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Oxidative/Nitroxidative Stress and Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a multifactorial, central nervous system, immune-mediated disease characterized by inflammation, demyelination, and neurodegeneration. Evidence suggests a steady rise in MS prevalence over the past five decades in the United States and around the world. Even with increased understanding of immunology, the specific etiological trigger of MS remains unknown. Evidence suggests that oxidative/nitroxidative stress is an important contributor to MS etiology, progression, and clinical symptoms. A multifaceted treatment approach aimed at counteracting oxidative/nitroxidative stress including MS disease–modifying medications, Mediterranean style diet, stress-relieving activities, smoking and alcohol cessation, exercise, and peer support programs is the best way to treat the disease.

Keywords Multiple sclerosis · Oxidative/nitroxidative stress · Axonal damage · Neuroinflammation · Demyelinating diseases · Immune dysfunction · Pain · Peer support programs · Antioxidants · Mitochondrial dysfunction · Cognitive and psychiatric disorders · Sleep disturbance · Neurodegeneration · Mediterranean diet · Ketogenic diet · Gut microbiota

Introduction

Multiple sclerosis (MS) is a multifactorial, central nervous system (CNS), immune-mediated disease that is characterized by demyelination, neurodegeneration, inflammation, and gliosis (Calabresi 2004; Hayes and Donald Acheson 2008; Weinshenker 1996). Evidence suggests a steady rise in MS prevalence around the world in the past five decades (Wallin et al. 2019). Indeed, over 700,000 and an estimated 900,000 adults were affected by MS in 2010 and 2017, respectively, in the United States (US) (Wallin et al. 2019).

MS is the leading progressive non-traumatic neurological disease of young adults (Zwibel and Smrtka 2011), and it reduces the sufferer's quality of life (Zwibel and Smrtka 2011). It is an expensive chronic disease to treat and manage. Indeed, using the data from 1999 to 2008, the total all-cause healthcare direct and indirect costs for MS ranged from just under $10,000 to over $50,000 per patient per year with prescription medications accounting for the majority of direct costs (Adelman et al. 2013).

Clinically, MS normally presents in multiple subtypes including relapsing-remitting MS (RRMS), the most common subtype noted by episodes of neurological dysfunction and subsequent remission, secondary progressive MS (SPMS), primary progressive MS (PPMS) which affects about 10–15% of MS patients, and progressive relapsing MS (PRMS) (Ghasemi et al. 2017). PPMS patients have no female predominance like RRMS and unlike RRMS are older at disease onset and have a faster accumulation of disability (Antel et al. 2012). PPMS and RRMS have been found to display identical lesion morphology under ultrahigh field magnetic resonance imaging (MRI), indicating a strong similarity in many respects despite differences in disease course and clinical features (Kuchling et al. 2014). Most RRMS patients (about 65%) will over time develop SPMS which is typically considered phase 2 of the disease (Ghasemi et al. 2017). PRMS is the least common MS subtype and occurs in about 5% of patients (Ghasemi et al. 2017). Despite the differences observed in MS phenotypes, such differences are mostly quantitative (Antel et al. 2012). MS phenotypes are believed to be part of a disease spectrum, and differences are influenced by individual genetics and environmental factors (Antel et al. 2012).

The specific elements that provoke MS pathogenesis remain unknown. This makes it hard to effectively treat the disease. The objective of this narrative review is to highlight the key role of oxidative/nitroxidative stress in MS pathogenesis,

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pathophysiology, and clinical symptoms. This could help improve our understanding of the disease and enhance strategies of treatment.

Oxidative/Nitroxidative Stress in MS.

Excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (such as superoxide, nitric oxide, and peroxynitrite), mitochondrial dysfunction, and poor or suboptimal antioxidant defense system lead to oxidative stress (OS) or nitroxidative stress (NOS), and these play a critical role in MS pathology (Haider 2015). Indeed, OS/NOS plays a critical role in the early phase of MS (Siotto et al. 2019) and on both the inflammatory and neurodegenerative components of the disease (Adamczyk and Adamczyk-Sowa 2016; Miller et al. 2019). Elevated levels of peroxynitrite formation in the CNS are implicated in MS pathogenesis (Cross et al. 1998), and research has found increased levels of OS markers (cholesteryl ester hydroperoxides) in plasma isolated from MS patients and impaired antioxidant mechanisms (Ferretti et al. 2005). The antioxidant, melatonin, has been shown to attenuate OS and increase the activity of antioxidative enzymes, superoxide dismutase, and glutathione peroxide in SPMS patients' red blood cells (Miller et al. 2013) as well as alleviate MS symptoms (Adamczyk-Sowa et al. 2014; Álvarez-Sánchez et al. 2017).

