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An overview on risk factors associated with Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a complicated neurological condition that has a high global prevalence, particularly among the elderly. The epidemiology, pathogenesis, risk factors, diagnosis, treatment modalities, preventive measures, and the most recent developments in gene therapy, immunotherapy, and nanomedicine are all included in this review of AD. AD is pathophysiologically characterised by several hypotheses, including the amyloid cascade theory, cholinergic theory, hyperphosphorylated Tau protein hypothesis, oxidative stress hypothesis, and metal ion theory. The development of AD is influenced by a number of factors, including genetics, environmental exposures, lifestyle decisions, vascular problems, metabolic disorders, neurological and behavioural illnesses, and inflammatory processes. Effective management requires accurate diagnosis and assessment, which includes a variety of psychiatric, neurological, physical, and cognitive examinations as well as biomarker analysis employing body fluid markers and neuroimaging techniques. N-methyl D-aspartate antagonists and cholinesterase inhibitors are the main treatments for AD, yet new developments in gene therapy, immunotherapy, and nanomedicine all present exciting possibilities for altering the course of the illness. Preventive tactics concentrate on risk variables that can be changed, like physical activity, drinking alcohol, quitting smoking, mental stimulation, controlling diabetes, controlling obesity, controlling blood pressure, participating in social activities, and receiving mental health care.

Keywords: Alzheimer's disease, Pathophysiology, Diagnosis, Treatment, Prevention

1 INTRODUCTION

Alzheimer's in one of the leading heterogeneous and genetically complex disease, influenced by both genetic and environmental risk factors leading to major threat in human community. This disease is categorized as Early onset (EOAD) and Late onset Alzheimer's (LOAD) disease which affects at least 27 million people worldwide (Silva et al., 2019). The pathophysiology of AD starts to occur before the sign of cognitive decline, and neuroscience researchers have started to focus on the preclinical stages of AD. Environmental, genetic, gender, age, lifestyle, vascular, metabolic, neurological, and inflammatory risk factors were found to be associated with the pathogenesis of AD (Armstrong, 2019).

The field of AD has greatly advanced due to several key conceptual changes, such as the transition from the syndrome, which was focused on signs and symptoms, to a biomarker diagnosis, which is based on the pathological hallmarks of the disease: Neurodegeneration, pathogenic tau, and amyloid β (Aβ) deposition (Scheltens et al., 2021). Consequently, in order to lessen the severity of the disease and enhance prognosis, early detection and prevention of AD are essential. CSF biomarkers and neuroimaging biomarkers employing PET or MRI are two of the current techniques for tracking AD pathology(Blennow, 2017; Huang et al., 2020; van Oostveen & de Lange, 2021). The currently approved FDA drugs in the market has various side effects. Several reports suggesting a significant rise in hepatotoxicity and gastrointestinal-related side effects, including nausea, vomiting, and diarrhoea, linked to the use of rivastigmine, galantamine, and memantine, donepezil, among patients have raised concerns. about the potential for adverse drug efficacy compromise caused by dosage rate(Ali et al., 2015; Weller & Budson, 2018).

Precision medicine requires integrating genetic, pharmaco-genomic, proteomic, and immune-genomic patient information to achieve the objective of "personalized medicine" and optimize therapy effectiveness for each individual (Deng & Nakamura, 2017). Moreover, a promising strategy to increase brain targeting specificity, brain bioavailability, and patient compliance is the use of nanomedicines for brain drug targeting (Wilson & Geetha, 2020). The study focus on an overall review of epidemiology, pathophysiology, risk factors, diagnosis, treatment and prevention of Alzheimer Disease.

2 EPIDEMIOLOGY OF ALZEIMER DISAESE

Alzheimer's disease is predicted to affect 12.7 million people aged 65 and over, according to a poll conducted by the Alzheimer's Association (Collaborators & others, 2019). According to reports, the global number of people with dementia climbed to 43.8 million in 2016, a 117% increase from 20.3 million in 1990 (Murray et al., 2020). It is anticipated that by 2050, a total of 152 million people with Alzheimer's and other dementias will be affected worldwide(Nichols et al., 2022). Deaths from Alzheimer's disease and related dementias rank fifth worldwide, accounting for 2.4 million deaths (Nichols et al., 2019). Alzheimer's disease incidence is decreasing due to breakthroughs in risk factors during the past century (Rajan et al., 2019). Despite this possible decreased incidence rate, the overall number of persons with Alzheimer's is likely to continue expanding because of the enormous increase in the number of adults aged 65 and over, the age group that is at elevated risk of Alzheimer's(Colby & Ortman, 2015; Guerreiro & Bras, 2015; US Department of Health and Human Services., 2016). Prevalence increases with advancing age, with rates of 0.97% among individuals aged 65-74 years, 7.7% among those aged 75-84 years, and 22.5% among individuals aged 85 years or older. Additionally, the prevalence is significantly higher among elderly women (7.1%) compared to men (3.3%) (Niu et al., 2017). By 2050, over 20% of the Indian population (319 million) would be 60 years or older, accounting for 15.4% of the global population (Iips, 2017). There is a concerning possibility that the number of dementia cases in India would rise due to its age risk factor (J. Lee et al., 2023). In 2019, the official mortality from Alzheimer's disease (AD) was 121,499, with 13.6 million persons affected (Association, 2019). With a pace of one person affected every three seconds, by 2050, the number of affected persons in a year will be 13.8 million, with 7.0 million being 87 years old (Hebert et al., 2013). Compared to men, female carriers of the apolipoprotein E ε4 allele, which is recognised as the biggest genetic risk factor for dementia and AD, have an increased chance of suffering from dementia (Neu et al., 2017). Additionally, it has been demonstrated that TGD (transgender) adults are 65% more likely to express subjective cognitive deterioration than cisgender adults.

3 PATHOPHYSIOLOGY OF ALZHEIMER DISEASE

3.1 AMYLOID CASCADE THEORY

Amyloid-β (Aβ), formed by proteolysis of its Aβ protein precursor (AβPP), is known to be released and aggregate extracellularly. This Aβ pool is assumed to promote Alzheimer's disease (AD) under the long-standing "amyloid cascade hypothesis" (ACH) theory of AD(Hardy & Higgins, 1992). In the brain tissues of AD patients, betasecretase (β-secretase) or gammasecretase (γ-secretase) proteolytically processes amyloid precursor protein (APP) to produce the peptide Aβ (Storey & Cappai, 1999). The accumulation of Aβ protein triggers a chain of events that cause nerve cell death and brain tissue damage, eventually leading to AD symptoms. The ACH2.0 theory of Alzheimer's disease was recently developed. In ACH, the disease is induced by secreted extracellular Aβ. In ACH2.0, it is started by Aβ protein precursor (AβPP)-derived intraneuronal Aβ (iAβ) and is triggered by iAβ created independently of AβPP (Volloch & Rits-Volloch, 2023). According to ACH2.0, Alzheimer's disease has two stages. During the initial, asymptomatic stage, extracellular Aβ is internalised and Aβ generated by gamma-cleavage of the C99 fragment of AβPP on intracellular membranes is retained, resulting in a lifelong accumulation of iAβ rather than plasma, membranes (Chafekar et al., 2008; Cook et al., 1997; Kumar-Singh et al., 2006; Wesén et al., 2017; Wild-Bode et al., 1997; Yajima et al., 2015). AβPP-independent iAβ production pathway is activated by iAβ upon reaching the T1 threshold in affected neurons within a restricted temporal window. This is likely the result of the elicitation of an integrated stress response mediated

by HRI and PKR. The second, fatal stage of AD, which involves tau pathology and culminates in neuronal death, is driven by a AβPP-independent generation of iAβ (Volloch & Rits-Volloch, 2023).

