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Mild Traumatic Brain Injury, Dementia, and Exercise

Increasing white matter integrity in the brain

Numerous studies have been carried out on mild traumatic brain injury (mTBI) and its treatment plans. This review covers the history of mTBI, differential diagnosis of the injury, and post-concussion syndrome (PCS). Furthermore, it explores the relationship between mTBI and aging, dementia, and Alzheimer's disease and how exercise relates to changes in white matter in the human brain. From the reviewed literature, it is possible to see the relationship between mTBI injury and white matter: mTBI may lead to structural changes in white matter fibre tract integrity. Exercise can be used to respond to cases of mTBI as it encourages the formation of new connections between neurons along with an increase in the production of new neurons. Aerobic exercise can lead to the replacement of damaged white matter as well as increased cognitive performance. This review demonstrates the possibility of using exercise to treat cases of PCS through white matter repair.

Keywords: mild traumatic brain injury, post-concussion syndrome, dementia, white matter

INTRODUCTION

Annually, about 18,000 Canadians experience a traumatic brain injury (TBI) that requires them to be hospitalized for treatment and monitoring (Brain Injury Centre Canada, 2011). In addition, there are 1.3 million Canadians who live with deficits acquired as a result of TBI (Brain Injury Centre Canada, 2011). The majority of these cases are reported as resulting from motor vehicle accidents, falls, and assaults often in urban areas. Overall, TBI led to spending about $151.7 million on treatment and care in the years 2000 and 2001 (Brain Injury Centre Canada, 2011).

DIFFERENTIAL DIAGNOSIS OF mTBI

According to Giza and Hovda (2001), a mild traumatic brain injury (mTBI) is a transient neurologic dysfunction that results from biomechanical force. Loss of

consciousness is a clinical hallmark of mTBI or concussion but it is not needed to make a diagnosis. The symptoms that are likely to be considered in the differential diagnosis may include confusion, dizziness, disorientation, headache, and visual disturbance (Giza & Hovda, 2001).

The diagnosis of cases of moderate or severe brain injuries is normally self-evident. Problems arise, however, when other life-threatening injuries that require immediate attention are present, such as physical trauma to other parts of the body: in these situations, the brain injury is normally missed (Giza & Hovda, 2001). While most physicians are familiar with mTBI management, there is difficulty in diagnosing and treating mTBI owing to the subtlety of deficits (Arciniegas, Anderson, Topkoff, & McAllister, 2005).

Diagnosis can involve brain imaging techniques such as computerized axial tomography (CAT), positron emission tomography (PET), and magnetic resonance imaging (MRI). To help clarify certain deficits, follow-up evaluation by physical, speech, and occupational therapists may be necessary (Giza & Hovda, 2001). Furthermore, differential diagnoses should involve consideration of other neurologic and psychiatric disorders (Giza & Hovda, 2001). The effects of negative expectations on cognitive performance in head injury, known as diagnosis threats, and development disorders should both be taken into consideration during the diagnosis of mild traumatic brain disorder (Suhr & Gunstad, 2002).

Lastly, carrying out a differential diagnosis of mTBI requires the understanding of the effect of concussion on brain metabolism. Henry et al. (2011) explored this and revealed that concussion leads to neurometabolic impairment, especially in the prefrontal and the motor cortices.

POST-CONCUSSION SYNDROME

Chen, Johnston, Collie, McCrory, and Ptito (2007) define post-concussion syndrome (PCS) as the continued occurrence of symptoms following mTBI. PCS symptoms include fatigue, headache, light-headedness, attentional and memory deficits, irritability, anxiety, and depression. The duration of symptoms is one of the key criteria for the clinical assessment of mTBI, however it is important to note that post-concussion symptoms are self-reported and are not always specific to concussions. The usefulness of PCS in the assessment of cerebral concussion remains unclear given that such symptoms are non-specific in nature and a large percentage of the normal population report identical symptoms in the absence of a history of concussive injury (Chen et al., 2007). There is a strong need for better-defined criteria and validated assessments of PCS. One way of doing this is by correlating self-rated PCS scales with other objective assessments, such as those provided by neuropsychological tests.

mTBI AND WHITE MATTER INTEGRITY

White matter consists of millions of bundles of axons (nerve fibres) that link neurons in distinct brain regions into functional circuits (Fields, 2010). The white colour comes from the insulation that encloses axons, called the myelin sheath. Myelin is necessary for the efficient and high-speed conduction of electrical impulses (Fields, 2010). Damage to white matter can weaken signal conduction and as a result can impair sensory, motor, and cognitive functions.

