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Causes, Identification & Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is one of the commonest neurodegenerative diseases characterized by genetic and environmental factors. The present work is based on the genetic mutations that are connected with early onset of AD and their diagnostic significance. The present study had a qualitative research approach and involved the analysis of the existing literature to determine the genetic variations in PSEN1 and PSEN2 genes and to compare the current diagnostic options. Four key mutations—p. These are Thr119Ile, p.Gly209Ala, p.Gly417Ala, and p.His169Asn mutations, which are associated with early onset of Alzheimer's disease. New research on neuroimaging and biomarkers has provided better accuracy in diagnosis in the initial stages. These genetic findings are then compared to other environmental and lifestyle factors in order to show the multifaceted relationship between the two and their impact on disease development and progression. The recognition of particular gene mutations improves the knowledge of the AD etiology and makes it possible to apply advanced diagnostic methods in practice, which points to the further development of personalized medicine in the treatment of AD.

Keywords: Alzheimer's Disease Genetics; Early-onset Alzheimer's; Diagnostic Biomarkers; PSEN1 and PSEN2 Mutations

Introduction

Alzheimer's disease is a chronic and generalized dementia that affects the brain and is manifested by loss of memory and thinking skills, behavioural changes and gradual decline in physical abilities. Alzheimer's disease is the most frequent form of dementia, and it affects about 6.7 million people in the United States of America; researchers estimate that by the year 2050, this number will have risen to 13.8 million due to the population's ageing process (Emil [1]). The financial impact of AD is high and is predicted to increase with a global cost of $355 billion in 2021 and more than $1 trillion by 2050 (Wong [2]). Such statistics refer to the need for such factors' investigation, as well as the condition identification with a high degree of efficacy and the effective approach determination to this condition, which significantly limits a patient's movements. A number of studies suggest that genetic, environmental, and behavioural factors may predispose to AD. Research shows that AD risk is 70 percent genetic; it is linked to the APP, PSEN1, and PSEN2 genes (Kabir, et al. [3]).

Carriers of ApoE ε4 genotype had a 12 times greater risk than non-carriers (Lozupone, et al. [4]). Environmental variables including air pollution and heavy metals and lifestyle factors like nutrition, exercise, and brain activity also contribute to AD development (Daiber, et al. [5]). Over time, diagnostic technologies and biomarkers have recognised Alzheimer's disease, which is alarming. Alzheimer's disease's pathology characteristics, amyloid plaques and neurofibrillary tangles, may be seen on MRI and PET scans (Matsuda, et al. [6]). Biomarkers in cerebrospinal fluid (CSF), including Aβ42, t-tau, and p-tau, may aid in diagnosing AD, even in pre-clinical patients (Mattsson, et al. [7]). New findings in blood-based biomarkers for AD also seem to hold hope for non-IV and affordable screening; the plasma Aβ42/40 ratio and p-tau217 have been shown to have high diagnostic performance (Hardy Sosa, et al. [8]).

It is important to understand the workings of Alzheimer's disease in order to find ways to treat and prevent it. Therefore, as the incidence of AD escalates, the socio-economic burden will increase and impact the healthcare systems and families all over the world. More advanced research in this area can result in discoveries that may help in the alleviation or control of the advancement of the disease, which is beneficial to millions of patients. Also, determining prognostic markers that can help in the early detection of diseases can greatly improve the patient's condition by intervening early.

The main purpose of this article is to give a comprehensive understanding of the factors, diagnosis, and possible therapies for Alzheimer's disease with an emphasis on recent findings. The specific objectives include Three GBA:

1. Reviewing genetic, environmental, and lifestyle risk factors for AD.
2. Comparing and contrasting diagnostic procedures and biomarkers existing and new.
3. Comparing and contrasting current interventions and exploring potential disease-modifying treatments. This research intends to help combat Alzheimer's disease by achieving these goals.

