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Metals in Multiple Sclerosis: Improvement or Progression

Fathi F[1]* and Ghaffari-Cherati M[2]

[1]*Department of Chemistry, Mazandaran University of Medical Sciences, Iran*

[2]*Department of Genetic, Mazandaran University of Medical Sciences, Iran*

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***Corresponding author:** Fathi Fereshteh, Department of Chemistry, Mazandaran University of Medical Sciences, Iran, Tel: +989112140421; Email: fereshtehfathi@gmail.com

Abstract

ZMultiple Sclerosis (MS) is autoimmune diseases that many factors can affect the appearance of progress in MS. Metals are important factors in this disease. The aim of this study is to investigate the effects or toxic effects in improving their nutritional and medicinal MS is in progress. A positive correlation between magnesium, calcium, copper and zinc levels with the recovery and negative correlation between blood lead levels and environmental mercury, iron aluminum prevalence and progression of the disease were reported. Identification and diagnosis of MS and its stage is very important. According to the role of metals in these diseases , elemental analysis for key metals such as zinc, calcium, iron, magnesium, aluminum, mercury and lead were noted as key in identifying the disease. This study is a systematic review article, search by keywords: multiple sclerosis, heavy metals in multiple sclerosis, lead poisoning and mercury poisoning in multiple sclerosis, magnesium, zinc, calcium, aluminum and iron in multiple sclerosis and through the web site of Pub Med, Science Direct, Google Scholar, Scoppus in the period 1980 to 2015 was conducted.

Keywords: Multiple sclerosis; Zinc; Copper; Magnesium; Iron; Mercury

Abbreviations: MS: Multiple Sclerosis; MRI: Magnetic Resonance Imaging; RRMS: Relapsing-Remitting Multiple Sclerosis; HCs: Healthy Controls; GDH: Glutamate Dehydrogenase; GAD: Glutamate Decarboxylase; MDD: Major Depressive Disorder; Ca-AEP: Calcium 2-Amino Ethyl Phosphoric Acid

Introduction

Studies on the effects of metals on autoimmune diseases such as multiple sclerosis (MS) started about 36 years ago [1]. Researchers have realized that types of nutrition and diets containing certain metals such as zinc and magnesium can be involved in improving MS symptoms such as muscle signals and thus, today, many physicians take into account level of such metals in the body. Shortage of metals such as zinc, magnesium and calcium can aggravate MS symptoms; however, such deficiencies can be overcome through nutrition and dietary habits, which can also be helpful in improving symptoms of the disease. Accordingly, increased levels of metals such as cadmium, copper, iron, lead and reduced levels of metals such as magnesium, zinc and calcium are considered to be characteristic markers of the disease and known to be involved in the etiology of MS by researchers [2]. Since within the course of MS, some evidence has been shown of shortage of certain metals such as zinc, magnesium, copper and excess of metals such as iron [3], paying attention to the metals involved in this disease can provide an effective treatment to improve it.

In addition, studies have shown that exposure to certain heavy metals speeds up the process of MS [4,5]. In fact, MS is a chronic inflammatory disease known as an autoimmune disease and a demyelinating agent in the central nervous system, namely the brain and spinal cord. Areas where myelin is lost are visible in magnetic resonance imaging (MRI) images in form of lesions [6]. Autoimmune demyelination is directed and developed through auto antibodies and T cells, which leads to the complete destruction of axons in the long term. The cause of the disease is not fully understood, although the onset of the disease might occur by environmental factors, type of diet and nutrition, infectious diseases and industry factors, as well as exposure to heavy metals such as mercury and lead [7]. Toxic heavy metals can cause major metabolic, neurological and immunological injuries in individuals. These metals can deposit on the myelin

sheath and cause changes in its protein or glycoprotein. This triggers the formation of auto antibodies and phagocytic actions damaging the myelin and causes the formation of plaques.