Oxidative/Nitroxidative Stress in MS Pathophysiology and Clinical Symptoms

Mitochondrial Dysfunction

Mitochondrial dysfunction plays a critical role in MS (Tobore 2019). Indeed, mitochondrial abnormalities including energy failure, DNA defects, abnormal gene expression, defective enzyme activities, and impaired DNA repair activity are involved in the development and progression of demyelination and neurodegeneration in MS (Mao and Reddy 2010). Mitochondrial DNA SNP, nt13708 G/A, is associated with a significantly increased risk of MS (Yu et al. 2008). Variants of the mitochondrial ATP6 and ND2 genes have been found to be associated with both MS and systemic lupus erythematosus (Vyshkina et al. 2008). Mitochondrial dysfunction is implicated as playing a major role in axonal degeneration in MS (Dutta et al. 2006).

OS plays a critical role in mitochondrial dysfunction in MS (Haider 2015). Indeed, OS triggers mitochondrial injury in MS patients and energy failure in the CNS of individuals susceptible to MS (Haider 2015). In an EAE model, OS mediated mitochondrial dysfunction induced by protein inactivation was critical in initiating the molecular events that resulted in apoptosis and neurodegeneration (Qi et al. 2006). Oxidative damage affects mitochondrial DNA, and oxidative damage to mitochondrial macromolecules resulted in a reduction in the activity of mitochondrial energy metabolism and enzyme complexes in chronic MS active lesions (Lu et al. 2000). Impaired permeability transition pore opening mediated by ROS and calcium dyshomeostasis play a key role in MS mitochondrial dysfunction and neurodegeneration (Su et al. 2013). Research on an EAE model found that focal intra-axonal mitochondrial injury precedes alterations in axon morphology and ROS and RNS provoked mitochondrial injury initiating focal axonal degeneration (Nikić et al. 2011). Indeed, attenuation of ROS and RNS reversed mitochondrial injury and axonal degeneration (Nikić et al. 2011).

Demyelination, Neurodegeneration, and Axonal Damage in MS.

OS plays a major role in MS demyelination and neurodegeneration (Lassmann and van Horssen 2016) and mediates MS neurodegeneration initiated by microglial activation (Gonsette 2008). In MS brain, OS triggers demyelination and neurodegeneration through oxidation of proteins, lipids, and DNA and by inducing mitochondrial injury, resulting in energy failure and further generation of ROS (Lassmann and van Horssen 2016). OS damages all types of glial cells and neurons, although neurons and oligodendrocytes are most sensitive to its effect (Lassmann and van Horssen 2016). Indeed, oligodendrocytes are highly susceptible to OS/NOS than astrocytes and microglia, due to their weak antioxidant defense and other risk factors resulting in selective oligodendrocyte death, and demyelination (Dutta et al. 2006). OS damage of oligodendrocytes and neurons is quite significant and is associated with MS active demyelination and axonal injury (Haider et al. 2011). Indeed, inhibiting peroxynitrite formation may protect oligodendrocyte against OS-induced toxicity (Li et al. 2011).

Diet

Diet and nutritional status play a role in the etiopathogenesis of MS (Armon-Omer et al. 2019; Jahromi et al. 2012). Antioxidant-rich food has been found to reduce the risks of MS while prooxidant food increases it. Indeed, MS is higher in people who consume a diet low in whole grains and high in animal fats, potato, sugars, meat products, and hydrogenated fats (Jahromi et al. 2012). Serum total antioxidant capacity is significantly lower in the MS patients and associated with disease severity (Armon-Omer et al. 2019). Antioxidant-rich diets from plants including fruits, vegetables, and plant protein, dietary fiber, vitamin C, cereal fiber, thiamin, calcium, riboflavin, and potassium significantly reduce the risk of MS (Ghadirian et al. 1998). Vitamin A, E, and B1 deficiencies are

involved in MS pathophysiology, and vitamin B9, B12, A, B1, and B3 may improve MS relapses, clinical symptoms, neurodegeneration, and inflammation (Khosravi-Largani et al. 2018). Also, potent antioxidants and immunomodulators such as vitamin D and B12 have been implicated in MS pathogenesis and severity (Bagur et al. 2017; Tobore 2020a). Indeed, elevated homocysteine level is believed to contribute to MS pathogenesis (Dardiotis et al. 2017) and vitamin B12 is known to attenuate homocysteine induced OS (van de Lagemaat et al. 2019). Supplementation of antioxidant-rich omega-3 and fish oils alleviates MS relapsing rate, the activity of pro-inflammatory agents, and improves MS patients' quality of life (AlAmmar et al. 2019).

