HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 3 (2024)

Environmental Influences on the Etiology, Prevention, and Therapies for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is ranked as one of the most important neurodegenerative disorders, causing devastating effects on populations of the aged across the world. Apart from causing cognitive and motor disturbances, this disease in the aged population presents a significant challenge in diagnosis and treatment. Although some advances have been made in the understanding of pathophysiology, the etiology of AD comprises a complex interplay among genetic and environmental factors. Genetic predisposition is not the sole cause of AD; major players are also environmental factors, which most commonly include exposure to neurotoxic agents like heavy metals, pesticides, and metal-based nanoparticles. It leads to abnormal accumulation and aggregation of β-amyloid peptides, along with phosphorylation of tau proteins in AD, which play major roles in defining the disease characteristics. Furthermore, AD pathogenesis encompasses the environmental factors that cause oxidative stress and epigenetic changes. Current research fits within the frame of understanding the role of these environmental factors in epidemiological and experimental data. The development of genome-wide and exposome-wide studies has established insight into gene-environment interaction. This means that the development of this research is paramount in promoting the role of precision medicine in neurodegenerative diseases. This paper integrates the very disparate insights from human epidemiological studies and experimental models into the building of a more comprehensive understanding of AD. It is through the examination of the synergistic effects of biometal dyshomeostasis, GE interactions, and environmental etiologies that approaches to intervention are made more probable in alleviating these devastating illnesses and managing patient outcomes.

Introduction

Metals are an essential trace element that finds its place in every tissue of the human body and is a key player in many enzymatic reactions as well as vital biological processes. Among the vital biological processes, the interactions of this element within the brain matter very significantly for neurotransmitter synthesis, energy supply, and gene expression. More significant is the fact that the function of Metals is not just confined to basic metabolic processes; it is involved in neural development and the preservation of brain health. This indicates that an optimal Metal level is warranted because both its deficiency as well as the surplus leads to several neurological disorders and crippled cognitive functions. For example, Copper, Zinc, Iron, and Manganese are not only a part of the redox reaction (Figure 1) but are also cofactors for very important enzymes, cytochrome c oxidase and superoxide dismutase. This indicates the fact that these metals play a dual role—that of a nutrient and simultaneously as a modulator of brain functions.

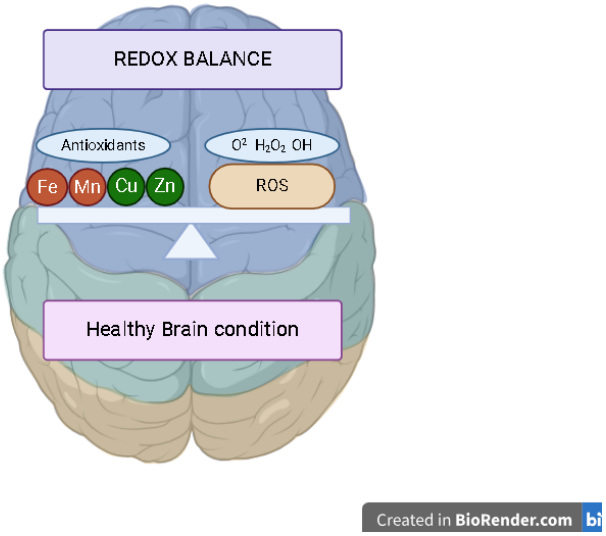

Figure 1. Optimal redox balance between metal Antioxidants and Reactive Oxygen Species. Source: Samynathan, 2024. Description: This image shows the antioxidant minerals iron, manganese, copper, and zinc in balance with the redox signaling process which represents a healthy brain.

Recent evidence has identified the importance of biometal dyshomeostasis in AD, especially with imbalances in essential metals like calcium, magnesium, and copper, which drive mechanistic ways in the progression of the disease, such as amyloid-beta aggregation and tau protein dysfunction (Islam et al., 2022; Kepp, 2017). This imbalance of metal, further compounded by the barrier mechanism caused by the selective permeability of the brain that is induced by the blood-brain barrier (Figure 2), provides important insight into potential therapeutic targets in metal-protein interactions (Harilal et al., 2020; Zhang Z. et al., 2016).