The relationship between white matter integrity and mTBI has been studied and is well documented by various researchers. Investigation by Gao and Chen (2011) on the morphologies of spared neurons in the cortex after mTBI reveals that mTBI leads to limited tissue lesions and cell death. However, mTBI causes widespread, significant synapse degeneration in the cortical neurons that are spared. This widespread loss disrupts neural circuitry leading to neurologic dysfunction. Thus, for proper diagnosis, treatment, and management of mTBI, it is important to detect neuron damage in cerebral white matter after TBI (Bazarian et al., 2007).

It is well known that mTBI leads to long-term cognitive and emotional difficulties along with behavioural disturbances (Gao & Chen, 2011); however, the lack of direct evidence-based neural correlates of the disorder has largely hampered treatment and diagnosis of mTBI. Unlike severe TBI, mTBI does not lead to significant tissue lesions or cavities in the cortex. Furthermore, neuro-imaging through magnetic resonance has always produced negative results, indicating that the damage is beyond the resolution of current scanning technologies (Gao & Chen, 2011).

Researchers and clinicians have attempted to use several tools (e.g. MRI and CAT) to study the damage caused to white matter, but these tools have not been sufficient. According to Cubon, Putukian, Boyer, and Dettwiler (2011), most athletes who experience mTBI experience rapid onset of short-lived neurological impairment without structural changes as measured using MRI and CAT. Indeed, researchers have recently reported that lesions to white matter tracts are underdiagnosed when using conventional imaging techniques (Inglese et al., 2005). Diffusion tensor imaging (DTI) has provided a solution to this problem. DTI is an objective tool that can be used to assess severity and recovery functions after a concussion. It involves assessing the white matter fibre tract integrity (Cubon et al., 2011). Diffusion tensor changes are a sign of brain damage. A way to measure these changes is by using an analysis called tract-based spatial statistics (TBSS), which can evaluate axonal injury of the white matter skeleton by effectively detecting structural changes from mTBI (Cubon et al., 2011).

SIMILARITY TO AGING, ALZHEIMER'S DISEASE, AND DEMENTIA

Dementia is a general term used to describe loss of memory as well as other human intellectual abilities. This loss normally interferes with one's daily life. The most common form of dementia is Alzheimer's disease (Tremblay et al., 2013). Another

term known as mild cognitive impairment (MCI) has also been used to refer to the form of dementia that does not interfere with one's daily life. The greatest known risk factor of this disease is aging. Indeed, adults over 65 years of age comprise the majority of the patients with this disease. According to Tremblay et al. (2013), Alzheimer's disease normally worsens over time. In the early stage, memory loss is the main symptom, but in the later stages, patients normally experience loss of other intellectual abilities. Numerous studies have been conducted to establish the relationship between Alzheimer's disease and mTBI with several showing that older adults who have had cases of mTBI are more likely to exhibit brain changes that are suggestive of Alzheimer's disease (Jellinger, 2004; Van Den Heuvel, Thornton, & Vink, 2007; Tremblay et al., 2013).   A study by Tremblay et al. (2013) on the correlation between cognitive decline in late adulthood and sports concussions sustained in early adulthood revealed physical brain anomalies in otherwise healthy former athletes. The researchers posited that these anomalies were a result of earlier mTBI and, therefore, suggested that mTBI may result in cognitive decline later in life. These patterns of decline are often associated with abnormal aging in those without history of mTBI (Tremblay et al., 2013). In a meta-analysis of seven case-control studies, Mielke et al. (2014) found that those who sustained an mTBI without loss of awareness were significantly more likely to develop MCI later in life. This risk increase was significant even after adjustments for education, alcohol consumption, and familial history of Alzheimer's disease.

