Review

Molecular basis of dementia

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Abstract

Dementia is a set of symptoms characterized by deterioration of memory and cognitive functions. Dementia diseases include Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, and mixed dementia. This disease represents an escalating social issue, particularly in a society with an increasing elderly population. In 2019, 271,998 people succumbed to dementia, making Alzheimer's disease the sixth most prevalent cause of death. The pathophysiology of Alzheimer's disease is complex and not fully understood. It is a multifaceted disease, with its pathogenesis influenced by a combination of genetic, environmental, and lifestyle factors. One of the genes involved in the pathogenesis of the disease is the apolipoprotein E (*APOE*) gene, which is one of the most common risk factors for Alzheimer's disease. The significance of other genes, including presenilin genes (*PSEN1* and *PSEN2*), the *TREM2* gene, the *MAPT* gene, and the *APP* gene, linked to various forms of dementia, is also emphasized. Another issue is the growing number of identified genetic variants within genes implicated in the onset of dementia. Dementia diseases are also characterized by chemical alterations in the brain, including the accumulation of abnormal excitotoxic proteins, varying degrees of inflammation, and metabolic disorders. This review summarizes current research in the field of dementia and highlights the significance of molecular factors in its pathogenesis. Gaining insight into the pathogenic mechanisms of dementia may allow for faster diagnosis of the disease and facilitate the creation of more efficient patient care plans.

Keywords: Dementia, genetic factors, biochemical factors, dementive diseases, risk factors, pathogenesis

1. Introduction

Dementia is a set of symptoms marked by the progressive deterioration of memory and cognitive functions. Dementia affects millions of individuals worldwide, posing significant challenges for both patients and their caregivers (Chertkow et al., 2013). The World Health Organization (WHO) recognizes dementia as a public health priority. According to WHO predictions, approximately 50 million people globally live with dementia, and this number is expected to triple by 2050 (World Health Organization, 2021). Since age is a contributing risk, dementia emerges as the leading cause of reduced years of healthy living due to disability in individuals aged 60 and above (World Health Organization, 2023).

With the ongoing aging of societies, dementia could pose significant challenges for healthcare systems and manifest as a substantial social and economic issue. As reported by Wimo et al. (2019), the annual global societal expenses related to dementia were estimated at US$1,313.4 billion for 55.2 million individuals affected by dementia, equivalent to

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US$23,796 per person with dementia (Wimo et al., 2023). According to data from the Institute for Health Metrics and Evaluation, in Poland in 2019, 585,000 individuals suffered from Alzheimer's disease (AD), the most prevalent form of dementia, and related diseases, making up 1.5% of the population (GBD, 2019). Additionally, it is important to acknowledge that dementia does not only impact the individuals affected but also those around them. As addressed by Feast et al., family caregivers view dementia and its symptoms as demanding, leading to a perception of strain on relationships, violation of social norms, and the belief that individuals with dementia inevitably undergo a loss of their "personality" (Feast et al., 2016).

1.1 Symptoms of dementia

Dementia is characterized by a range of cognitive, emotional, and behavioral symptoms that progressively impact both the individual's daily functioning and the well-being of their family members (Cerejeira et al., 2012). These symptoms may vary depending on the type of dementia, but common symptoms include memory loss, marked by persistent forgetfulness and difficulty remembering new information. Affected individuals exhibit cognitive deterioration as dementia gives rise to difficulties in reasoning, problem-solving, and decision-making. They may have difficulty recalling recent events, names, or important details. Simple tasks that were once routine may become increasingly difficult. Dementia patients experience challenges in communication, including expressing thoughts verbally and comprehending spoken or written language. Feelings of frustration and isolation can arise in individuals with dementia due to these symptoms. Additionally, patients who have dementia may experience mood changes (e.g., depression, anxiety, or irritability), impaired motor skills, and confusion (Cerejeira et al., 2012; Kim et al., 2021; Schneider, 2022; Atri, 2019; Arvanitakis & Bennett, 2019; Arvanitakis et al., 2019; Elahi & Miller, 2017; Aarsland, 2020; Prendecki et al., 2020). Early recognition of these symptoms is essential for timely diagnosis and pharmacological intervention. Family members, friends, and healthcare professionals play a key role in observing and responding to these changes, improving the quality of life of individuals affected by dementia.