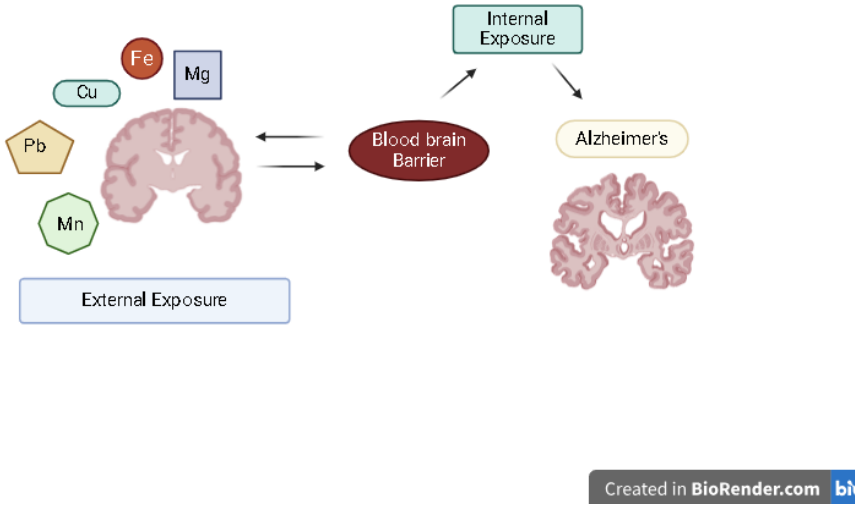

Figure 2. Process of biometal dyshomeostasis through the blood-brain barrier. Source: Samynathan, 2024. Description: This image shows the transportation of metals through the blood-brain barrier ultimately leading to the development of Alzheimer's.

An additional important mechanism is the dysregulation of metals and genetic susceptibility to environmental insults, through which diseases such as Alzheimer's and Parkinson's can occur. Gene-environment interactions are the central point that links the concept of genetic predisposition with the impact of factors in the environment that may alter the onset and development of both neurodegenerative diseases: Alzheimer's and Parkinson's (Patel, 2016; Gatz et al., 1997). Now, novel developments in genomic and exposome research make clear how lifelong exposures and genetic makeup combine to alter disease risk and progression (Wild, 2005; Rappaport, 2011). This makes the environmental factor, particularly that which is linked to lifestyle choices and chemical exposures, relevant since it has been noted to influence the onset of neurodegenerative diseases years before manifesting clinical symptoms. There is, therefore, the need for increased research, to strengthen exposure definition and validate biomarkers that may be useful in the early diagnosis of these conditions with certainty (Vineis et al., 2017; Barnes and Yaffe, 2011).

Moreover, animal models, particularly rodent models, have provided a great deal of usefulness in understanding pathogenic processes and as a way to validate mechanisms of G × E interactions in human studies. This is important since the model may bridge the theoretical and practical therapeutic applications. These allow an environment of control where cumulative impacts of genetic and environmental interactions are studied over a shortened period.

Methodology

The primary objective of this research was to synthesize knowledge and identify gaps in the understanding of environmental influences on the etiology, prevention, and therapies for Alzheimer's Disease (AD). This study aimed to integrate findings from various epidemiological and experimental sources to offer a comprehensive view of the role that environmental factors play in AD progression and management. This study was conducted through an extensive literature review, utilizing a range of academic databases and online resources including PubMed, JSTOR, NIH, and specific neurology and environmental health journals that are accessible online. The selection criteria for the literature included relevance to Alzheimer's Disease, a focus on environmental factors, and recency to ensure the inclusion of the latest findings up to 2024. Studies selected ranged from epidemiological research, genome-wide, and exposome-wide association studies, to experimental models involving both human subjects and animals.

The methodology involved the qualitative synthesis of findings from selected articles to determine the role of metals, pesticides, and lifestyle factors in the etiology and progression of AD. Information regarding genetic susceptibility and the impact of environmental factors was extracted and analyzed to establish connections between exposure and disease outcomes. The review focused on how these factors influence the development of AD pathologies such as amyloid-beta aggregation and tau protein phosphorylation. Once again, No physical experimentation was undertaken in this study. The research was entirely based on secondary data analysis of previously published studies. As such, no new empirical data were collected, and the study did not involve direct interaction with subjects or the environment. Therefore, no ethical approvals were required for this study, as it did not involve any experimental procedures or primary data collection in a physical lab setting.

This analysis underscored the complex relationship between genetic predispositions and environmental factors like metal toxicity and lifestyle choices in the pathology of Alzheimer's Disease. The literature suggests that chronic exposure to certain metals and lifestyle-related factors may exacerbate genetic vulnerabilities, leading to earlier onset and faster progression of the disease. The findings from this review contribute to the understanding of potential therapeutic targets and preventive measures, emphasizing the significance of controlling environmental exposures as part of a comprehensive strategy against AD. This methodology section confirms that the study was conducted as a non-empirical literature review and that all findings and discussions are derived from secondary data analysis, focusing on published research concerning the environmental influences on Alzheimer's Disease, therefore there will be no need for ethical considerations.

