**Correspondence to*:
Dr. Iole Robuffo,
CNR Sezione di Chieti,
66100 Chieti, Italy.
e-mail: iole.robuffo@cnr.it

KEYWORDS: *cytokine, chemokine, microglia, inflammation, IL-1, IL-6, IL-17, IL-12, IL-23*

INTRODUCTION

Cytokines are numerous pleiotropic peptides secreted in response to insults including antigens. These polypeptides mediate immune and inflammatory responses (1). Cytokine synthesis occurs through gene transcription (mRNA) followed by cell activation (2). Cytokines can act in concert with other cytokines, and some may have a stimulatory effect, while others an inhibitory effect (3). In addition, they can mediate physiological immune states, but can also induce inflammation with serious consequences. In the central nervous system (CNS), even if the number of white immune cells is low, cytokines play an important role, both physiological and pathological, during inflammatory states (4).

In neuroinflammatory pathological states, microglia are involved, a producing source of cytokines that can cause alteration of homeostasis, tissue damage, destruction of neurons, and pathological changes (5). However, it is uncertain whether cytokines may play a role in brain tissue degeneration.

The cells that make up the CNS are of different types. For example, glial cells include astrocytes, microglia, and oligodendrocytes that produce various cytokines and chemokines that mediate homeostatic processes (6). Astrocytes generate some cytokines such as IL-17 and IFN-γ, and the chemokine CCL2 (7). The oligodendrocytes that generate the myelin sheath that surrounds axons mediate fast signaling between neurons and may be an immune target (8). Microglia, which are myeloid cell types that are similar to peripheral blood monocytes, have the function of engulfing the remains of decaying cells and also the microorganisms that manage to cross the blood-brain barrier (BBB). Activated microglial cells produce several pro-inflammatory cytokines such as IL-1, TNF, and IL-6 which damage the CNS (9). Moreover, activated microglia also produce IL-12 and IL-23, cytokines involved in the phagocytosis of cellular debris and microorganisms, promoting tissue regeneration (10).

CONCLUSIONS

Here in this short letter, we report that neuroinflammation involves immune cells that when activated by various biological, chemical, or physical stimuli produce hypo-inflammatory immune cytokines that can damage brain tissue. At present we do not know whether anti-inflammatory cytokines such as IL-37 and IL-38 can be produced by microglia mimicking the functions of monocytes/macrophages, which produce anti-inflammatory cytokines.

Conflict of interest
The author declares that they have no conflict of interest.

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COVID-19 AND PAIN

S.K. Kritas*

Department of Microbiology and Infectious Diseases, Aristotle University of Thessaloniki, Macedonia, Greece.

Correspondence to:
Dr. S.K. Kritas,
Department of Microbiology and Infectious Diseases,
Aristotle University of Thessaloniki,
54250 Macedonia, Greece.
e-mail: skritas@vet.auth.gr

ABSTRACT

SARS-CoV-2 causes COVID-19, which includes acute respiratory tract infections with a variety of manifestations such as pneumonia and bronchiolitis which are accompanied by other symptoms such as wheezing, cough, respiratory distress, and pain. The novel Coronavirus has caused millions of deaths and increasing challenges for healthcare professionals globally. When the virus enters our organism through nasal mucosa it is identified by the innate immune system such as macrophages and mast cells, therefore producing pro-inflammatory cytokines including IL-1β, IL-6, and TNF. The production of cytokines mediates fever, malaise, depression, anxiety, loss of appetite, hyperalgesia, and pain. Here in this paper, we report the interrelationship between COVID-19 and pain.

KEYWORDS: *COVID-19, SARS-CoV-2, inflammation, cytokine, IL-1β, IL-6, TNF, immune, pain*

INTRODUCTION

In December of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surfaced in the city of Wuhan, China, causing the coronavirus disease (COVID-19) which then spread quickly and became a global pandemic (1). On January 30th, 2020, The World Health Organization declared the COVID-19 outbreak to be an International Public Health Emergency (2). As of January 24th, 2021, there have been over 98 million confirmed cases of Covid-19 globally and it has led to more than 2 million deaths (3). The pandemic has had a great impact on society, the economy, and has presented challenges for healthcare professionals globally.