1.2 Risk factors of dementia

The increasing incidence of dementia is not solely associated with the age of patients; various other risk factors contributing to the development of this condition have also been recognized. These factors encompass genetic predispositions, lifestyle elements such as alcohol and smoking, level of daily stress, physical activity, lower educational attainment, and the presence of chronic diseases (arterial hypertension, diabetes) (Kuo et al., 2020; Zhang et al., 2021; Albai et al., 2019). Research on AD indicates that infections such as gastrointestinal infections, sepsis, and pneumonia may also pose as risk factors for dementia (Fink et al., 2021; Lei et al., 2022; Piekut et al., 2022).

1.3 Types of dementia

The varied pathophysiological alterations in the brains of individuals with dementia has allowed us to distinguish several dementia types, including AD, vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and mixed dementia (Husebo et al., 2016). Each dementia type exhibits unique symptoms and progression patterns, emphasizing the importance of accurate diagnosis for tailored care (**Fig. 1**).

1.4 Alzheimer's disease

AD, the predominant form of dementia, accounts for 60-70% of dementia cases (World Health Organization, 2023). It is a multifactorial disease characterized by the degeneration of brain cells. AD does not have a single, identifiable cause; rather, it arises from a combination of factors, including the individual's age, genetic predispositions, protein accumulation and aggregation in the brain, as well as vascular, immunological, environmental, and lifestyle factors (Breijyeh & Karaman, 2020).

Regarding genetic factors, particular emphasis is placed on variations in the apolipoprotein E (*APOE)* gene, specifically 4ε. The neurological changes observed in the brains of individuals with AD involve

the accumulation of amyloid-beta (Aβ) proteins, while the aggregation of phosphorylated tau proteins contributes to the formation of neurofibrillary tangles (NFTs). Additionally, the presence of additional risk factors for AD, including head injuries, obesity, cardiovascular changes, smoking, or infections, may accelerate and exacerbate the progression of the disease (Breijyeh & Karaman, 2020; Armstrong, 2019; Khan et al., 2020). More details are found in section 2: *Biochemical factors of different types of dementia*.

Given the multifactorial pathomechanism of AD, understanding the intricate interplay of these factors is crucial for unraveling the complexities of AD. Ongoing research aims to identify more specific causative mechanisms, paving the way for targeted interventions and potential preventive strategies.

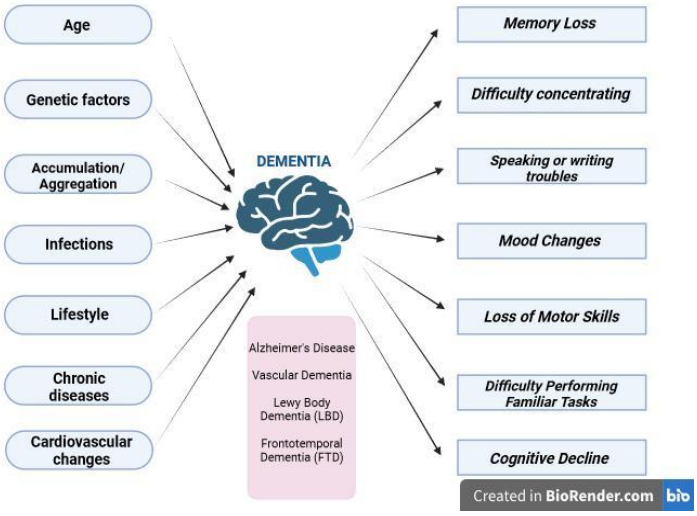

Figure 1. Risk factors and typical symptoms of dementia.