Mechanisms

Utilization and Synthesis of Metals in the Body

Metals are not naturally produced through the body's organs, but instead, they are digested through the human diet or smoking, synthesized in other organs, and then transported to the brain. Metabolically, the trace metals iron, copper, zinc, manganese, calcium, and magnesium are critical elements in brain function, and these elements are credited through specific processes: enzymatic, transmissive, and neuroprotective. (Jaishankar et al. 2014) Iron is needed in oxygen transport and its presence in hemoglobin, and tyrosine hydroxylase, among others, which are important for dopamine synthesis. Iron is transferred to the brain by transferrin, while its storage is mostly in ferritin. Copper facilitates neurotransmitter synthesis through enzymes like dopamine β hydroxylase, and in antioxidant defense through the enzyme SOD and CTR (Figure 3), as it is transported to the brain in the form of ceruloplasmin. Zinc influences the transmission of neurotransmission and regulates the activity of enzymes in synaptic vesicles, especially in the hippocampus, which is mediated by ZIP and ZnT transporters. Manganese is a cofactor for glutamine synthetase in ammonia detoxification and is transported in the DMT1. Calcium is an important ion in signaling and neuroplasticity, which is modulated by voltage-gated calcium channels and proteins such as calcineurin and calmodulin. (Krall et al 2021) Lastly, of the metals mentioned, magnesium is an element that protects NMDA receptor-related nerves by blocking the NMDA receptors from binding with glutamate in the brain, thus stopping the eventual excitotoxicity.

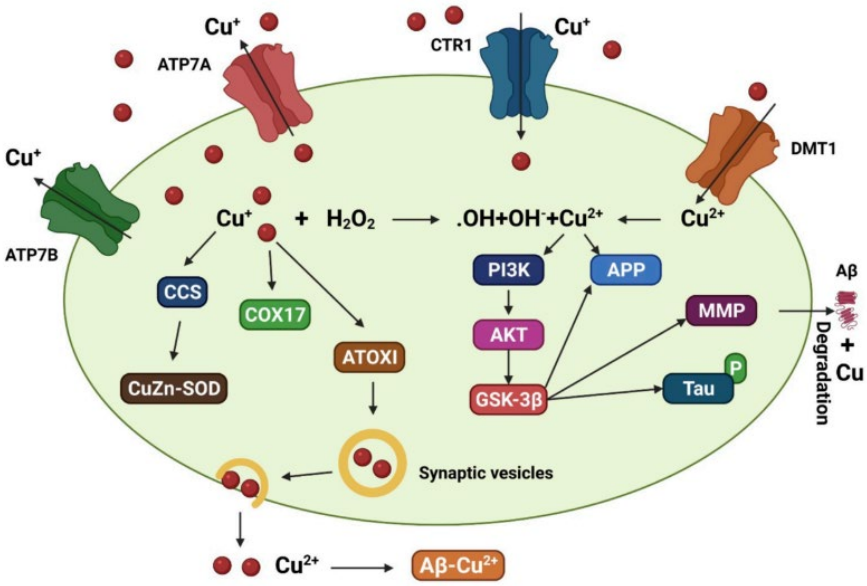

Figure 3. Copper transporter 1 (ctr1) transports copper ions into brain cells. Source: (Islam et al. 2022). Description: The usage and effects of metal pathways in the brain:

The proper functioning of metal pathways results in the structural integrity of the brain; hence causes efficient performance of neuronal activity upon binding to its receptors, which are important for brain functions of movement, cognition, and emotional regulation. (Wang et al. 2020) These bioinorganic pathways are the neuronic networks for the transportation of metals to the brain during obligatory functions such as the activation of enzymes, synthesis of neurotransmitters, and neuronal excitability regulation. (Nicoletti et al. 2021) Major

metal pathways that occur in the brain include systems for transport and regulation of iron, copper, zinc, manganese, and potentially harmful metals like lead and mercury. Iron is critical for cerebral oxygen transport through receptor-mediated transport across the blood-brain barrier by transferrin. Copper is transported across the human CTR1 protein and is homeostatically regulated to prevent toxicity. Highly abundant in synaptic vesicles of glutamatergic neurons, zinc is important in the modulation of transmission and synaptic plasticity, which involves processes in the induced activity of cognition and memory (Górska et al. 2023).

Other metals like lead, arsenic, and mercury, which are commonly found in e-cigarettes, vapes, and commercial pesticides, are toxic (figure 4); they can cross the blood-brain barrier and act like beneficial metals, which alter normal brain function. These metals can interfere with calcium homeostasis and evoke oxidative stress responses that result in neuronal damage. The concentration of metal ions within the brain is strictly regulated to accomplish different physiological functions. (Broadfoot 2022) Disturbances of these pathways, either through deficiency or overload, can lead to neurological disorders. For example, on one hand, iron accumulation is related to neurodegenerative diseases like Alzheimer's; on the other hand, copper and Zinc can lead to a disorder of neurodevelopment and neurodegeneration which can further escalate the symptoms of Alzheimer's.