Material and Method

This qualitative study uses secondary data to determine Alzheimer's disease's aetiology, diagnosis, and treatment. A literature review of reliable database research publications is the study technique (Cooper, et al. [9]). PubMed, Google Scholar, and ScienceDirect, which include a large number of peer-reviewed articles and research, were utilised to compile resources. Because these databases give reliable and complete data, the acquired data are trustworthy and complete. An awareness search approach was utilised to identify similar research works and publications. The following keywords and phrases were used to conduct a systematic search: "Alzheimer's disease causes," "genetic contribution to AD," "environmental risk factors for AD," "diagnosis," "biomarkers in AD," "neuroimaging in AD," "current treatment of Alzheimer's," and "novel therapies for Alzheimer's."Categorisation of the data was used in the evaluation and interpretation of the collected secondary data, whereby the process of content analysis was followed. By choosing this qualitative form of research, the author was able to focus more on the nature of the themes as well as the patterns present in the literature which in turn enabled the author to understand the multifaceted nature of Alzheimer's disease. Content analysis entailed categorising the information into coherent units, for instance, attributes, genes, environment, tests, and therapy.

This helped in the process of identifying common trends and major conclusions in other qualitative research, making it possible to evaluate the state of the knowledge in the field. While analysing the content of the collected data, the focus was on the quality and applicability of the sources. This was done to avoid Including articles from non-standardised websites and those with low scientific information about the studies mentioned. Furthermore, the emphasis was on the studies published in the last five years to reflect the current progress and discoveries in Alzheimer's disease. This article uses qualitative research and secondary data to review and extend the knowledge of Alzheimer's disease, causation, diagnosis, and management from an informed and comprehensive perspective. The methodologically sound process of making conclusions guarantees and gives an account of the existing knowledge in the scientific community about Alzheimer's disease.

Results and Discussion

Genetic, Environmental, and Lifestyle Factors Contributing to Alzheimer's Disease

Table 1 and Figure 1 depict some of the genetic mutations related to early-onset Alzheimer's disease (EOAD). Four mutations in the PSEN1 and PSEN2 genes were identified: PSEN1 mutations p. Thr119Ile, p.Gly209Ala, and p.Gly417Ala, and the PSEN2 mutation p.His169Asn. These mutations were observed in patients with the (AOO) between 37 and 64 years, and all the patients were ApoE ε33 carriers. The PSEN1 mutations are new; the PSEN2 mutation has an ExAC frequency of 0.0001648, which lets the confirming that it is rare (Giau, et al. [10]). The p.Thr119Ile mutation in PSEN1 was observed in a 64-year-old female patient with EOAD with the prediction of a PolyPhen2 score of 0.9, which is considered to be damaging, and the Sift score of 0.06, which is tolerant, suggesting that the mutation is likely pathogenic.

Table 1.

Genes	DNA Change	Protein Change	AOO	Gender	ApoE	ExAC	PolyPHen2	Sift Score	Provean	Family History	Clinical Features
PSEN1	c.356>T (Exon 5)	p.Thr119lle	64	F	ε 33	Novel	0.9(D)	0.06(T)	-2.37(N)	Unknown	EOAD
	c.626>T (Exon 7)	p.Gly209Ala	54	F	ε 33	Novel	1(D)	0(D)	-5.64(D)	Probable Positive	AD, depression
	c.1250>T (Exon 12)	p.Gly417Ala	37	M	ε 33	Novel	0.99(D)	0(D)	-5.33(D)	Unknown	AD with Parkinsonsm
PSEN1	c.505>T (Exon 6)	p.His169Asn	59	F	ε 33	0.0001648	0.925(D)	0.04(D)	-6.33(D)	Unknown	L:eft Dominant AD

