

The Main Cause and Prevention of Multiple Sclerosis and its Relation to Cancer

Introducing the Evolutionary Metabolic Hypothesis of Multiple Sclerosis (Emhms)

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Received: November 11, 2017; Published: November 22, 2017

Abstract

Multiple Sclerosis (MS) is a condition of demyelination of the nerve cells in the brain and spinal cord. It is possible that multiple factors are involved in causing multiple sclerosis, including DNA defects in nuclear and mitochondrial genomes, viral infection, hypoxia, oxidative stress, lack of sunlight, and increased macrophages and lymphocytes in the brain. This meta-analysis has gone through many researches and reviews to find the similarities and differences in the cause of MS and cancer. Our epidemiological review from 2014 - 2017 on Multiple Sclerosis and Cancer disease shows that, the outbreak of HIV/AIDS, Ebola in 2014 and infectious diseases has been the main cause of MS and cancer in African population, so mainly the native population of Africa do not get cancer and MS because of their primitive lifestyle. This research has concluded that the environmental temperature is an important factor causing multiple sclerosis and cancer. The high rate of these two diseases in Australian population is due to the hole in Ozone layer in this island. Therefore; the best place for the prevention of cancer and multiple sclerosis is to live in the equator line of the earth like our first ancestors (*Homo sapiens*). The role of mitochondrial metabolism, environmental temperature and distance from the equator has been discussed in this research, and the amounts of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) i.e. the increase in cellular inflammation, is the most possible cause of multiple sclerosis and cancer in men and women.

Keywords: Multiple Sclerosis; RNS; ROS; Epidemiology; Cellular Inflammation; Temperature; Hypoxia; Mitochondria; Cancer; Native Lifestyle

Introduction

Multiple Sclerosis Definition

Multiple sclerosis is a demyelinating condition in which the insulating covers of nerve cells in the brain and spinal cord are damaged [1]. This damage interferes with the ability of parts of the nervous system to communicate and function properly, which results in mental, physical and often psychiatric disorders [2-4]. The most specific symptoms might include double vision, blindness in one eye, muscle weakness, trouble with sensation, or trouble with coordination [1]. MS takes several forms, with new symptoms either relapsing or progressive forms. Between attacks, symptoms may disappear completely. however, permanent neurological problems often remain, specifically as the disease advances [5]. While the cause may not be clear, the underlying mechanism has been thought to be either destruction by the immune system or failure of the myelin-producing cells [6]. Proposed causes for this include genetics and environmental factors such as viral infections [3,7]. Multiple Sclerosis is mainly diagnosed based on the signs and symptoms and the results of medical tests [8]. There is no known cure for multiple sclerosis. Treatments attempt to improve function after an attack and prevent new attacks [3]. Medications used to treat MS, while modestly effective, can have side effects and be poorly tolerated. Physical therapy can help with the patients' ability

to function [1]. Many people choose alternative treatments [9]. The long-term result is difficult to foresee, with good outcomes more often seen in women, those who develop the disease early in life, those with a relapsing course, and those who initially experienced few attacks [10]. Life expectancy is on average 5-10 years lower than unaffected population [2].

In 2013, about 2.3 million people were affected globally with rates varying widely in different regions and among different populations [11,12]. That year approximately 20,000 people died from MS, up from 12,000 in 1990 [13]. The disease usually begins between the ages of 20 and 50 and is twice as common in women as in men [14]. MS was first described in 1868 by Jean-Martin Charcot. The name multiple sclerosis refers to the numerous scars that develop on the white matter of the brain and spinal cord [15].

Infectious agents and T-cells

Many microbes have been proposed to trigger MS [3]. Moving at an early age from one location in the world to another alters a person's subsequent risk of MS. An explanation for this could be that some kind of infection, produced by a widespread microbe rather than a rare one, is related to the disease [7]. Proposed mechanisms include the hygiene hypothesis and the prevalence hypothesis. The hygiene hypothesis proposes that exposure to certain infectious agents early in life is protective, the disease being a response to a late encounter with such agents [2]. The prevalence hypothesis proposes that the disease is due to an infectious agent more common in regions where MS is common and where in most individuals it causes an ongoing infection without symptoms. Only in a few cases and after many years does it cause demyelination [21].

