Low-Dose Ionizing Radiation Therapy: A Novel Treatment for Post-Concussion Syndrome?

Paul A. Oakley

Abstract
A subset of victims who experience concussion suffer from persistent symptoms spanning months to years post-injury, termed post-concussion syndrome (PCS). Problematically, there is lack of consensus for the treatment of PCS. Concussion injury involves a neurometabolic cascade leading to oxidative stress and neuroinflammation which parallels the oxidative stress loading occurring from age-related neurodegenerative conditions. Historical and recent evidence has emerged showing the efficacy of low-dose radiation therapy for many human diseases including neurodegenerative diseases such as Alzheimer’s disease (AD).

Due to the pathognomonic similarities of oxidative stress and neuroinflammation involved in PCS and neurodegenerative disease, treatments that prove successful for neurodegenerative disease may prove successful for PCS. Recently, low-dose ionizing radiation therapy (LDIR) has been documented to show a reversal of many symptoms in AD, including improved cognition. LDIR is thought to induce a switching from proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype. In other words, a continual upregulation of the adaptive protection systems via LDIR induces health enhancement. It is hypothesized LDIR treatment for PCS would mimic that seen from early evidence of LDIR treatment of AD patients who suffer from similar oxidative stress loading. We propose the application of LDIR is a promising, untapped treatment for PCS.

Keywords
post-concussion syndrome, low-dose ionizing radiation, concussion, treatment

Introduction
Concussion is a traumatically induced transient disturbance of brain function that involves a complex pathophysiological process. It is understood to be a mild traumatic brain injury (mTBI) where most patients recover quickly, within 7–10 days. Some patients, however, do not fully recover and have persistent symptoms, so-called post-concussion syndrome (PCS) that may last for months or years after the initial injury.

The treatment of acute concussion involves rest with light and graded activity, but there is a lack of consensus for the treatment for those concussion patients whom experience lingering and persistent symptoms (PCS). Here, we present the rationale for a novel treatment for concussion, particularly PCS, that is, low-dose ionizing radiation (LDIR) therapy.

Neurometabolic Cascade of Concussion Parallels Other Neurodegenerative Diseases
Current understanding of concussion involves a neurometabolic cascade as the main pathophysiological process leading to the sequelae of C/PCS. One aspect consistent across concussion injury and neurodegenerative conditions such as Alzheimer’s disease (AD) involves the role of oxidative stress and neuroinflammation.
Oxidative stress is a disturbance in the prooxidant-antioxidant ratio that favours oxidants. A more current explanation includes the fact that it also leads to a ‘disruption of redox signalling and control and/or damage’. Adaptive oxidative stress responses are activated by molecular redox switches that initiate the activation of multiple gene expressions of defence systems to counteract the challenge. This results in redox homeostasis or a ‘reset’ of redox balance.

Oxidative stress is a normal and vital phenomenon, and under normal conditions it is considered a ‘eustress’, meaning it is physiologic. However, when circumstances initiate the production of excessive oxidant levels, such as occurs in age-related, gradual evolution of neurodegenerative disorders or in the acute neurometabolic cascade of concussion, this becomes non-physiologic; that is, pathologic. Thus, pathogenic oxidative stress, so-called oxidative distress, is the common underpinning for both age-related neurodegenerative diseases and acute neurologic brain injury such as concussion.

**LDIR Therapy for Neurodegenerative Diseases**

Recently, there has been interest in LDIR treatment for patients suffering from neurodegenerative diseases including, for example, AD. In 2016, Cuttler et al described the successful application of LDIR for an 81-year old female with advanced AD. After receiving 5 head CT scans over 3 months, the patient displayed improvements in cognition, speech, movement and appetite. In 2017 and 2018, two updates reported that the patient continued to do well after ‘booster scans’. Most recently, a case series of 4 advanced AD patients were treated with the same initial treatment protocol as the original case; three of the four patients had significant clinical improvements in behaviour and wellbeing as reported by caregivers and family members.

**LDIR Therapy for Concussion**

Due to the pathognomonic similarities of oxidative stress and neuroinflammation involved in C/PCS and neurodegenerative disease, treatments that prove successful for neurodegenerative diseases may also prove effective for C/PCS. The use of the Parkinson’s medication amantidine, for example, increases the availability of dopamine by facilitating its release and inhibiting its reuptake; preliminary studies show this medicine can improve symptoms and quality of life in PCS patients.

The similarities in pathogenesis of increased oxidative stress in neurodegenerative disease and C/PCS taken together with early evidence of successful treatment to AD patients from LDIR suggest this treatment could be effective in the treatment of PCS. Since most patients suffering from concussion recover relatively quick, this treatment may be particularly promising for the subset of patients who fail to recover; this ranges between 11% and 39% of concussed patients whom develop PCS (depending on differences in diagnostic classification). Since concussion is not an age-relative deterioration process like neurodegenerative diseases, ongoing or booster treatments would not be necessary. Low-dose ionizing radiation treatment would be a limited treatment protocol for concussion, but could prove to expedite the recovery process, again, particularly for PCS patients.

