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REVIEW

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Toxic Environmental Factors and their Association with the Development of Dementia: a Mini Review on Heavy Metals and Ambient Particulate Matter

Fevronia Antoniadou¹, Theodora Papamitsou¹, Dimitros Kavvadas¹, Dorothea Kapoukranidou², Antonia Sioga¹, Vasileios Papaliagkas³

¹Laboratory of Histology and Embryology, Aristotle University of Thessaloniki, Thessaloniki, Greece;

²Laboratory of Physiology, Aristotle University of Thessaloniki, Thessaloniki, Greece

³International Hellenic University, Laboratory of Physiology, Sindos, Thessaloniki, Greece

Corresponding author: Dr Theodora Papamitsou, Laboratory of Histology and Embryology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; thpapami@auth.gr Tel.: 2310999075 ORCID: <https://orcid.org/0000-0002-0709-540>

ABSTRACT

Introduction: More and more studies are trying to establish a connection between dementia and environmental pollution. Dementia, most commonly associated with Alzheimer's disease, is a chronic, progressive, neurodegenerative disorder that is directly associated to aging. Although the etiology of the disease is not fully understood, it is recognized as a multifactorial one. Genetic and environmental factors contribute to the development of various forms of dementia. Both predisposing genes and environmental pollution have been shown to affect brain function through a variety of mechanisms.

Aim: The purpose of this bibliographic work is «ecological consciousness» of modern societies to be awakened, to identify the harmful environmental factors and to highlight their involvement in the causal pathogenesis of the most debated disease, dementia. **Methods:** Trying to achieve this aim, the available bibliography was reviewed and selected for further study. In particular, recent bibliographic data and scientific papers were selected, mainly from the last five years. The information was collected using the keywords «environmental pollution», «toxic agents» and «etiology of dementia», with particular emphasis on «Alzheimer's disease». The data were selected mainly from medical research databases. In particular, they were selected by PubMed, BioMed Central and Science Direct. **Conclusion:** According to the results of this study, long-term exposure of individuals to pollutants may be associated with an increased risk of dementia. However, we must be cautious in our conclusions, as further reliable studies are needed to confirm the stated evidence. Among other things, health

professionals are responsible for promoting health, preventing and encouraging lifestyle change, so that the progressively growing elderly population remains autonomous, healthy and active.

Keywords: Dementia, Alzheimer disease, toxic agents, heavy metals, air pollution.

1. INTRODUCTION

Dementia is the disease that has taken on unprecedented dimensions in recent years. The number of patients suffering from dementia is expected to increase dramatically. According to the World Health Organization, the number of people suffering from dementia is estimated to be tripled over the next 30 years (1). In the USA, in 2010, Alzheimer's disease was the fifth leading cause of death in the elderly (2). This increase is expected mainly in developing countries. Already, 58% of people with dementia live in low- and middle-income countries, but, by 2050 this will increase to 68% (3). Dementia affects the elderly, although the number of cases starting before the age of 65 is constantly increasing (3). In Europe, the number of people suffering from dementia is estimated to rise from 7.7 million in 2001 to 15.9 million in 2040. A similar increase is projected in terms of the European cost for tackling the disease, which is expected to soar to 43% between 2008 and 2030, amounting to more than € 250 billion. Dementia is the third most expensive disease after cardiovascular disease and cancer, due to the increased costs required for its prevention, diagnosis, treatment and management (4).

The most distinct characteristic of dementia is a gradual decline in mental capacity, with memory loss appearing as the most severe symptom either in the early stages or in advanced stages of the disorder (5). Memory function has a catalytic role for the formation of personality, since it allows communication, the acquisition of skills and survival in the best possible way (5). Depending on the degree of disturbance of the patient's daily life, the disease is divided into three degrees of severity. In the initial stages, the mild degree that limits the daily life of the patient, his domestic and social activities. The degree of moderate severity, that patients are in need of intermittent supervision. In the final stage, the severity of the disease requires constant care and supervision of the patient (6). The most common form of dementia is Alzheimer's disease (65-70% of all cases), followed by Lewy body dementia and vascular dementia.