Evidence for a virus as a cause include the presence of oligo-clonal bands in the brain and cerebrospinal fluid of most people with MS, the association of several viruses with human demyelination encephalomyelitis, and the occurrence of demyelination in animals caused by some viral infection [22]. Human herpes viruses are a group of viruses which has been thought to trigger MS disease. Individuals having never been infected by the Epstein-Barr virus are at a reduced risk of getting MS, whereas those infected as young adults are at a greater risk than those having had it at a younger age [7]. Although some consider that this goes against the hygiene hypothesis, since the non-infected have probably experienced a more hygienic upbringing, others believe that there is no contradiction, since it is a first encounter with the causative virus relatively late in life that is the trigger for the disease. Other diseases that may be related include measles, mumps and rubella [2].

Apart from demyelination, the other sign of the disease is inflammation. The inflammatory process is caused by T cells, a kind of lymphocyte that plays an important role in the body's defenses [3]. T cells gain entry into the brain via disruptions in the blood-brain barrier. The T cells recognize myelin as a foreigner which can be dangerous and attack it, which is the explanation why these cells are also called autoreactive lymphocytes [2]. The attack of myelin starts inflammatory processes, which triggers other immune cells and the release of cytokines and antibodies that are soluble factors. Further breakdown of the blood-brain barrier causes a number of other damages such as swelling, activation of macrophages, and more activation of cytokines and other destructive proteins [3]. Inflammation can potentially reduce transmission of information between neurons in at least three ways. The soluble factors released might stop neurotransmission by intact neurons. These factors could lead to or enhance the loss of myelin, or they may cause the axon to break down completely [2]. In parasitic attacks, normal cells produce more hydrogen peroxides to fight the parasite, which causes the ROS to increase inside and outside the cell. This process affects mitochondria to produce more ROS which in conclusion will damage mitochondrial DNA and functioning and cell respiration.

Oxidative damage

In aerobic organisms, the energy needed for biological functions is produced in the mitochondria via the electron transport chain. In addition to energy, reactive oxygen species (ROS) with the potential to cause cellular damage are produced. ROS can damage DNA, RNA, proteins and polyunsaturated fats in the cell membrane. ROS are produced as a normal product of cellular metabolism. Specifically, one main cause of oxidative damage is hydrogen peroxide (H_2O_2), which is converted from superoxide that leaks from the mitochondria. Cata-

lase and superoxide dismutase ameliorate the damaging effects of hydrogen peroxide and superoxide, respectively, by converting these compounds into oxygen and hydrogen peroxide which is later converted to water, resulting in the production of benign molecules. However, this conversion is not 100% efficient, and residual peroxides persist in the cell. While ROS are produced as a product of normal cellular functioning, excessive amounts can cause damage [16]. Memory abilities decline with age, evident in human degenerative diseases such as Alzheimer's disease, that is accompanied by an accumulation of oxidative damage. Current researches show that the accumulation of ROS can decrease an organism's fitness because oxidative damage is a contributor to senescence. In particular, the accumulation of oxidative damage may lead to cognitive dysfunction (CD), as demonstrated in a research in which old rats were given mitochondrial metabolites and then given cognitive tests. Outcomes showed that the rats performed better after receiving the metabolites, suggesting that the metabolites reduced oxidative damage and improved mitochondrial function [17]. Accumulating oxidative damage can then affect the efficiency of mitochondria and further increase the rate of ROS production [18]. This process continues till it reaches a damaging amounts which leads to mitochondrial DNA damage. The accumulation of oxidative damage and its implications for aging depends on the particular tissue type where the damage is happening. Additional experimental results suggest that oxidative damage is responsible for age-related decline in brain functioning. Older gerbils were found to have higher levels of oxidized protein in comparison to younger gerbils. Treatment of old and young mice with a spin trapping compound caused a decrease in the level of oxidized proteins in older gerbils but did not have an effect on younger gerbils. In addition, older gerbils performed cognitive tasks better during treatment but ceased functional capacity when treatment was discontinued, causing oxidized protein levels to incline. This led researchers to conclude that oxidation of cellular proteins is potentially important for brain function [19].