The central nervous system is very sensitive and if exposed to toxic substances and heavy metals like mercury, such metals become accumulated in the brain and CNS, liver and kidneys. Due to the impenetrability of cerebrospinal barrier, concentration of metals is observed to be lower in the cerebrospinal fluid than in blood. Metals can bind to sulphydryl groups (-SH) and OH, Cl and NH_2 in proteins, enzymes, coenzymes and cell membranes, causing problems in the immune system [8]. Moreover, metals can act as immunosuppressive drugs or agents towards abnormal activation of the immune system. For instance, an imbalance in mercury and lead can produce autoimmune responses (through imbalance in Th1 and Th2 that trigger the production of antibodies to fight antigens. Gold, mercury, platinum and palladium could increase autoimmune responses by IgE [9].

Studies on animal models have shown that lead exposure through damage to the nervous system proteins could cause the incidence of neurological diseases such as MS, which has been mostly reported in areas where people may be at a potentially greater lead exposure risk. Accordingly, there exists great number of MS cases in such areas. Here we review the results of studies carried out so far in relation to the positive role of certain metals in improvement of the disease and negative role of some other metals in the exacerbation of MS so that a major step can be taken towards the treatment of MS symptoms through nutritional therapy or use of medications containing metals effective in the improvement of the disease.

Materials and Methods

This review article aimed to examine and discuss the results in a number of studies obtained from the databases Pub Med, Science direct, Google Scholar, Scopus in the period 1990 to 2015 using the keywords of multiple sclerosis, metals in multiple sclerosis, zinc and magnesium, calcium and vitamin B12, aluminum, mercury and lead in multiple sclerosis.

Results

In various studies on the treatment of MS patients, findings are observed on the nutrition performance with certain metals such as magnesium, zinc, copper, vitamin B12 or treatment with drugs containing these metals. Studies have shown that magnesium is one of the most important metals involved in MS. Appropriate level of magnesium in the body is essential for nerve function, muscle contraction and bone health [10]. Also, cells need magnesium to transport potassium and calcium from the cell wall. In addition, magnesium protects cells from aluminum, mercury, lead, beryllium, and nickel. Accumulation of iron, cadmium, aluminum and lead in the kidneys and brain occurring due to magnesium deficiencies, may lead to oxidative stress in such organs.

Magnesium inhibits acetylcholine release and reduces its activity and polarization. Therefore, low level of magnesium in the body causes uncontrollable muscle contractions. Magnesium, prescribed as magnesium aspartate, magnesium citrate, magnesium lactate and magnesium chloride, is effective in controlling chronic symptoms. These symptoms include muscle spasms, weakness, muscle atrophy, rapid eye movement, and hearing loss [10]. In 1990, Yasui et al. [11] conducted some studies in Japan on the level of magnesium in 4 patients with MS and 5 controls. The results showed lower magnesium level in central nervous tissues and visceral organs except for the spleen in MS patients, as compared to that in the control group. This suggests that magnesium levels should be monitored in patients with MS.

The important point to note is that magnesium-containing diets have proven to have a significant impact on the treatment of patients with MS. Accordingly, experiments conducted by Rossier et al. [12] in the United States on a 35-year-old woman with secondary progressive MS during the years 1998 to 2000 showed that the dietary containing magnesium and oral magnesium glycerophosphate slightly treated hip and knee spasm and hyperextension in the patient after a short period of time. Therefore, a patient with MS could be treated by receiving 100 mg of elemental magnesium, while other antispasmodics are unable to do so.

Magnesium plays an important role in relieving fatigue which is one of the critical symptoms in MS patients. This has been confirmed in reports by Bitafaran et al. [13] on the relationship between nutrition and fatigue in MS patients. Similarly, the study conducted at the Neurological Research Center, Imam Khomeini Hospital, Tehran, on 101 relapsing-remitting multiple sclerosis (RRMS) patients showed that only magnesium and folate intake influences the reduction of fatigue. The researchers found that a diet containing less magnesium and folate was associated with extreme fatigue in MS patients. In fact, fatigue is one of the common symptoms among MS patients, affecting about 75-90% of such population. Factors such as inflammatory cytokines, analysis of axons, reduced metabolism of the brain areas and excess energy consumption causes fatigue in patients. Low intake of folate and magnesium, leads to fatigue in MS patients, receiving of which can improve symptoms in these patients.