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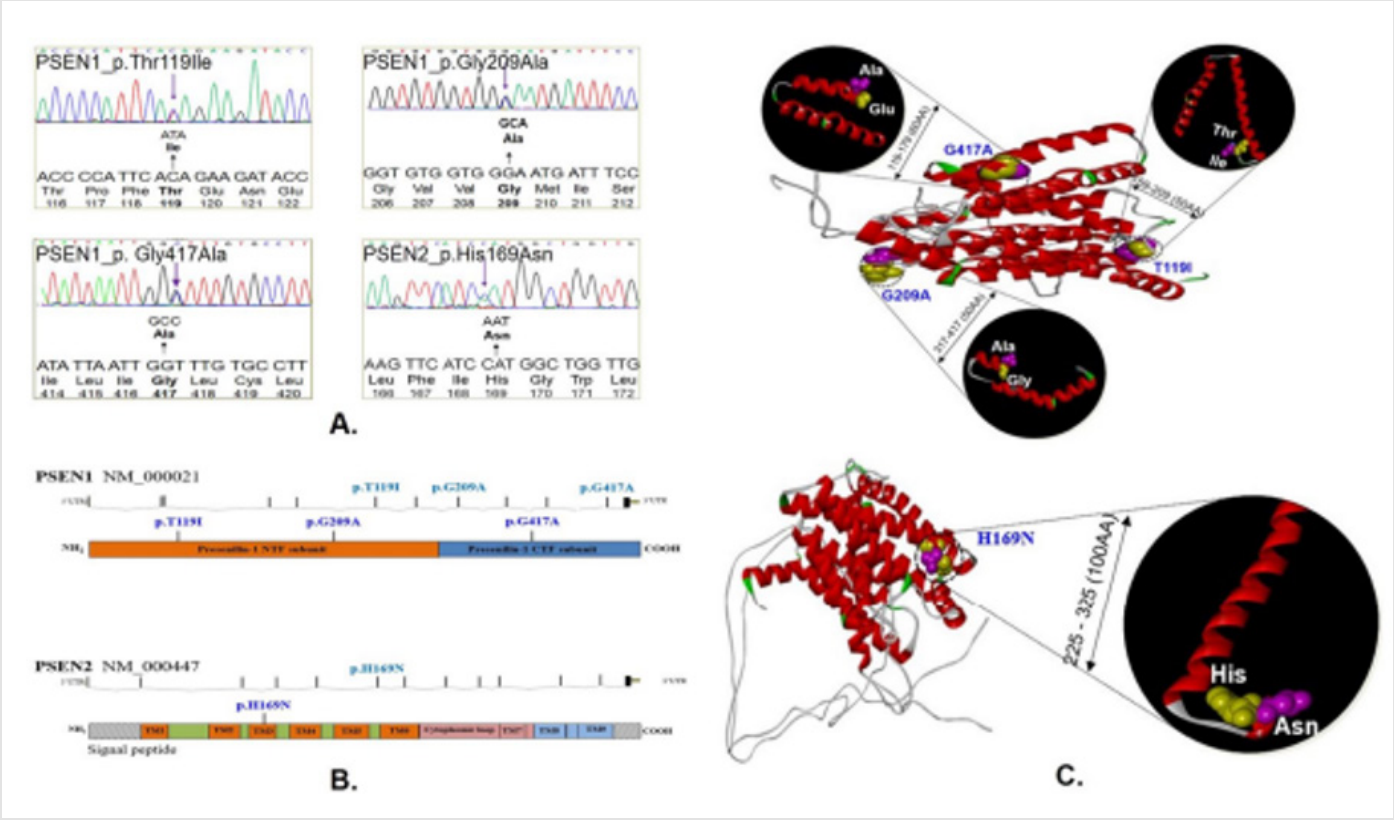

Figure 1:

A. DNA sequencing data of the four mutations found in PSEN1 and PSEN2 genes.

B. Location of PSEN1 and PSEN2 mutations in the genomic DNA and protein structure.

C. Possible protein structure changes associated with PSEN1 and PSEN2 mutations, highlighting normal (yellow) and mutant (pink) protein structures. (Giau, et al. [10]).

Likewise, the p.Gly209Ala mutation was identified in a 54-year-old female suffering from Alzheimer's disease and depression, with a PolyPhen2 score of 1 and a Sift score of 0, which is damaging. The p.Gly417Ala mutation in PSEN1, detected in a 37-year-old male with Alzheimer's disease and Parkinsonism, displayed a PolyPhen2 score of 0.99 (damaging) and a Sift score of 0 (damaging), suggesting a significant impact on protein function (Giau, et al. [10]). The PSEN2 p.His169Asn mutation, present in a 59-year-old female with left-dominant Alzheimer's disease, showed a PolyPhen2 score of 0.925 (damaging) and a Sift score of 0.04 (damaging), indicating its pathogenic potential. The mutational changes described in Figure 1C show changes in the protein conformations of PSEN1 and PSEN2. These changes probably interfere with normal protein function and cause disorders related to Alzheimer's disease.