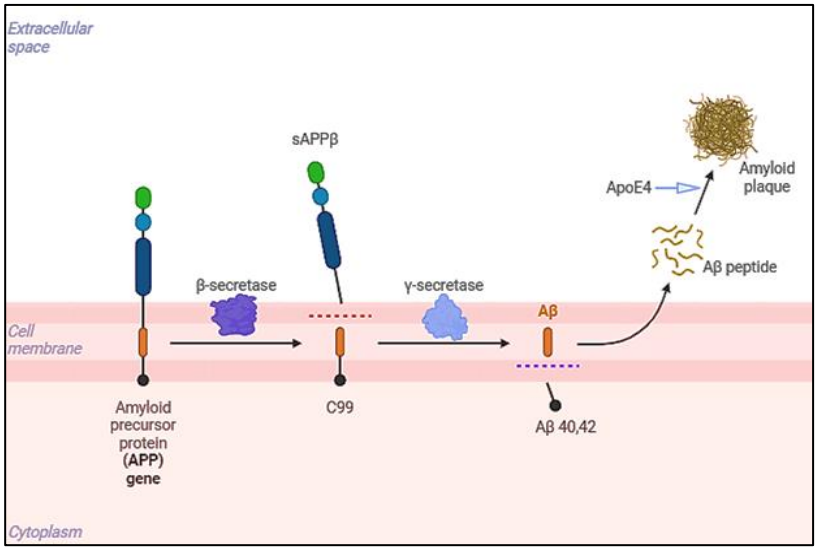

FIGURE 1: AMYLOID CASCADE THEORY

3.2 HYPERPHOSPHORYLATED Tau PROTEIN HYPOTHESIS

Neurofibroblast tangles (NFTs) are an insoluble filament that grow in the cytoplasm of neurons, particularly in the axoplasm. They are the second common morphologic sign of AD and are primarily composed of hyperphosphorylated tau protein(Alavi Naini et al., 2015; F. P. Chong et al., 2018; Gao et al., 2018; Iqbal et al., 2005; Neumann et al., 2011; Sajjad et al., 2018; Šimić et al., 2016; Trushina et al., 2019). The tau hypothesis states that tau tangles arise before Aβ production and that microtubule instability and the neurotoxic effects of P-tau and associated aggregation are the main causes (initiating factors) of neurodegeneration in AD. The oligomeric tau hypothesis states that the toxic form of tau is tau oligomer which causes neuronal loss memory impairment in initial stages of Alzheimer disease (Arnsten et al., 2021; Berger et al., 2007; Gerson et al., 2014; Kametani & Hasegawa, 2018; Lasagna-Reeves et al., 2011; Ward et al., 2012). A diverse group of protein kinases are involved in phosphorylation of tau protein and these group increases the progression of AD as a result of Aβ oligomer formation or neuroinflammation (Avila, 2006; Domise et al., 2016; Qi et al., 2016). The connection between the tau and amyloid theories could be due to GSK-3 being activated through either overexpression of the enzyme or the impact of Aβ oligomers. GSK-3 phosphorylates tau, and its function is involved in the synthesis of Aβ and Aβ-mediated neuronal death (Hernandez et al., 2013; Hooper et al., 2008).

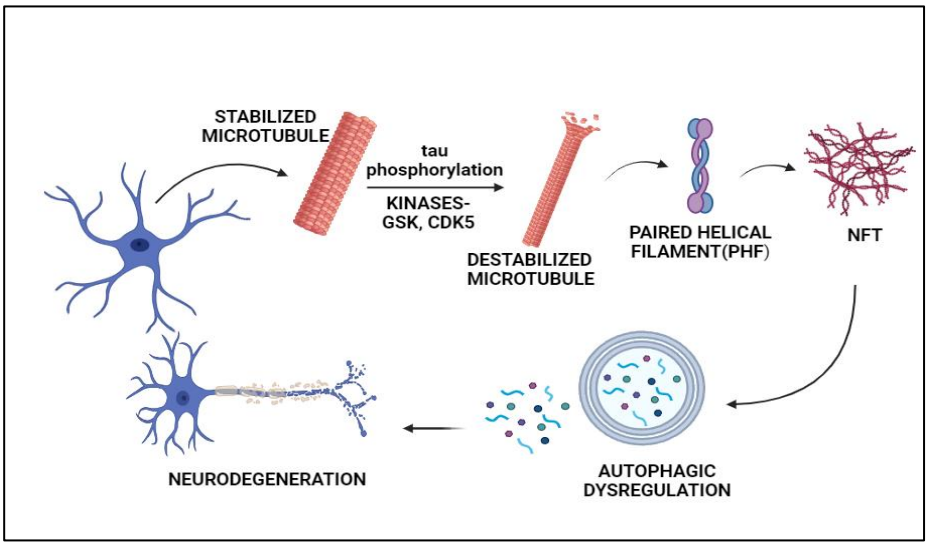

FIGURE 2: HYPERPHOSPHORYLATED Tau PROTEIN HYPOTHESIS

3.3 CHOLINERGIC THEORY

The Meynert nucleus in the basal forebrain is a primary source of cortical acetylcholine, which has been linked to severe neuronal loss in AD patients (Doucette et al., 1986). The cholinergic hypothesis is based on three key concepts: decreased presynaptic cholinergic markers in the cerebral cortex, significant neurodegeneration of the nucleus basalis of Meynert (NBM) in the basal forebrain, which causes cortical cholinergic innervation, and the opposing effects of cholinergic antagonists and agonists on memory decline, with the former worsening and the latter improving (Hampel et al., 2018). The ChAT (enzyme choline acetyltransferase) enzyme synthesizes Ach (acetylcholine) from choline and acetyl-coenzyme A in cholinergic neurons, which is then transported to synaptic vesicles via the vesicular acetylcholine transporter (VAChT) (Babic et al., 1999; H Ferreira-Vieira et al., 2016). Cholineacetyltransferase levels are reduced in the parietal and frontal cortex by up to 75%, and in the hippocampal and temporal cortex by up to 90% (Burns et al., 1997). Research suggests that the brain cortical cerebrospinal fluid acetylcholine levels were substantially lower in AD patients, which was linked to cognitive decline (Jia et al., 2004). The M2 decline and the M3 are maintained at normal levels, while the muscarinic receptors may be reduced to some extent or at normal levels. Conversely, there is a reduction in nicotinic receptors (Monczor, 2005). The onset of AD's neuropsychiatric symptoms is significantly correlated with cholinergic depletion.