Studies have shown that, compared with healthy controls (HCs), women with MS reveal lower levels of folate, magnesium, vitamin E and other nutrients with antioxidant or anti-inflammatory properties. Folate and Vitamin B are water soluble and help to build red blood cells. Thus, foods such as spinach, pumpkin seeds, soybeans, fish, flour and rice, bananas and dried figs containing abundant magnesium and foods such as spinach, black eye beans, lentils, asparagus, broccolis, oranges and whole wheat bread containing abundant folate are recommended to MS patients. In addition, foods with high fat or small amount of

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vitamin D can reduce magnesium absorption, as one factor that increases the risk of MS in cold areas and areas away from the sun [14].

Study on the effects of zinc on MS patients has begun about 35 years ago. Zinc plays an essential role in the inhibition of destructive immune reactions against T lymphocytes and also, in the predisposing inflammatory responses of MS. Zinc as an antioxidant can protect cell membranes and myelin. Moreover, it reduces the activity of glutamate dehydrogenase (GDH) and also, glutamate decarboxylase (GAD) enzymes in glutamate catabolism. Vertebral column is an area of the central nervous system that contains metal ions, including zinc, copper and iron in synaptic terminals of its neurons. Many studies show low zinc levels in patients with MS. Zinc deficiency causes thymus impairment, decreased thymulin activity, decreased T cell proliferation and altered Th1/Th2 equilibrium against a Th2 response [15]. Thus, it seems that zinc in the diet of patients with MS can be useful in the elimination and reduction of muscle contractions, and effectively reduce the muscular symptoms of the disease and fatigue in patients.

Certainly, physicians should note that magnesium-rich foods mentioned earlier are useful for the health of their patients. MS prevalence is lower in people who consume a lot of seafood (which contain very high zinc levels). Wong et al. (1980) in an experiment on 25 patients with MS showed that plasma zinc levels were lower in these patients than in controls [16]. Moreover, in the study conducted by Sadeqi et al. in Kerman on 58 MS patients and 39 healthy subjects, it was demonstrated that changes in concentration of zinc and copper in patients with MS is correlated with age, gender, and duration of illness and degree of disability. In addition, serum zinc concentration was observed to be low in MS patients as compared to the control group.

The zinc level in both the control group and MS patients group was also observed to be greater among males than females [17]. The noteworthy point is that such a decline in zinc and copper levels was observed in comparison with the control group (males and females) in patients under 45 years, whereas no changes in zinc and copper levels occurred above 45 years [18]. As the disease progresses, the level of zinc is lowered in MS patients. Zinc supplementation has been suggested since the definition of this disease in the 1880s. The evidence suggests that zinc may reduce the duration of colds and thus, is important for viral infections such as colds that may be invasive to MS [19]. On the other hand, based on studies on the effect of zinc on depression, zinc deficiency leads to behavioral changes such as learning and memory and changes in nutrition functions. Another problem of MS patients is major depressive disorder (MDD).

Studies show that about 20-50% of MS patients suffer from depression during the illness. Depression symptoms are not correlated with disease severity and also, location of lesions as well as neurological symptoms and disability in patients. Mousavi et al. [20] demonstrated that serum zinc and magnesium levels is lower in MS patients compared with the control group [21]. What mentioned above is a number of positive effects of zinc on memory function and mental states in patients and surely, physicians are recommended to prescribe zinc, either medicinal or nutritional, in order to reduce stress or mental depression caused by the disease during the treatment [22].

Studies have shown that impaired metabolism of iron and copper play an important role in the pathogenesis of degenerative nervous diseases [23]. Like zinc, copper is a redox-active metal that plays an important catalytic role in active antioxidant enzymes and formation of free radical. Copper and zinc deficiency in various animal types may reduce myelination, and it has been shown that copper and zinc deficiency plays an important role in the onset and progress of neurological diseases. Palm et al. [22] reported increased plasma zinc concentration in 50 patients with MS in Sweden [24]. In another study by Johnson (2000), the accumulation of copper, cadmium and Iron along with zinc, magnesium, vitamin B6 and D deficiency was investigated in the pathogenesis of MS in patients in Washington. The summary of results show that excess copper decreases zinc absorption and copper also inhibits synthesis of uric acid by xanthine oxidase, causing abnormally low levels of uric acid in the spinal fluid.