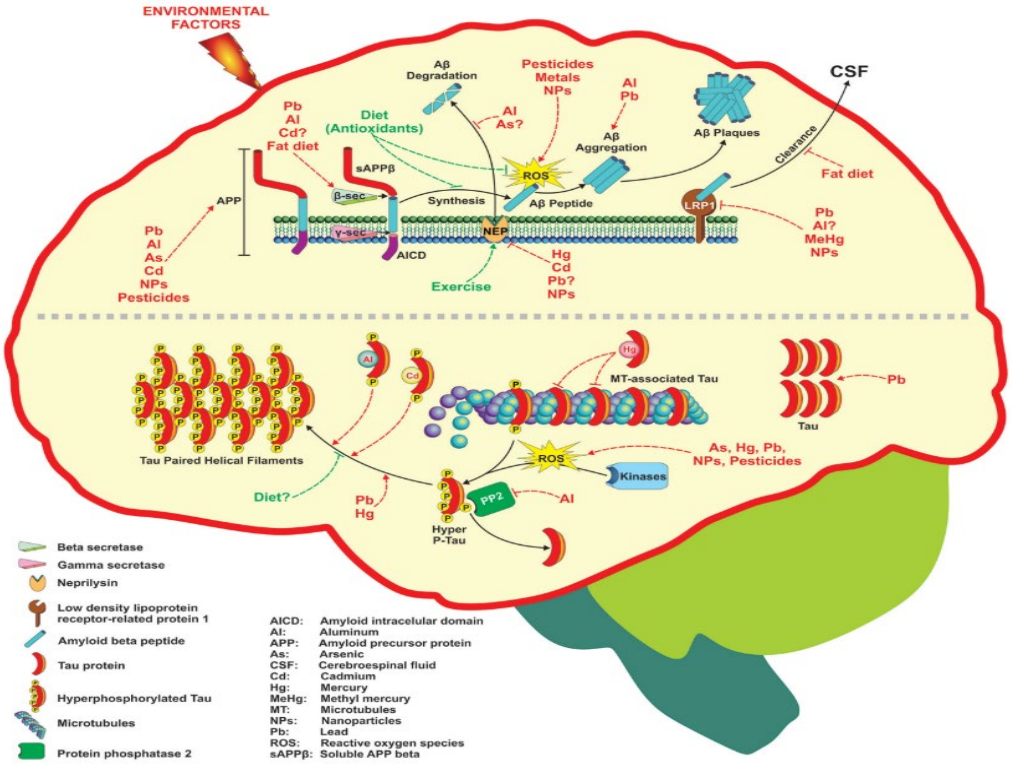

Figure 4. The synthesis of toxic metals, Lead, aluminum, arsenic, cadmium, and pesticides which cause tau hyperphosphorylation and subsequently, its formation as neurofibrillary tangles. Source: Chan et al., 2015. Description: The reaction that metals partake in the brain to synthesize tau protein.

Alzheimer's Pathology

Alzheimer's disease is a neurodegenerative disease that primarily affects the geriatric population. The two main mechanisms of development for AD are the build-up of beta-amyloid plaques outside neurons and the formation

of neurofibrillary tangles inside neurons. These buildups can lead to disruptions in communication between neurons and can cause brain atrophy, but mostly the loss of neurons, especially in parts of the brain that control memory retention and body function such as the Hippocampus and the Cerebral Cortex.

Role of Metal Toxins

AD, in this case, occurs when toxic metals and pesticides accumulate in the brain. These substances cause damage, especially to areas in the brain like the hippocampus and the cerebral cortex that are majorly associated with memory and cognitive functions. These mechanisms interfere with normal cellular functions through problems like oxidative stress and inflammation, which originate from interfering with normal cellular mechanisms, causing neuronal damage and death. (Wen et al. 2023) As neurons die, affected regions of the brain shrink in a process known as brain atrophy, which leads to significant changes in brain function and structure, leading to beta-amyloid plaque formation and tau protein transformation into neurofibrillary tangles. It is a neurodegenerative disease related to age but ties closely with the amount of exposure over time to toxic metals. As this process goes on, the patients start losing their cognitive abilities. This is because the regions in which the neurons are lost comprise the most crucial part where memories come from and are picked. (Wen et al. 2023) As such, the symptoms of AD start appearing, marked initially by severe memory loss, confusion, changes in behavior and personality, and cognitive and executive function. The continued exposure to toxic substances and chemicals worsens progressive neurodegeneration; it indeed creates a vicious cycle for such impairments.

