Oxidative Stress in Multiple Sclerosis Disease (Review Article)

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Abstract

Background: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, in which the myelin sheaths got injured. The prevalence of MS is on grow, as well as, it affects the young ages. Females are most common to have MS compared to males. Oxidative stress is the situation of imbalance between oxidants (free radicals and reactive oxygen species (ROS)) and antioxidants in a living system, in which either the oxidants are elevated or antioxidants are reduced, or sometimes both. ROS and oxidative stress have been implicated in the progression of many degenerative diseases, which is important in cracking the unrevealed mysteries of MS. In this review article, some of the proposed mechanisms that link oxidative stress with MS disease would be described.

Keywords: Oxidative stress, ROS, multiple sclerosis, antioxidants

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Introduction

Multiple sclerosis (MS) is a neurological disease that causes a wide range of symptoms that impair movement and perception [1]. It is an inflammatory disease of the central nervous system (CNS) that causes an injury in the myelin sheaths Figure (1), leading to demyelination and thus, consequently, a series of neurologically dysfunction known as relapses [2]. Once it causes a relapses, it's called relapses-remitting multiple sclerosis (RRMS) and it is the most common subtype of MS. Another subtype is secondary progressive multiple sclerosis (SPMS) and is, often, follows RRMS when the patient is no

longer has exacerbations and has a continuous accumulation of disability with time. The primary progressive multiple sclerosis subtype (PPMS) is recognized by disease progression without remarkable exacerbations.

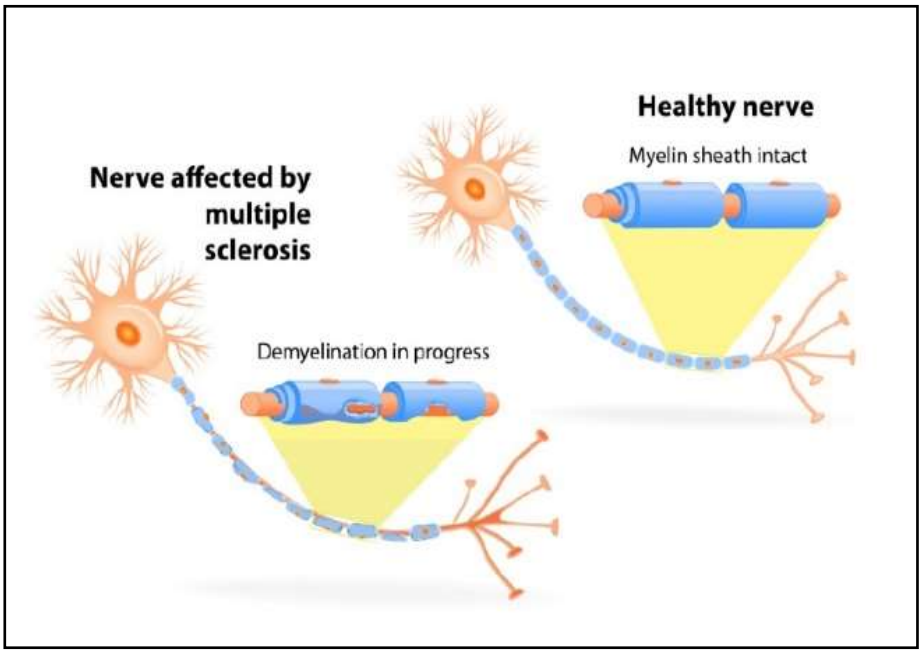

Figure (1): Myelin sheaths in normal and MS nerves [4]