In addition to Reactive Oxygen Species, due to high metabolic rate of the neurons and central nervous system, the amounts of Reactive Nitrogen Species (RNS) can go high as well. Reactive nitrogen species (RNS) are anti-microbial molecules derived from nitric oxide and superoxide produced through the enzymatic activity of nitric oxide synthase 2 (NOS₂) and NADPH oxidase. Reactive nitrogen species act along with reactive oxygen species (ROS) to cause damage to the cells and also neurons, causing nitrosative stress. Therefore, these two species are referred to as ROS/RNS [20].

- $\text{NO (nitric oxide)} + \text{O}_2^{\cdot-} \text{ (superoxide)} \rightarrow \text{ONOO}^- \text{ (peroxynitrite)} - \text{ONOO}^- + \text{H}^+ \rightarrow \text{ONOOH (peroxynitrous acid)} \rightarrow \cdot\text{NO}_2 \text{ (nitrogen dioxide)} + \cdot\text{OH (hydroxyl radical)}$
- $\text{ONOO}^- + \text{CO}_2 \text{ (carbon dioxide)} \rightarrow \text{ONOOCO}_2^- \text{ (nitrosoperoxy carbonate)} - \text{ONOOCO}_2^- \rightarrow \cdot\text{NO}_2 \text{ (nitrogen dioxide)} + \text{O=C(O}\cdot\text{)O}^- \text{ (carbonate radical)}$
- $\cdot\text{NO} + \cdot\text{NO}_2 \rightleftharpoons \text{N}_2\text{O}_3 \text{ (dinitrogen trioxide)}$

Evolutionary Metabolic Hypothesis of Cancer (EMHC)

The first living cells on Earth are thought to have arisen more than 3.5×10^9 years ago, when the Earth was not more than about 109 years old. The environment lacked oxygen but was presumably rich in geochemically produced organic molecules, and some of the earliest metabolic pathways for producing ATP may have resembled present-day forms of fermentation. In the process of fermentation, ATP is made by a phosphorylation event that harnesses the energy released when a hydrogen-rich organic molecule, such as glucose, is partly oxidized. The electrons lost from the oxidized organic molecules are transferred via NADH or NADPH to a different organic molecule or to a different part of the same molecule, which thereby becomes more reduced. At the end of the fermentation process, one or more of the organic molecules produced are excreted into the medium as metabolic waste products. Others, such as pyruvate, are retained by the cell for biosynthesis. The excreted end-products are different in different organisms, but they tend to be organic acids. Among the most important of such products in bacterial cells are lactic acid which also accumulates in anaerobic mammalian glycolysis, and formic, acetic, propionic, butyric, and succinic acids [45,46].

The first cell on the earth before the entrance of the bacteria did contain nucleus and used the fermentation process to produce ATP for its energy. Then an aerobic proteo-bacterium enters the eukaryote either as a prey or a parasite and manages to avoid digestion. It then

became an endosymbiont. As we observe, the fermentation process used the glucose or even glutamine to produce ATP, but the aerobic process used the glucose, fat and protein to produce more ATP than the previous one. The symbio-genesis of the mitochondria is based on the natural selection of Charles Darwin. Based on Otto Warburg Hypothesis, in nearly all cancer cells, the mitochondrion is shut down or are defected and the cancer cell do not use its mitochondrion to produce ATP [47]. This process of adaptation is based on Lamarckian Hypothesis of Evolution and the normal cells goes back to the most primitive time of evolution to protect itself from apoptosis and uses the fermentation process like the first living cells 1.5 billion years ago. Therefore, cancer is an evolutionary metabolic disease which uses glucose as the main food to produce ATP and Lactic Acid. The prime cause of cancer is the abundance of Reactive Oxygen Species produced by mitochondria that is a threat to the living normal cell and causes mitochondrial damage mainly in its cristae [48].