2. Biochemical factors of different types of dementia

Dementia manifests in various forms, each characterized by distinct biochemical foundations. Common types of dementia, such as AD, DLB, and FTD, share macroscopic changes resulting in the loss of neurons in the brain, yet they vary in terms of location **(Fig. 2)**. AD, the most prevalent form of dementia, is distinguished by the accumulation of Aβ plaques and the presence of NFTs comprised of hyperphosphorylated tau proteins. The key distinction lies in the location of these structures; plaques typically form outside cells, while NFTs are generally found within cells. The imbalance between production and clearance of these proteins hampers neuronal function, resulting in synaptic dysfunction, neuronal loss, and cognitive decline (Kao et al., 2020). Recent research emphasizes the role of neuroinflammation and oxidative stress in AD pathogenesis. VaD arises from compromised blood flow to the brain, frequently stemming from strokes or other vascular issues. At the biochemical level, diminished cerebral blood flow induces hypoxia, triggering the release of inflammatory mediators and oxidative stress. This cascade of events contributes to the degeneration of white matter and the development of cognitive impairment. In DLB, abnormal aggregates of the alpha-synuclein protein, referred to as Lewy bodies, accumulate in the brain. These aggregates interfere with cellular function, impairing neurotransmitter release and leading to neuronal death. The biochemical intricacies of DLB also encompass mitochondrial dysfunction and impaired protein clearance mechanisms. FTD is characterized by the degeneration of the frontal and temporal lobes, leading to personality changes and language impairment. Biochemically, FTD is associated with abnormalities in tau, TDP-43, and FUS proteins. Dysregulation of these proteins disrupts cellular functions, contributing to the neuronal loss observed in FTD patients. Understanding the diverse biochemical pathways implicated in various types of dementia is crucial for developing targeted therapeutic strategies.

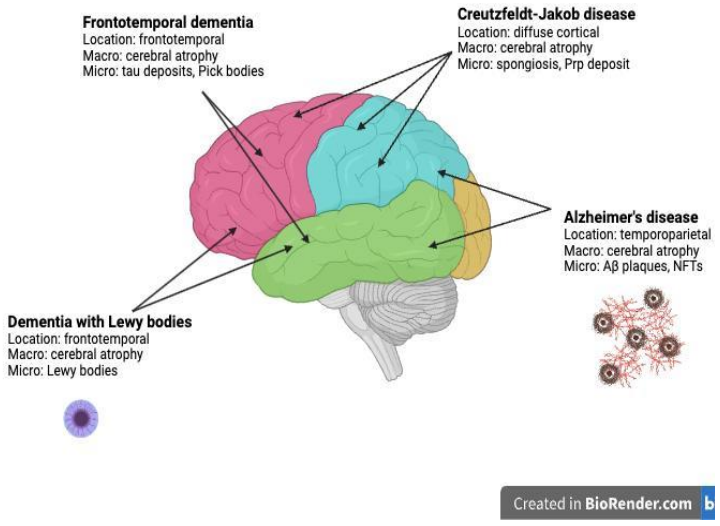

Figure 2. Common types of dementia.

2.1 Biomarkers in neurodegenerative diseases

Advancements in diagnostic techniques and early identification are made possible through the potential for a lifetime diagnosis of the disease using diagnostic biomarkers, both in imaging studies and laboratory tests of cerebrospinal fluid (CSF). A biomarker is a naturally occurring molecule, gene, or characteristic that allows the identification of a specific pathological or physiological process, disease, etc. The extracellular and intracellular protein deposits, known as plaques, consist of Aβ peptides. These peptides exist in two forms: the shorter Aβ 1-40 (Aβ1-40) and the longer Aβ 1-42 (Aβ1-42), typically undergoing proper metabolism and degradation. In individuals with AD, there is a disruption in Aβ metabolism, leading to an accumulation of excess peptides, primarily Aβ1-42, which aggregate to form the plaques (Pasieka et al., 2021). The assessment of Aβ1-42 levels is widely acknowledged as a crucial indicator of an abnormal condition associated with Aβ metabolism (Hampel et al., 2021). NFTs, or tangles, represent the second distinctive histopathological feature of AD, following Aβ deposits. These intracellular structures consist of aggregates of hyperphosphorylated tau protein (Moloney et al., 2021).

In the 2018 NIA-AA recommendations, biomarkers in neurodegenerative diseases are categorized into biomarkers indicating pathological Aβ deposition, biomarkers associated with tauopathy (neurofibrillary degeneration), and indicators of neurodegeneration (Jack et al., 2018). A distinctive feature of AD is a reduction in the concentration of Aβ protein in the CSF. In individuals who later develop AD, a significant decrease in Aβ1-42 is observed as early as 5-10 years before the onset of cognitive impairment symptoms (McGrowder et al., 2021). It is important to highlight that Aβ peptides of various lengths, including Aβ1-40, are present in the CSF. To account for individual differences in Aβ synthesis, the Aβ1-42/Aβ1-40 ratio can be calculated, providing a more accurate assessment compared to measuring the levels of these biomarkers individually (Hampel et al., 2021). Moreover, studies have demonstrated that the Aβ ratio results for both lengths exhibit a stronger correlation with positron emission tomography (PET) imaging studies (Pemberton et al., 2022).