Therefore, high concentration of copper causes superoxide to be greater produced. On the other hand, women need zinc more than men, and during growth, low melatonin levels, important for zinc absorption, and high copper levels causes zinc absorption to be impaired [25]. Also, observations of Forte et al. in Italy on 60 patients showed low copper levels in MS patients [26]. Since copper plays a role in transmission of pulses in the muscular and nervous system, thus, reduced copper level causes some problems. Studies showed that copper level is lower in glutathione peroxidase than in the control, proving that zinc and copper homeostasis disorder in patients may be due to the use of steroids in the treatment, which require to be replaced by more suitable alternatives. Copper is an important element and involved in dopamine metabolism, which is a neurotransmitter.

In this regard, Masoud & Fakharian [25] conducted a study on 35 patients with typical symptoms of MS in Kashan, Iran. They investigated the discrepancy in serum magnesium and copper levels in MS patients in comparison to the healthy controls and concluded that serum magnesium, copper and zinc levels is lower in the MS patients than in the control group ($P<0.001$). Moreover, it was observed that women, as compared to men, in the both groups of controls and MS patients had higher mean levels of serum copper and zinc ($P <0.001$), but lower mean levels of serum magnesium ($P<0.0001$) [27]. Copper is an important element in foods such as beans, nuts, grains and organ meats and in fruits such as bananas, which can help to improve MS-related neuromuscular symptoms. However, it should be noted that

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excess copper, due to interference with zinc and accumulation in the brain and also, elimination of some proteins can cause other hazards. Therefore, patients are recommended to take precautions and refer to the doctor for consumption of copper.

One special physiological condition in patients with MS is abnormal lipid levels in white matter caused by deficiency of vitamin D and calcium during demyelination.

Vitamin D affects the activity of the phospholipids. Ca^{2+} ion controls several membrane properties associated with myelin structure and its stability [28,29]. The solubility of brain phospholipids can be affected by calcium and magnesium ions. At the molecular level, calcium is able to tightly bind to phospholipids, which is involved in myelin stability. Based on studies by Kreutz, who investigated the impact of calcium on the spatial structure of various phospholipids [30], and Wolman and Weiner, who had shown that changes in calcium ion concentration can affect the myelin structure [31], Goldberg (1974) pointed out that vitamin D and calcium have an important role in the prevalence of MS [32]. In a study in Japan in 1993 conducted by Yasui on 4 patients with MS and 5 healthy controls (HCs), calcium levels in 26 districts of the CNS and in the white matter were measured by the neutron activation analysis (NAA) and it was found that the concentration of calcium was higher in MS patients than the HCs (634±34μg/g against 608±8μg/g).

However, no significant difference was observed between the patients and the control regarding the content of calcium in the gray matter, brainstem and vertebral column, and the difference between the two groups was only observed in the white matter. The studies showed that calcium deposition in the CNS produces calcium hydroxyapatite (Ca-Hy) for stimulation of CNS disorder. It is worth noting that reduced level of calcium and magnesium occurs as a result of increased level of aluminum and manganese. On the other hand, a chronic magnesium deficiency causes reduction in number of lymphocytes, particularly T Lymphocytes, leading to abnormal immune system. This provides induction of cytokines (IL2) for the diversity of T cell proliferation. In MS with abnormal immunity, levels of magnesium and calcium, which play an important role in the activation of T cells, are lower in white matter that raises the possibility of involvement of these elements in the disease process [33]. If lipid deficiency occurs during puberty, a weak structure of myelin occurs in an adult's central nervous system, causing myelin sheath to break. Therefore, according to the studies, vitamin D and calcium have been shown to reduce the risk of MS.

