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Alzheimer's Disease (AD): Risks, Treatments, Prevention, and Future Implementations

Tanzeel Huma[1,2*], Rukhsana Nawaz[3], Xiaohua Li[4], Andrew Willden[2]

[1]The University of the Lahore, Lahore, Pakistan
[2]Kunming Institute of Zoology, University of Chinese Academy of Sciences, Kunming, China
[3]Department of Clinical Psychology, College of Medicine and Health Sciences, UAE University, Abu Dhabi, the Emirate of Abu Dhabi
[4]Nanchang University, Nanchang, China
Email: *tanzeelhuma@outlook.com

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Abstract

Alzheimer's disease (AD) is the most common type of dementia found among geriatric populations worldwide and is growing quickly in low- and middle-income countries. Alzheimer's disease affects approximately 36.6 million people, and that number is expected to double over the next two decades. Those most susceptible to Alzheimer's are over the age of 60, though other associated factors such as sex, poor nutrition, education, impaired functional status, body mass index, diabetes, depression, smoking, alcohol, fish intake, and pesticide exposure have been reported, though none are clear. Gaining a better understanding of the etiology of AD requires multiple-site-targeted therapy to control the disease at the initial level. On the other hand, evidence suggests that risk factors for AD are modifiable. Hence reduction in associated risk factors may require very long follow-ups to make people aware of their effect on AD incidence. If these factors are effective in preventing the progression of AD, the target populations could be affected at the early stages of AD or even patients with more advanced disease.

Keywords

Alzheimer's Disease, Geriatric Population, Dementia, Age

1. History of Alzheimer's Disease

As described nearly a century ago by **Alois Alzheimer**, Alzheimer's disease (AD) is characterized by an early deterioration in memory followed by progressive impairment of other cognitive domains and concurrent large-spectrum

psychological and behavioral symptoms [1]. Prior to the description of AD, the disease was primarily characterized as simple dementia. The mistake is natural, given that AD is the most common form of dementia in geriatric populations, and accounts for 50% to 80% of all dementia cases [2]. Impairments like dementia or AD have long been associated with advanced age. In roughly 2000 BC ago, ancient Egyptian seemed to be aware that advanced age was associated with significant memory disorder [3], while over a millennia later, Solon wrote in his book that judgment could be impaired by physical pain, violence, drugs, and old age [4]. Curiously, there are some references to diseases like AD being distinct from dementia; for example, writers of Greek and Roman history presume the fabled stories of Agamemnon were true, but they identified psychopathology other than dementia. Unfortunately, these references disappeared by the middle ages—perhaps in an era marked by plague, religious warfare, and upheaval dementia did not inspire much interest or concern. Coincidentally, during this period, there were religious proscriptions against medical dissection. With the rise of the enlightenment and renewed interest in understanding the human body and mind and a more open-minded attitude towards learning about either, there became renewed interest in understanding dementia. In the early 20th century, Alzheimer was investigating a 51-year-old woman who exhibited an unusual form of amnesia and an inability to answer questions and some other unusual symptoms. After her death, Alzheimer's post-mortem examination of the body showed some novel features, notably distinctive plaques and tangles in the brain that we now know as neuritic plaques and neurofibrillary tangles. For a large part of the 20th century following this discovery, the only way to diagnose AD was to wait for the patient to die and examine the brain, and for most of this time, little progress was made in actually understanding the etiology of the disease.

2. Diagnostic Criteria for Alzheimer's Disease

The development of diagnostics for AD was comparatively slow. For half a century after discovering the disease, the symptoms we now associate with Alzheimer's were presumed to be part of the normal aging process. By the 1960s, there were some documented connections between cognitive decline and the presence of neuritic plaques and neurofibrillary tangles. This set the foundation for understanding AD as a complex disease with externally visible symptoms that could be diagnosed. By 1984, neurologists and pathologists had in place a series of guidelines to follow for diagnosing an individual's symptoms as assessed by family and friends and a basic neurological assessment [5]. Unfortunately, AD manifests itself differently in each individual, making such assessments haphazard. There are, however, some common symptoms, including memory loss—forgetting an event, repeating sentences and statements, misplacing things or placing them in illogical locations, forgetting names of family members, etc. —disorientation and misinterpretation of spatial relationships, problems with

speaking, writing, reasoning and concentration, changes in personality and behavior, depression, or difficulty performing normal daily tasks [6].