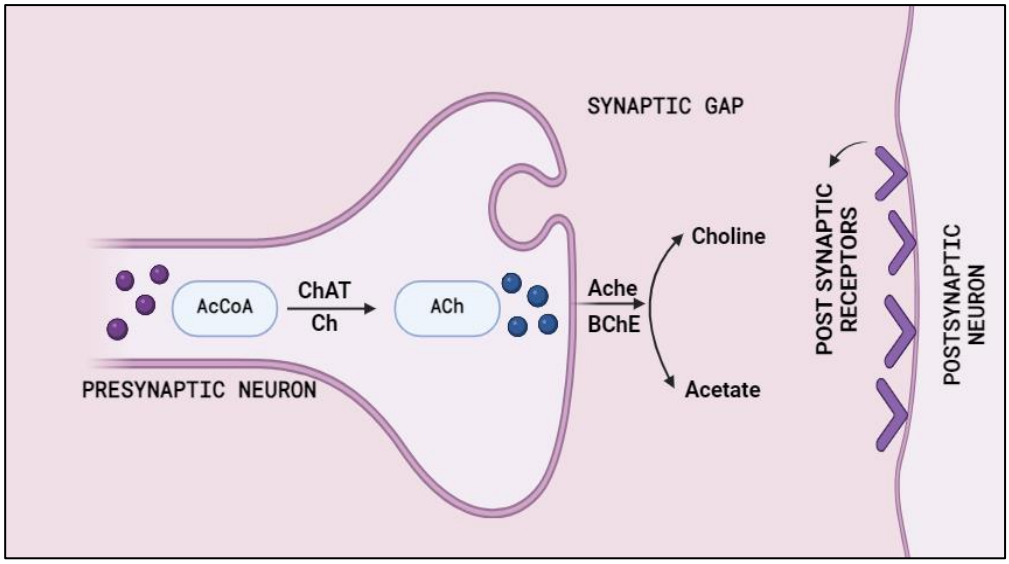

FIGURE 3: CHOLINERGIC THEORY

3.4 OXIDATIVE STRESS HYPOTHESIS

Oxidative stress is a crucial factor in the pathogenesis of Alzheimer's disease (Bai et al., 2022; Ionescu-Tucker & Cotman, 2021; Mandal et al., 2021; Roy et al., 2023; C. Sharma & Kim, 2021). The brain is an extremely energy-demanding organ, and in order for it to continue its many metabolic functions, the redox reactions that contribute to its energy production must continue. Additionally, this increases OS's susceptibility to the brain. Physiological levels of reactive oxygen species (ROS) are necessary for a cell to function properly (Manoharan et al., 2016). Three primary mechanisms of oxidative stress lead to a development of AD: macromolecule peroxidation, Aβ metal ion redox potential, and mitochondrial dysfunction. These mechanisms impact cell homeostasis, ROS production, and the up-regulation of Aβ and p-tau(X. Chen et al., 2012; Gella & Durany, 2009; Kregel & Zhang, 2007; Valko et al., 2005). One such significant OS-related condition is mitochondrial dysfunction (MD). MD affects the metabolism of glucose and calcium, which shortens the average life span of neurons (Butterfield & Boyd-Kimball, 2020; Misrani et al., 2021; Wilkinson & Landreth, 2006).

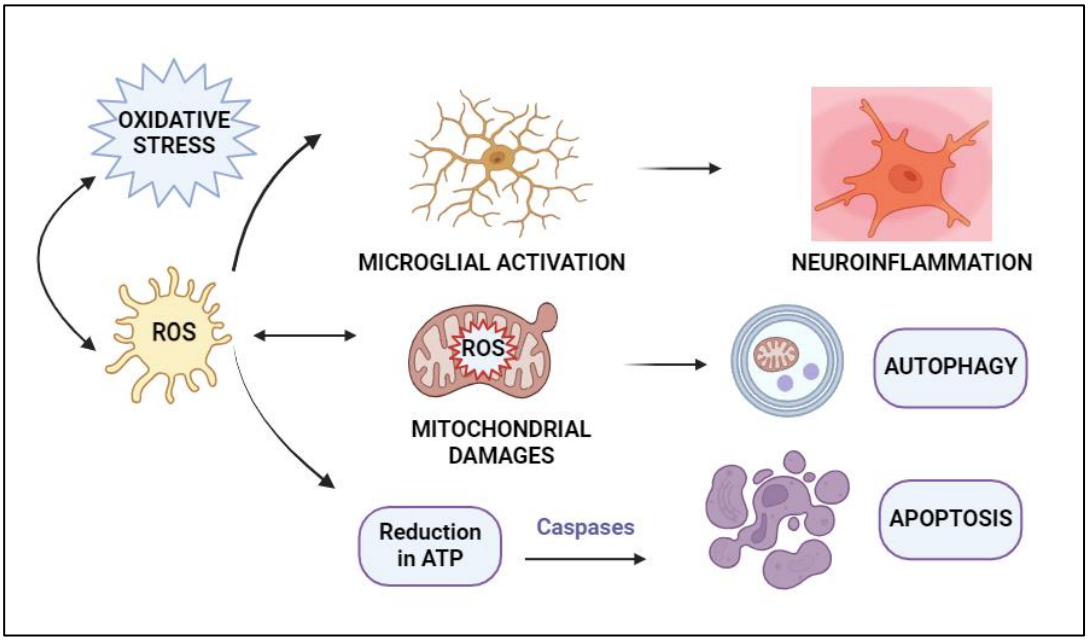

FIGURE 4: OXIDATIVE STRESS HYPOTHESIS

3.5 METAL ION THEORY

Metal ion homeostasis is critical for the brain's regular functions. These bio-metals in general are involved in variety of biological processes, including neurotransmitter production, mitochondrial synthesis, oxidation, metabolism, cell division, and synaptic plasticity (Prashanth et al., 2015; Todorova & Blokland, 2017). Aβ overproduction, tau hyperphosphorylation, and their aggregation/accumulation can be encouraged by abnormal deposition of metal ions in various brain areas. In addition, excessive production of metals results in oxidative stress. One of the main causes of the improper distribution of copper, zinc, iron in the brain is the abnormalities of the associated metal transporters (Adlard & Bush, 2018; L. Wang et al., 2020).