The environment in which we live is considered responsible for many diseases that appear from time to time and afflict all societies. The first reports of the connection between the environment and the health of individuals have been made by the father of medicine, Hippocrates. Hippocrates was the first to deal on how the natural environment affects human health. Studying his work, the reader realizes that Hippocrates considers the human body an integral part of the environment (7).

Environmental risk factors may have a key role in accelerating or slowing the onset and progression of dementia (8). Environmental risk factors include mostly air pollution and chronic exposure to various metals, as the aggressive rate of anthropogenic activity releases excess amount of pollutants into the environment. As a result, a large group of the population is exposed not only to basic metals, such as copper and aluminum, but also to toxic metals, more specific, mercury and lead which disrupt cellular homeostasis. This study is structured in a specific way in order to present the association of dementia with these heavy metals. The implication of ambient particulate matter to Dementia is also analyzed (Table 1).

2. AIM

The purpose of this bibliographic work is «ecological consciousness» of modern societies to be awakened, to identify the harmful environmental factors and to highlight their involvement in the causal pathogenesis of the most debated disease, dementia.

3. METHODS

During the review of literature, studies were selected by searching in reputable scientific databases such as PubMed BioMed Central, Science Direct, NCBI.

The eligibility criteria required a recent publication year, namely publications of the last 5 years, with the exception of a few previous publications of key information. The status of the first author was taken into account, as well the duration and follow-up of the clinical study, the geographical location that took place, its design, the size of the sample and the year in which it was conducted. Full-text publications were preferred.

The exclusion criteria were the year of the study, the size and the monitoring time of the sample. Posts that re-

stricted the ability to display full text were also excluded. However, the restriction on English language publications may have led to the exclusion of possible relevant studies in other languages, which contained important information.

The aim of the study is not to describe dementia and brain diseases, but to cite the findings regarding the environmental risk factors. An additional goal is to study the most recent research on the aforementioned study topics and compare them with the knowledge gathered so far, which has been collected by experts, in order to arrive at a poised conclusion in regards to brain toxicity of heavy metals.

4. TOXIC ENVIRONMENTAL FACTORS

Exposure of individuals to heavy metals such as aluminum, copper, mercury and lead has been shown to have serious effects on brain function (9). Below we will study the effect of the main environmental toxic factors which appear to have a direct effect on the occurrence of different types of dementia.

4.1. Aluminum (Al)

Aluminum is not found on a pure form in nature, but in the form of minerals from which it is extracted. It is the third most abundant element in the earth's crust and the first of the minerals. The British Davy, in 1807, was the first to support the existence of aluminum, while the Dane Oersted managed to isolate the metal. Although aluminum is abundant in the earth, its bioavailability is limited due to its insoluble nature. The content of aluminum that can be found in water and underground is extremely low. The rare exposure to aluminum maintains a low concentration load in the biosystem, however in pathological conditions, its concentration is increased (10).

From a toxicological aspect, the main aluminum compounds are considered to be aluminum oxide Al_2O_3 , aluminum hydroxide $Al(OH)_3$ and KOH and NaOH. Aluminum is absorbed primarily by the lungs and to a lesser extent by the gastrointestinal tract. After its absorption it is found in the blood stream, bound to proteins, in a percentage of 50% and mainly with albumin and transferrin. Insoluble aluminum salts do not display toxicity in contrast to soluble aluminum salts which show significant toxicity (11).

Exposure to high levels of aluminum leads to neuronal degeneration. In Alzheimer's disease, a high concentration of aluminum is observed in the degenerate neurons. Injection of aluminum into the cerebrospinal fluid of experimental animals has been found to cause progressive encephalopathy and degenerative lesions of nerve fibers, similar to those observed in people with Alzheimer's disease. This poses a strong evidence that aluminum is one of the causes of neurodegenerative disorders. Aluminum compounds combined with mercury compounds, can act synergistically in the degeneration of glial cells (12).