Materials and Methods

This research is based on many studies and researches to find the similarities and differences in causing the Multiple Sclerosis, and the main reason behind the progression and demyelination of the axons of neurons.

Peizhong Mao., *et al* in 2011 stated the relationship of multiple sclerosis with mitochondrial damage in neurons and proposed it as a mitochondrial disease. It is reasonable that mitochondrial dysfunction is the key contributor to neurodegenerative process of this disease. We propose that the inflammation may be initiated by infection or by intrinsic imbalance such as cellular energy failure and increased oxidative stress in neurons or oligodendrocytes, and tissue response to this inflammation that controlled by DNA defects in nuclear and mitochondrial genomes in MS patients [23].

Mahad and Lassman in 2010 proposed that it is mitochondrial damage which leads to the progression of multiple sclerosis [24].

Lukas Haider in 2015 indicated that Inflammation, Iron, Energy Failure and Oxidative Stress role of mitochondrial damage in the Pathogenesis of Multiple Sclerosis [25].

In 2013, Kimmy Su and colleagues did a research on the role of mitochondria in multiple sclerosis. They have summarized some of the extensive work done investigating the effects of mitochondrial dysfunction on neurodegenerative processes in MS, with particular emphasis on the PTP, its modulator CyPD, and mitochondrial ROS sensor and amplifier p66. Thus, MS is not a mitochondrial disease, such as certain inherited mitochondrial diseases but they believed mitochondrial dysfunction is a critical component of axonal injury within the acute focal inflammatory lesions and in the progressive neurodegenerative phase of the illness [26]. There are many evidences that hyperbaric oxygen therapy can be beneficial in treatment of Multiple Sclerosis [27].

In 2011, Jack van Horssen and colleagues did a research on the cause of multiple sclerosis and they concluded that the increase of ROS in MS pathogenesis and evidence is emerging that free radicals play a key role in various processes underlying MS pathology [28].

Multiple Sclerosis and Ketone Bodies One research of MS in a mouse model found that a ketogenic diet suppressed inflammatory markers. The reduced inflammation led to improvements in memory, learning and physical function, which is a breakthrough in treatment of MS [29]. This shows the relationship between ketone bodies in the brain and reduction in ROS which leads to improvements in myelin degeneration.

As with other nervous system disorders, MS appears to reduce the neuron's ability to use sugar as a fuel source. Due to this reduction, replacing the amounts of carbohydrate by fats in the diet is crucial, since the ketone bodies can be a safe fuel for the neuronal activities and also beneficial in the reduction of ROS/RNS damage potential to myelin sheath and also central nervous system. One 2015 review discussed ketogenic diet potential to assist with energy production and cell repair in MS patients [30].

Additionally, a controlled study of 48 people with MS found significant improvements in quality of life scores, cholesterol and triglycerides in the groups who followed a ketogenic diet or fasted for several days [31]. This research study shows how going on a fasted state

can be beneficial in multiple sclerosis treatment, since when the body goes on fasting, the healthy cells can turn into cannibalism state and digest the damaged cells which is beneficial for the regeneration of the new healthy cells.

In 1985, Konat GW and colleagues performed a research and concluded that H₂O₂ and ROS in the brain cause the degeneration and damage of myelin sheath of adult rats. This is an important result that explains how T cells cause damages to the myelin sheath since white cells produce H₂O₂ to fight parasitic attacks which leads to the death of parasites and damages to the myelin sheath of the neurons [32].