The virus is highly transmissible in humans, by droplets, through speaking, sneezing, and coughing, in close parameters, or by surface contact (4). SARS-CoV-2 causes acute respiratory tract infections and older individuals and those with a weakened immune system and comorbidity are at higher risk for experiencing severe complications. Symptoms of COVID-19 can range from mild to severe and include shortness of breath, dry cough, fatigue, fever, pneumonia, respiratory failure, systemic inflammation, and pain (5).

COVID-19 can cause acute and chronic pain, with the latter becoming increasingly apparent as a long-term symptom. For this, coping with residual pain is an important aspect of treatment, to improve the quality of life for patients. Pain accompanying COVID-19 is linked to inflammation and the "cytokine storm", with the rapid release of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF), and this article aims to explore this relationship between COVID-19 and pain.

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SARS-CoV-2 and the Innate Immune System

SARS-CoV-2 enters the body through nasal mucosa, where it replicates and infects the nasal cavity (6). It can continue to replicate down the respiratory tract, from the throat, to bronchia, and into the lungs, causing severe COVID-19, and potential brain infiltration and death (6). A prompt innate immune response to SARS-CoV-2 can lead to virus clearance and immune memory. An immediate and active immune response can contain and clear the virus, while a delayed response and increased inflammation can lead to serious complications, such as pneumonia, and death (4). Those with a weakened or compromised immune system are at higher risk for severe disease.

Upon entry, the virus is recognized by the innate immune system including mast cells (MCs) and macrophages. MCs are innate immune cells that are ubiquitous in the body, which are highly heterogeneous and function differentially in response to diverse stimuli (7). After activation, MCs release histamine, proteases, and proinflammatory cytokines and chemokines. This can be protective and help to clear infection, but an overactive response with proinflammatory mediators can be damaging, exacerbating inflammation, and leading to severe disease.

Macrophages are innate immune cells which intervene immediately when the microorganism enters the body. SARS-CoV-2 activates macrophages through Toll-like receptors (TLRs), and they produce pro-inflammatory cytokines which aggravate COVID-19 and generate pain.

COVID-19 infection can cause an exaggerated inflammatory response deemed the "cytokine storm". In response to SARS-CoV-2 entry, macrophages and MCs initiate signaling cascades and activate transcription factors, which induce pro-inflammatory cytokines including IL-1, IL-2R, IL-6, IFN-γ, IP-10, MCP-1 and TNF (5,8). A sudden increase in these pro-inflammatory cytokines, and the subsequent convergence of macrophages, neutrophils, and T cells to the infection site, creates the "cytokine storm", which can lead to tissue and vascular damage, organ failure, lung injury, and death (9).

Evidence proposes the "cytokine storm" is involved in patients with severe COVID-19 and is a common cause of mortality and complications, with studies finding significantly heightened levels of IL-1β, IL-6, and TNF in living and deceased patients (5,10,11).

COVID-19 Pain

COVID-19 is often accompanied by pain, with the most frequently reported pain symptoms including headache, widespread myalgia, and back and neck pain. In fact, myalgia and headache are often the first symptoms experienced by patients. Inflammation plays a vital role in the development of pain.

Muscle pain has been reported to affect 21-36% of patients (12,13) and is associated with inflammation. The release of pro-inflammatory cytokines during "the cytokine storm" can activate the formation of pain mediator prostaglandin E2 (PGE2), which is induced by IL-1β on macrophages.

COVID-19 induced headache operates by similar mechanisms as migraines and common headaches. Inflammation causes nociceptive sensory neurons to become activated in response to cytokines. Other possible causes could include viral neuroinvasion, hypoxia, or thrombosis.