These factors contribute to normal development of myelin, especially during puberty; therefore, the direct effect of sunlight in sunny areas can reduce MS [34]. In regions such as northern Europe with low sunlight, vitamin D-containing foods such as fish and fish oil should be consumed. Increased vitamin D and calcium cause reduced rate of continuous relapses. In 1941, a form of calcium, calcium 2-amino ethyl phosphoric acid (Ca-AEP) was discovered by a biochemist named Chargaff. He found that Ca-AEP is a critical component in the structure of cell membrane, serving as a shield surrounding nerve cells, and is effective in maintaining and controlling autoimmune conditions. This element is essential for sensitivity of the cell membrane in MS that binds to fatty acids and electrolytes of cell membranes and produces cellular electric charge. Ca-AEP was first used by the Health Organization in Germany in 1967 to treat MS. Also, Ca-AEP is a neurotransmitter that plays an important role in the treatment of patients with autoimmune responses induced by auto antibodies, toxins, viruses and free radicals. In a study, a nutritional treatment including calcium, magnesium and vitamin D was investigated on a group of young people with MS for a period of 1-2 years. The results showed that in these patients, with approximately 22-37 years of age, calcium and magnesium were effective in myelin structure and stability.

Lack of requirement of calcium, magnesium and vitamin D during development of the central nervous system causes abnormal lipid composition and myelin instability. Treatment of these patients with calcium and magnesium has been effective in the form of dolomite tablets and liver oil. Moreover, Ca-AEP binding to calcium urate leads to reduction in bone calcium loss and increased bone strength and also, improves the functioning of cell membranes, in bone tissues and decreases bone fractures in patients with MS [35]. Therefore, it seems essential to consider the effect of vitamin D and calcium in the body, especially in Iran where people mostly suffer shortage of this vitamin in the body, an issue in need of being taken into account by physicians through conducting studies on metals essential to body such as zinc, copper, magnesium and calcium, as well as enzymes and coenzymes involved with them along with their function mechanism. It seems that the prevalence of MS is associated with abnormal metabolism of selenium or GSH-PX activity. Vitamins E and Se inhibit lipid peroxidation, resulting in lowered damage to myelin, which is made mostly of lipids. Selenium plays an important biological role as part of the GSH-PX enzyme, which is one of the main antioxidants of the immune system. This element is rapidly excreted by urine and in combination with the blood and selenocysteine-containing proteins.

Lipid peroxides, that cause damage to the cell membrane such as lysosome membranes, are metabolized either straightly through glutathione peroxidase (GSH-PX), an enzyme containing selenium, or indirectly by glutathione reductase (GssG-Rd). Therefore, modified lipid peroxidation, similar to what occurs due to selenium deficiency, causes altered activity of leukocytes. Moreover, selenium deficiency increases lipid peroxidation by reducing the GSH-PX activity, which increases the oxidative risk of brain cell membranes. In other words, other antioxidant mechanisms such as superoxide dismutase, catalase, glutathione S-transferase and Vitamin E may partly compensate for selenium deficiency and therefore, alter the progression of oxidative damage [36].

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Wikstrom et al. (1976) reported low mean level of selenium in the blood of all patients with MS in high-risk areas such as Finland. In another study conducted in Denmark, Jensen et al. (1980) showed higher blood selenium levels in the MS patients compared to the control subjects which was not significant. On the other hand, serum selenium levels in the MS patients did not show less significant differences than that in the healthy subjects [37]. Korpela et al. [36] investigated serum selenium concentration and activity of glutathione peroxidase (GSH-PX). Studies on 9 females and 6 males aged 29-66 years showed that in patients with rapidly progressive MS, the mean level of lipid peroxides is higher than in healthy controls, whereas in patients with remitting or slowly progressive MS, no significant differences were observed between selenium levels and serum lipid peroxide. Serum selenium concentration is not correlated with the GSH-PX activity and also, there is no association between serum selenium and lipid peroxide concentrations [38]. The GSH-PX activity in serum is a sensitive identifier for the body selenium content, which faster responds to changes in selenium intake by nutrition, as compared to the GSH-PX activity in blood or red blood cells. Therefore, during the reduction of the selenium level, a significant positive correlation was observed between serum selenium and the GSH-PX activity.