Recent advances in neurobiology and the pathogenesis of neurodegenerative diseases as well as the immense achievements of studies on human genetics paved the way for some updated diagnostic criteria and guidelines that were incorporated in 2011. The most important changes include the identification of three stages of Alzheimer's disease before memory loss, and the search for Biomarkers test to confirm the presence and absence of the disease. These stages are mapped out to correspond to the severity of the disease. The first, **Stage 1 [Mild]** can last 2 - 4 years [7]. During this period, patients with AD are less energetic and spontaneous, experience minor memory loss, exercise poor judgment, repeat sentences, and may withdraw or avoid new places in favor of familiar ones. Next, **Stage 2 [Moderate],** the longest stage, lasting 2 - 10 years [8], is marked by the affected individual who becomes clearly disabled, requires help in performing numerous tasks. Patients at Stage 2 may become more disconnected from their family and confused, forgetting recent events, family history, and even encounter difficulty recognizing familiar people. Similarly, speech problems increase, and patients may encounter problems in understanding reading and writing, and may invent new words. As the patients become aware of this loss of control, they may become dejected, short-tempered and restless. The final stage of the AD, **Stage 3 [Severe]** can last up to 3 years [9], during which patients encounter severe losses in basic functions, even losing their ability to feed themselves, speak, recognize people, and control bodily functions, e.g., swallowing or bowel and bladder control. By this point, memory worsens and may become almost non-existent, and patients sleep often and grunt or complain. At this stage, constant care is critical. In a weakened physical state, patients may become susceptible to other illnesses such as skin infections or respiratory problems, particularly when they are unable to move on their own [10].

The second aspect of the new diagnostic criteria is that patients suspected of either having or being susceptible to having AD should undergo a biomarker test. While several studies have attempted to numerous potential biomarkers, the two accepted markers identified for Alzheimer's disease include beta-amyloid and Tau proteins, and their level in blood and cerebrospinal fluid determine the disease at the early stages [11].

3. Prevalence and Age Factor

Current epidemiological forecasts predict that AD will have a marked impact on both the medical system and society at large due to the prevalence of AD dementia and the distribution of Alzheimer's being most reported in patients 60 - 65 years old [12] [13], which will continue to form a much larger share of the population in developing and developed countries worldwide. While the early onset of Alzheimer's can occur much earlier than 60 years of age, the frequency of dementia is relatively low at this early stage, and there is an exponential in-

crease in the dementia with age (reaching almost 50% of those in 85 years of age). This risk increases even further past 85, from 12.5% per year after 90 years of age, 90 - 94 years age group to 21.2% per year in the 95 - 99 years old age group, and to 40.7% per year in those at least 100 years of old.

The age association is especially troubling in terms of medical care. The severe progressive nature of AD leading to worsening functional and cognitive decline and increased risk of the disease is becoming a major determining factor in the institutionalization of the elderly. This heterogeneity may result from differences in localized severity of brain damage or variations in patient's personalities, life history, environmental risk factors and socio-economic conditions that may also be the cause of metabolic cognitive syndrome (MetS), which is also linked with the AD.

4. Potential Causes of Alzheimer's Disease

An adult human brain contains 100 billion neurons and 100 trillion synapses which allow the signals to travel throughout the brain circuits and create thoughts, memories, skills and movement [14]. In AD, interference causes disturbance in the function of these neurons and synapses, the number of synapses declines, neurons die and information transfer at synapses begins to fail. Precisely why this occurs is not clear. What we currently know is that AD is a chronic multi-factorial brain disorder that develops in response to multiple risk factors including environmental factors, chemical imbalances in the brain, hereditary factors and other brain development abnormalities. Studies on AD have noted a clear autosomal dominant pattern in people reported for AD before 65 years of age and people with inherited autosomal dominant genes who have not yet developed symptoms [15]. Currently, three genes mutations have been described that may lead to early forms of AD—amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2). Mutations in these genes seem to alter the proteolytic processing of amyloid precursor protein, leading to an increased production of the β-42, which forms the core of neuritic plaques and has been shown to act as a neurotoxin [16].