Evolution and Multiple Sclerosis as of 2010, the number of people with MS was 2 - 2.5 million which is approximately 30 per 100,000 globally, with rates varying widely in different regions [12]. The estimation has resulted in 18,000 deaths that year. In Africa, rates are less than 0.5 in 100,000, while they are 2.8 per 100,000 in South East Asia, 8.3 per 100,000 in the Americas, and 80 per 100,000 in Europe. Rates goes over 200 per 100,000 in certain populations of Northern European descent. The number of new cases that develop in one year is about 2.5 in 100,000 [14].

Studies on population and geographical patterns have been common [33] and have led to a number of theories about the cause [34,35]. MS usually appears in adults in their late twenties or early thirties but it can rarely start in childhood and after 50 years of age [14]. The primary progressive subtype is more common in people in their fifties. Similar to many autoimmune disorders, the disease is more common in women, and the trend may be increasing [36]. As of 2008, globally it is about two times more common in women than in men. In children, it is even more common in females than males, while in people over fifty, it affects males and females almost equally [33].

Due to ecological aspect of Multiple Sclerosis incidence, the colder the environment, the incidence of multiple sclerosis increases. There has been some important researches resulted in the amount of ROS and the temperature [37]. The body's reaction to cold stress is controlled by the CNS. However, the brain itself can be cooled, which affects its own viability as well as its ability to control the various systems in terms of thermoregulation. The effects that cold environments have on the brain are multiple, but the area with the greatest interest deals with the hypoxic sparing effect that cold temperature has on brain function. Hypoxia increases the amounts of ROS in myelin sheath with can cause damage and demyelination [38]. One deep study by L M Tiede and colleagues in 2011, showed that when the amounts of oxygen are below the normal amounts in neurons, the mitochondrial reactive oxygen species increases [39].

All above lines indicate the role of environmental temperature on the brain tissues and neuronal activities. In lower temperature far from the equator, the incidence of hypoxia in neurons increases which can be resulted in more production of ROS by mitochondria in neurons which can be detrimental to myelin sheath and can cause damage to neurons.

As we can observe in figure 1, the cancer incidence is high in the developed countries where the change in the evolutionary nutrition has occurred. The green spots are where the diet of the population is the same as or near the hunter gatherers diet and ketogenic diet. In Australia and New Zealand where the Ozone layer has the largest hole, the melanoma and other cancer incidence is high [IARC's World Cancer Report, 2014].