The biological role of selenium is related to GSH-PX that reduces peroxides and therefore, protects brain cell membranes against oxidative damages. Selenium concentration and GSH-PX activity are high in the brain. As a result, selenium may play a role in the brain anti-oxidative deficiency. This is while serum selenium levels cannot show its amount in the brain and CSF. Monestier et al. [37] noted in their study that treatment with D-penicillamine or quinidine causes autoantibody production against chromatin antigens in mice, which is similar to monoclonal autoantibody production induced by mercury injected into mice [39]. Schwartz et al. (1998) discussed how exposure to toxic particles with low molecular weight causes protein or glycoprotein changes in the myelin sheath which in turn, induces the formation of auto antibodies and phagocytoses damaging the myelin and causes formation of plaques. Metals such as mercury (with methyl mercury injection) can produce antibodies for nervous proteins and glycoproteins such as MBP and GFAP that enter into the central nervous system after the destruction of blood-brain barrier and bind to MBP or proteolipid protein (PLP) and enhance autoimmune response. While in 1996, Chang came to the conclusion that mercury deposits on the myelin sheath and destroys it [36].

Mercury is one of the most toxic non-radioactive elements, which is commonly absorbed along with its derivatives by seafood (fish) as organic mercury, and also widely exists in various products including disinfectants, dental instruments, beauty creams, etc. In case of chronic mercury exposure, due to short half-life of mercury in blood, the use of 24-hour urine is a more accurate method to measure mercury concentration. Mercury, as a potent neurotoxin, affects basal cell functions through strong bond with selenohydryl and sulphydryl groups on the albumin molecules in cell membranes, receptors and intracellular signal bindings. The toxicity of mercury is due to production of free radicals and potential change of the cell redox reaction. Low levels of mercury may stimulate phosphorylation and hence, intracellular signaling pathway. Moreover, mercury inhibits and destroys construction of cytoskeleton in nerve cells [40,41].

Monnet et al. [40] studied the prevalence of apoptosis (programmed cell death) among several rat brain cultures and found that mercury increases spontaneous apoptosis in immature cultures, especially astrocytes [42]. In another study conducted by Shenker et al. in 2000 at the Dentistry University of Pennsylvania on 22-40-year-participants, it was shown that mercury is able to induce a cascade of apoptosis in human T lymphocytes [43]. Duxbury et al. [42] stated that mercury is toxic to oligodendroglial cells of human head and damages to oligodendrocytes occur through apoptosis, especially when the cells are exposed to small concentrations of HgCl2 [44]. However, throughout previous years around 1998, Bangsi et al. [43] in Canada studied a number of dental restorations performed from 1991 to 1994 on about 353 MS patients by means of the amalgam (an instrument to fill teeth in dentistry) and found a large number of MS patients associated with dental amalgams [45]. Mercury levels in MS patients compared to healthy subjects is higher, expressing the notion that high levels of mercury in the serum used may increase the prevalence of MS disease.

Recent studies suggest that mercury used in dental equipment may lead to nephron toxicity, neurological behavioral changes, autoimmune and oxidative stress. It should also be noted that the relationship between MS and chronic exposure to mercury through dental equipment, i.e. dental fillers, was mentioned in a report presented by Golding (2007) in Canada [41]. Due to the high prevalence of MS and industrial pollution in Isfahan, some studies in 2012 investigated the possible relationship between serum levels of mercury and developing MS. There was a significant difference between the serum levels of mercury in healthy subjects and patients suffering from MS. The difference was also observed between males and females. In addition, abnormally high levels of mercury were noticed among the MS patients. According to a wide study carried out by a number of nephrologists (from 5 April, 2003 to 31 July, 2006) on 1718 patients suffering from MS in Isfahan, Iran, a relatively high and rising epidemiological risk was observed in the province. Regarding this study, the prevalence of MS in Isfahan Province was 43.8 per 100,000 persons and the incidence of MS was 3.64 per 100,000 persons.