The majority of human exposure to aluminum derives from food, drinking water and alcoholic beverages (11). The use of certain pharmaceutical and cosmetic products, is the main source of aluminum since Al is one of the key ingredients of deodorants, and various personal hygiene products (10). Its intake is estimated at 10-100 mg per day, mainly from meat, cereals, dairy products and fish. Concen-

trations have also been reported in tea leaves, with higher concentration levels in young leaves, in the autumn and summer. Other sources of Al are food additives, containers, cookware and food packaging. Dietary intake of aluminum is minimal compared to amounts consumed through other sources, such as the use of aluminum cookware and utensils for cooking and storing food (10).

Aluminum is responsible for Neurochemical changes. Some of the cellular processes involved in neurodegeneration are oxidative stress, apoptosis and the formation of neurofibrillary tangles (NFT). A possible mechanism is the increase in the nitrosylation of tyrosine residues in cytoskeletal proteins such as tau proteins, mediated by peroxide dissolution, leading to the formation of neurofibrillary tangles (24). The presence of nitrotyrosine has been demonstrated in Alzheimer's disease proving its involvement in oxidative damage. Through oxidative stress it leads to neurodegeneration, and also causes the apoptosis of astrocytes, which contributes to the transportation of fluids and ions from the extracellular space to the blood vessels. With the fluids' loss, the neurotrophic support is reduced. This consequents to neurotic death. Apoptosis is considered to be the main toxicity mechanism of aluminum in nerve cells (10). Mitochondrial dysfunction marks the initial stage of aluminum neurotoxicity and is a prerequisite for this vicious cycle (13).

A possible mechanism for the initiation and development of these diseases could be the disturbed homeostasis of basic metals and the appearance of unfolded or incorrectly folded proteins which are basically the main culprits to several diseases. Aluminum has the ability to bind to negatively charged phospholipids in the brain, which contain polyunsaturated fatty acids and make them vulnerable to reactive oxygen species (ROS). Aluminum stimulates lipid peroxidation mediated by iron ions in the Fenton reaction, which causes ROS production, formation of trivalent iron ions, loss of cellular homeostasis and oxidative stress. The above disorders are observed in glial, astrocyte and microglial cells. Aluminum is an inhibitor of the cells' antioxidant enzymes which support the defense. The charge of the peroxide is neutralized by trivalent aluminum ions Al^{3+} forming the $Al-O_2$ complex which leads to the increase of the oxidizing capacity of O_2 (14, 15).

Regarding inflammatory reactions, aluminum induces the expression of transcription factor $NF-\kappa B$, the precursor of interleukin- 1β and phospholipase A2, which are involved in proinflammatory and pro-apoptotic signaling mechanisms. Aluminum increases pro-inflammatory cytokine levels such as $TNF-\alpha$ and $IL-1\alpha$ (15).

In addition to the above, aluminum is also involved in the apoptosis of nerve cells, as mentioned. It releases cytochrome c from mitochondria, reduces an anti-apoptotic molecule of Bcl-2 nerve cells in the mitochondria and endoplasmic reticulum, induces the displacement of the Bax pro-apoptotic protein and the activation of the executive caspase-3. These events mark the beginning of apoptosis. Aluminum has also been shown to lead to apoptosis by activating the SAPK / JNK kinase signal transduction pathway (stress-activated protein kinase or c-jun N-terminal kinase) (15).

Aluminum, in its oxidizing state as Al^{3+} , has a high affinity for organic and inorganic phosphates, carboxyls and deprotonated groups. Al^{3+} ions display a strong positive charge and a relatively small ionic radius, compared to other metal ions such as Ca^{2+} , Zn^{2+} and Na^+ . Thus it is bound strongly to metal-binding amino acids, such as histidine (His), tyrosine (Tyr), arginine (Arg), or phosphorylated amino acids and acts as a crosslinking agent. The binding of Al^{3+} to phosphorylated amino acids is strong, thus the accumulation of highly phosphorylated cytoskeletal proteins, including neurofibrillary and microtubule-associated proteins (MAPs) (15).