The following Figure 2 describes a web of environmental influences which could be a cause of AD or may have impacts on Alzheimer's disease. It details how aspects like lead (Pb), aluminium (Al), cadmium (Cd), arsenic (As), and mercury (Hg), the pesticides and nanoparticles (NPs) worsen AD pathology. These pollutants cause a rise in ROS, which results in inflammation and oxidation stress, Aβ peptides formation and tau protein hyperphosphorylation (Mir, et al. [11]). This aggregation is important in the development of amyloid plaques and neurofibrillary tangles, the principal pathological features of AD, which is a major pathology found in the brain. On the other hand, diet, exercise and antioxidants work less rigorously by promoting the clearance of Aβ and also decreasing the level of oxidative stress, thus implying that the risk of getting AD might be reduced. On the other hand, fats, especially high-fat diets, and inactivity are known to promote the development of Aβ peptides (Khemka, et al. [12]). This figure also explains why the environmental and lifestyle factors need to be considered in the treatment of AD because the hypothesis holds that they equally contribute to the progression of the disease and its severity. Modifiable risk factors include the DASH diet that is rich in antioxidants, regular exercise, and cognitively stimulating activities to reduce the risk of AD suggesting the feasibility of prevention.

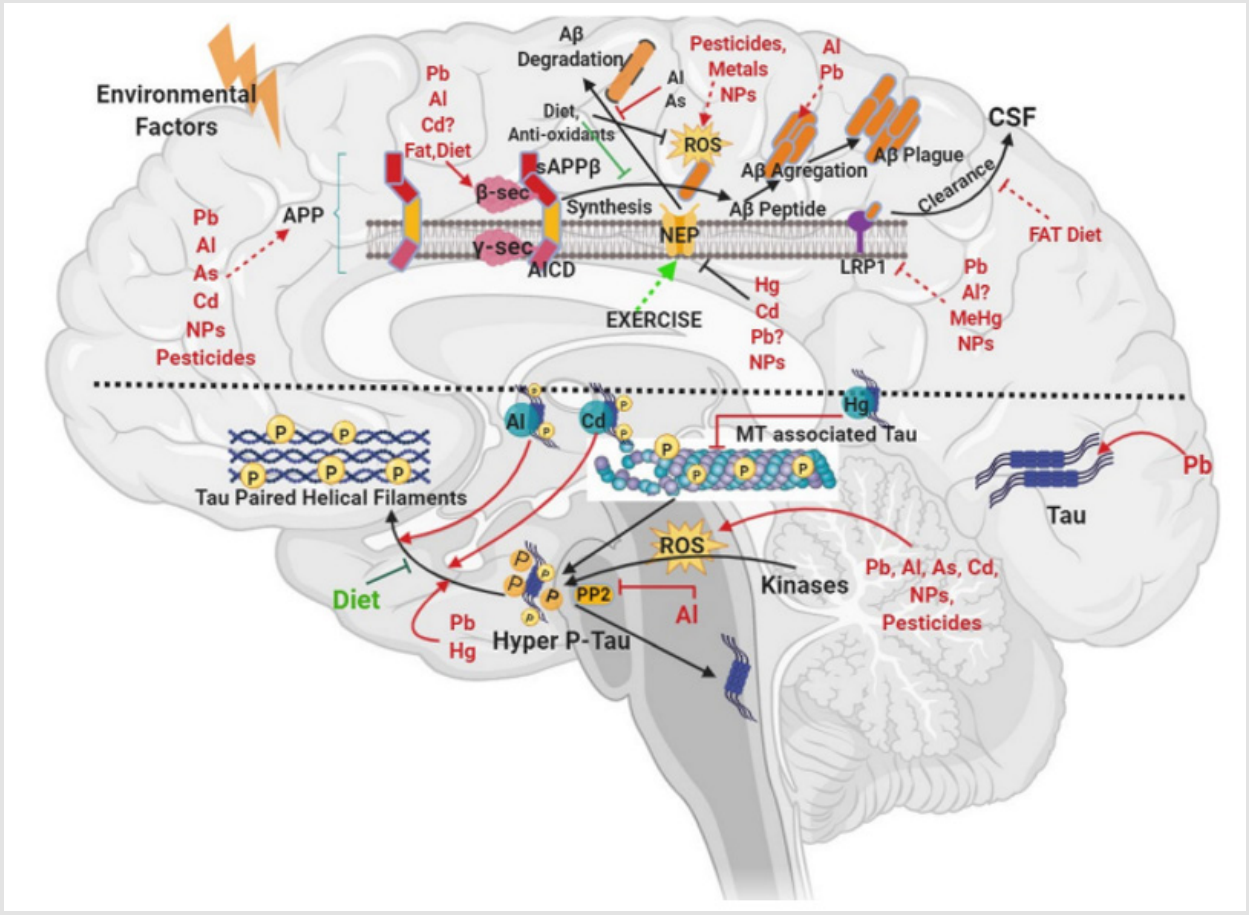

Figure 2: Mechanism of Various environmental factors associated with Alzheimer's disease (Mir, et al. [11]).

Efficacy and Accuracy of Diagnostic Tools and Biomarkers

Diagnostic resources and biomarkers for Alzheimer's disease (AD) have been advanced, which, in turn, has promoted early detection of the disorder. Since MRI and PET are important in demonstrating amyloid plaques and neurofibrillary tangles, which are characteristic of AD, this field is crucial in neuroimaging. According to previous research, PET scans can recognize amyloid alterations in more than 90% of Clin clinically diagnosed AD patients; its sensitivity is approximately 88%, and specificity is 87% (Kolanko, et al. [13]). CSF markers such as Aβ42, t-tau, and p-tau are very useful in the diagnosis of AD and have been identified to be of great