The meaningful statistics reveal the urgent need of the country, especially the province, for immediate action against this particular disease [46]. Despite the potential risks, people

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must observed health cares in the face of this dangerous metal in their environment and physicians should also examine individuals' living place to place and their exposure to toxic metals by any means and strive to reduce the disease or remove its causes. Visconti et al. presented a report in 2005 in Rome and pointed out that the average concentration of molybdenum in 12 MS patients' serum was higher compared to the control subjects [47]. It seems that this finding is consistent with those obtained by Zapadniuk (1992, Ukraine), indicating the relationship between molybdenum and MS. Furthermore, it should be noted that molybdenum can be removed by phlebotomy [48]. A recent increase in prevalence and incidence of MS among the residents of the eastern slopes of Mount Etna was attributed to their exposure to volcanic ash containing rare elements and this indicates the role of trace elements as a leading environmental factor in the MS pathogenesis.

Nicoletti et al. [47] in an article published in 2014 showed that children living in Etna, who are naturally exposed to high absorption of arsenic, manganese, vanadium and uranium, are not affected by volcanic activities in comparison to those who are living in other parts of the island of Sicily in Italy. They also showed that local foods may be the most likely ways to attract and be exposed to rare elements [49].

Iron overload in patients suffering MS could make the disease severe. Therefore, consumption of red meat and seafood, such as oysters which are rich in iron, aggravates MS symptoms, particularly among males. Magnetic resonance imaging (MRI) is introduced as a standard method to estimate the disease activity and to evaluate the therapeutic effects. MRI also is a powerful tool in detecting and determining the amount of iron overload in the brain. It is considered as a standard method to estimate the disease and to evaluate therapeutic effects. Iron overload in cells, white matter, brainstem and thalamus is revealed as a signal intensity decrease in T2 sequence [50].

Studies have shown that the signal intensity decrease in T2 sequence is associated with brain atrophy, the disease process and physical disability in people suffering from MS. It is observed that iron level is high among the MS patients and this leads to iron deposition and sediment in the brain. As a matter of fact, since the 1980s, the researchers found high levels of iron in MS patients' brains [51]. After the discovery of magnetic resonance imaging (MRI), the researchers could obtain images of iron accumulation in brain. There are different causes of abnormal iron overloads in MS patients, including blood-brain barrier dysfunction, decreased iron clearance caused by axonal dysfunction and axon inflammation or disorders in regulating transporter proteins as a result of inflammation [52]. Abo-Krysha [51] in an experiment on 20 MS patients showed that there was no significant difference between serum levels of iron among MS patients and the control group; however, serum transferrin level was higher in patients than the control group. These are indicative of iron dysfunction. Levin et al. conducted tests in Kansas, US, to determine iron and ferritin levels in patients' cerebrospinal fluid and concluded that ferritin level is higher in these patients [53]. Ge et al. [52] performed a study on patients with MS at the Medical Center of New York and measured the accumulation of iron in gray matter.

In an article, Forte et al. (2005) having a study on 60 MS patients in Rome, Italy, concluded that the serum level of iron was higher in patients compared to the control groups. Exely et al. in 2006 in Staffordshire (UK) examined urine iron levels of urine discharge in 10 patients with MS and 10 healthy subjects and demonstrated that iron level is high in these patients. Moreover, Iranmanesh et al. [54] conducted a study in Kerman and measured the serum levels of zinc, iron and copper of 25 patients with MS. They expressed that the serum level of iron was higher in patients than the control group [55]. Abnormal blood-brain barrier permeability can lead to gradual penetration of blood compounds to the central nervous system. Therefore, MS is sometimes considered as a blood-brain barrier disease; however, in general, the extent of iron accumulation in gray matter structures and lesions would provide knowledge about the progression of disability in MS disease and express the extent of lesion accumulation and the level of cell death. Several studies have been conducted on the accumulation of iron in gray matter and white matter using MRI images.