COVID-19 not only produces classic respiratory virus symptoms, but a growing amount of evidence continues to show neurological symptoms such as headache, anosmia (loss of smell), ageusia (loss of taste), nausea, myalgia, confusion, and disorientation (14-16), as well as the development of persistent pain. Following SARS-CoV-2 infection, the rapid release of cytokines such as IL-1β, IL-6, and TNF, can mediate fever, malaise, depression, anxiety, loss of appetite, hyperalgesia, and pain.

Chronic pain is characterized by hyperalgesia, sensitivity to thermal and mechanical noxious stimuli, and allodynia, sensitivity to non-noxious stimuli. Altered neuronal plasticity can affect sensitization in the peripheral and central nervous system (CNS), heightening perceptions of pain and leading to chronic pain. Pro-inflammatory cytokines can act on pain-sensing nociceptors in the neurons of peripheral tissues and cause pain sensitivity.

COVID-19 pain occurs when SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is a protein that acts as an entry point for virus to infect cells. ACE2 receptor is present in different cells, including the epithelium of the nose, mouth, and lungs. The virus uses a "spike" surface protein to bind to ACE2 and allow it to infect the cells, resulting in an imbalance of ACE2 and lung injury (17). SARS-CoV-2 has been detected in cerebrospinal fluid and can produce neurological symptoms, and ACE2 has also been detected in neurons and microglia in mice in the spinal dorsal horn. There, ACE2 is associated with pain alleviation (18), but a reduction of ACE2, which has been used by the virus, can lead to the accumulation of Angiotensin II (Ang II) with low levels of Angiotensin-1-7, causing COVID-19 pain (17).

Cytokines in Pain

Cytokines are small, protein-based signaling molecules involved in the communication between cells in immune responses (19). They can have autocrine, paracrine, or endocrine actions, and can be pro-inflammatory or anti-inflammatory. During SARS-CoV-2 infection, activated immune cells, such as MCs and macrophages, produce pro-inflammatory cytokines including IL-1β, IL-6, and TNF. The production of these cytokines exacerbates inflammation and creates fever, destruction of tissue, pain, and may lead to shock and death (20). Overwhelming inflammation is harmful to the host and plays a central role in pain development. Some pro-inflammatory cytokines have been associated with pain amplification, with evidence showing a strong correlation with IL-1β, IL-6, and TNF.

The pro-inflammatory cytokine IL-1β has been seen to start and maintain chronic pain. IL-1β is expressed in dorsal root ganglion (DRG) neurons in response to nociceptive stimulus after CNS injury (21,22). It has been associated with increased production of PGE2 and substance P, which can create inflammatory nociception, and injection of IL-1β has also been shown to initiate hyperalgesia (23,24). Because of its implication in pain, IL-1β could provide future opportunities in therapy if it can be blocked.

IL-6 is active in neuropathological events, and evidence has shown that it is associated with neuropathic pain behavior. IL-6 is normally present in low levels in the brain, and a substantial increase results with neurological disorders such as Alzheimer's disease and Parkinson's disease, brain ischemia, and brain cancer. But at the same time, IL-6 is important for regeneration (25), oligodendrocyte differentiation (26), and acts as a neurotrophic factor (27). IL-6 has been seen to facilitate and exacerbate pain after nerve injury (28). In a rodent model of sciatic cryoneurolysis (SCN), a valid neuropathic pain model, IL-6 was seen to increase in the brain after SCN and cause sensitivity to noxious and non-noxious stimulus after intrathecal infusion (29). It has also been linked to nociceptor and central sensitization (30,31).

TNF is another cytokine that is a pain mediator. It acts on different signaling pathways, regulating NF-kB and apoptotic pathways, and activates stress-activated protein kinases (SAPKs) in the brain. Its two receptors, TNFR1 and TNFR2, are found in glia cells and neurons, and TNFR1 signaling contributes to inflammation, tissue degeneration, and the development and continuation of neuropathic pain (32). Increased TNF levels are seen at sites of peripheral nerve injury (33) and endoneurial injection has been shown to initiate symptoms of pain without injury (34).