A broad range of environmental components may exacerbate damage to the brain and contribute to either the severity or risk of AD. For example, some environmental factors interact with the genetic liability in a negative manner to produce disorders. In terms of genetic risks, since mental illness can run in families, family history provides strong evidence that AD is more likely to develop in first degree relatives who have a parent, brother or sister with Alzheimer's than those who do not have a first-degree relative with Alzheimer's [17] [18]. Those who have more than one first-degree relative with Alzheimer's are at an even higher risk of developing the disease [19]. Other studies show that illiterate people are at higher risk for AD than those who are highly educated [20]. According to the cognitive hypothesis, additional years of education may increase the connection between neurons and activate the brain to compensate for the early brain

changes of Alzheimer's by using alternate routes of neuron-to-neuron communication to complete a cognitive task [21] [22]. Other studies suggest that other modifiable factors, such as remaining mentally [23] and socially active, may support brain health and possibly reduce the risk of Alzheimer's and other dementias [24] [25], though further follow-up studies are needed to verify these possibilities.

5. Diet, Chemicals, and Alzheimer's

Many studies have investigated whether exposure or ingestion of certain compounds may alter the risk for AD. For example, formaldehyde is found in paint, cloth and medicinal and industrial products. The level of human endogenous formaldehyde is maintained at a low concentration (0.01 - 0.08 $mmol \cdot L^{-1}$ in blood) under normal physiological conditions, but the concentration increases as individuals age, especially once they are over 65 [26].

Dietary components that are ingested maybe change the chemistry of amyloid in the brain in meaningful ways; for example, copper is an essential element in diets, and an important trace metal for the immune system, blood vessels, nervous system, and bones. Copper predominately enters the body via drinking water and from food sources like nuts, meat, shellfish, fruits and vegetables. Essentially, copper is prevalent and necessary. However, some studies found that copper exposure over long periods can create chemical imbalances and increase the production of toxic proteins and clumps, thus forming the plaques associated with the physical brain changes that accompany AD [27]. Study results indicate that diet with high saturated fat content increase LD Aβ levels, whereas a diet with low saturated fat decreased these fractions and total serum cholesterol level in mid-life is a recognized risk factor for AD [28]. Accordingly, fish consumption is linked to the risk of AD in that consumption of fish provides some protective effect, likely due to the long-chain omega-3 fatty acid that acts as supplements against cognitive impairment [29]. Finally, a meta-analysis of 15 studies showed that those who consume alcohol have a higher risk of developing AD as compared to those who do not [30].

Though the existing studies report numerous potential factors, there is still keen evidence supporting the association of AD and brain disorders with the environmental, social, psychological and biological factors. The potential behind these reports cannot be ignored and should be evaluated. Accordingly, a vital objective of further research is examining tobacco toxicity and its potential relationship with gene interactions and brain disorders [29]. One study reported that several genes together with environmental factors may interact with cannabis to increase the risk of psychosis [31], though again there need to be comparative studies examining the potential roles of nicotine and cannabis, preferably that evaluate other known risk variables.