In 2006, Halliwell [56] in a review article stated that hydrogen peroxide takes an electron when exposed to free iron and reform it as free radical OH. This free radical can react with oxygen and other molecules in brain and generate more free radicals. The generated radicals can attack lipid membranes, proteins and DNA and lead to apoptosis. On the other hand, Gilgun [57] stated that these radicals can damage myelin and axons [60]. Iron chelators can reduce the free radical toxicity through binding to free iron available in the blood circulation and preventing this (free) iron to take part in the Redox reactions. The most important chelating agents are DMPS and DMSA [61]. The risky presence of cadmium can be removed by chelators and abundant iron through phlebotomy, especially in males. Likewise, lead, molybdenum, arsenic and aluminum can cause MS. In this regard, lead and arsenic can be removed by chelators. Since parathyroid hormone is effective in the absorption of magnesium, adequate generation of this hormone is beneficial in preventing MS [62].

Aluminum is also one of toxic metal that affect the central nervous system. Aluminum is also involved in the performance of enzymes such as succinate dehydrogenase and Delta amino levulinate dehidrasi. The role assumed for aluminum in deteriorating brain diseases such as Alzheimer and Parkinson's diseases is based on this metal potential to increase intracellular brain ROS (reactive oxygen species), the presence of aluminum in the old plaques, the accumulation of amyloid, a slight increase of aluminum in the brains of patients suffering from Alzheimer's disease [63]. In a study carried out in Milan, Italy, Fulgenzi et al. [61] through genetic analysis and MRI study of MS patients

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treated with chelation (EDTA) for 15 years, reported an increased level of aluminum in their urine.

Moreover, aluminum level goes up in patients who are on dialysis. Also, in Alzheimer's disease and other nervous system diseases such as MS, high aluminum levels have been observed in the urine. In fact, researchers have found that aluminum can be involved in MS. Verbal problems are the most significant consequence of exposure to aluminum. Therefore, elevated levels of aluminum are one of the important experiments in diagnosis of this disease. Injection of an aluminum-bound drug (deferoxamine 500mg) greatly helps in the removal of the metal and treatment of the disease. Therefore, according to the evidence and tests available in relation to MS patients, this point can be observed that paying attention to places of residence and jobs is highly effective to inform or propose appropriate approaches for prevention and treatment of the disease. This is due to the fact that exposure to hazardous and toxic metals increases the risk of damage to the myelin sheath and causes the number of patients to increase. Various methods exist for measuring the elements for controlling the MS disease, among which is the ICP-MS method.

The method was used by Tamburo et al. [63] to determine the concentrations of 21 elements, including silver, aluminum, arsenic, barium, cadmium, cobalt, chromium, copper, iron, lithium, manganese, molybdenum, nickel, lead, rubidium, antimony, selenium, strontium, uranium, vanadium and zinc in hair of 48 remitting-relapsing MS patients, as compared with healthy controls. The results showed that the most common elements in the analysis of hair of healthy controls were Zn>Fe>Cu, respectively. Similarly, hair analysis in the patients with MS also showed the same order of elements. Yet in another study conducted at Al-Zahra Hospital in 2012, the same technique was used to examine blood samples of 40 patients with MS, and levels of zinc, rubidium, iron and boron were measured and examined in blood samples of the patients and healthy controls [64].

Discussion and Conclusion

Given the crucial role of metals in the initiation, progression and diagnosis of MS, it can be said that physicians should conduct fundamental research on the patient's workplace and exposure to heavy and toxic metals, and recommend some experiments to patients during diagnosis and treatment of the disease to evaluate levels of basic metals.

This is important to note that several methods have been considered in the diagnosis of MS: first, urinary excretion analysis methods due to the presence of

a) Indicators of oxidative damage markers

b) High iron presence and

c) high aluminum presence, and second, hair strand mineral analysis in order to determine low or high levels of heavy metals in the body, since hair is exposed to the internal environment of the body, such as blood and extracellular fluid.

Further, toxic, hazardous elements can be removed for this disease by the chelators previously mentioned.

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