help. When CSF Aβ42 is low, combined with high t-tau and p-tau, the estimated diagnosing accuracy of AD is 85-90% (Abu Rumeileh, et al. [14]). Recent developments in the biomarkers for screening have involved the use of blood, which is non-invasive and considerably less expensive. Plasma Aβ42/40 ratio and p-tau217 are reliable biomarkers, and the provided diagnostics showed sensitivity and specificity that are close to those of CSF biomarkers (d'Abramo, et al. [15]). These diagnostic techniques help in early diagnosis of AD, even in the preclinical stages, hence improving management. Thus, further studies and confirmation of these biomarkers will determine accurate diagnosis and overall improvement of the patient's outcomes.

Effectiveness of Existing Treatments and Emerging Therapies

The current treatment options for AD are primarily focused on managing symptoms, and no cure directly stops Alzheimer's disease from progressing. Donepezil, rivastigmine and galantamine are commonly used drugs that, in turn, enhance mood swings and other cognitive dysfunction due to the increased content of acetylcholine in the cortical area. Such drugs work in about 50% of the patients, giving slight enhancement in cognitive abilities and daily activities for a limited time only (Farooq, et al. [16]). Another recommended drug is memantine, which belongs to the group of NMDA receptors and helps to reduce the excitotoxicity related to the malfunctioning of neurons caused by glutamate. It is generally administered to patients at a mid- or severe stage of the disease; the medication stabilizes the condition in about 45% of cases (Atri [17]). Recent advancements entitle the

use of biologics, the most recent of which is aducanumab, a monoclonal antibody that binds to amyloid-beta plaques. Approved controversially by the FDA in 2021, aducanumab has shown potential in reducing amyloid plaque burden, although the clinical benefits regarding cognitive decline remain debated (Karran [18]). Emerging therapies focusing on tau pathology, synaptic protection, and inflammation are in various stages of clinical trials, aiming to offer disease-modifying outcomes. These developments reflect a growing understanding of AD's multifactorial nature and promise more targeted interventions in the future.