Ketogenic diet (KD) attenuates OS by modulating uncoupling proteins and elevating levels of antioxidant enzymes (e.g., catalase and glutathione) via inhibiting histone deacetylases and activating the Nrf2 pathway (Storoni and Plant 2015). It also improves mitochondrial function and has been suggested to be potentially useful in attenuating neurodegeneration in MS (Storoni and Plant 2015). A pilot study found that it alleviates fatigue and depression, promotes weight loss, and attenuates serologic pro-inflammatory adipokines in patients with RRMS (Brenton et al. 2019). A murine model of experimental autoimmune encephalomyelitis (EAE) found that KD improves cognitive ability and motor function and attenuates pro-inflammatory agents and OS (Kim et al. 2012).

Also, gut microbial dysbiosis is implicated in MS pathology (Cekanaviciute et al. 2017; Chen et al. 2016; Ochoa-Reparaz et al. 2017). Indeed, MS patients have a special or different gut microbiota (Chen et al. 2016; Schepici et al. 2019). Evidence suggests that *Parabacteroides distasonis*, which promoted anti-inflammatory IL-10 cells expressing IL-10+FoxP3+ Tregs in mice and human CD4+CD25+ T cells, were reduced in MS patients and *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*, which provoked increased proinflammatory activity in monocolonized mice and human peripheral blood mononuclear cells, were elevated in MS patients (Cekanaviciute et al. 2017). MS patients have also been found to have elevated gut microbial populations of *Streptococcus*, *Flavobacterium*, *Dorea*, *Pedobacteria*, *Mycoplana*, *Pseudomonas*, *Eggerthella*, and *Blautia* and reduced microbial populations of *Prevotella*, *Coprobacillus*, *Bacteroides*, *Sutterella*, *Adlercreutzia*, *Lactobacillus*, *and Faecalibacterium* (Schepici et al. 2019). Transfer of microbiota from MS patients into germ-free mice led to heightened severity of symptoms of EAE and reduced quantity of anti-inflammatory IL-10+ Tregs (Cekanaviciute et al. 2017). Restoring the microbial population in patients with RRMS attenuated inflammation and reactivated the immune system (Schepici et al. 2019).

Importantly, diet has a profound effect on the composition of the gut microbiome (Schepici et al. 2019; Singh et al. 2017). Indeed, diet modulates health partly through its effect on gut microbiome (Wu et al. 2011). Mediterranean diet is an antioxidant-rich food, and adherence reduces the risk of developing MS (Sedaghat et al. 2016). In addition, Mediterranean diet modulates gut microbiome and adherence is associated with increased levels of certain bacteria taxa including fecal *SCFAs*, *Prevotella*, other *Firmicutes*, *Lactobacillus*, and *Bifidobacterium* and decreases in *Clostridium* (De Filippis et al. 2016; Singh et al. 2017).

Also, diet plays a role in obesity and a high BMI and obesity are associated with increased risks of MS (Ghadirian et al. 1998; Langer-Gould et al. 2013; Mokry et al. 2016). Evidence suggests that OS is a cause, mediator, and consequence of obesity (Tobore 2020b) and OS has been suggested to be the underlying mechanism that links obesity to MS (Tobore 2020a).

Psychiatric Disturbance and Cognitive Dysfunction

Neuropsychiatric symptoms are prevalent in MS patient population (Murphy et al. 2017b; Skokou et al. 2012). Both biological and psychosocial factors play a role in neuropsychiatric symptoms in MS, and risk factors include female sex, family history of major depression, age (less than 35 years), and stress (Skokou et al. 2012). Psychiatric disorders particularly depression are strongly associated with reduced quality of life for MS patients (Amato et al. 2001; Biernacki et al. 2019; Fruewald et al. 2001).

Increased inflammation and OS/NOS play a critical causative role in the pathophysiology of MS and major depression (Morris et al. 2018a). Indeed, significant correlation between elevated OS/NOS and the initiation of MS relapses and the number of MS relapses as well as correlation between OS/NOS levels and severity of major depression indicate an underlying causative role of OS/NOS in both diseases (Morris et al. 2018a). OS plays a critical role in the etiology and pathophysiology of psychiatric disorders (Hassan et al. 2016; Moniczewski et al. 2015; Ng et al. 2008; Salim 2014; Smaga et al. 2015; Tsaluchidu et al. 2008) and contributes to depression in MS (Katarina et al. 2018). Coenzyme Q10 (CoQ10) supplementation in RRMS patients treated with interferon-β1a 44 μg is associated with attenuating OS and inflammation and improving depressive symptoms (Moccia et al. 2019).