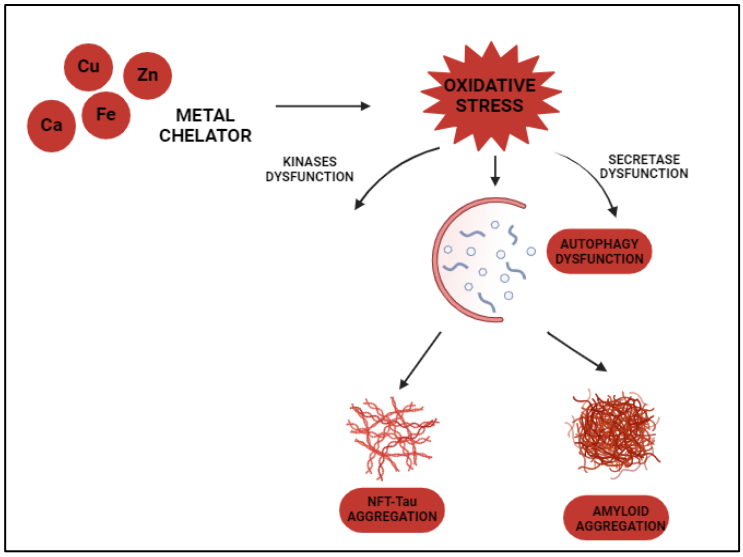

Figure 5: METAL ION THEORY

4 RISK FACTORS ASSOCIATED WITH ALZHEIMER

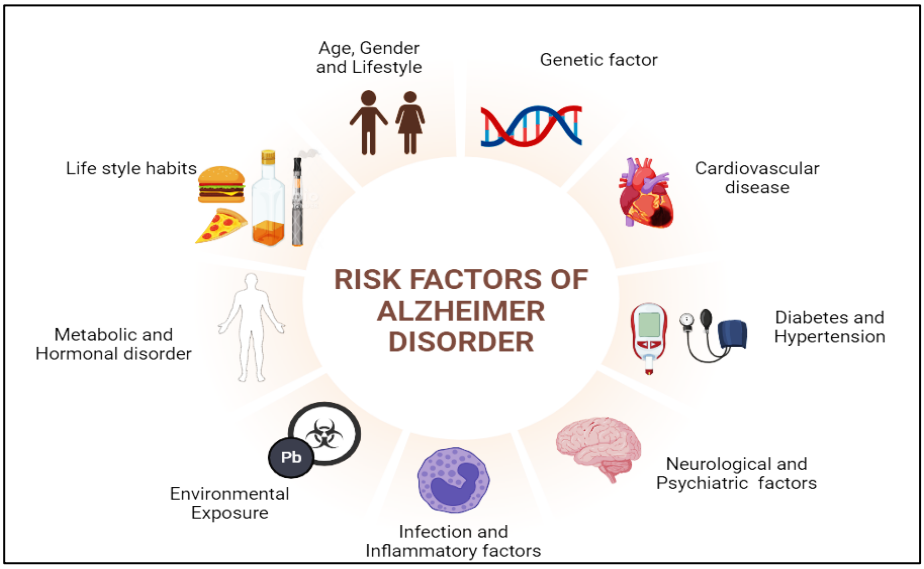

FIGURE 6: MULTIPLE RISK FACTORS ASSOCIATED WITH ALZHEIMER'S DISEASE

4.1 GENETIC FACTORS

Over the last decade, due to advent of recent high-throughput technologies such as Genome Wide Association Studies (GWAS), Genome Wide Linkage Scans (GWL), and Genome Wide Expression profiling (GWE) have been broadly used to recognize the unknown genetic risk factors (Bush & Moore, 2012). The GWAS in Alzheimer's disease have revealed susceptible genes such as *PSEN1, APP, PSEN2, ABCB1, APBB2, APOE, TGFβ1, APBB2, BDNF, SORL1, IL1B* and *CD33* associated with disease pathogenesis (Husain et al., 2019). Here we have discussed in detail about the major genes related with to Alzheimer's disease. Table 1 provide the list of genes, their chromosomal locations, and other information about the genes (Zerbino et al., 2018)

TABLE 1: GENES INVOLVED IN DEVELOPMENT OF ALZHEIMER'S DISEASE

Genes symbol	Gene Synonyms	Chromosomal location	Total Exons	Transcript length (BPs)	Protein (Amino Acids)	UniProtKB	Consensus Coding Sequence	Molecular Mass (Da)
Apolipoprotein E *(APOE)*	*AD2*	19q13.32	04	1166	317	P02649	CCDS 12647	36154
Amyloid beta precursor protein *(APP)*	*AD1, AAA, ABPP*	21q21.3	18	3583	770	P05067	CCDS 13576	86943
Presenilin 1 *(PSEN1)*	*AD3, PS1, FAD, PSNL1*	14q24.2	12	6018	467	P49768	CCDS 9812	52668
Presenilin 2 *(PSEN2)*	*AD3, AD3LP,PS2*	1q42.13	13	2249	448	P49810	CCDS 1556	50140
Sortilin-Related Receptor *(SORL1)*	*LRP9,LR11, SorLA*	11q24.1	48	10863	2214	Q92673	CCDS 8436	248426
Brain-Derived Neurotrophic Factor *(BDNF)*	*ANON2, BULN*	11p14.1	1	4766	247	P23560	CCDS 7866	27818

Transforming Growth Factor β1 *(TGFβ1)*	*CED,DPD1, IBDIMDE*	19q13.2	7	2780	390	P01137	CCDS 33031	44341
GRB2 Associated BindingProtein 2 *(GAB2)*	*Pp100, KIAA0571*	11q14.1	10	6052	638	Q9UQC2	CCDS 8259	74458

4.1.1 APOLIPOPROTEIN E (APOE)

This gene encodes for Apolipoprotein E, widely studied for functions in the lipid metabolism and they are observed on chromosome no 19q13.2. They contain pleiotropic molecule which controls the actions like transport of lipids, synaptic function, intracellular signalling, Aβ trafficking and also in immune regulation (Bekris et al., 2010).The *APOE* has three common alleles which are called ε4,ε3, and ε2, among which the e3allele is frequently observed in more than half of the overall population. This gene has been linked with both sporadic late-onset and familial late-onset AD in various ethnic groups. The genotype highly associated with higher AD risk is APOE ε4 and the mechanism underlying the toxicity of APOE in brain tissue are not completely understood. The other mechanisms include APOE ε4-mediated tau hyperphosphorylation, isoform-specific toxicity, APOE ε4-mediated amyloid aggregation is studied in recent years (Hashimoto et al., 2012). APOE are generally expressed in various organs with high expression in the liver and in brain. The cell types which express *APOE* in the brain are mainly the astrocytes and microglia.

4.1.2 AMYLOID PRECURSOR PROTEIN A4 (APP)

APP gene encodes for Amyloid beta precursor protein, they are localized in chromosome no *21q21*.3 comprising 18 exons. This gene is alternatively spliced into several products and named based on their amino acid length (*APP563, APP714, APP 695, APP770* and *APP 751*) differentially expressed in tissues. There are 3 main Isoforms relevant to AD, namely *APP695*which is restricted to the central nervous system and *APP770* and *APP751* might be expressed in both the system (Dewji et al., 2015). This protein classified under type-I integral membrane protein resembling as signal transduction receptor. They are widely expressed in several tissues and mainly intense in the synapses of neurons. APP protein and their derivative the Aβ have been documented to be translocated exclusively in the mitochondria and concerned in their dysfunction.

4.1.3 Presenilin 1 (PSEN1)

This gene encodes for polytopic membrane protein, they are observed in *14q24.2* comprising 12 exons, encoding 467 amino acids. These proteins are part of the γ-secretase complex (Sánchez et al., 2011).In Early onset Familial AD mutations are most frequently observed *PSEN1*gene. AD associated with the *PSEN1* is autosomal dominant neurodegenerative disorder categorized by Parkinsonism and Dementia, generation of Aβ intracellular domain and in modulation of notch signalling (Cai et al., 2015). Totally 197 variants in the *PSEN1* gene have been preliminarily linked with F-AD in that 185 are responsible to cause the familial AD and majority of them are missense mutations. These mutation carriers are more probable to have atypical features such as seizures, spastic paraparesis and early myoclonus.