It is worth noting that the optimal biomarker or combination of biomarkers may vary based on factors such as the stage or type of dementia. Assessing markers in the CSF and utilizing markers in neuroimaging studies, within the appropriate clinical context, enables early disease diagnosis and enhances the differentiation between various types of dementia.

2.2 Cerebrospinal fluid analysis

Table 1 provides a summary of CSF levels for three biomarkers: Aβ42, total tau (t-tau), and phosphorylated tau (p-tau). The assessment of Aβ42 levels is an important indicator of an abnormal condition associated with Aβ metabolism. In a functional Aβ metabolism pathway, amyloid is continuously degraded and present in the CSF. However, in AD, where the degradation is impaired, amyloid persists in the brain, leading to the formation of Aβ plaques.

Table 1: Cerebrospinal fluid markers for differential dementia

Dementive diseases	Biomarkers in cerebrospinal fluid		
	Amyloid-beta	**Total tau**	**Phosphorylated tau**
Alzheimer's disease	significantly reduced	significantly increased	significantly increased
Dementia with Lewy bodies	reduced	increased	increased
Frontotemporal dementia	reduced	increased	no changes
Vascular dementia	reduced	no changes	no changes
Other dementia	no changes	varied changes	varied changes

Consequently, a characteristic feature of AD is a reduction in the concentration of Aβ protein in the CSF (Mulder et al., 2010). Unlike Aβ, levels of t-tau and p-tau proteins in the CSF increase in individuals with advanced neurodegeneration and cognitive impairment. In FTD, there is a decrease in CSF Aβ42 and an increase in CSF t-tau levels, while CSF p-tau levels remain within the normal range (Verwey et al., 2010). In DLB, CSF levels of Aβ42 are slightly decreased, alongside increased levels of CSF t-tau and p-tau. In VaD, CSF Aβ42 is decreased, but CSF t-tau and p-tau remain within the normal range. Patients with Creutzfeldt-Jakob disease (CJD) exhibit markedly elevated CSF t-tau levels, while CSF p-tau levels are relatively normal. In psychiatric disorders (PSY), CSF levels of Aβ42, t-tau, and p-tau are all within the normal range (Schoonenboom et al., 2012).

2.3 Amyloid precursor protein metabolism

Amyloid precursor protein (APP) is abundantly expressed in both the liver and the central nervous system. Under physiological conditions, it plays a role in neuronal migration, adhesion, protein transport and axon repair. According to the amyloid cascade hypothesis, APP undergoes proteolysis by secretases, with the predominant physiological pathway involving α and γ secretase (90%) and the amyloidogenic pathway involving β and γ secretase (10%). The amyloidogenic pathway results in the formation of Aβ (40-42 amino acids), an extramembrane fragment with a propensity to aggregate. Aβ is the primary component of senile plaques, contributing to increased neuronal apoptosis and likely playing a role in the development of AD (Zheng & Koo, 2011).

Additionally, Aβ fragments have the ability to interact with and disrupt the function of many receptors and components in the extracellular environment. They can interfere with certain glutamatergic and cholinergic receptors, thus hindering cell-cell communication (Patterson et al., 2008). Furthermore, they can impact the Trk-B receptor, the primary receptor for BDNF - a fundamental neurotrophic factor highly responsible for neuroplasticity. BDNF has been shown to be diminished in numerous psychiatric and neurodegenerative disorders (Jerónimo-Santos et al., 2015).

2.4 Summary of biochemical factors in AD

Aβ exerts adverse effects such as synapse dysfunction, heightened oxidative stress (affecting both oxidant and antioxidant components, disrupting the redox balance), inflammation (triggering microglial activation and escalating the production of proinflammatory cytokines), mitochondrial dysfunction (penetrating into mitochondria) and inducing apoptosis (Buccellato et al., 2021; Olufunmilayo et al., 2023). Another hallmark of AD is the presence of NFTs, formed by agglomerates of hyperphosphorylated tau protein and located within the cells (Basheer et al., 2023).

3. Genetic factors of dementia

Numerous studies suggest that dementia diseases can be likened to the "butterfly effect," influenced by a multitude of factors throughout one's lifespan (Martens et al., 2022). Given genetic heterogeneity, we find ourselves in a situation where the disease phenotype is shaped not only by a single mutation but also by a combination of various genes (Jellinger, 2022). Furthermore, it cannot be definitively asserted that individuals with one copy of the faulty gene will inevitably develop the disease. We can only refer to an "*elevated risk of disease*." If it is determined that we possess defective copies of genes associated with an increased disease risk, we can undertake appropriate measures to postpone the onset of potential symptoms or alleviate them when they appear (prevention) (Martens et al., 2022).