Also, cognitive impairment, particularly impairment in processing speed, executive functions, attention, visuospatial perception, and episodic memory, is prevalent and considered a core feature of MS pathology (Di Filippo et al. 2018; Rao 1995). Indeed, about 45 to 65% of MS sufferers are affected by cognitive problems at some time in the disease course (Rao 1995). In MS patients, N-acetyl-cysteine has been found to positively modulate cerebral glucose metabolism, which is associated with improvements in cognition and attention

(Monti et al. 2020). Reduced potent CNS antioxidant, glutathione, has been found in different MS types and is associated with cognitive impairment severity (processing speed and learning and memory deficits) (Hughes 2014). Similarly, reduced glutathione is associated with a decline in executive function with aging in healthy adults (Hajjar et al. 2018). In schizophrenia, OS-induced prefrontal oligodendrocyte precursor cell dysfunctioning is theorized to be the causal factor that drives the etiology of cognitive symptoms (Maas et al. 2017). In an experimental model of MS, vitamin D3 using its antioxidant properties attenuated OS and improved cognitive deficits (spatial learning and memory deficits) (Tarbali and Khezri 2016).

Neuroinflammation

MS is strongly associated with neuroinflammation (Rosenberg 2002). Inflammation promotes OS and vice versa, suggesting a self-perpetuating vicious cycle (Ortiz et al. 2013). Levels of ROS and RNS can dramatically increase under inflammation conditions, overcoming the antioxidant defenses within lesions, and may result in damage in proteins, cell mitochondria, nucleic acids, and lipids, and cell death (Park et al. 2010). Indeed, oxidative damage to mitochondrial macromolecules develops concomitantly with inflammation in the CNS and plays a role in the reduction of mitochondrial enzyme complex activity and energy metabolism in chronic active lesions of MS, potentially resulting in cell death or degeneration (Lu et al. 2000). OS is implicated in the initiation of inflammation in the acute phase of MS (Adamczyk et al. 2017), and in RRMS patients, melatonin has been shown to promote an insulated cytokine microenvironment and mitigate inflammatory response by decreasing Th1 and Th22 responses in patients (Álvarez-Sánchez et al. 2017).

Inflammation-induced OS in activated microglia and macrophages plays an important role in demyelination and OS-induced tissue injury that results in MS pathogenesis (Fischer et al. 2012; Ortiz et al. 2013), and OS is implicated in inflammation-induced MS demyelination and neurodegeneration (Wang et al. 2014). ROS may damage myelin sheaths and promote macrophage activity on myelin sheaths (Smith et al. 2006). ROS and NO released during inflammation have been implicated in the damage from OS to DNA in MS lesions and in nearby neurons around these lesions contributing to the development of MS clinical disability (Vladimirova et al. 1998). Macrophages and microglia express myeloperoxidase and promote ROS production during myelin phagocytosis in the white matter, and demyelination in MS has been found to be associated with significantly increased myeloperoxidase activity in homogenates of MS white matter, indicating an intricate relationship between inflammation and OS in contributing to axonal injury within plaques (Gray et al. 2008).

Sleep Disturbances

Sleep disturbance is prevalent in MS (Bøe Lunde et al. 2012), and it is a predictor of poor quality of life (Merlino et al. 2009). Sleep disturbance in MS is strongly associated with depression, anxiety, fatigue, and pain (Vitkova et al. 2016, 2014). Inflammation and OS/NOS play a role in the pathophysiology of poor sleep and circadian abnormalities in neuropsychiatric disorders including MS and sleep disturbance promotes further inflammation, OS/NOS in a vicious cycle (Morris et al. 2018b). Evidence suggests that MS patients have higher serum levels of total oxidant status and melatonin uses its antioxidant properties to improve poor sleep quality in MS patients (Adamczyk-Sowa et al. 2014). Also, sleep is an important resting state with antioxidant properties, responsible for attenuating OS produced during wakefulness (Teixeira et al. 2019; Villafuerte et al. 2015). Indeed, poor sleep in MS could amplify OS/NOS and worsen disease severity (Tobore 2019).

Pain

Pain is common in MS and accounts for a significant portion (approximately 30%) of all drugs uses to treat MS symptoms (Solaro et al. 2013; Solaro and Messmer Uccelli 2011). MS patients can experience different types of pain simultaneously and at any interval in the disease (Solaro and Messmer Uccelli 2011). Chronic neuropathic pain in MS is one of the most frequent symptoms associated with reduced quality of life (Murphy et al. 2017a).