4.1.4 PRESENILIN 2 (PSEN2)

This gene is localized on chromosome no 1 at *q42.13* position comprising 13 exons encoding totally 448 amino acids. This gene product is a major component of atypical aspartyl protease termedas γ-secretase and responsible for Aβ cleavage. They are widely expressed in a multiple tissues including the brain first and foremost in neurons. This protein consists of total nine transmembrane domains and also a large loop like structure is observed between the $6^{th}$and 7^{th}domains (Cacace et al., 2016).The mutation associated with this gene tends to boost the proportion of Aβ42 to Aβ40 in humans, demonstrating that the PSENs adjust the way γ-secretase cuts the Amyloid Precursor Protein. The above region has been documented to be variably affected by these precise presenilin mutations (Wolfe, 2012). The mutations found in *PSEN2* gene are rare compared to *PSEN1* mutations those observed in familial AD (Żekanowski et al., 2003).

4.1.5 SORTILIN-RELATED RECEPTOR (SORL1)

The *SORL1* gene product is a receptor which participates in the vesicle trafficking from cell surface to the golgi bodies and the endoplasmic reticulum. This pathway is mainly significant in the processing of APP and also in the production of Aβ peptide (Willnow & Andersen, 2013). They are observed on chromosome *11q24.1* comprising 48 exons and highly associated as a risk

factor in late-onset AD. The previously published studies on *SORL1* gene expression documented that, they are differentially expressed in AD subjects compared with healthy controls (Giri et al., 2016).

4.1.6 BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

The *BDNF* gene is a candidate gene for diseases which are involved in memory loss due to long-term plasticity in the hippocampus region, a major function which breaks down during the EOAD. They are most widely distributed neurotrophin protein in the central nervous system, and play a major role in neuronal survival and synaptic plasticity (Egan et al., 2003).The *BDNF* gene expression from the Post-mortem studies documented severe decrease in the frontal cortex, temporal, and hippocampus regions of AD. They are released as mixture of pro and mature BDNF in the brain (Hempstead, 2015).There are several studies supporting that neurotrophic factors play a major role in AD etiology, among which is *BDNF* gene. Their protein and mRNA levels were found to be reduced in the post-mortem brain of AD subjects when compared with controls, with no alterations in TrkB levels (Mufson et al., 2002).These types of reduction in levels were also reported in subjects with mild cognitive impairment which is an initial AD stage.

4.1.7 Transforming-Growth Factor β1 (TGFβ1)

This gene belongs to *TGFβ* superfamily, they include various groups of multi-functional cell signalling highly conserved proteins playing major role such as cell growth differentiation, control, involve in embryogenesis process, neuroprotection and in immune suppression (Zimmerman & Padgett, 2000). In homosapiens, the *TGFβ* superfamily includes TGFβ1, 2 and 3 which are modulators in apoptosis and cell survival (Sánchez-Capelo, 2005).The TGFβ 1, TGFβ2 and TGFβ3 encodes for three protein isoforms such as the TGFβ1, TGFβ2 and TGFβ3 with high structural and functional similarities (Fujio et al., 2016). *TGFβ1* is highly conserved and the most abundant isoform which interacts with a high affinity transmembrane receptor complex which comprises the *TGFβ* type-I receptor, activin-like kinase 5 (ALK5)and *TGFβ* type-II receptor subunits (Radaev et al., 2010).

4.1.8 GRB2 Associated Binding Protein 2 (GAB2)

The GAB2 protein belongs to the family of adapter and scaffolding proteins, and found highly expressed in the central nervous system especially in hypothalamus and prefrontal cortex(Okun et al., 2010). They participate in various signalling pathways such as, cell differentiation, proliferation, cell-survival and apoptosis. Mainly in AD the GAB2 protein interacts with PI3K-AKT signalling pathway, which in turn reduces the tau phosphorylation for preventing neuronal loss and in the formation of neurofibrillary tangles (NFTs) (Pan et al., 2010).The functional analysis from GWAS studies documented alterations in *GAB2* expression which in turn affects the GSK3 dependent phosphorylation of tau protein and also in the development of neurofibrillary tangles (Davinelli et al., 2011).

4.2 ENVIRONMENTAL AND LIFESTYLE RISK FACTORS

4.2.1 Education and Cognitive Reserve

Reduced educational attainment can impact cognitive reserve and is a controllable risk factor for Alzheimer disease and related dementias (A. T. C. Lee et al., 2018; J. Lee et al., 2023; Sommerlad et al., 2020). One of the most common modifiable risk factors for AD is reduced educational, notably not having completed secondary school, which has a prevalence of 40% worldwide(Livingston et al., 2017). The cognitive reserve hypothesis, which suggests that AD's early symptoms may be less noticeable in more highly educated individuals, leading to a delay in diagnosis until neurodegeneration is more advanced, suggests a potential link between higher education and faster disease progression (Doraiswamy et al., 1995; Gerritsen et al., 2018; Pavlik et al., 2006; Sobral & Paúl, 2013; Sommerlad et al., 2020).

4.2.2 Occupational and Environmental Exposures

Electromagnetic field (EMF) has been shown to have an impact on a number of bodily functions, such as calcium homeostasis and the brain's ability to produce melatonin, although the precise mechanism by which it causes AD is yet unknown (Davanipour & Sobel, 2009; Garc\'\ia et al., 2008; Sobel et al., 1995, 1996; Terzi et al., 2016). Individual exposed to low to high EMF has higher risk of acquiring AD (Feychting et al., 2003; Park et al., 2005; Qiu et al., 2004; Savitz et al., 1998). Exposure to pesticide has been reported to cause neurodegeneration. Since most insecticides target the nervous system of insects, they also have neurotoxic effects on non-target species like humans because of parallels in brain function. In addition to insecticides, certain fungicides and herbicides have neurotoxic qualities(Mie & Rudén, 2023; Organization & others, 2021; ROUSSELLE et al., n.d.). Exposure to lead alters both the epigenetic composition and the epigenetic regulators in the brain and its various areas(Bihaqi et al., 2011; Dou et al., 2019; Eid et al., 2016). Occupational exposure to lead was linked to somewhat higher, but not statistically significant, risks of AD (odds ratio = 1.12, 95% Cl: 0.63–2.00) in a case-control study of clinically proven AD(Gun et al., 1997).

4.2.3 Tobacco Smoking and Alcohol Consumption

Environmental tobacco exposure, commonly known as passive smoking, has been linked to an increased risk of dementia and Alzheimer's disease (Barnes et al., 2010; R. Chen, 2012). Cigarette smoke contains four metal ions and five aromatic hydrocarbons that can influence the myeloid beta (Aβ) peptide's aggregation process. It was demonstrated that toluene modifies the hydrophobic and oligomeric form of Aβ. Pb (IV) was found to have an effect on the development of dummers and trimers of Aβ among the metals (Rusanen et al., 2011; Wallin et al., 2017). Smoking leads to oxidative stress which triggers elevated production of amyloid-b and abnormal tau protein phosphorylation (Campos et al., 2016; Mondragón-Rodr\'\iguez et al., 2010; Praticò et al., 2002). Alcohol can change the microbiota, leading to neuroinflammation and disrupting immunological function. Elevated ethanol concentrations are linked to greater Aβ buildup and precursor protein synthesis. However, there is controversy regarding the link between alcohol use and cognitive effects since some studies suggests that moderate alcohol intake may have a protective effect while other points out its negative effects((WHO) & others, 2019; Anstey et al., 2009, 2019; Haller et al., 2018; Lobo et al., 2010; Sabia et al., 2018; Stampfer et al., 2005; Toda et al., 2013).