Aluminum has also been shown to accumulate in neurons, where it inhibits sodium (Na^+) / calcium (Ca^{2+}) exchange mechanisms and thus intervenes to the overload of the mitochondria with cytoplasmic Ca^{2+} . Increased levels of intra-mitochondrial Ca^{2+} leads to the opening of Mitochondrial Trifunctional Protein (MTP), which is considered to be the main trigger for neuronal damage. This is followed by the release of cytochrome c, which is a mitochondrial protein and an important apoptotic factor.

4.1.1. Recent research on Aluminum

Based on the above, aluminum is fairly regarded to be a neurotoxic agent. However, the association of aluminum with the etiology of various serious neurological disorders, such as Alzheimer's disease, remains unclear. Despite this uncertainty, there are several epidemiological reports in the scientific literature regarding exposure to aluminum and the risks of neurological disorders. An important reason for this uncertainty is the small number of examinees, due to the ethical concerns of the tests performed on humans.

There have been many studies in mammals, especially to those that have been exposed to aluminum throughout their lives, so that the effects of aluminum can be fully observed (16). Exley C, et al, in their recent study on human brain tissue, argue that high aluminum concentration in the brain is not an inevitable result during the process of aging (17). Wang, Z., et al, in a meta-analysis of 10,567 people, found that chronic aluminum exposure was associated with an increased risk of Alzheimer's disease (18). In contrast, an earlier study by Forster DP, et al, found no significant association between aluminum exposure and the incidence of Alzheimer's disease (19). Also, in a meta-analysis, Virk SA, et al, do not support the causal role of aluminum in the pathogenesis of Alzheimer's disease (20).

4.2. Copper (Cu)

As the brain displays low levels of antioxidant activity and becomes vulnerable to oxidative stress, free copper concentration levels must be kept minimum in order for a neuronal integrity to be sustained.

Copper contributes to the maintenance of life, the development and function of the nervous system, the formation and maintenance of myelin and finally is actively involved in various biochemical cycles, as it forms a building block of several proteins and enzymes. Its concentration in high quantities causes toxicity. The organs of copper accumulation are mainly the liver and the brain. Copper toxicity has an important role in the pathogenesis of Alzheimer's disease and in the general loss of cognitive function. It has also been shown that people who consume high-fat foods

Aluminum (Al)	Exley C, et al (31)familial Alzheimer's disease, autism spectrum disorder and multiple sclerosis. Detailed statistical analyses showed that aluminium was significantly increased in each of these disease groups compared to control tissues. We have confirmed previous conclusions that the aluminium content of brain tissue in Alzheimer's disease, autism spectrum disorder and multiple sclerosis is significantly elevated. Further research is required to understand the role played by high levels of aluminium in the aetiology of human neurodegenerative and neurodevelopmental disease.	2020	"Al is not an inevitable aging factor for human brain"	NO
	Wang Z, et al (32)	2016	"Al is associated with increased risk of Dementia"	YES
	Forster DP, et al (33)medical history, cigarette smoking, and exposure to aluminium. Design–A case-control study in which 109 cases of clinically diagnosed PDAT and 109 controls matched for age and sex were compared for exposure to the risk factors. Odds ratios (ORs	1999	"No correlation was found"	NO
Copper (Cu)	Virk SA, et al (34)	2015	"None etiological factor was found"	NO
	Yu F, et al (41)which is an important pathological component in the brains of Alzheimer's patients. Cu(II	2015	"Cu is neurotoxic and affects negatively human brain at any level"	YES
	Xu J, et al (43)	2017	"Cu could be therapeutic to a certain level"	NO
Mercury (Hg)	Geier DA, et al (52)	2019	"Hg is linked with the cognitive impairment of the elderly"	YES
	Sun YH, et al (53)	2015	"Increased Hg could increase the chance of developing Alzheimer's Disease"	YES
Lead (Pb)	Zhao ZH, et al (61)	2018	"Pb is linked to impaired memory and learning"	YES
	Schafer JH, et al (62)tibia lead, and homocysteine levels by cross-sectional analysis of data among subjects in the Baltimore Memory Study, a longitudinal study of 1,140 randomly selected residents in Baltimore, Maryland, who were 50-70 years of age. Tibia lead was measured by 109Cd K-shell X-ray fluorescence. The subject population had a mean ± SD age of 59.3 ± 5.9 years and was 66.0% female, 53.9% white, and 41.4% black or African American. Mean ± SD blood lead, tibia lead, and homocysteine levels were 3.5 ± 2.4 µg/dL, 18.9 ± 12.5 µg/g, and 10.0 ± 4.1 µmol/L, respectively. In unadjusted analysis, blood lead and homocysteine were moderately correlated (Pearson's r = 0.27, p < 0.01	2005	"High levels of Pb in the blood is related to high homocysteine levels which leads to an increased risk of Dementia"	YES
Particulate Matter (PM)	Chen H, et al (65)	2017	"Residents living near busy highways had a higher incidence of dementia"	YES
	Kioumourtzoglou MA, et al (66)	2016	"Strong correlations were found between long-term exposure to PM2.5 and neurodegenerative diseases"	YES
	Wu CH, et al (2)	2015	"Long-term exposure to PM10 or ozone was significantly associated with an increased risk of Alzheimer's disease and Vascular Dementia"	YES

