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Review Article

Correlation of Neurodegenerative Diseases with Oxidative Stress and Nutrition

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A B S T R A C T

Technology or ease of doing work might be the greatest boon to this era, but it is still a bane for our health and life. Sitting in front of laptops or computers for several hours (sedentary lifestyle), using cell phones, watching television, skipping meals or eating junk/ fast food, lack of physical activities, stress, etc. increase the risk of many lifestyle diseases. All the above-mentioned habits increase the count of free radicals in our body and due to a lack of endogenous and exogenous antioxidants, the body cannot combat oxidative stress. Thus, the chances of occurrence of several chronic diseases like cancer, atherosclerosis, cardiovascular diseases, neurodegenerative diseases, rheumatoid arthritis, chronic inflammations, etc. increase. There are several factors contributing to neurodegeneration of the brain and neurons, in which oxidative stress plays an important role. This review article is the compilation of research done by several other researchers on Neurodegenerative Diseases (NDDs) and is primarily focused on better understanding a few basic questions like the correlation of oxidative stress and nutrition to neurodegeneration, NDDs, their different types, symptoms and causes followed by establishing a relation between oxidative stress and nutrition with the help of several studies carried out by researchers in this context.

Keywords: Antioxidants, Atherosclerosis, Cardiovascular Disease, Chronic, Intervention, Oxidative Stress, Sedentary

Introduction

'Neurodegeneration' is a term formed by the combination of two words - 'neuro', signifying nerve cell and 'degeneration', signifying progressive damage.[1] Neurodegenerative diseases (NDDs) lead to the loss of nerve cells, causing either sensory dysfunction (dementia) or functional loss (ataxia).[2] NDDs cause progressive damage in neural cells and neuronal loss, thereby compromising motor or cognitive functions.[3] The causes of many NDDs are still a mystery and even though researchers found about a few of them, their mechanisms of action are still not properly known. Some of these causes are increased levels of free radicals and decreased levels of endogenous antioxidants i.e. oxidative stress (OS), protein misfolding, protein degradation, membrane damage, mitochondrial dysfunctioning, excitotoxicity, high levels of lipids in the brain, DNA damage, genetic mutations, apoptosis, inflammation, etc.[4] General symptoms of neurodegeneration are memory loss, frequent headaches, impairment in daily physical and functional activities of life, cognitive decline, difficulty in balance, speech loss,

inattentiveness or apathy, anxiety, agitation, behavioural and mood issues (depression or other psychological problems), tremors (involuntary shaking of legs, hands, head, etc.), and in severe cases, fits and body paralysis have also been observed.[5]

Common NDDs

Some of the NDDs commonly occurring worldwide are:

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive, chronic and incurable condition, causing cells of the brain to degenerate (waste away) and die. It is the most common reason for the occurrences of dementia - a continuous decline in behavioural, thinking and social skills which hinder the ability of an individual to function independently. The key symptom of AD is memory loss which is an early sign of this disease. At first, the individual usually has a problem in remembering recent conversations or events but with the disease progression, it worsens along with the development of other symptoms like difficulty in multitasking, concentration, making judgments and decisions, change in personality and behaviour and so on.[6] In a study, it was stated that the main causes of AD are deposition of protein aggregates, neurofibrillary tangles or intracellular tau (τ), extracellular amyloid plaques (Aβ) and synaptic connections being lost in several regions of the brain. The peptides of neurotoxic Aβ oligomer get accumulated which along with τ proteins, effectuate neurodegeneration, hence, leading to impaired synaptic connection, neuroinflammation, neuronal loss, neurotransmitter imbalance, dendritic alterations and many more complications.[7]

Parkinson's Disease

Parkinson's disease (PD) is the second leading NDD after AD in the elder population which causes stiffness, shaking and difficulty in coordination, balance, and walking. It occurs when nerve cells present in an area of the brain known as substantia nigra, responsible for controlling movement or locomotion die or any impairment occurs in them.[8] The nerve cells present in this region, responsible for making the chemical dopamine, start to die. The emergence of insoluble inclusions in nerve cells called Lewy bodies comprising generally of synuclein is a major indicator of PD. Regulation and control of voluntary actions are the major functions of neurons, thus their deterioration can cause impaired motor functions, postural instability, bradykinesia, rigidity, and tremors, when stationary.[7]