CONCLUSIONS

COVID-19 produces a range of symptoms, from cough, fatigue, and fever, to pneumonia, respiratory failure, systemic inflammation, and pain. The most common pain symptoms include headache, myalgia, neck pain, and back pain, and inflammation plays an important role in the development and persistence of pain. The release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF are involved in severe cases, which can lead to the "cytokine storm". These cytokines act on nociceptors in the neurons of peripheral tissues, leading to pain sensitivity. The "cytokine storm" can lead to heightened levels of pain, as well as the continuation of pain. Excessive inflammation produced by the release of proinflammatory cytokines IL-1β, IL-6, and TNF is associated with pain sensitivity. IL-1β is expressed in DRG neurons after CNS injury, activating the pain mediator PGE2, and initiating and maintaining chronic pain. After nerve injury, IL-6 can cause pain sensitivity to noxious and non-noxious stimulus and moreover, TNF signaling has been associated with inflammation and the development of pain. However, more research is necessary to expand the role that these proinflammatory cytokines, and other inflammatory compounds, play in the development and maintenance of chronic pain in COVID-19.

Conflict of interest

The author declares that they have no conflict of interest.

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POST-TRAUMATIC STRESS DISORDER IN ORTHOPEDIC TRAUMA PATIENTS

G. Ronconi[1*] and A.J. Williams[2]

[1] Territorial Patient Clinic, Fondazione Policlinico Gemelli, Rome, Italy;
[2] Consultant, Viale Unità d'Italia 73, Chieti, Italy.

Correspondence to:
Gianpaolo Ronconi, MD,
Territorial Patient Clinic,
Fondazione Policlinico Gemelli,
Rome, Italy.
e-mail: gianpaolo.ronconi@policlinicogemelli.it

ABSTRACT

Orthopedic trauma patients show a higher prevalence of post-traumatic stress disorder (PTSD) when compared to the general public. Studies have shown that between 20-50% of trauma survivors with musculoskeletal injuries will suffer from PTSD. Emotional distress can present immediately after the traumatic experience or there may be delayed onset, and pretraumatic, peritraumatic, and posttraumatic risk factors have been identified as contributing to the development of PTSD. Therapist-delivered trauma-focused psychological therapy has been successful for treating PTSD, and early identification after trauma is important for initiating the treatment in order to improve outcome and limit disability. With their role as the first care providers to orthopedic trauma survivors, orthopedic surgeons can assist with this process by identifying at-risk patients and those who may be exhibiting symptoms of PTSD, and referring them to appropriate mental healthcare providers.

KEYWORDS: *PTSD, trauma, orthopedics, disorder, stress, musculoskeletal*

INTRODUCTION

Orthopedic trauma is a severe injury to the musculoskeletal system that can be life-threatening and traumatic for the patient, as well as being a major cause of disability. Trauma can occur from accidents of blunt or crushing force, falls, military combat, sports injuries, natural disasters, and violent crime, amongst others. The physical damage that is incurred during orthopedic trauma can be life-changing, limit mobility and recovery, and can be a long and demanding process (1). Additionally, these injuries are often sudden and difficult for the patient to experience and cope with on an emotional level. In fact, more than half of trauma survivors experience psychological distress after being treated for their injuries, and some will go on to struggle for years and even decades (2).

Post-traumatic stress disorder (PTSD) occurs in people who have experienced or witnessed traumatic or life-threatening events and is a common psychiatric condition that affects orthopedic trauma patients after injury. In the past, PTSD was mainly attributed to veterans of war, who had returned from combat with "shell shock". The disorder was primarily associated with war until 1980, when it became a formal diagnostic entity (3,4). Now PTSD is a well-defined condition and one of the most commonly diagnosed mental health disorders. The American Psychiatric Association defines PTSD as a disturbance, regardless of its trigger, that "causes clinically significant distress or impairment in the individual's social interactions, capacity to work or other important areas of functioning" (4). The Diagnostic and Statistical Manual 5th edition (DSM5) lists behavioral symptoms as: re-experiencing, avoidance, negative cognitions and

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mood, and arousal (4). These encompass the possible symptoms that can occur in survivors, including flashbacks, recurrent dreams and thoughts, intrusive memories, hypersensitivity and hypervigilance, feelings of guilt, blame, and sadness, withdrawal from activities and social interests, insomnia, or self-destructive behavior.