Progressive relapsing multiple sclerosis (PRMS) is the rarest and most progressive subtype of MS [3], see Figure (2). Multiple sclerosis is considered as the most epidemic of demyelinating diseases, as well as, it is the most common of the CNS disorders that causes a permanent disability in young adults [5, 6]. World health organization (WHO) has estimated that over 2 million people are suffering from MS in the world [7]. The rate of the prevalence in the world is about 100 to 150 per 100000 populations, presented in the ages between 20 and 40 years with a higher percentage in women than men. It is thought that the prevalence of MS increases as the distance from the equator increases [1]. A study on the epidemic of MS in 2008 have shown an average of low to high prevalence in the Middle East region, this wide variety depends on several factors such as environment and ethnicity [8]. One study has been found on the prevalence of multiple sclerosis in Iraq, 2005, showed that MS is found in a quite noticeable percentage. Also, region distribution shows a variation between cities of Iraq suggests the involvement of environmental factors in the incidence of MS [9]. The rates of growing epidemiology of MS drive the need for investigation on the mechanisms and physiological pathways of the disease to get the better understanding picture, and ultimately better ways for preventing and treatment. In this article, some of the physiological changes of oxidative stress will be demonstrated.

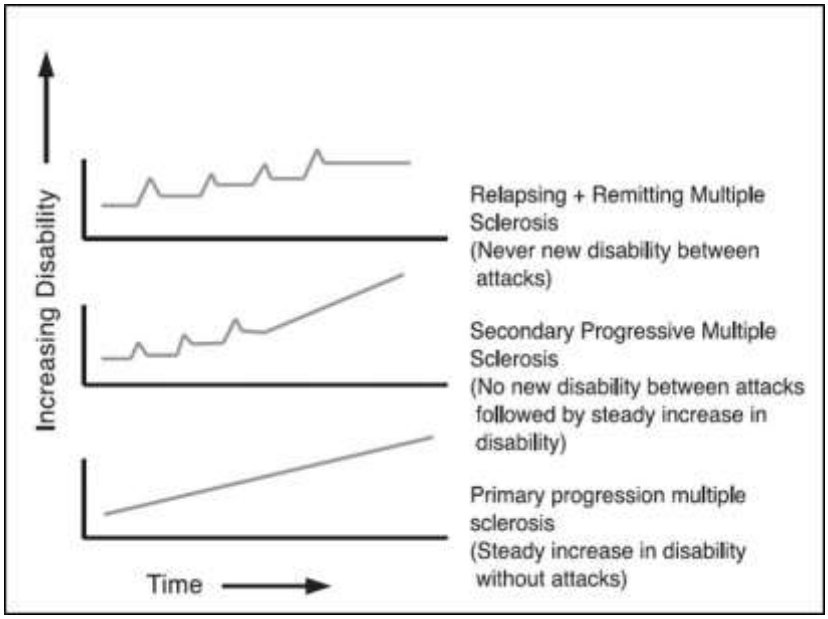

Figure (2): Types of MS [10]

Clinical Features

The signs and symptoms of multiple sclerosis are wide diverse as it can influence any part within the central nervous system including the brain, spiral cord, brainstem, and optic nervous. Even though the main event involves demyelination, there is inflammation, edema, axonal loss, and gliosis, all of which are responsible for the lesion symptomatology. The most common clinical signs and symptoms are visual loss from optic neuritis, alteration, or loss of sensation due to envelopment of spinothalamic or posterior column fibers, abnormalities of cranial nerve function secondary to brainstem lesions, tremors, and incoordination of gait or limbs basically related to cerebellar or spinocerebellar fiber participation, and limb weakness and spasticity related to disruption of corticospinal tracts. Also, urinary bladder, bowel, and sexual dysfunction occur in over 65% of patients. Depression, fatigue, heat intolerance, and cognitive disturbances are common in MS patients [11,12], see Figure (3).