Huntington's Disease

It is a genetic disorder which causes the neurons of the brain to breakdown progressively, thus proving to be fatal for an individual.[9] It is an autosomal dominant disorder that occurs due to hereditary repeat extention of CAG trinucleotide in the huntingtin gene on chromosome no. 4. This results in mutation in the huntingtin protein, which leads to the production of an adversely prolonged chain of repeating glutamine units. Huntington's disease is marked by psychiatric, cognitive, and motor malfunctioning. Mutant huntingtin at the cellular level leads to neuronal dysfunction and death via various processes, involving direct toxicity of mutant protein, transcription and mitochondrial function, and disrupted proteostasis. Changes in the striatum have been seen with involvement of the cortex at early macroscopic levels with disease progression. Currently, there are no disease-modifying treatments.[7]

Multiple Sclerosis

Multiple sclerosis (MS) is a disease of potential disability of the brain and spinal cord (Central Nervous System). It is considered an autoimmune disease as myelin (protective sheath), covering nerve fibres, is attacked by the immune system causing communication malfunctioning between the brain and the rest of the body. Thus, it can cause deterioration or permanent damage to nerves. Various signs or symptoms depend on the degree of nerve damage and the types of nerves affected. Some patients when in severe condition cannot walk independently or at all, while others may experience long periods of remission without showing any new symptoms. The accurate causes of MS are still unknown. Treatments of MS can help in speedy recovery from attacks, manage symptoms, and can modify the course of the disease but there is no proper cure.[10]

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), the most common motor neuron disease, is also called Lou Gehrig's disease. ALS is a fatal disorder, marked by progressive degeneration of upper and lower motor nerve cells in the cortex, brain stem, and spinal cord. Out of total cases, approximately 90% are sporadic (SALS) i.e. with no clear genetic relations while 10% are found to be familial (FALS) cases, a result of the mutation in gene codes for superoxide dismutase. Extended hexanucleotide repeat (GGGGCC) is identified as the most common genetic mutation found in the non-coding area of C9Orf72 gene on chromosome 9p21. Mitochondrial dysfunctioning, excitotoxicity, oxidative stress, neuronal inflammation, and endoplasmic reticulum stress are the various factors reported in the pathogenicity of ALS. OS-mediated lipid peroxidation, protein injury and oxidation of RNA and DNA have been seen in patients. Moreover, OS biomarkers are exclusively found in SALS patients' urine, cerebrospinal fluid, blood, and individual tissues.[7] Signs of ALS in earlier stages are generally unnoticed by individuals but symptoms such as difficulty in carrying out daily activities like walking; weakness, cramping, twitching in feet, hands, legs and ankles or tongue; increased clumsiness; uncontrolled outbursts of laughing or crying; cognitive

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changes; fatigue; pain and so on can be observed with time.[11]

Oxidative Stress

Oxidative stress (OS) is an imbalance between the accumulation and production of reactive oxygen species (ROS) in the body and the capability of their detoxification by the biological system. ROS plays important physiological roles (cell signalling) and is generally produced as a by-product of the metabolism of oxygen. In spite of this, xenobiotics and environmental stressors (UV, ionising radiations, pollutants and heavy metals) have a large contribution in increasing ROS production, thereby creating an imbalance causing cellular and tissue damage (oxidative stress).[12] Hydrogen peroxide (H_2O_2), superoxide radicals (O_2^-), singlet oxygen ($^1O_2$), and hydroxyl radicals (OH^-) are generally considered ROS, produced as by-products of metabolism. Apoptosis, protein phosphorylation, immunity, transcriptional factors and differentiation etc, all depend on the production of ROS.