PTSD is diagnosed after a month of experiencing symptoms following the distressful experience and is a serious mental health disorder that can greatly affect quality of life.

This review will discuss the association of PTSD in orthopedic trauma patients and the implications for treatment and orthopedic surgeons.

Prevalence and Assessment

PTSD has a greater prevalence amongst orthopedic trauma patients in comparison to the general public, affecting between a fifth to half of survivors with musculoskeletal injuries (2,5-11). One particular study focusing on orthopedic trauma survivors showed that half of the 580 respondents showed symptoms for PTSD (10). In another interesting review of studies for skeleton and pelvis injuries, it was shown that more than 25% of survivors had PTSD symptoms after acute orthopedic trauma (12). Furthermore, Starr et al. suggested that the phrase "The emotional problems caused by the inury have been more difficult than the physical problems," may be useful for signaling PTSD in orthopedics (10).

Symptoms of PTSD may appear soon after injury, but often do not present immediately. A diagnosis can be made after one month of recurring symptoms, but those symptoms can persist or develop months or years after the trauma, with one study showing significant numbers of PTSD patients continuing or starting to experience symptoms at 12 months after injury (9).

PTSD is assessed by screening instruments and structured clinical interviews, with the latter being more successful in assessment and for treatment purposes as well (13). Screening should be established at important intervals, during the acute care phase, and at 3 months after the time of injury, a critical time indicator for long-term symptoms (14). A detailed history and mental status examination is important for determining the nature of the patient's PTSD.

Risk Factors

Not everyone who experiences a traumatic event will go on to develop PTSD, and some risks factors are useful for predicting patients who may be susceptible (15). The origins of PTSD can be diverse, with pretraumatic, peritraumatic, and posttraumatic factors involved (16).

Patients who have injuries sustained by high-energy mechanisms can be at greater risk of developing PTSD (17). Other indicators include low post-trauma cortisol levels (18), a history of prior trauma and PTSD (19), smoking (20), level of social support, and the perceptions of threat to life (21). The female gender has been shown to have worse outcomes of PTSD after trauma (22). In addition, younger age has been correlated with a higher risk for PTSD (21,23,24).

Pain is not only physical, but emotional as well, and emotional distress can have many negative health consequences and can be a factor for developing PTSD. It has been seen in studies of vehicle accident patients, where pain was linked with PTSD morbidity (25) and where it was shown that reduced pain-levels could lead to reduced PTSD symptoms (26). Another study showed that PTSD can be predicted by pain intensity at the time of discharge from hospital, and pain can provoke and worsen symptoms when it is felt and associated with the traumatic experience (27).

Another factor is the memory extent of the traumatic event (28), as well as the patient's reaction during the event. Dissociation and emotional numbness are some reactions that fall under the label of peritraumatic dissociation, which can predict PTSD (19), although some studies have shown conflicting results (29).

It was also shown that level of severity and type of orthopedic injury can play a role in developing PTSD, and the need for more physical care in hospital may be linked with the need for greater mental health care (9).

Additionally, there may be a correlation between the nature of the traumatic experience and rates of PTSD. Studies have shown that victims who had experienced violent crime and accidents where pedestrians had been hit by motor vehicles are at higher risk for PTSD afterwards (17).

Finally, a patient's psychological history can show warnings, as pre-existing psychiatric disorders, such as depression or anxiety, are a risk for developing PTSD and disability (30,31).

Treatment and Management

Treatment options for PTSD are available in the form of therapy and behavioral and pharmacological treatments. Pharmacotherapeutics have limited success, as they are used in PTSD to treat symptoms and not the underlying pathophysiology of the condition, which must be addressed (32).