Progressive Exposure to Toxic Metals on Genetics

The interaction between genetic predispositions and environmental toxins is a key area of research in understanding AD. Genetic factors can influence a person's immunity to metal toxicity and their capacity for metal detoxification. For example, variations in genes related to metal transport and storage, such as those encoding for metallothioneins and transport proteins like transferrin, can affect how metals are absorbed, distributed, and excreted by the body. Genes that regulate antioxidant defenses and DNA repair mechanisms also play a significant role in modulating the effects of metal exposure. Individuals with certain genetic makeups may have a reduced ability to counter the oxidative stress induced by metal exposure, thereby increasing their risk of developing AD. (Asiminicesei et al. 2024) The concept of gene-environment interactions is crucial in understanding the impact of long-term exposure to toxic metals on the risk of Alzheimer's Disease. Genetic predispositions can either exacerbate or mitigate the effects of environmental toxins. For example, the presence of the APOE ε4 allele, a well-known genetic risk factor for AD, has been suggested to influence the neurotoxic effects of metals like aluminum and mercury. Research indicates that APOE ε4 carriers may experience more pronounced cognitive decline following exposure to these metals compared to non-carriers. Additionally, epigenetic modifications triggered by metal exposure can alter gene expression without changing the DNA sequence, potentially affecting multiple pathways involved in AD pathogenesis as the exposure to the environmental toxins progresses through time. These modifications can occur throughout an individual's life given the time they had been exposed to such toxins.

Causes of AD

Alzheimer's Disease is a complex neurodegenerative disorder that affects the elderly, leading to progressive cognitive decline and memory loss. The causes of AD are not fully understood but are generally acknowledged to be a result of a combination of genetic, environmental, and lifestyle factors. AD has a strong genetic component, particularly in early-onset cases, which typically occur before the age of 65. Environmental factors also play a critical role in the development of Alzheimer's Disease. Exposure to neurotoxic agents such as heavy

metals and industrial chemicals has been linked to increased AD risk. Lifestyle choices can significantly impact the risk and progression of Alzheimer's Disease. Factors such as diet, physical activity, and alcohol consumption have been shown to influence the onset and severity of AD.

Genetic Influences

Genetics are believed to play a major role in Alzheimer's disease initiation and development, especially in early-onset cases. Toxic metals can cause breaks in the DNA strands and cross-linking, which prevents DNA replication and transcription. This can lead to mutations, which may cause genetic disorders in children. The most renowned genetic risk factor is the presence of the apolipoprotein E (APOE) ε4 allele (Figure 5). One who possesses one ε4 allele has an increased risk of developing AD, and this continues further with two alleles. Apart from APOE, there are several other genes, such as PSEN1, PSEN2, and APP, which directly are known to influence amyloid-beta production, the key pathogenic factor responsible for Alzheimer's disease. These genetic markers can ultimately result in early aggregation of amyloid-beta peptides, forming plaques, thus disturbing the cell functions and triggering neurodegeneration. (Lanoiselée et al. 2017)

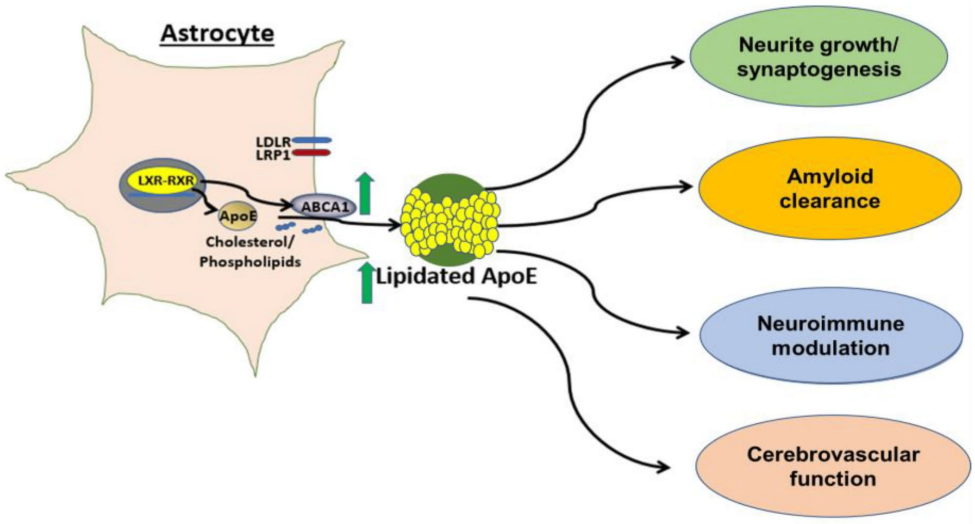

Figure 5. Production of lipidated Apolipoprotein E (ApoE) and its subsequent effects, such as promoting neurite growth, amyloid clearance, neuroimmune modulation, and improved cerebrovascular function. Source: (Suidan, Ramaswamy 2019). Description: astrocyte producing ApoE protein in regular function.