Therefore, their presence is required at low levels for normal functioning of the body. An increase in ROS levels leads to a harmful impact on important cellular structures like proteins, nucleic acids, and lipids. Thus, they are responsible for the inception of several chronic diseases like CVDs, cancer, diabetes, atherosclerosis, and various metabolic disorders. Based on enzymatic components, cells deploy an antioxidant defence system such as superoxide dismutase (SOD), glutathione peroxidase (GP_x), and catalase (CAT), for protection from ROS-induced cellular damage.[12]

Correlation of Oxidative Stress with NDDs

Niedzielska E et al. stated that OS plays a major role in the pathogenesis of neurodegenerative disorders.[13] It was found in clinical and preclinical studies that NDDs are marked by lower levels of antioxidant defense biomarkers and higher levels of OS biomarkers in the brain and peripheral tissues. Neuronal cells are hypersensitive to OS due to its anatomical and metabolic functions like:

- A high amount of OS and glucose consumption is required by a large number of glial cells (present in the brain) in order to generate an ATP pool for normal brain functioning
- Redox metals like Fe, Cu, etc. in the brain generate free radicals leading to OS[13]
- The presence of neuronal biochemical composition comprises a pool of unsaturated lipids, it is susceptible to ROS therefore, liable to peroxidation and oxidative modification
- Damaged mitochondria and activated microglia act as a reservoir of ROS. Certain genetic mutations in people make them susceptible to gaining free radicals[14]

Oxidative Stress and Alzheimer's Disease

Singh A et al. stated that OS plays a significant role in AD as ROS have deleterious effects on biomolecules, especially, proteins.[7] Evidence shows that neuronal damage due to oxidative imbalance might play a central role in AD. Indications were found in studies that there is a relation between OS and protein oxidation, DNA/RNA oxidation and elevated levels of byproducts of lipid peroxidation. Accumulated Aβ aggregates play an important role in OS, leading to mitochondrial dysfunction and failure of energy production. Reduced levels of antioxidants like vitamins C and E, uric acid, and antioxidant defense enzymes like catalase, superoxide dismutase, and so on are also seen in AD patients. Besides ROS, RNS (Reactive nitrogen species) has also been observed in AD patients. In the brains of AD patients, the elevation of RNS along with modifications has been found in the astrocytes and nerve cells.

Oxidative Stress and Parkinson's Disease

Through the reports, it was indicated that ROS and OS involvement might play a significant role in PD occurrence. The exact mechanism and pathway of PD are still not clear, although it was demonstrated and believed in many types of research that particularly, substantia nigra in patients suffering from PD are observed to have increased levels of oxidised proteins, DNA, and lipids, along with decreased glutathione levels. Inflammatory markers such as transforming growth factor (TGF)-β; interleukin (IL)-1β, IL-6, IL-10, and so on, and tumour necrosis factor (TNF)-α in microglia were found to be repressed and inoperable in PD patients. RNS apart from ROS is evidenced to play a significant role in nitrosative stress. NO (nitric oxide) produced by NOS, is found in extreme quantities in cells and extracellular spaces around dopaminergic neurons produced by nitric oxide syntheses (iNOS or nNOS). Many enzymes in addition to complex I and IV of electron chain transport in mitochondria are obstructed by NO, and thus, elevate levels of ROS. Toxicity mediated by metals also plays an important role in ROS elevation, enhances OS in the environment of the cell and causes neuron damage, and ultimately may increase PD progression.[7]

Oxidative Stress and Amyotrophic Lateral Sclerosis

Several factors have been reported in ALS such as dysregulation/ dysfunctioning of mitochondria, stress in endoplasmic reticulum, excitotoxicity, neuroinflammation, and OS. OS-mediated lipid peroxidation, protein injury, and RNA and DNA oxidation have been found in patients with ALS. Also, biomarkers of OS have been profoundly observed in urine, blood, cerebrospinal fluid (CSF), individual tissues, or in combination with one or more biomolecules such as

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malondialdehyde (MDA) modified protein, lipid peroxidation product and so on of SALS patients. ROS may lead to calcium homeostasis, mitochondrial DNA mutations, and membrane permeability, along with enhanced lipid oxidation and protein carbonylation, resulting in NDDs like ALS.[7]

Correlation of Nutrition with NDDS

It has been seen in various studies that many of the major disorders like AD and PD, increase as a function of age and their aetiology may partially include lifestyle determinants such as decreased sensitivity to insulin, obesity, and metabolic syndrome. Unfortunately, among clinicians and physicians, there is a distinct lack of knowledge on where nutritional recommendations can be used with traditional approaches in neurogerontology.[15] Although the cure for NDDs is not there, all the therapeutic interventions are focused on managing the symptoms and improving the quality of life in patients.[16]