An effective treatment that is considered the leading choice for PTSD patients is therapist-delivered trauma-focused psychological therapy. Single session interventions were commonly used in the past for preventing mental health

conditions after trauma but were shown to have little effect in preventing PTSD, indicating that multiple sessions are necessary. However, this option is not always accessible or feasible for all trauma survivors, as there may be a lack of qualified therapists, the cost may be a problem, and transportation and time off work are limiting factors.

Trauma-based cognitive behavioral therapy has been shown to be effective in treatment (33,34). Eye movement desensitization and reprocessing, a therapist-guided psychotherapy treatment involving recall of the traumatic experience with controlled movement of the eyes, has had successful results (35,36).

Prolonged exposure therapy, which confronts fear stimuli and reconstructs memories associated with it, and cognitive processing therapy are strongly recommended treatments for PTSD (37).

For short-term PTSD recovery some options include holistic approaches, pastoral care, coping skills, mindfulness, peer visitation, and educational resources (2). Social support can be a valuable tool for long-term recovery, and support groups are available to unite survivors who have experienced similar trauma (2,38).

Following a traumatic injury, early identification of emotional distress and mental health disorders is vital for initiating treatment, reducing long-term symptoms, and improving outcome (39). Orthopedic trauma patients should be screened for mental health problems during their time of care in hospital (40), and routine follow-up should be provided at determined intervals, such as 1- and 3-months post-discharge. Early detection of problems can be identified with better screening methods, such as the Psychosocial Screening Instrument for Physical Trauma Patients (PSIT), developed by Karabatzakis et al (41).

In addition, educational information for patients about PTSD may be included at discharge with recommendations for recognizing symptoms and proceeding with follow-up (9,14).

The Role of the Orthopedic Surgeon

Raising awareness of PTSD within the orthopedic community is an important step in limiting the effects of PTSD for trauma survivors. Early identification of risk factors is crucial for prevention and treatment.

The role of the orthopedic surgeon is to treat the physical symptoms of the musculoskeletal injury and restore function, not to treat the affective disorders that may accompany such injury. However, orthopedic surgeons are at the front-line in treating trauma survivors at the beginning of a potentially long physical and emotional recovery process, the critical timeframe where early identification and diagnosis of PTSD can be greatly beneficial. Identifying psychological distress early is advantageous in determining outcome.

For this reason, educational training concerning PTSD should be provided to orthopedic surgeons. Knowledge of risk-profiles can help surgeons identify the warning signs for PTSD, and subsequently refer patients to appropriate professionals to assist them with treatment. Orthopedic surgeons can also pay attention to patients who are slow in recovery, especially those continuing to experience pain after healing, who may be dealing with psychological problems that are negatively affecting their recovery (42).

CONCLUSIONS

PTSD is a common psychological disorder that accompanies orthopedic trauma patients. It has physical, social, and psychological consequences that can greatly affect the quality of life for the patient. PTSD does not necessarily occur immediately after injury; it can have a delayed onset and present months to years after trauma. Early identification of risk factors and warning signs and screening at discharge, one-month post-discharge, and preferably at determined intervals afterward, can help initiate treatment and recovery. Educational training programs should be initiated for orthopedic surgeons, the first care providers for orthopedic trauma survivors, to aid the early detection process and treatment course for PTSD.

Conflict of interest

The authors declare that they have no conflict of interest.

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

M. Trimarchi*

Department of Medicine and Surgery, Neuroscience Centre of Milan, University of Milan, Italy.

Correspondence to:
M. Trimarchi,
Department of Medicine and Surgery,
Neuroscience Centre of Milan,
University of Milan, Italy.
e-mail: trimarchi.matteo@hsr.it

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.

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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, a time of complex neuroinflammatory cascades. In addition, studies have shown that cognitive decline affects between15 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 (40-42).

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 to be accounted for.

CONCLUSIONS

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 author declares that they have no conflict of interest.

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