4.2.4 Diet and Nutrition

Modifying one's diet can reduce risk factors for Alzheimer's disease, such as obesity, hypertension, and diabetes. This could be a public health strategy to prevent age-related neurodegeneration and dementia in later life (den Brink et al., 2019; Valls-Pedret et al., 2015; Wu et al., 2019). The Western diet is often heavy in calories, sugar, fattyacid, salt, and food additives. Following a Western diet can worsen cognitive decline and raise the chance of Alzheimer's disease (Allès et al., 2019; Jackson et al., 2016). A high consumption of SFA (Saturated fatty acid) is linked to a higher risk of AD as well as metabolic diseases like type 2 diabetic mellitus (T2DM). There are also reports of modest cognitive impairments caused by it (Baranowski et al., 2018; Busquets et al., 2017;). Similarly, long term intake of simple carbohydrate rich food has negative effect on cognition and triggers the progression of AD (Carvalho et al., 2012; C. P. Chong et al., 2019;).

4.2.5 Physical Activity and Exercise

The epidemiological research has demonstrated that a higher level of physical activity protects against AD dementia and, on the other hand, a lower level of physical activity is linked to an increased risk of acquiring AD dementia (Abbott et al., 2004; Buchman et al., 2012; de Bruijn et al., 2013; Kishimoto et al., 2016; Middleton et al., 2011; Tan et al., 2017). An increased risk of Alzheimer's disease (HR, 1.36; 95% CI, 1.12-1.65) and new-onset dementia (HR, 1.40; 95% CI, 1.23-1.71) was linked to physical inactivity over the ten years prior to dementia diagnosis (Kivimäki et al., 2019). Previous research suggests that APOEε4 allele carriers may have larger decreases in brain Aβ due to physical activity than ε4 non-carriers. Exercise and PA can lower tau phosphorylation and hippocampus tau pathology in experimental models of Alzheimer disease

4.3 VASCULAR RISK FACTORS

4.3.1 Hypertension and Cerebrovascular Disease

Blood pressure represents one of the most extensively researched risk factors for dementia, including AD. Hypertension poses a risk for endothelial damage, vascular inflammation, arteriolosclerosis, infarcts, among other clinically invisible diseases (Blevins et al., 2021; Carnevale et al., 2016; L. Nelson et al., 2014; Petrea et al., 2020; Yu et al., 2020). Hypertension affects the blood-brain barrier (BBB) and causes inflammation, potentially contributing to vascular dementia and AD (Canavan & O'Donnell, 2022; Santisteban et al., 2023). A microvascular conditions called Alzheimer's disease is partially caused by the build-up of the lethal β-amyloid peptide (Aβ) in the brain. This deposit results in complex cerebromicrovascular damage and weakens the neurovascular unit (Cortes-Canteli & Iadecola, 2020; Zlokovic, 2011). A meta-analysis study found that while diastolic hypertension was not substantially linked to AD risk, systolic hypertension—defined as a blood pressure of greater than 160 mmHg—was related with an increased risk of AD(Abell et al., 2018; Freitag et al., 2006; Lennon et al., 2019). Additionally, APOE did not have a moderating effect and hypertension was not linked to amyloid-beta 1-42, according to a cerebrospinal fluid biomarker analysis. On the other hand, tau was directly linked to hypertension, and the APOE genotype altered ptau-181(Faraco et al., 2016; Kester et al., 2010; Tian et al., 2012). Cerebral amyloid angiopathy (CAA) is a prevalent type of vascular illness that contributes to dementia. Parenchymal amyloid-β-related processes converge with vascular pathways to synergistically enhance tau and promote cognitive loss(Arvanitakis et al., 2016; Jack et al., 2013; Rabin et al., 2022).

4.3.2 Atherosclerosis

Numerous vascular risk factors, including age, obesity, smoking, hypertension, hypercholesterolemia, hyperhomocysteinemia, diabetes mellitus, and APOE4 isoforms, are shared by atherosclerosis and AD, according to epidemiological studies (Gorelick et al., 2011; Roher et al., 2011). Fragments of the atherosclerosis plaque can be released, leading to ischemia damage and cerebrovascular occlusions which in turn causes vascular cognitive impairment (Alistair, 2002; Sakamoto et al., 2001). The pathophysiologic cascade leading to AD pathology has been related to chronic brain hypoperfusion and hypoxia caused by

atherosclerotic stenosis, atherosclerotic stiffness, and higher vascular resistance of the small and large arteries(Bos et al., 2011; Kalaria et al., 2012; Koike et al., 2010). Advanced atherosclerosis can cause brain hypoxia, which increases Aβ cleavage from the APP by upregulating the β- and γ-secretase enzymatic pathways(L. Li et al., 2009; Tesco et al., 2007; X. Zhang et al., 2007).

4.3.3 Heart Failure and Cardiac Dysfunction

A population-based cohort study revealed that Heart is linked to a higher chance of acquiring AD, a disorder characterized by a predominance of temporal lobe atrophy (Qiu et al., 2006; Vogels et al., 2007). The pathophysiology of brain and cardiac problems in AD patients is thought to be shared by mutations in the PSEN gene and aggregation of Aβ proteins (Gianni et al., 2010; D. Li et al., 2006; Sanna et al., 2019; Stamatelopoulos et al., 2015; Takeda et al., 2005; Troncone et al., 2016). Moreover, patients with heart failure (HF) have a constantly active sympathetic nervous system, which is known to be a component of upstream signaling cascade that modifies intracellular Ca2+ homeostasis and closely regulates the survival and function of neurons. Alzheimer's disease and other neurodegenerative illnesses are characterized by Ca^{2+} dyshomeostasis (Dridi et al., 2023; Lacampagne et al., 2017; X. Liu et al., 2012).

4.3.4 Stroke and Transient Ischemic Attacks (TIAs)

Incidence rates of dementia after ischemic stroke were 1.5 times higher in the presence of stroke history as opposed to first-time occurrence. Deterioration of cognition is correlated with ischemic lesions of the left hemisphere as it controls language and generalized cognitive function (Basso et al., 1981; Desmond et al., 2000; Schneider et al., 2003). The presence of p25, a CDK5 activator, leads to an increase in toxic Aβ levels in the brains of Alzheimer's patients after Ischemic stroke(Chi et al., 2013; Gamaldo et al., 2006; Tolppanen et al., 2013). Recurrent stroke, pre-stroke cognitive impairment, development of apathy, hypertension and diabetes mellitus are risk factors for dementia following a stroke(Leys et al., 2005; Pendlebury & Rothwell, 2009; Pohjasvaara et al., 1998).

4.3.5 Hyperlipidemia and Dyslipidemia

Dyslipidemia has been identified as a significant risk factor for AD. Moreover, the onset of dementia is strongly associated with low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and Triglycerides (TG) (Ancelin et al., 2013; Bailey-Downs et al., 2013; Ferretti et al., 2012). Hyperlipidemia can negatively impact brain health by affecting the vascular that supports it(Dichgans & Leys, 2017; Etherton-Beer, 2014). Serum triglyceride levels in midlife can indicate the onset of Aβ and tau pathology in cognitively normal people(Burgess et al., 2006; Nägga et al., 2018; Raffaitin et al., 2009).