Cholesterol metabolism in the brain of AD patients is disturbed which is associated with neuronal death and neurodegeneration. Increased HDL and decreased LDL in the plasma of AD patients have been found in studies. Diets with low LDL and high HDL levels can promote synapses and neuron maintenance in the brain. A cholesterol-rich diet causes the production of excess free radicals leading to OS, ultimately promoting NDDs. Therefore, it is suggested to take low LDL and high HDL content in diet along with food groups rich in antioxidants.[17]

The prevalence of NDDs is increasing at a higher rate in Western countries as compared to Eastern countries due to modified lifestyles. Hence, nutraceuticals can be an effective measure to treat NDDs as they slow neuronal degeneration progress. It is possible because they can pass through the blood-brain barrier (BBB) with their antioxidant, anti-inflammatory, and anti-protein aggregation properties. They can also repress abnormal mitochondrial dynamics (multifaceted along with a high bioavailability rate)[18]

Nutrition and Alzheimer's Disease

Various researchers have shown over the decade that disturbances in metabolism such as metabolic syndromes and obesity are threat factors in the development of AD and dementia.[19] Wang J et al. explained the function of selenium in the antioxidant system and also showed through their studies that less amount of selenium is associated with AD incidence.[20]

Micronutrients like polyphenols possess important antioxidant, anti-carcinogenic, and anti-inflammatory activities. It was suggested that resveratrol, a polyphenol found in grapes, has anti-amyloid properties (observed in the AD mouse model), but after the experiment, it was concluded that a combination of several bioactive metabolites present in the extract of juice and not resveratrol alone, may ameliorate AD pathology.[21]

Brain areas of AD patients had been found to have impaired glucose metabolism[22] which on supplementing with ketone bodies was reversed and helped in better cognitive performance in animal models.[23] Farah BA conducted a clinical case study of the effect of caprylic triglyceride, a medium-chain triglyceride which instigates ketosis, in an old man of age 70 years probably having mild AD.[24] The results showed that ketogenic treatments were cognitively effective in AD. Cognitive decline in the elderly population has been related to hypovitaminosis and AD is critically associated with low vitamin D levels.[25] Wengreen H et al. stated that it is necessary to maintain an optimum nutrient supply for proper brain function.[25] Randomised intervention, epidemiologic analyses, and mechanistic studies provide insight into the positive effects of docosahexaenoic acid (DHA) as well as micronutrients (B, C, D and E vitamins) in helping neurons to cope with AD and dementia.[26]

Increased cholesterol levels, diabetes, and hypertension are also involved in the development of AD.[27] Edible mushrooms can help in the mitigation of AD and other age-related NDDs by providing many health benefits including immune-modulating response.[28]

Nutrition and Parkinson's Disease

It was found in many studies that exclusion or inclusion of one or the other food components or groups either trigger PD or can provide neuroprotection.[29] Consumption of dairy products (except yoghurt and cheese) can increase the chances of PD. Further, a stronger correlation between PD and milk consumption was also reported.[29]

Shen C et al. stated in their preliminary research that individuals consuming a huge quantity of products from dairy might have low levels of serum uric acid.[30] Uric acid and serum urate are inversely proportional to PD risk and disease duration. The serum urate effect on neuroprotection is limited to men. Phytochemical (present in fruits and vegetables) intake leads to a reduction in functional decline connected with ageing and may slow PD advancement.[31] Epidemiological studies revealed that large consumption of fish, vegetables, and fruits was conversely proportional to the risk of PD. Dietary patterns, which are characteristics of a Mediterranean diet, are evolving as promising options for neuroprotection in PD.[20] Vegetables and fruits are generally reservoirs of antioxidants, comprising vitamins A, B (riboflavin), C, and E, which are observed in very less amounts in PD patients. A reduction in peroxidase, glutathione-peroxidase activities, and glutathione in the substantia nigra of PD patients' postmortem thus suggests that a failure of metabolism in antioxidant mechanisms and chemical activities can cause peroxidation of lipids and characteristics of Parkinsonism.[29]