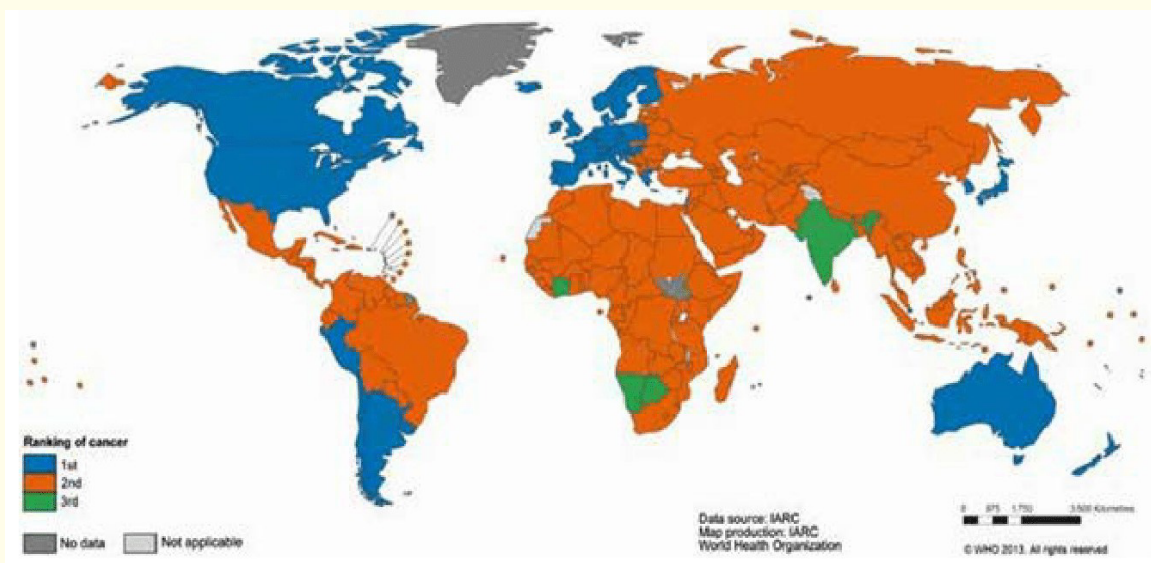


Figure 1: Ranking of cancers as a cause of premature mortality for both sexes ages 30 to 69 years [IARC's World Cancer Report, 2014].

In most developed countries, a substantial proportion of people are overweight, an observation confirmed by recent statistical estimates that the global frequency of excess body weight in adults increased by more than 25% between 1980 and 2013. Overall, about 35% of the adult population of the world is overweight. This is an obvious cause for concern, given the established knowledge –based on numerous and consistent studies –that overweight increases the risk several cancers, including cancers of the colorectal, pancreas, gall bladder, and breast. Going overweight is the result of increasing the consumption of sugar and also the change in evolutionary nutrition. [World Cancer Report, 2014]

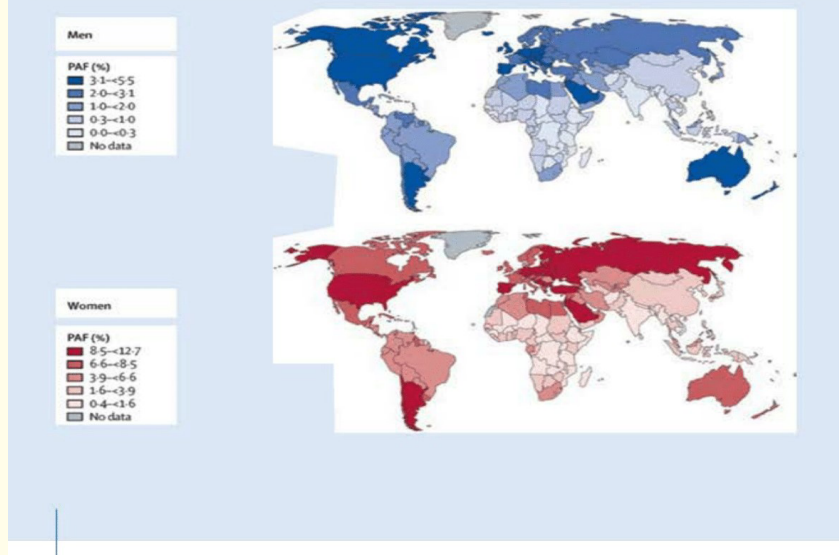


Figure 2: Shows that as the distance from the equator increases, the probability of Multiple Sclerosis incidence increases as well.

Comparing the cancer incidence with the Multiple Sclerosis, we observed the incidences are very the same in the world populations. In the cold areas, the two happens simultaneously. The Multiple Sclerosis incidence arises in the cold areas far from the equator. As we go far from the equator, cancer incidence arises as well. However; in Eskimos where they consume hunter gatherers diet which is like the ketogenic diet with the high consumption of saturated fats, the cancer incidence is rare. Cancer incidence has the close relation to the diet, but Multiple Sclerosis incidence has the close relation to the temperature and diet. Both of them are Evolutionary metabolic diseases.

Discussions

Multiple Sclerosis and Cancer

Increasing the amounts of Reactive Oxygen Species (ROS) in tissues especially by the metabolically process of mitochondria of normal cells, can lead to the damage of mitochondria which has been proved to be the main reason behind turning normal cells into cancer cells [40].