6. Genetic Basis of Alzheimer's Disease

This is an irreversible, progressive brain disease due to the development of amy-

loid plaques and neurofibrillary, or tau, tangles which results in the loss of connections between nerve cells and the death of nerve cells. Scientists have found evidence of a link between Alzheimer's disease and genes on four chromosomes, labeled as 1, 14, 19, and 21. Early-onset Alzheimer's disease occurs in people aged 30 - 60 and represents less than 5% of all people with Alzheimer's. Most cases are caused by an inherited change in one of three genes: APOE $\varepsilon 2$, APOE $\varepsilon 3$ and APOE $\varepsilon 4$, resulting in a type known as early-onset familial Alzheimer's disease, or FAD. For others, the disease appears to develop without any specific, known cause. A child whose biological mother or father carries a genetic mutation for early-onset FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child has a very strong probability of developing early-onset FAD and it is caused by any one of a number of different single-gene mutations on chromosomes 21, 14, and 1. Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP), on chromosome 14 causes abnormal presenilin 1 (PSEN1) to be made, and on chromosome 1 leads to abnormal presenilin 2 (PSEN2). Each of these mutations breaks APP, a protein whose precise function is not yet fully understood. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of the disease. Critical research findings of early-onset Alzheimer's have helped identify key steps in the formation of brain abnormalities typical of the more common late-onset form of Alzheimer's. Genetics studies have helped explain why the disease develops in people at various ages. NIA-supported scientists are continuing research into early-onset disease through the Dominantly Inherited Alzheimer Network (DIAN), an international partnership to study families with early-onset FAD. By observing the Alzheimer's-related brain changes that occur in these families long before symptoms of memory loss or cognitive issues appear, scientists hope to gain insight into how and why the disease develops in both its early- and late-onset forms.

Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in the mid-60s and later. The causes of late-onset Alzheimer's are not yet completely understood, but they likely include a combination of genetic, environmental, and lifestyle factors that affect a person's risk for developing the disease. Researchers have not found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor—having one form of the apolipoprotein E (APOE) gene on chromosome 19—does increase a person's risk. APOE comes in several different forms, or allele APOE $\varepsilon 2$ is relatively rare and may provide some protection against the disease. If Alzheimer's disease occurs in a person with this allele, it usually develops later in life than it would in someone with the APOE $\varepsilon 4$ gene. Dozens of studies around the world have shown that when a person has one type of the APOE gene, called APOE4, it increases their odds of getting Alzheimer's at some point in their lives. But the link isn't completely clear-cut. Some people who have APOE4 don't get Alzheimer's. And others have the disease even though they don't have APOE4 in their DNA. In other words, though the APOE gene clearly

influences Alzheimer's risk, it's not a consistent sign that someone will have the disease. Scientists need to learn more about the connection.

Using a relatively new approach called genome-wide association study (GWAS), researchers have identified a number of regions of interest in the genome—an organism's complete set of DNA, including all of its genes—that may increase a person's risk for late-onset Alzheimer's to varying degrees. By 2015, they had confirmed 33 regions of interest in the Alzheimer's genome. A method called whole genome sequencing determines the complete DNA sequence of a person's genome at a single time. Another method called whole exome sequencing looks at the parts of the genome that directly code for the proteins. Using these two approaches, researchers can identify new genes that contribute to or protect against disease risk. Recent discoveries have led to new insights about biological pathways involved in Alzheimer's and May one day lead to effective interventions.

A blood test can identify which APOE alleles a person has, but results cannot predict who will or will not develop Alzheimer's disease. It is unlikely that genetic testing will ever be able to predict the disease with 100 percent accuracy, researchers believe, because too many other factors may influence its development and progression. Currently, APOE testing is used in research settings to identify study participants who may have an increased risk of developing Alzheimer's. This knowledge helps scientists look for early brain changes in participants and compare the effectiveness of treatments for people with different APOE profiles. Most researchers believe that APOE testing is useful for studying Alzheimer's disease risk in large groups of people but not for determining any one person's risk. Genetic testing is used by researchers conducting clinical trials and by physicians to help diagnose early-onset Alzheimer's disease. However, genetic testing is not otherwise recommended.

Alzheimer's disease strikes early and fairly often in some families-often enough that experts single it out as a separate form of the disease. It's called early-onset familial Alzheimer's disease. By studying the DNA of these families, researchers have found that many of them have flaws in related genes on chromosomes 1 and 14. A few of the families share a difference in one gene on chromosome 21.