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Intake of diet having nicotine-consisting vegetables from the Solanaceae family (including potatoes, peppers, and tomatoes) which are edible worldwide was connected with a decreased threat of Parkinson's in women and men who never had tobacco or cigarettes.[32] Vegetables of the cruciferous family (like cabbage, broccoli, and cauliflower) are also rich in antioxidants possessing neuroprotective capability. Naturally occurring isothiocyanates like sulforaphane and erucin are found in cruciferous vegetables which have potent antioxidant properties. When the 6-hydroxydopamine mouse model was treated with sulforaphane, it improved motor deficits and saved dopaminergic neurons in the mouse.[33]

DHA shields neurons from inhibition of NO production, an influx of calcium and cytotoxicity. Activities of antioxidant enzymes, glutathione reductase, and glutathione peroxidase can be increased by DHA. Moreover, supplementation of DHA reduces apoptosis in dopaminergic cells and replaces omega-6-PUFAs in the brains of mice after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. Other nutrients like soy protein, caffeine, tea, and controlled use of wine and beer can help in reducing the proliferation of PD.[29]

Studies proving a Relationship between Neurodegenerative Diseases, Oxidative Stress, and Nutrition

In a study, it was demonstrated that curcumin can improve and reinstate the levels of DOPAC (3,4-Dihydroxyphenylacetic acid), dopamine, tyrosine hydroxylase, etc. and enhance neurobehavioural function, hence it was suggested that possibly through anti-apoptosis, antioxidant, and anti-inflammatory capabilities, curcumin provides neuroprotection in PD.[34] Nirankari S et al. conducted a few experiments to find the neuroprotective performance of quercetin on brains of rats oxidatively damaged by treatment. From this, they found that in the rats treated with arsenic, when supplied with quercetin, the antioxidant defense enzymes like SOD, GSH, etc. and the action of nitric oxide synthase enzyme were restored to normal levels.[35] Also, a change in the histo-architectural level of brain tissues due to arsenic treatment of rats was found to be normalised by simultaneous treatment with quercetin. Thus, as a prophylactic intervention, quercetin could reverse the neurotoxic activity of arsenic by decreasing OS. Trovato A et al. demonstrated in their research that lion mane mushroom (H. erinaceous) reduces the deposition of amyloid plaques and neurofibrillary tangles in mice as well as human models. Therefore, it can reduce the proliferation of AD. It can also prevent PD and neuroinflammation by providing other neuroprotective functions.[36]

A study was regulated in 23 centres in 10 European countries to exemplify the function of dietary, biological, lifestyle and environmental factors in the aetiology of chronic diseases. The results from this study show that smoking is directly, while caffeine is indirectly proportional to PD progression. Similarly, dairy products except cheese and yoghurt show a strong positive association with PD risk.[30] Zhao L et al. provided preclinical evidence of APP (amyloid precursor protein)/ PS1 (presenilin 1) double transgenic AD mice where oral administration of apigenin improved damaged memory and learning in mice which were associated with AD.[37] Therefore, apigenin-containing food like parsley, thyme, onions, celery, citrus species, etc. seem to provide another alternative for therapy or prevention of AD. A hospital-based study provides evidence of an inverse relation between antioxidants (such as vitamins C and E, and carotenoids) and PD. They, by neutralising RONS, play an important function in shielding cells against damage through oxidation and hence, dietary patterns with a high intake of vegetables, fruits, and fish can be associated with a lower risk of PD progression and risk.[38] Sengupta T and Mohankumar KP conducted research and found that long-term consumption of a large amount of 2-phenylethylamine also called β-PEA (PEA containing products like wine and chocolate) causes behavioural and neurochemical alterations leading to hallucinations, schizophrenia, and is capable of causing Parkinsonism, although, small amounts of PEA have no impact on rat models.[39]

Conclusion

Neurodegeneration is a pathophysiological condition that is not completely curable. There are several factors behind the development of NDDs but OS is one such major element. OS can be combated by including antioxidant-rich foods in our diet like fruits, vegetables, nuts, and fishes. After a certain age, the oxidant defense mechanism (endogenous antioxidants) weakens. Stress, weak immunity, or several other changes in lifestyle are some underlying components responsible for that. Therefore, one should consume endogenous antioxidants to combat OS and reduce the risk of chronic diseases like NDDs, cancer, diabetes, etc. Moreover, endogenous antioxidants can slow down the progression of chronic diseases, and therefore, can be used in therapeutics.

Conflict of Interest: None

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