Discussion

The discussion section of this present research paper offers a critical analysis of the current study's findings with a view to understanding what is already known concerning Alzheimer's disease, particularly with regard to genetic markers for the disease as well as its pathological processes. In this research, five gene mutations, namely p.Thr119Ile, p.Gly209Ala, p.Gly417Ala, and p.His169Asn in the PSEN1 and PSEN 2 genes, were established to have early onset Alzheimer's disease. This concurs with the work by (Giau, et al.[10]), who stressed that similar mutations are pathological in nature, thereby lending an endorsement to the genetic factors articulated in Alzheimer's disease studies (Kabir, et al. [3]).Using genetic factors as the focus of the current study, it is crucial to note that context them within the continuum model of risk factors pointing to Alzheimer's disease proposed by (Mir, et al. [11]) and Khemka, et al. [12]. While the present research does not explore these wider risks directly, it implies the two-hit hypothesis and genetic susceptibility with environmental precipitants in reference to the multifactorial model of the disorder as described in the literature (Daiber, et al. [5]).The current findings also reveal new knowledge on the age of onset and the severity of the diseases accompanying such genetic mutations that have not been notified in prior research carried out by other researchers. This adds a further layer of nuances to the extreme geneticist view of Alzheimer's disease, which is instrumental in crafting a differential diagnosis and individualized regime to treat the ailment.

The results of the study corroborate the usefulness of neuroimaging methods and biomarkers, such as the Aβ42/40 ratio and p-tau217), in early Alzheimer's disease diagnosis. These findings support d'Abramo, et al. [15]'s gradual alterations and improve Alzheimer's disease diagnosis (Matsuda et al., in press; Hardy-Sosa, 2022). The genetic variables found in this study suggest the following next research avenues: The combined impact of genetic susceptibilities and avoidable variables like diets and environmental contaminants need more study (Daiber, et al. [5,11]). Such interactions may assist develop more effective Alzheimer's disease prevention and therapy (Khemka, et al. [12]). The confirmation of these diagnostic findings suggests that clinical practise should continue to improve biomarker or screening procedures to provide early detection and interventional treatment that may change the course of the illness (Mattsson, et al. [7]).

Conclusion and Recommendations

In conclusion, Alzheimer's disease (AD) is still a tough nut to crack in healthcare, especially in the neurodegenerative diseases subclass and comes with many challenges clinically and fiscally. Through this article, the author has explained how AD is characterised by genetic and environmental as well as lifestyle factors that play a role in eliciting the disease. Thus, the present diagnostic capabilities are enabled by much more accurate MRI and PET, CSF and new blood biomarkers that allow the detection of the disease even in the early stages. This helps in early involvement in the condition's progression and possibly changing it in the process. However, the therapeutic landscape pertains to the treatment of the symptoms and does not cause a shift in the course of the disease. Another recent example is the emergence of a probable change in the management strategy with the approval of aducanumab, even though its effectiveness and cost-effectiveness remain topics for discussion. Thus, the future of AD research targeting is expected to expand to a set of mechanisms and factors such as tau aggregates, neuroinflammation, and synaptic dysregulation. Further research into such fields is necessary to achieve prior goals and create better-curing interferences for Alzheimer's disease that not only help the patients to stabilise or worsen the condition but also help to slow down or even stop the development of the disease.

Recommendations

Based on the nature of Alzheimer's disease and the lack of optimal therapeutic solutions that can address it, several suggestions can be made regarding the continued development of research and improvements in existing treatment methods. First of all, it is necessary to increase the funding for biomarker discovery to improve the strategies for detecting the disease at an early stage and tracking the further developments of the process. That way, it will also be easy to develop better diagnostic technology that involves non-invasive biomarkers in patients with AD. Second, beyond amyloid-based therapies, more is needed. To find other AD pathogenesis targets including tau protein, synapse, and inflammation, further research is needed. This might help provide a more comprehensive strategy that could change the disease's course further. Third, studies should recruit varied patients to assess interpatient variability and identify beneficial treatment results. This will assist create P4 regimens that target the patient's genetics, environment, and lifestyle. Finally, financing and collaboration between academics, industry, and government are essential for teaching new ideas and transferring research to practice quicker. These areas must be prioritised to fight Alzheimer's.

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