Table 1. Findings about the correlation among Dementia and toxic environmental factors (Aluminum, Copper, Mercury, Lead and Particulate Matter).

in combination with taking copper supplements are at risk of memory impairment (21).

Since the beginning of the 20th century, there has been a significant increase in the use of copper for the construction of water pipes in developed countries (21). During World War I and World War II, its use was limited. After 1950 the use of copper pipes took off, reaching 90% of the plumbing of homes in the United States. At the same time, the Alzheimer's disease epidemic began in developed countries (21).

Another source of inorganic copper that is common in the developed world is the intaking copper through dietary supplements. A high-fat diet combined with elevated copper levels is considered to be a significant risk factor. Copper has been linked to oxidative stress and the destruction of nerve cells. Elevated homocysteine levels are also a risk factor for Alzheimer's disease; homocysteine interacts with copper during the oxidization of cholesterol and results to

neurons' destruction as well. The apolipoprotein E4 allele poses a risk factor for Alzheimer's disease, while apoE2 is a protective factor and apoE3 remains neutral. Certain alleles of the ATP7B protein gene, also known as the Wilson disease gene, increase the risk of Alzheimer's disease. In Wilson's disease the cytotoxic effect of copper is achieved by the production of free radicals, which destroy cell membranes by fat peroxidation. ATP7B gene controls free copper levels, which have been shown to be elevated in people with Alzheimer's disease (21).

A high concentration of copper and zinc has been found at amyloid plaques deposited in the brain tissue. There is also a high concentration of copper and zinc in the cerebrospinal fluid in people with Alzheimer's and Parkinson's disease (22). Maintaining copper homeostasis in the brain at normal levels is important, since copper can catalyze O2 activation by creating reactive oxygen species (ROS). The result of these potent oxidizing agents is a variety of

oxidative damage including lipid peroxidation, DNA oxidation, protein oxidation, and advanced glycosylation of end products (AGEs). Neurodegenerative disorders exacerbate the already increased oxidative stress, which is an early event in the development of Alzheimer's disease and is associated with normal aging. Oxidative stress is enhanced by the pathological increase in the interactions of divalent copper oxide with the A β peptide, and then the produced interactions promote the production of reactive oxygen species (23).

Studies focusing on the interaction of divalent copper oxide with t-protein or phosphorylated t-protein and their portions are rather limited. According to *in vitro* studies, the ability of t-protein to bind to copper also contributes to oxidative stress, as does the binding of β -amyloid peptide to copper (23).

A high-fat diet, along with inorganic copper intake, is considered an important risk factor for Alzheimer's disease. This hypothesis is difficult to be studied in humans. The studies are only applied experimentally to animal models, on the permitted extension, and therefore they are limited. The degree of absorption of copper depends mainly on its chemical state but also on the presence of compounds such as zinc and iron. Zinc has a competitive effect against monovalent copper. Zinc intake seems to have a beneficial effect, as its deficiency poses a risk factor for the disease (21).