4.4 METABOLIC AND HORMONAL RISK FACTORS

4.4.1 Obesity and Metabolic Syndrome

The metabolic syndrome (MetS) is a group of symptoms and indicators that includes a number of vascular risk factors, including dyslipidemias, abdominal obesity, arterial hypertension, and insulin resistance. Along with insulin resistance and obesity, it raises the likelihood that AD and other neurological disorders may develop in older people (Luque-Contreras et al., 2014; Milionis et al., 2008; Misiak et al., 2012; Solfrizzi et al., 2011). Obesity has been linked to a higher risk of dementia, independent of type 2 diabetes(Kelly et al., 2008; Whitmer et al., 2008). An investigation into the dietary risk factors of AD discovered that in the frontal cortex of the 3xTg AD mouse model, a high-fat diet (HFD) increases Aβ and tau pathology. Alzheimer's disease susceptibility is higher in APOE4 carriers than in carriers of other genotypes due to their higher levels of total cholesterol and low-density lipoproteins (Elosua et al., 2003; Tejedor et al., 2014; Torres-Perez et al., 2016; Zade et al., 2013). Hippocampal inflammation, NFTs, and Aβ plaques are observed in the mouse model of HFD-induced obesity (Julien et al., 2010; Puig et al., 2012; Shie et al., 2015).

4.4.2 Diabetes Mellitus

The type 2 diabetes mellitus group with mild cognitive impairment was subjected to a multivariable analysis, and the results showed that age greater than 75 years was highly susceptible to dementia (Ma et al., 2015). Brain insulin resistance plays a critical part in the pathophysiology of AD (de la Monte & Wands, 2005; Steen et al., 2005). Low production of acetylcholine transferase due to improper insulin levels and insulin receptor desensitisation may lower Ach in diabetic patient's neurons, leading to Alzheimer's disease (Kroner, 2009; Rivera et al., 2005). Insulin may have an impact on the management of Aβ aggregates; it may promote the extracellular release of Aβ by lowering the expression of the GSK3β, BACE1, and APP genes and favouring the insulin-degrading enzyme (IDE) and ADAM-10 (Devi et al., 2012; Pandini et al., 2013).

4.4.3 Hormonal Changes in Aging

Menopause is a neuroendocrine transition state that occurs in midlife and ends with reproductive senescence. It is characterized by neurologic symptoms, including altered sleep patterns, stress, depression, distortion of estrogen-regulated thermoregulation, and alterations in several cognitive regions(Brinton et al., 2015; Scheyer et al., 2018). Ageing and AD were associated with

increased expression of nonfunctional splicing variants of estrogen receptor alpha in the hippocampus, with higher expression levels in elderly female than in males (Foster, 2012; Ishunina et al., 2007; Rettberg et al., 2014). In addition, estrogen receptor polymorphisms linked to cognitive decline in women(Ryan et al., 2014; Yaffe et al., 2009). Low testosterone levels are frequently linked to heart attacks, strokes, depression, and cardiovascular disease. Because of this, older men with low sex hormone levels are more susceptible to cognitive decline and may therefore be more likely to develop dementia (Carcaillon et al., 2014; Ford et al., 2018; Lv et al., 2016).

4.5 NEUROLOGICAL AND PSYCHIATRIC RISK FACTORS

4.5.1 Traumatic Brain Injury (TBI)

The most prevalent risk factor for non-familial, sporadic types of AD is traumatic brain injury (TBI) (Srinivasan & Brafman, 2022). TBI can damage the blood-brain barrier, resulting in infiltration of leukocytes and stimulation of microglial cells. Moreover, neurodegenerative disease development in TBI patients has been linked to β-amyloid pathology, chronic neuroinflammation, mitochondrial function, tau deposition, vascular injury, and white-matter deterioration (Barkhoudarian et al., 2011; Faden & Loane, 2015; Franz et al., 2019; Maroon et al., 2015). APP overexpression indicates diffuse axonal damage in traumatic brain injury (TBI). Following damage, animal models have shown increased amounts of Aβ40, Aβ42, and Aβ deposits due to amyloidogenic processing of APP (Tajiri et al., 2013; Tran et al., 2011). P-Tau immunoreactive NFTs have also been seen among youngsters a few weeks to months after their most recent concussion (Mckee & Daneshvar, 2015). Long-term TBI survivors' tau deposits have also been linked to the later emergence of neuropsychiatric disorders (Takahata et al., 2019).

4.5.2 Depression and Anxiety Disorders

In a large-scale, community-based, longitudinal study spanning 4.5 years and involving over 4,000 dementia-free individuals over 55, there was a substantial correlation between baseline anxiety and subsequent AD (Santabárbara et al., 2019). The hypothalamic-pituitary-adrenal (HPA) axis may be impaired in elderly patients with depressive disorder as evidenced by higher cortisol levels compared to age-matched controls (Lebedeva et al., 2018; Murri et al., 2014). Additionally, BDNF levels, which are essential for neuronal survival, sinaptic integrity, and neuroplasticity, were found to be lower in elderly patients with depressive disorders (Diniz et al., 2014; Nunes et al., 2018; von Bohlen und Halbach & von Bohlen und Halbach, 2018). Anxiety disorders have been linked to three major hallmarks of AD: cognitive impairment, neuronal death, and cerebral amyloid deposition (M. Johansson et al., 2020). Moreover, Anxiety may contribute to dementia and vascular disease by causing hypercoagulability, hypertension and atherosclerosis (Esler, 2017).

4.5.3 Psychosocial Stress and Cortisol Dysregulation

Neurodegenerative diseases are preceded by ageing and stress. Furthermore, regardless of age, APOE genotype, sex, or anxiety symptoms, elevated cortisol levels have been linked to a in global cognition, episodic memory, in cognitively healthy older persons with Aβ positive PET imaging (Pietrzak et al., 2017). In this case alzheimer's disease is a result of both a dysfunctional HPA axis and accumulation of glucocorticoids (Blennow et al., 2006; McEwen, 2007; Querfurth & LaFerla, 2010). The levels of APP, BACE, and C99 increase in response to stress or glucocorticoids, suggesting that stress induces APP processing towards the amyloidogenic pathway, which could explain the elevated amounts of Aβ (Catania et al., 2009; K.-W. Lee et al., 2009)

4.5.4 Sleep Disorders

Research has revealed a correlation between sleep fragmentation and declines in cognition and memory. Adults over the age of 70 who sleep for extended periods of time (>8 hours) are more likely to develop dementia, especially if they have AD (Larsson & Wolk, 2018; Sindi et al., 2018; W. Xu et al., 2020). Specifically, higher levels of sleep fragmentation were linked to higher declines in memory (Manousakis et al., 2018; Sethi et al., 2015; Shin et al., 2014). Studies on humans and animals have shown that insufficient sleep promotes the aggregation and production of amyloid-b (Ab), a crucial element in the pathophysiology of AD.