OS/NOS plays a critical role in different types of pain (Little et al. 2012; Salvemini et al. 2011) including neuropathic pain (Kim et al. 2004; Park et al. 2006; SINISCALCO et al. 2007; Yowtak et al. 2013, 2011). Research indicates that lipoic acid, a potent antioxidant, can improve whole-brain atrophy rate in SPMS patients (Spain et al. 2017), suppress matrix metallopeptidase 9 activity, and disrupt T cell migration into the CNS in MS patients (Yadav et al. 2005) and it has been found in a case study to be effective in the treatment of MS-induced neuropathic pain (Kulaklı 2018). US Government approved medication for MS, dimethyl fumarate, has been found to attenuate nociceptive hypersensitivity triggered by peripheral nerve injury by activating antioxidant response-nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, attenuating neuroinflammation, and mitochondrial OS mechanisms involved in promoting nociceptive hypersensitivity (Li et al. 2020). CoQ10 supplementation in RRMS patients treated with interferon-β1a 44 μg is associated with attenuating OS and inflammation and with clinical improvement in pain symptoms (Moccia et al. 2019).

Conclusions and Clinical Recommendations

MS is a complex, multifactorial disease, and OS/NOS play a critical role in the disease pathogenesis and progression. Aside from the factors described above, OS/NOS has been implicated as the underlying mechanism in many factors involved in MS including neurotransmitters alteration, Epstein-Barr Virus (EBV), human herpes 6 (HHV6), smoking, mycoplasma pneumonia, lower insulin-like growth factor-1 (IGF-I), lower growth hormone (GH), MS relapse and disability, visual impairment, thyroid dysfunction, sex hormones, and altered hypothalamic pituitary adrenal (HPA) axis (Tobore 2020b; Tobore 2019). Armed with the understanding of the critical role of OS/NOS in MS, an integrated or heterogeneous approach to attenuate OS/NOS is likely to confer the best therapeutic benefit. This includes sleep quality improvement; exercise; disease-modifying drugs; stress-relieving activities including yoga, meditation, and social or peer support programs; smoking and alcohol cessation; and antioxidant-rich diet.

Regular exercise boosts endogenous antioxidant defense systems and is linked with improvement in fatigue and quality of life of MS patients (Motl and Gosney 2008; Pilutti et al. 2013; White and Castellano 2008). As adjunct therapy, stress-relieving activities including yoga and meditation should be recommended as they attenuate OS (Tobore 2020a), reduce fatigue (Shohani et al. 2020) and pain, and improve quality of life in MS patients (Tavee et al. 2011). More MS peer support programs should be created and expanded, and patients should be encouraged to participate as it may help improve quality of life and MS-related psychological functions including depression, anxiety, and stress (Ng et al. 2013). Melatonin uses its antioxidant properties to improve sleep and depression in MS patients (Adamczyk-Sowa et al. 2014) and should be recommended for MS patients with reported sleep-related problems.

Pro-oxidant foods (Tobore 2020a) should be avoided, and adherence to antioxidant-rich diet particularly the Mediterranean diet, which decreases OS (Tobore 2020b), reduces MS risk (Sedaghat et al. 2016), and improves the quality of life and severity of the disease (Katz Sand et al. 2019), is strongly recommended. Supplementation of antioxidant-rich omega-3 and fish oils should be encouraged as it has been found to reduce MS relapsing rate, pro-inflammatory agents, and improve MS patient's quality of life (AlAmmar et al. 2019). Antioxidant supplementation including vitamins A, E, B1, B9, B12, and B3 should be recommended in cases of deficiency as this may improve MS relapses, clinical symptoms, neurodegeneration, and inflammation (Khosravi-Largani et al. 2018). CoQ10 supplementation (500 mg/day) is recommended to reduce MS-related fatigue and depression (Sanoobar et al. 2016). Importantly, caution must be applied in the use of supplements and preference should be given to antioxidant-rich diet because excessive antioxidant supplementation could promote OS. Indeed, excessive vitamin C can aggravate MS symptoms because of the promotion of Fenton reaction (Khosravi-Largani et al. 2018).

In conclusion, OS/NOS plays a critical role in MS etiopathogenesis, and progression and treatment strategies should employ an integrated approach aimed at reducing OS/NOS. However, MS remains a complex disease that involves other factors including genetics that cannot be accounted for by OS/NOS. So, more and continued research is necessary to better and more effective treatment of the disease.

Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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