Environmental Factors

Environmental factors are involved in the development and progression of AD. For instance, chronic exposure to heavy metals, including lead, mercury, and aluminum, is correlated with AD. It is those metals that can accumulate within the brain tissue and are thought to contribute to oxidative stress and amyloid-beta aggregation like the mechanisms seen with certain pesticides in Parkinson's disease. (Wang et al. 2021) There is sufficient evidence to show that air pollution, in particular from fine particulate matter, is associated with a higher increase in the rate of cognitive decline via neuroinflammatory and oxidative stress pathways.

Lifestyle Contributions

Human Interest Lifestyle factors contribute significantly to the risk of developing Alzheimer's. Among the modifiable risk factors are a sedentary way of life and obesity. These are the causes of the reduction of neurotrophic factors vitally important for neuron survival and proper functioning. It is in that light that saturated fat and sugar intake may exacerbate the effects of insulin resistance, which is being increasingly viewed as a contributor to the pathophysiology of AD. Insulin resistance has been called "type 3 diabetes," but not all investigators support this view. Another factor is smoking and heavy alcohol intake. These inflame the brain, as it is, in all the other neurodegenerative diseases. The toxins from cigarettes are harmful above a certain threshold as metals such as aluminum, chromium, lead, and zinc are found in tobacco, cigarette paper, and cigarette filters. (Bernhard et al. 2005) Moderation in alcohol use and stopping smoking reduce these risks and are important components of precautionary health plans. (Decourt et al. 2022)

A. Therapeutic approaches include:
    a. Dietary changes
    b. Regular physical activity
    c. Cognitive training (puzzles, reading, music, etc.)
    d. Social engagement
    e. Adequate sleep
    f. Avoidance of smoking
    g. Limiting alcohol consumption

Preventing Early-Onset Alzheimer's in Regards to the Environment

Water and Diet: It is very important to make sure that drinking water is safe through filters that control heavy metals. Organic foods may help one reduce the intake of high levels of pesticides in the body. A diet rich in fruits and vegetables may further decrease residues of pesticides in your system.

Occupational Health: Safety protocols require that people working in industries that pose potential exposure to heavy metals and pesticides must be specified. Regarding this, the right protecting gears need to be used, and there should be good ventilation at the workplace. (Axe, 2024)

Routine Testing: Routinely undergo blood tests for heavy metals, particularly if you live or are otherwise located in heavily industrialized areas or rely on well water. This would provide you with an option for early detection and management of health conditions that could be contracted in case of contamination.

Nutritional Support: Nutrient intake can also protect against toxic metal-induced damage. Some of the antioxidants, like vitamins C and E, omega-3 fatty acids, and selenium, are capable of combating the effects of damage induced by toxic metals. A diet rich in varied nutrients will enhance your body's defenses.

Public Awareness and Policy: Lobby for stricter policies regarding the use and disposal of heavy metals and pesticides so that there is less exposure at grassroots levels. Through participation in local and national movements that push for the regulation of environmental pollution, there will be changes in policy by better provision of safe environments. (Vandenberg et al., 2023)

Early Diagnosis and Monitoring: Persons at high risk of exposure should undergo standard cognitive screening periodically. Early detection of any decline in cognitive functions would facilitate an intervention and management kind of program in due time to possibly ameliorate the negative effects on brain health resulting from exposure to metals and pesticides.

Current AD Treatment through the Candidate Gene Approach

Researchers select specific genes (candidates) to pinpoint the exact gene to which a specific disease has been related so far. These are called candidate genes. In the exact case example of Alzheimer's disease, the most well-known candidate gene is 'APOE' which stands for 'apolipoprotein E' as the gene mentioned here in one of its alleles or variations is called 'APOEε4', and it accordingly shows the risk of the concerned disease. To study these genetic factors in a controlled environment, researchers often use transgenic animals—usually mice or rats. These animals are genetically engineered to carry human versions of specific genes or gene variants. For example, mice might be engineered to carry the APOEε4 allele to study its effects on Alzheimer's disease progression. The Transgenic animals are then exposed to a controlled environment, which might include diet, exposure to toxins, physical activity, and more. Researchers can then figure out how genetic predispositions (carrying certain alleles like APOEε4) and environmental factors combine to influence the likelihood of developing a disease. The most prevalent limitation is the difference in the model organisms between humans and rodents. The biological process and the onset of diseases may be quite different among species, leading to findings with a limited general implication for human conditions. (Perkovic et al., 2021) Human diseases are often influenced by multiple genetic and environmental factors, and the given combination of them may matter. This complexity can hardly be represented within controlled environments. Furthermore, Techniques for making transgenic animals by the introduction, deletion, or modification of genes may not replicate natural genetic variation within the genome. Additionally, overexpression of gene knockdown does not reflect the participation of the gene in normal human physiology. (Mocellin & Provenzano, 2004)