4.6 INFLAMMATORY AND IMMUNE-RELATED RISK FACTORS

4.6.1 Chronic Inflammation and Immune System Dysregulation

Maladaptive immune responses may be important drivers of AD pathogenesis, according to the theory that inflammatory mechanisms contribute to AD neuropathology and the genetic link of numerous immune-specific genes (CR1, TREM2, and CD33) (Katsel & Haroutunian, 2019). Elderly people frequently experience infection and inflammation, and preclinical research has shown that inflammation induced AD pathologic hallmarks in mice that alone possessed ApoE4 (Marottoli et al., 2017; Miklossy, 2008). An imbalance between pro- and anti-inflammatory responses, as well as the advancement of neurodegeneration and vascular pathology in the brain, may be accelerated by systemic inflammation (Franceschi & Campisi, 2014; Sankowski et al., 2015).

4.6.2 Autoimmune Diseases

The second most common cause of dementia in younger individuals, after neurodegenerative dementia, is autoimmune dementia, which accounts for 20.3% of cases (Kelley et al., 2008). In SLE (systemic lupus erythematosus), autoantibodies, such as aPL, are likely to target vascular endothelial cells, triggering the coagulation cascade and inflammatory response. This can lead to thrombosis, which can gradually impair neural activity, diminish cognitive function, and eventually cause vascular dementia (Denburg & Denburg, 2003; Z. Zhao et al., 2018).

5 DIAGNOSIS AND ASSESSMENT

Diagnosis and Assessment is crucial in prevention and treatment of Alzheimer Disease. Table 1 outlines conventional diagnostic and assessment methods for Alzheimer's disease, including physical and neurological examinations, psychiatric evaluations, cognitive assessments, and laboratory tests.

TABLE 1a: CONVENTIONAL DIAGNOSTIC AND ASSESSMENT METHODS FOR ALZHEIMER

DIAGNOSTIC METHOD	DESCRIPTION	ANALYSIS	REFERENCE
Physical examination	A comprehensive physical examination to evaluate general health.	Assessment of vital signs, neurological function, and sensory/motor abilities, review medications that may cause cognitive impairment	(Apostolova, 2016; Arvanitakis et al., 2019;)
Neurological examination	Neurological assessment to assess reflexes, coordination, motor function and Sensation	Assessment of cranial nerve function, gait, seizures, myoclonus, Cerebellar ataxia, spastic paraparesis, Apraxia and sensation.	(Bulut et al., 2018; El-Tallawy et al., 2022;)
Psychiatric evaluation	1. Evaluation of behavior, mood, and mental health symptoms—such as psychosis, depression, or anxiety—that may coexist with Alzheimer's disease. 2. Neuropsychiatric Inventory (NPI)-Conducting interviews with patients and caregivers to assess instrumental activities of daily living (IADLs) and functional impairment in activities of daily living (ADLs).	Clinical interview and observation by a psychiatrist to evaluate behavior, mood, and psychiatric symptom and question regarding ability to perform daily activity	(Devanand et al., 2022; Di Iulio et al., 2010;)
Cognitive assessment	Assessment of cognitive function using standardized tests such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock drawing test, DemTect	Assessments of memory, attention, language, praxis, visuospatial abilities, and executive function are administered and scored using cognitive tests.	(Folstein et al., 1975; Kalbe et al., 2004;)
Laboratory test	Erythrocyte sedimentation rate, C-reactive protein, thyroid hormones, vitamin B12, folic acid measurement, complete blood count serum creatinine and urea concentration, lipid profile, glucose, albumin, haemoglobin, infectious markers and electrolyte measurement	Blood testing is a crucial part of the evaluation process since it aims to rule out clinical conditions may mimic Alzheimer's symptoms	(van der Flier & Scheltens, 2005)

6 TREATMENT APPROACHES

Currently, only two types of medications are approved to treat Alzheimer's disease: cholinesterase inhibitors (naturally occurring, synthetic, and hybrid analogues) and N-methyl d-aspartate (NMDA) antagonists i.e., Galantamine, Donepezil, Rivastigmine, and

Memantine (J. Liu et al., 2019; Singh & Sadiq, 2019). Aducanumab and Lecanemab are the two anti-Aβ monoclonal antibodies that the FDA approved in 2021 but Aducanumab has been discontinued by its manufacturer Biogen to reprioritize its resources in Alzheimer's disease. In this section we overall summarize the currently available treatments of Alzheimer disease. Table 2 highlights the drugs and their targets for AD.

TABLE 2: DRUGS TARGETS FOR AD

S.NO	DRUG NAME	MECHANISM OF ACTION
1	Estrogen	Enhances ApoE synthesis and secretion
2	Scyllo-inositol	Aβ aggregation Reduction
3	MK0752 (clinical trials)	Inhibition of γ-Secretase
4	Indomethacin	attenuates neuroinflammation and cognitive impairment
5	CTS-2166 (clinical trials)	Inhibition of β-Secretase
6	NABT-5102A (clinical trials)	Prevention of Aβ aggregation
7	Probucol	Suppress lipoprotein-Aβ secretion and Neuroinflammmation
8	Pioglitazone, Rosiglitazone	Inhibition of β-Secretase
9	Semagacestat	γ-Secretase inhibition and reduces reduces Aβ40 and 42
10	Estrogen	Prevents dementia through enhancing prefrontal and hippocampal activity

6.1 GENE THERAPY

Gene therapy possesses the capability to rectify the genetic anomalies that underlie the pathogenesis of diseases at the molecular level (Choong et al., 2016). The latest gene therapy advances involve innovative vectors for improved delivery of therapeutic genetic material. Notable advances include the development of highly- specific viral vector designs, nanoparticles, engineered microRNA, polymer-mediated gene delivery, plasmid transfection, and in vivo CRISPR-based therapeutics (Pena et al., 2020).

6.2 IMMUNOTHERAPY

Immunotherapy, which comprises a variety of tactics such the creation of antibodies (vaccines) or passive antibodies that prevent progression of AD. In order to induce the release of antibodies, adjuvants are typically administered in conjunction with antigens during active immunotherapy. While the purpose of passive immunotherapy is to achieve the same benefits as active vaccination by directly injecting foreign antibodies into an animal or human (Alshamrani, 2023; Huang et al., 2023; Jucker & Walker, 2023; Ng et al., 2020; C. Song et al., 2022; Valiukas et al., 2022).

7 PREVENTION STRATEGIES OF AD

The listed modifiable risk factors in table 6 for cognitive impairment and dementia are accompanied by evidence-based management strategies, reflecting a comprehensive approach to prevention. Ranging from lifestyle adjustments like physical activity and dietary modifications to targeted interventions for conditions such as hypertension and depression, these insights emphasize the multifaceted nature of dementia risk reduction.

8 CONCLUSION

In summary, there are plenty of opportunities for improved patient care as the field of Alzheimer's disease research and therapy continues to advance quickly. There is increased hope for better results due to developments in our understanding of the underlying mechanisms of the disease and the creation of novel diagnostic and therapeutic approaches such gene therapy, immunotherapy, and nanomedicine. Collaborative efforts across scientific disciplines and sectors are critical for accelerating development and converting research findings into effective treatments. In the future, sustained funding for research and innovation will be necessary to address the intricate problems presented by Alzheimer's disease and enhance the quality of life for those who are impacted by the illness.

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