Alzheimer's disease (AD) is the most commonly diagnosed form of dementia in the elderly. Family history is the second strongest risk factor in AD, following advancing age as the first. Rare, highly penetrant pathogenic mutations in the genes *APP*, *PSEN1*, and *PSEN2* cause the early-onset familial form of AD. The genetic variants leading to the highly prevalent late-onset AD are complex and heterogeneous, with the commonly occurring $\varepsilon 4$ allele in the gene *APOE* being the most well-established risk. Taken together, however, the four genes explain less than 50% of the heritability in AD. Recent efforts to explain the remaining heritable risk factors employing genome-wide association studies (GWAS) have revealed a number of novel AD genes, which implicate a range of diverse neuroimmunological pathways eventually leading to AD. In this chapter, we review

the most significant genetic findings and ongoing genetic studies in AD, with emphasis on the strongest novel AD genes arising from the recent GWAS reports (Developing Therapeutics for Alzheimer's disease).

7. Treatment Methods to Cure Alzheimer's Disease

In brief, during AD neurons are the chief cells being destroyed. In the brain, neurons connect and communicate at the synapse, where tiny bursts of neurotransmitters carry information from one cell to another. AD disrupts this process, eventually destroying synapses and killing neurons, thereby damaging the brain's communication network and leading to gradual degradations in cognitive and motor function. Curing the disease would then necessitate first stopping the process that leads to the death of neuron cells, and then finding a way to actually regrow damaged or dead neurons. The potential difficulty in this venture is enormous, thus no wonder at the moment there are no specific strategies that can fully cure the disease. Instead, there are three potential venues that if pursued correctly may help to inhibit the disease's progression.

7.1. Prevention

To prevent the onset of AD, there are several possibilities: direct genetic manipulation; inhibition of β-amyloid production; or inhibition of β-amyloid aggregation. Currently, the main drug used for this purpose is cholinesterase, which works by slowing down the disease activity that breaks down key neurotransmitters, *i.e.* donepezil, galantamine, rivastigmine, and tacrine.

7.2. Arresting Progress

Given the nature of AD, the disease's progress can be arrested by using anti-inflammatory drugs, antioxidants/free radical scavengers, and other neuroprotective methods. Arresting Progress seems to be quite promising and moderately successful in that it can delay the risk and time of the disease.

7.3. Symptomatic Treatment

Since we neither know enough of the underlying causes of AD to develop a targeted treatment nor have the technical capacity to actually reverse the damage caused by the disease, the extant treatments focus on the replacement of neurotransmitter (acetylcholine, glutamate and serotonin) losses during the course of AD. Cholinesterase inhibitors have proven a successful approach in delaying cognitive deterioration, and the serotonergic system can be manipulated by the use of atypical antipsychotics have proven a viable strategy for the treatment of some non-cognitive symptoms, but again until the bases and risks for AD are more clearly understood, these are merely palliative care and not an actual solution.

8. Conclusions and Future Direction

Alzheimer's has a troublingly double-edged sword. On one hand, we do not

clearly understand it or how to cure it, and on the other, for reasons unknown incidences of AD keep growing. Accordingly, researchers are constantly looking for new ways to treat the disease. At the moment, a promising focus is working on pre-symptomatic Alzheimer's subjects, carrying genetic determinants which eventually will develop into Alzheimer's or asymptomatic subjects which are at a risk of AD with biomarkers of AD pathology. Working with these populations informs how to avoid the risks before they develop further, theoretically offering novel opportunities for new treatment options. Other research groups are also working on nonhuman primate Alzheimer models and try to understand the underlying nature of AD and the efficacy of novel treatment options.

Now, there are so many things that we have to keep in mind while exploring this factor. Researchers need to find the missing links in all this process. If we focus on the dietary habitat, then the history of the AD began 20 years ago, when the trend of Coca-Cola and diet soft drinks started. These drinks contain a high amount of formaldehyde. Maybe a case repot will help us to solve it. There are some studies in mice and rats, which show that formaldehyde does not have any effect, and the accumulation of beta amyloid plaque was not observed. But, more research is needed to study the effect of formaldehyde in non-human primates and resolve such issues.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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