Current AD Treatment

Chelation therapy for Alzheimer's disease subjects to chelate heavy metals from the body by using chemical compounds that form stable bonds with metal ions which are administered through IV or orally. The effectiveness and safety of such an intervention are very questionable. The heavy metal body burden and the bioavailability of chelating agents differ widely between patients, which may lead to a remarkably high variability of therapy outcomes. This progressive disease makes it challenging to lower metal concentrations within neural tissues, which are continually and gradually degraded, most likely leading to the control of the symptoms and cognitive decline. (Hegde et al., 2009)

Recent Advances in AD Treatments

Lecanemab (trade name Leqembi), which received FDA approval at the start of 2023, is designed to specifically target and clear soluble amyloid beta protofibrils from the brain. According to clinical trials, it is capable of decreasing amyloid burden and minimizing cognitive and everyday functional decline by between 26% to 37%. (Mcmillan, 2023)

Pros: Lecanemab targets specifically soluble amyloid beta protofibrils, which are believed to be one of the principal pathogenic drivers of Alzheimer's; Reduces Amyloid Burden: It has been proven in clinical trials to be capable of reducing the amyloid plaques in the brain in a significant manner; and slows Decline: Clinical studies have found it capable of reducing cognitive and functional decline by 26% to 37%, which results in a potentially better quality of life for patients.

Cons: As with many drugs, there may be associated side effects, which include infusion-related reactions and, more seriously, even conditions such as ARIA (amyloid-related imaging abnormalities); As a newly approved drug, it can be costly to obtain and not yet accessible in all areas; and its long-term effects and overall safety profile require more research.

Another breakthrough method for treating the problem is the use of gamma-wave and ultrasound technology, specifically the MRgFUS treatment. The production of such technology as goggle-like units or LED panels and stereos designed to stimulate some brain waves (Figure 6). According to preliminary research, such technology is capable of decreasing brain volume loss and decelerating cognitive and functional loss without any side effects which are usually associated with drug therapy. This method temporarily disrupts the blood-brain barrier and makes it viable for drugs to penetrate the barrier and cross into brain tissue. (Trafton, 2022)

Pros: Utilizes devices such as goggles or LED panels and stereos, which are non-invasive compared to administering a drug therapy; Promising research has discovered that it is capable of slowing cognitive decline and brain volume loss in a way that is without the side-effects normally seen in conventional drug therapies; and has the potential to be used in conjunction with other treatments to create a more rounded therapeutic approach.

Cons: While demonstrating great promise, gamma-wave technology is still in the early stages of research, and more research is needed to solidify its effects; As a new technology, it may not be widely available at this time, and the devices needed for regular usage may be cumbersome or even impractical for some patients; The long-term effects and efficacy of stimulating brain waves to open the blood brain barriers in this manner are unknown; and the primary concern with disrupting the BBB is the risk of unwanted substances entering the brain. This could lead to inflammation or infection.

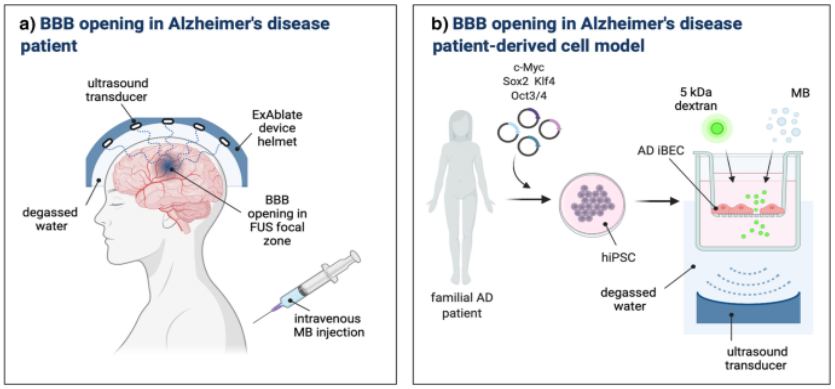

Figure 6. Materials Used in MRgFUS and BBB Opening in Cell. Source: (Wasielewska, 2022). Description: Shows how the MRgFUS method works to open BBB by using ultrasound waves.

The treatment pipeline for Alzheimer's disease is broad, with all classes of therapeutic interventions currently being probed. These are not only amyloid-targeting strategies, but also other anti-inflammatory agents, as well as existing agents for different diseases including cancer, Parkinson's disease, and diabetes in the pipeline for testing for use in Alzheimer's disease. (MedXpress, BrightFocus)

Pros: A huge range of therapeutic interventions are being explored, from anti-inflammatory agents to repurposed drugs from other diseases such as cancer, Parkinson's, and Diabetes; Diversification of research into other classes of drugs increases the chances of finding more effective treatment options; and Such diversification in research helps in the deepening of understanding of Alzheimer's pathology and possible treatment options.