4.2.1 Recent research on Copper

Regarding exposure to copper, several studies highlighted the role of copper as a cofactor in increasing the activity of β -amyloid protein toxic plaques and tau protein deposits. Disorder of copper homeostasis seems to promote the onset of Alzheimer's disease, as in its occurrence, copper levels are found to be elevated. At normal levels of nutritional intake, copper, as an essential trace element, helps to enhance brain function.

Yu F, et al, observed that divalent copper enhances the effect of β -amyloid protein on microglial activation and subsequent neurotoxicity (23). The study of Xu J, et al, reinforces the view that low copper levels are consistent with the cause of neurodegeneration and may well contribute to the pathogenesis of Alzheimer's disease. They also claim that copper therapy could help treat Alzheimer's disease. In conclusion, the question of whether excess or insufficiency of copper levels is responsible for the pathogenesis of Alzheimer's disease remains controversial (24).

4.3. Mercury (Hg)

Mercury is one of the most toxic natural elements, it is ten times more neurotoxic from lead and causes a numerous health problem. There is no safe threshold level of exposure and ideally it should not be detected as it does not provide anything beneficial to the human body. The half-life of mercury is 30-60 days, while in the brain it reaches about 20 years. The binding of elemental mercury to the brain after oxidation is due to selenium, which probably contributes to the retention of mercury for a longer period of time (25).

Studies have shown an association between mercury and Alzheimer's disease. Neurotransmitters such as acetylcholine, serotonin, dopamine, glutamate-one of the most important excitatory neurotransmitters of the central nervous system-and norepinephrine are inhibited in patients with

Alzheimer's disease. The same inhibition occurs in conditions of mercury toxicity. In Alzheimer's disease, there is a malfunction in the production of enzymes β -secretase, γ -secretase, cyclooxygenase-2, cytochrome-o-oxidase, protein kinases, monoamine oxidase, nitric oxide synthetase, acetylcholine transferase and caspases. These dysfunctions can be attributed to mercury toxicity. Immune and inflammatory responses to Alzheimer's disease also occur when cells are exposed to mercury. Mercury can inhibit DNA synthesis in the hippocampus, and has been linked to genetic mutations in the presenilin 1 and 2 genes found in Alzheimer's disease. Mercury toxicity causes disorders of minerals and vitamins, such as calcium, copper, iron, magnesium, selenium, zinc and vitamins B1, B12, E and C, a situation encountered in patients with Alzheimer's disease. Aluminum seems to increase mercury's toxicity (26).

Organic forms of mercury can easily penetrate blood-brain barrier and enter the neurons, resulting in neuronal loss and free entry of toxic metals and substances into the brain. Methylmercury, alongside with elemental mercury, leads to the extravasation of plasma proteins and to a greater extent of degenerative lesions of the sensory nerves, compared to motor nerves, possibly due to the disturbance of cellular metabolism. Exposure to relatively low concentrations of mercury in the air as vapor, has been shown to inhibit the polymerization of tubulin in the brain, which is a necessary protein for the formation of microtubules (25).

Mercury accumulates in all nerve cells, has a devastating effect on energy production and can damage the detoxification process, causing either death or chronic malnutrition in the cells. Exposure of cells to mercury leads to changes in membrane's permeability, changes in the macromolecular structure and DNA destruction. It is also blamed for causing oxidative stress and mitochondrial dysfunction, which can lead to changes in calcium homeostasis and increased lipid peroxidation (25). Evidence suggests that mercury could be a causative agent of Alzheimer's disease. Further investigation is needed.

4.3.1. Recent research on Mercury

Geier DA, et al, in their study provide epidemiological data, which linked the increase of ethyl-mercury levels in the blood with the cognitive impairment of the elderly (27). Also, Sun YH, et al, conducted a study in which they discovered that individuals who were exposed to mercury via dental amalgam, had an increased ratio of 1,132 on developing Alzheimer's disease, in comparison to those who were not exposed at all (28).