**LDIR Mechanism of Action for Brain Disorders/Concussion**

As discussed, the common denominator between neurodegenerative disorders and C/PCS is oxidative stress and neuroinflammation. Low-dose ionizing radiation is thought to induce a switching in the central nervous system from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype.

Indeed, low-dose radiation exposures induce an upregulation in the innate adaptive protection systems (APS). As illustrated by Cuttler, when LDIR exposures are performed in a repeated fashion, a continual upregulation induces health enhancement (Figure 1). A burst of LDIR damages the tissues of the patient and causes reactive oxygen species (ROS). The body’s APS subsequently ‘over-repairs’ the damage caused; that is, it repairs the induced radiation damage as well as other endogenous damage that was pre-existing (e.g. neurodegenerative/PCS oxidative stress and neuroinflammation). This results in an enhanced level of...
oxidative homeostasis or an improved level of cognitive functioning.

**Conclusion**

The application of LDIR is a promising, untapped treatment for PCS. The risks are non-existent as the radiation doses are in the range that have been shown to enhance health in previously and recently documented human studies. It is expected that LDIR treatment for PCS will mimic that seen recently in the LDIR treatment of patients suffering from neurodegenerative diseases that have similar oxidative stress loading such as AD.13

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Paul A. Oakley  https://orcid.org/0000-0002-3117-7330

**References**

1. Harmon KG, Clugston JR, Dec K, et al. American medical society for sports medicine position statement on concussion in sport. Clin J Sport Med. 2019;29(2):87-100.
2. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017;51(11):838-847.
3. Hadanny A, Efrati S. Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions. Expert Rev Neurother. 2016;16(8):875-887.
4. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery. 2014;75(4):S24-S33.
5. Sies H. Oxidative stress: Introductory remarks. In: Sies H, eds. Oxidative stress. London: Academic Press; 1985:1-8.
6. Sies H, Jones D. Oxidative stress. In: Fink G, ed. Encyclopedia of stress. 2nd ed. Amsterdam: Elsevier; 2007:45-48.
7. Sies H. Oxidative eustress and oxidative distress: Introductory remarks. In: Sies H, ed. Oxidative stress. Eustress and distress. Elsevier Inc.; 2020:3-12.
8. Doss M. Low dose radiation adaptive protection to control neurodegenerative diseases. Dose-response. 2013;12(2):277-287.
9. Cuttler JM. Application of low doses of ionizing radiation in medical therapies. Dose-response. 2020;18(1):1559325819895739.
10. Cuttler JM, Moore ER, Hosfeld VD, Nadolski DL. Treatment of Alzheimer disease with CT scans: A case report. Dose-response. 2016;14(2):1559325816640073.
11. Cuttler JM, Moore ER, Hosfeld VD, Nadolski DL. Update on a patient with Alzheimer disease treated with CT scans. Dose-response. 2017;15(1):1559325817693167.
12. Cuttler JM, Moore ER, Hosfeld VD, Nadolski DL. Second update on a patient with Alzheimer disease treated by CT scans. Dose-response. 2018;16(1):1559325818756461.
13. Cuttler JM, Abdellah E, Goldberg Y, et al. Low doses of ionizing radiation as a treatment for Alzheimer’s disease: A pilot study. J Alzheim Dis. 2021;80(3):1119-1128.
14. Reddy CC, Collins M, Lovell M, Kontos AP. Efficacy of amantadine treatment on symptoms and neurocognitive performance among adolescents following sports-related concussion. J Head Trauma Rehabil. 2013;28(4):260-265.
15. Voormolen DC, Cnossen MC, Polinder S, von Steinbuechel N, Vos PE, Haagsma JA. Divergent classification methods of post-concussion syndrome after mild traumatic brain injury: Prevalence rates, risk factors, and functional outcome. J Neurotrauma. 2018;35(11):1233-1241.
16. Calabrese E, Dhawan G, Kapoor R, Kozumbo W. Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose. Hum Exp Toxicol. 2019;38(8):888-898.
17. Feinendegen LE, Pollycove M, Neumann RD. Low-dose cancer risk modeling must recognize up-regulation of protection. Dose-response. 2009;8(2):227-252.
18. Pollycove M. Radiobiological basis of low-dose irradiation in prevention and therapy of cancer. Dose-response. 2006;5(1):26-38.
19. Pollycove M, Feinendegen LE. Radiation-induced versus endogenous DNA damage: possible effect of inducible protective responses in mitigating endogenous damage. Hum Exp Toxicol. 2003;22(6):290-306.
20. Löbrich M, Rief’N, Kühne M, et al. In vivo formation and repair of DNA double-strand breaks after computed tomography examinations. Proc Natl Acad Sci USA. 2005;102:8984-8989.