In this meta-analysis research, the main cause of Multiple Sclerosis has been proposed which is increasing the amounts of ROS and Reactive Nitrogen Species (RNS) in brain tissue by mitochondrion inside neurons, which can cause damage to myelin sheath and neurons.

Neurons and astrocytes are largely responsible for the brain's massive consumption of O₂ and glucose. The brain represents only 2% of the total body weight and yet accounts for more than 20% of the total consumption of oxygen [41].

Partly reduced forms of oxygen are highly active since the free radical is so unstable and has to either accept or be a donor of electrons. There are many different varieties of partially reduced reactive oxygen species (ROS) including superoxide, hydrogen peroxide, and the hydroxyl radical. ROS includes both oxygen radicals and non-radicals that are easily converted into free radicals that is O₃, H₂O₂ and 1O₂. Reactive Oxygen Species have different reactive capabilities, and one of the most reactive ROS is the hydroxyl radical OH•. Because of the high reactive activity of ROS, they chemically interact with biological molecules leading to changes in cell function and cell death. As a result, oxygen has the potential to be poisonous, and aerobic organisms survive its presence only because they contain antioxidant defenses [42].

Cancer and Multiple Sclerosis are similar in the cause and treatment by some extent. The main reason behind the cause of cancer is mainly the incline of ROS in the cells and mitochondrial damage [43]. The main cause of multiple sclerosis which has mentioned in this meta-analysis research is increasing the amounts of ROS/RNS in neurons which is detrimental to CNS and myelin sheath as well. In multiple sclerosis the amounts of glucose consumption by neurons decline which may be due to the mitochondrial damage in neurons. But in cancerous cells, the main nutrient that these cells use is glucose to ferment in cytosol and produce ATP and Lactic acid [44].

In previous line in this article, this is mentioned that ketone bodies and ketogenic diets can be used to treat multiple sclerosis, and ketone bodies is beneficial for the adverse effects of ROS/RNS to neurons and also myelin sheath degeneration. This is important for the cancer, that ketone bodies are beneficial for the adverse effects of lactic acid production of cancer cells and also weakening cancer cells [44].

There are not enough studies which have mentioned the relationship between multiple sclerosis and cancer in patients; however, one research study has found that the incidence of cancer in multiple sclerosis patients can rise up to 85 percent. The relation between multiple sclerosis and breast cancer is 200 percent [45,46].

Conclusion

Increasing ROS/RNS in neuronal areas of the brain is very important in the cause of multiple sclerosis. Parasites like certain viruses, bacteria or parasitic microorganisms cause the incline in ROS/RNS which causes the damage to the mitochondria, myelin and mitochondrial DNA. The role of the environment and the distance from the equator is apparent in the incidence of MS. Cold weather is detrimental to the health of nervous system, since in lower temperature below 37C degrees causes hypoxia in the brain and increases the MS incidence. In multiple sclerosis the amounts of glucose consumption by the neurons decreases, this shows glucose as the main source of energy is not useful. A Ketogenic diet which includes 80 percent fat mostly in the form of medium chain triglycerides (MCT) can increase ketone bodies and be protective to the neurons and myelino-genesis. Furthermore, as we already showed, the epidemiology of cancer shows that the incidence is very low in the native American Indians, African Massai populations, Eskimos and Alaska populations which consume native diets mainly saturated fats, MCTs, medium protein by hunting and very low carbohydrates. Multiple Sclerosis and Cancer Are Evolutionary Metabolic diseases which can be treated by specific Keto-Diet plus Vial Ozone Therapy (VOT). Therefore; we suggest living in the equator line of the earth, using ketogenic diet (80% saturated fat, 15% protein with the lowest glutamine, 5% complex carbohydrates) as the main diet, would be the best way to the prevention of the MS and cancer disease.

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Volume 2 Issue 5 November 2017

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