4.4. Lead (Pb)

Various epidemiological researches and studies in animal models prove the etiological association between Alzheimer's disease and lead exposure (29). Lead appears to be one of the environmental factors causing the levels of the precursor amyloid protein APP and β -amyloid A β to increase. Exposure to lead in prenatal and early childhood has been shown to increase biomarkers involved in Alzheimer's disease in adulthood. In particular, exposure at an early age is associated with a decrease in H3K9Ac histone over time (30).

A possible mechanism by which environmental factors can alter the expression of Alzheimer's predisposing genes,

is via epigenetic routes. Epigenetic mechanisms refer to genome change, affecting gene expression without altering the underlying DNA sequence. Animal studies showed that lead may be associated with epigenetic changes including DNA methylation and histone modifications (29).

Lead is highly toxic and bioaccumulative. Even exposure to acceptable lead levels could cause neurophysiological dysfunction and reduce peripheral nerve conduction rate. Exposure to lead is associated with severe cognitive and learning deficits. Lead is a risk factor for increased hippocampal gliosis, a state associated with the development of Alzheimer's disease. Rats exposed to lead during their early life showed increased amyloidogenesis and senescent plaque accumulation (31).

Inorganic lead behaves like calcium, mimicking its action in various systems. It replaces calcium ions and ensures the ability to penetrate the blood-brain barrier, resulting to accumulation in astroglial cells. It destroys immature nerve cells and prevents the formation of myelin. In addition, it disrupts the release of neurotransmitters, such as protein kinase C, which, among other basic functions, is involved in learning and memory processes. Lead also causes iron deficiency and anemia, exacerbates calcium and copper deficiency and competes with zinc, mainly in its enzymatic functions (29, 30, 31).

4.4.1. Recent research on Lead

The findings show that lead exposure has a long-term effect and may increase the risk of Alzheimer's disease. The presence of lead in the blood, results in its intervention in many organs and functions of the body, but also to the central nervous system, which is by far the most vulnerable. Zhao ZH, et al, reported in their study that rats exposed to lead showed deficits in work, as well as impaired memory and learning (32). In an earlier study, Schafer JH, et al, reported that in a large, general population sample, high levels of lead in the blood were found to be related to homocysteine levels. According to the data, both lead and homocysteine are associated with an increased risk of dementia (33).

4.5. Ambient Particulate Matter (PM)

The air pollution particles, which belong to the category of submetric particles (UFT, Ultrafine Particles) with a diameter of less than 0.1 μm , display high velocity and penetrate the capillaries and the brain. Chronic exposure of the individual to these particulate matter, leads to inflammation and causes cell damage (34).

Inhalation of gases and airborne particles causes inflammatory responses, increasing microglycemic activity and production of active oxygen forms. Particles less than 0.1 μm in diameter reach the brain directly through the olfactory bulb to the cortical and subcortical centers of the frontal lobe and cause damage. Inevitably, a vicious cycle of inflammation, capillary damage and further silent inflammation is developed, and an increase in pro-inflammatory cytokines is observed, which promotes astroglial and neuronal death (34).

4.5.1. Recent research on Ambient particulate Matter

Various studies have shown that PM_{2.5} particulate matter, in addition to being associated with a wide range of diseases, may also be responsible for a variety of neurode-

generative diseases, such as Alzheimer's disease. Chen H, et al, in a cohort study of a large population group, found that residents living near busy highways had a higher incidence of dementia (35). Kioumourtzoglou MA, et al, also reported strong correlations between long-term exposure to PM_{2.5} and neurodegenerative diseases such as Alzheimer's disease (36). Finally, Wu CH, et al, found that long-term exposure to PM₁₀ or ozone was significantly associated with an increased risk of Alzheimer's disease and Vascular Dementia (2).

5. PERSPECTIVES AND CHALLENGES OF FUTURE RESEARCH

Dementia is a degenerative disease that could be treated, if not avoided, by minimizing exposure to various risk factors. From this standpoint we made an attempt to study some of the toxic agents which pose a great threat for developing neurodegenerative diseases. More specific, we put "under the microscope" heavy metals and ambient air pollutants by comparing old and new studies.