   Other studies have looked at amyloid-beta deposition, which is a key post-mortem indicator of Alzheimer's disease. According to Jellinger (2004), both human post-mortem and non-human experimental studies show amyloid-beta deposition after head injury. This has been confirmed in a recent study by Mielke et al. (2014).

EXERCISE AND WHITE MATTER INTEGRITY

Apart from the known benefits of exercise such as a reduction of cardiovascular disease risks and the strengthening of muscles and bones, exercise has been used in the management of Alzheimer's disease to benefit the brain (Tremblay et al., 2013). Specifically, it is used with the intention of improving memory performance and other cognitive functions while also delaying the onset of the disease.

   According to Baker, Freitas, Leddy, Kozlowski, and Willer (2012), increased blood flow to the brain may trigger biochemical changes that lead to the production of new connections between neurons as well as the production of new neurons. Exercise appears to protect newly formed neurons by triggering the release of a nerve growth factor. This facilitates the formation of functional connections with neurons in proximity (Leddy, Kozlowski, Fung, Pendergast, & Willer, 2007). Importantly, exercise has been shown to contribute to the development of white matter for both new and aging neurons.

Numerous animal studies have indicated that exercise has several benefits beyond neurogenesis (Leddy et al., 2007). Some of these benefits include an increase in the production of neurotransmitters and angiogenesis, which is the development of new blood vessels. A meta-analysis conducted by Leddy et al. (2007) showed that training increases the cognitive performance of individuals between the ages of 55 and 80. This is an age group that is often associated with low levels of cognitive performance due to aging (Jellinger, 2004). Another meta-analysis demonstrates that exercise boosts cognitive performance through fitness training for adults over 65 years who suffer from cognitive impairment as a result of dementia (Jellinger, 2004). Furthermore, physical activity has been used to enhance neurogenesis for the management of Parkinson's disease and dementia (Jellinger, 2004).

According to Leddy et al. (2007), however, patients with post-concussion symptoms should not be involved in exercise due to the potential re-emergence of symptoms. On the other hand, extended rest may also lead to PCS patients experiencing deconditioning and secondary effects, including depression. Leddy et al. (2007) further suggest that PCS may be reduced by the patients' being submitted to aerobic exercise.

Studies investigating rehabilitation programs also indicate that progressive exercise treatment helps in reducing PCS symptoms by aiding the flow of blood in the brain (Baker et al., 2012). Patients put under an exercise regimen have reported increased cognitive performance compared to their counterparts who are not involved in training. Another example in a rehabilitation setting is a study by Riggs et al. (2016) that explored neurocognitive outcomes of exercise in children. Their study utilized DTI to examine exercise outcomes in children who were treated with radiation for brain tumours. The intervention was found to increase recovery from the radiation-induced side-effects. Radiation makes the brain unable to produce new brain cells, including white matter. The inability of the brain to produce new cells has, therefore, caused some cancer patients who are treated by radiation to lose memory and cognitive ability. The study suggests that exercise helps prevent post-radiation treatment memory decline by increasing blood flow to the hippocampus, a brain structure used in learning, navigation of space, and memory. The duration of these exercises and the exercise routines, however, need to be selected and planned with great care to prevent an exacerbation of symptoms.

CONCLUSIONS, LIMITATIONS OF CURRENT RESEARCH, FUTURE DIRECTION
This paper highlights the relationship between mTBI and white matter. It further reveals the possibilities of using exercise to treat the effects of mTBI. There is a need for further studies on the exact mechanism through which exercise repairs white matter that is destroyed due to mTBI. Future studies should take advantage of DTI to help isolate specific locations where exercise enhances neurogenesis. Future

studies should also attempt to measure the outcome of aerobic exercise interventions on the white matter integrity in patients and athletes who have had one or more concussions.

Finding parallels between white matter changes in patients with dementia and in patients with mTBI can not only lead to the development of novel interventions to treat lingering PCS symptoms that follow mTBI, but also help advance the understanding of the underlying neural mechanisms that lead to white matter atrophy in both patient populations.

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