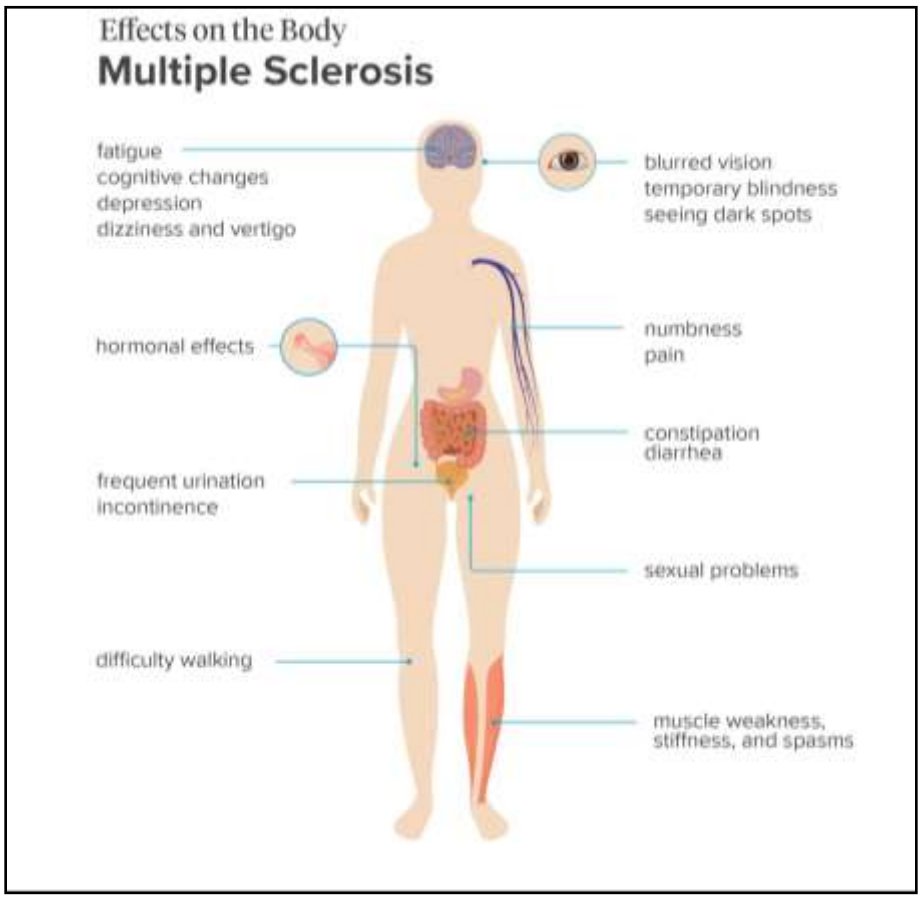

Figure (3): Common Symptoms of Multiple Sclerosis. Image credit: Stephen Kelly, 2019

Oxidative stress

Free radicals and reactive oxygen species (ROS) are highly oxidant materials within the human body [13]. ROS, at normal levels, perform a redox signaling function [14, 15]. However, when the level of ROS elevated the harmful effects start to appear within the cells including; lipid peroxidation, proteins specific site oxidation, and DNA alternations, which collectively result in sabotaging the cell and developing pathological conditions [13]. For maintaining the harmless level of ROS, the body contains a defense system called antioxidants [16, 17]. The antioxidant materials are defined as "any substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of" that substrate" [18].

Oxidative Stress and MS

Abbas *et al*. (2021) have reported a significant elevation of monoamine oxidase (MAO) activity in sera of MS patients [19]. MAO is known to release the ROS, hydrogen peroxide, as a side product for the oxidation of dopamine [20].

Melnikov *et al.* (2016), have found that serum level of dopamine is reduced significantly in MS patients who under relapses compared to healthy people [21].

Dopamine reduction could be explained by the work of Abbas *et al*. (2021), in which the

over activity of MAO results in the reduction of dopamine, which essentially becomes a source of ROS in MS disease. In MS disease, the need for extra adenosine triphosphate (ATP) is needed in the chronically demyelinated axon which can push the mitochondria to exceed its limit, and since the mitochondria are a major source of ROS at normal conditions, then the mitochondrial overloading would lead to elevate the mitochondrial ROS percentage [22].

Both chronic and acute active MS lesions have consistently been shown to contain Nitrate ions (NO3-). But, the presence of NO3- was not detected in chronic inactive lesions. This indicates that chronic lesions contain oxidative stress in spite of the lack of pathological inflammation. On the other hand, myeloperoxidase has shown to be elevated in microglia of acute MS lesions but not chronic MS lesions [23].