Cons: With such a large number of different treatments being explored, efficacy can be highly variable among the treatments, with not all of them being successful; The huge diversity of research involves high investment, which can be an expensive and resource-intensive affair; and approval of new uses of existing drugs or for entirely new treatments is a complex and time-intensive regulatory process.

Results

This literature review has confirmed the vital influence of environmental factors in the etiology, prevention, and treatment of Alzheimer's Disease (AD). Results also indicated that genetic factors interact strongly with environmental toxins, including neurotoxic metals such as lead, mercury, and aluminum, which in certain genetic backgrounds predisposed to increased risk for AD and possibly to an earlier onset of the disease. The malfunction of metal homeostasis was specially observed in AD progression, also the amyloid-beta accumulation and tau protein hyperphosphorylation, hallmarks of AD pathology. Both the diet and air pollutants played a crucial role in the progression of AD, a diet rich in antioxidants exhibits potential, however, conversely pollutants show deleterious impacts when the exposure is prolonged. The review discussed the possibility of chelation therapy to reduce metal overload in neuronal tissues, although its effectiveness was non-uniform. Suggested preventative strategies included minimizing neurotoxin exposure and adopting healthy lifestyle choices. In conclusion, these data consolidate the importance of embracing both genetic and environmental factors as part of comprehensive AD prevention and treatment strategies, advocating the need to further investigate and develop precision medicine approaches to managing neurodegenerative diseases.

Conclusion

This study demonstrated the involvement of environmental factors in the pathogenesis, progression, and treatment of Alzheimer's Disease (AD). From an extensive literature review of the current knowledge, it is evident that genetics is influenced by environmental exposures, specifically toxic metals that modulate AD risk and progression. The evidence strongly supports the notion that environmental factors are unequivocally relevant to the disease pathogenesis, and metal dysregulation and oxidative stress are significant factors in the neurodegeneration leading to the main AD mechanism amyloid-beta plaques and tau protein tangles.

The outcomes of this study not only advance the knowledge of the complex factors involved in AD, but also open avenues for innovative preventive and therapeutic measures against the disease. For example, chelation therapy and lifestyle changes have been demonstrated to ameliorate the effects of environmental toxins, suggesting that combined management strategies may affect disease symptoms in a significant manner. Moreover, the ability of medicine to intervene based on the individual genetic and environmental circumstances may revolutionize the way patients with this disease are being treated.

There are however, remaining knowledge gaps, particularly the direct causal mechanisms involving specific environmental exposures to AD and the long term safety of the emerging therapies. It is thus imperative that the research in this field does not cease, particularly emphasis on experimental studies that can elucidate the mechanisms by which environmental factors modulate AD. Experimental studies should also be directed at the optimization of therapeutic interventions that target environmental exposures in even wider ranges.

To conclude, the present research indicates the importance of environmental factors in Alzheimer's disease. Only through continued study will we be able to unmask the full extent of environmental impacts on AD and develop preventive and treatment strategies that can lift off the burden of this disease from patients, families, and the world.

Limitations

While this review is extremely comprehensive, there are limitations that must be fully recognized with respect to the scope and the limitations of the literature and findings used. First, the scope of this paper is limited to Alzheimer’s disease and does not include other neurodegenerative diseases, although there are likely overlapping etiological factors and potential treatments in between several diseases. This focused approach allows for

a more in-depth examination for AD specifically, but may leave out broader knowledge that can be applicable for other neurodegenerative diseases.

The construction of this paper faced challenges of its own. One challenge was that it was constructed entirely of primary data sources, meaning that this paper was restricted in terms of interpretation and synthesis of original data and while I tried to include the most recent studies, this field is rapidly evolving, meaning that some newer findings may not have necessarily been available at the time.

FInally, the sources themselves present their own set of limitations. Many studies in the AD field involve small sample sizes over a short period of time which may not capture long-term effects.There is also a variation, albeit small, in how studies measure and report exposures and outcomes, which might lead to potential inconsistencies in making firm conclusions when compiled and analyzed. Furthermore, the research relies heavily on animal subjects, which may not be accurately representative of human anatomy and pathophysiology.

Acknowledgment

I extend my heartfelt gratitude to all my academic advisors that helped me write this paper with their guidance and critical insights which were extremely valuable in shaping this study. The expertise and encouragement of Dr. Jobin Varkey, Dr. Virgel Torremocha, and Jothsna Kethar have been a source of motivation and inspiration throughout my entire project.

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