Due to the unprecedented acceleration of urban development, heavy metals are the main culprits of toxicity in the environmental systems. Their impact on public health goes hand to hand to the probable sources of pollution, especially in urban areas. Future research should emphasize on the connection among the prevalence of dementia and the probable sites of heavy metal contamination. Zhao L., et al, observed that industrial activity in Southeastern China led to an increased level of heavy metals in the soil-rice system. Farmland soils are displaying an alarming accumulation of Cu, Zn and Pb, due to fertilizers and urban pollution, and that could lead to hazardous levels of heavy metals uptake in biological systems. An intriguing study found out that atmospheric dust carries heavy metal particles at various sizes, and this kind of contamination could be detected by measuring the contamination in urban road-deposited sediments. These observations prove that future studies should focus on the source of contamination and the manifestation of dementia. A distinct well-designed questionnaire might be helpful in order to clarify whether or not the participants have been exposed to heavy metals and if this kind of exposure is the main reason for developing the disease. As there are innumerable sources of contamination, future researchers should try to evaluate the participants by their work and living places, their everyday habits, the sources of food, vitamins uptake, probable hazardous spots and many other factors.

Ambient air pollutants are also a major problem regarding public health and a significant risk factor for developing dementia. Human activities are responsible for the soaring levels of air pollution, especially in low-income countries, which suffer severe consequences. It has been calculated that air pollution's death toll rises up to seven million deaths annually. Similarly to heavy metals, future researchers should establish an undeniable connection among the prevalence of dementia and polluted sites. Governments and scientists should collaborate in order to achieve a declining rate of air pollution. Society should also be educated on their everyday habits in order to minimize the pollution. Meta-analyses and epidemiological studies of large

scales, might be able to persuade the public for the danger of developing dementia due to atmospheric contamination. This should motivate each one to adopt environmental consciousness, in an attempt to protect public health. Apart from review studies and surveys, a more direct approach to this investigation could be the processing of tissue and blood samples of individuals, from a designated group of patients. However, this approach displays a limitation in regards with the number of participants, since it is rather challenging to gather a significant amount of people and receive samples for further study.

A concise presentation of the findings regarding the relation among Dementia and the highlighted toxic factors is presented at Table 1. In the case of Mercury, Lead and Ambient Particulate Matter, there is no doubt that they pose a serious threat for developing dementia. Future studies should focus on presenting further evidence on the matter. Potential findings could be beneficial not only to health specialists and researchers who want to treat and cure these kinds of diseases, but also to the society, since they could act as a protective shield against various risk factors that threaten public health. Aluminum and Cooper on the other hand, displayed a contradictive behavior in regards with their effects on dementia. The scientific community has studied thoroughly the effects of Aluminum and Cooper on humans but their relation to these neurodegenerative diseases remains obscure. Hopefully, future studies will shed light on this matter and add extra knowledge on this long-lasting arduous effort of scientists.

6. CONCLUSION

Given the enormous dimensions of the socio-economic impact caused by the increased amount of people suffering from dementia, some of the basic environmental risk factors were investigated. The aim of the investigation was to avoid or minimize the unpleasant effects on human health by analyzing in depth those environmental culprits who are responsible for the incidences of this disease.

The data collected suggest that elevated levels of particulate matter in the atmosphere and the accumulation of heavy metals in the body disrupt cellular metabolism, antioxidant defenses and immune responses, leading to the onset and progression of the disease. However, in some cases, writers found rather contradictive results. These were the cases of aluminum and copper (Table 1). Especially for aluminum, regardless its conspicuous negative effects on brain and neuron system, many researchers could not find enough evidence to support its correlation to Dementia. For copper, results were similarly contradictive. On the other hand, mercury, lead and ambient air pollutants were clearly associated to Dementia, as was expected due to their neurotoxicity (Table 1). However, further robust, time-consuming studies with repeated environmental exposure evaluation are needed in order to confirm the stated evidence and clarify the picture regarding aluminum and copper.

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