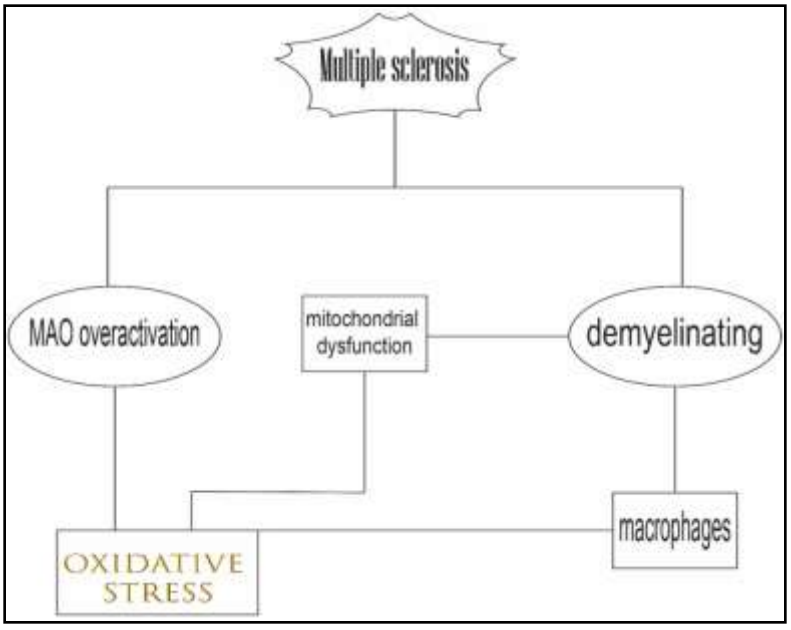

Figure (4): Possible pathways from MS to oxidative stress

Fischer *et al*. (2012), have found that segments of the NADPH oxidase 2 (NOX2), p22phox, and gp91phox, expression is intense at the lesion edge of MS patients. It might result from the microglia density growing and overexpression of these molecules in each cell. To a lesser extent, the macrophages at demyelinated areas also expressed the p22phox and gp91phox [24]. NOX2 is an important source of ROS, in which the enzyme catalyzes the electron reduction of molecular oxygen to superoxide anion which follows a rapid conversion to H_2O_2 [25]. NOX plays a central role during inflammation as a defender through the generation of ROS, during phagocytosis NOX2 produces $O_2^{\bullet -}$ which follows subsequent conversion to H_2O_2 by the action of the enzyme superoxide dismutase (SOD), and used by myeloperoxidase and other peroxidases to produce strong microbicidal chemicals, such as HOCl [26]. The

enhancement expression of p22phox and gp91phox in lesions of MS patients could be a pathway for oxidative stress amplification. In another study established by De Rasmo *et al.* (2020), the Peripheral blood mononuclear cells (PBMCs) of MS patients were isolated and investigated for H_2O_2 concentration. The workers have reported an increase in the production of H2O2 of PBMCs in MS patients and elevated H_2O_2 is associated with dysregulation of optic atrophy 1 (OPA1) [27]. The OPA1 is a protein that regulates the dynamic of mitochondria and controls apoptosis [28]. Živković *et al*. (2016), have reported overexpression of angiotensin-converting enzyme (ACE) and angiotensin type 2 receptor (AT2R) in MS patients (AT2R overexpression was more significant in female subjects, which made the workers suggest that genotype is female-specific factor of risk for MS) [29]. The angiotensin (AT) is a peptide intermediated sequential system that regulates minerals homeostasis in the circulation which includes renin and aldosterone as well [30]. ACE catalyzes the conversion of AT1 peptide to AT2 [31]. The over-activation of AT2R by AT2 has shown to induce the increase of the formation of ROS,[32] and inflammatory cytokines [33]. Park *et al*. (2013), have reported the involvement of AT2R in the oxidative damages in the brain throughout increasing the activity of NOXs enzymes [34].

Conclusions

Multiple sclerosis is a disease of wide symptoms and signs which differ by the difference of lesion location. This would lead to a subsequent complications for the cells, that these lesions could develop oxidative stress. Once oxidative stress arises, cells would be vulnerable to oxidative destruction, hence the antioxidant treatment of MS patients should take a major part of disease therapy.

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Ethical clearance: The study was approved by the academic ethical committee, Mustansiriyah University.

Conflict of interest: Nill

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