3.1 Alzheimer's disease

Early-onset AD (EOAD), also referred to as familial AD (fAD), is currently recognized to result from dominant mutations in three genes: *PSEN1*, *PSEN2*, and *APP*. Most often, we are dealing with a mutation in the *PSEN1* gene. Defects in the *PSEN2* gene are sporadic, and mutations in the *APP* gene are even rarer (Paulson & Igo, 2011). Mutations in *PSEN1* and *PSEN2* genes encode presenilin 1 (PS1) and 2 (PS2), whose protease products play a crucial role in the cleavage of APP. A subset of cases is attributed to a mutation in the gene responsible for the precursor protein APP, located on chromosome 21. Individuals with trisomy of chromosome 21, such as those with

Down syndrome, have three copies of the gene encoding APP. Consequently, the incidence of AD is more prevalent in this population compared to individuals with the typical number of chromosomes (Jorde et al., 2014).

Another form of AD is late-onset AD (LOAD), which occurs more frequently than EOAD. The genetic component of its pathogenesis involves various allelic variants of the apoE locus, encoded by the *APOE* gene, particularly the most significant variants of this locus – ε2, ε3, and ε4 (Jorde et al., 2014). The *APOE* isoforms differ by only one amino acid (Martens et al., 2022). The presence of the ε4 variant, in a single copy, increases the risk of AD by 2-5 times, and when present in two copies, the risk increases by 5-10 times. The level of risk varies based on the ethnic origin of the population (Jorde et al., 2014). Additionally, with this variant, the age of onset is typically earlier. Despite ε4 being present in 50-70% of AD cases, it is not the causative gene. Conversely, ε2, which is relatively uncommon, has the strongest protective effect (Martens et al., 2022). Presently, in the pathophysiology of AD, *APOE* is implicated in symptoms like tau-induced neurodegeneration, microglial and astrocyte reactions, and the disruption of the blood-brain barrier (Jorde et al., 2014).

Genome-wide association studies (GWAS) have uncovered additional genes linked to the risk of AD, including *TREM2*, *INPP5D*, *CLU*, *CR1*, *SPI1*, *ABCA7*, *EPHA1*, and *MS4A*. These genes are associated with the functioning of the immune system. For instance, the *TREM2* gene encodes a surface receptor that prevents Aβ aggregation by activating microglia, which facilitate endocytosis. Research methods emphasize the importance of investigating the neuroimmune axis in AD for a comprehensive understanding of the intricate pathogenic mechanisms and the development of effective treatment and diagnostic methods (Ward et al., 2022; Bellenguez et al., 2022).

3.2 Vascular dementia

VaD arises from various conditions that disrupt blood flow and oxygen supply to the brain, leading to damage in the brain's blood vessels. Cerebral small vessel disease (cSVD) is notably linked to a heightened risk of dementia. The pathogenesis of cSVDs is associated with genetic factors such as: *NOTCH3*, *HTRA1*, and *COL4A1/2* genes (Cho et al., 2022).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the prevailing form of cerebral small vessel disease, resulting from genetic alterations in the *NOTCH3* gene (Cho et al., 2022). CADASIL is associated with various manifestations, including stroke, white matter (WM) disease, microbleeds, and vascular dementia (Mizuno et al., 2020). Individuals carrying mutations in the *NOTCH3* gene face an elevated risk of developing vascular dementia compared to those without the mutation in the general population (OR, 5.42; 95% CI, 3.11-8.74) (Cho et al., 2022).

The *NOTCH3* gene is a large gene comprised of 33 exons located on chromosome 19p13.1. It codes for a single-pass transmembrane receptor (Notch3) abundant in epidermal growth factor repeats (EGFRs) within the extracellular domain. This receptor is expressed in vascular smooth muscle cells (VSMCs) and pericytes, playing a role in maintaining the homeostasis of mesenchymal stem cells derived from vertebrae (VMSCs) (Ferrante et al., 2019). In CADASIL, the function of the *NOTCH3* gene is heightened, indicating a pro-aggregation mutation. This occurs through the addition or subtraction of cysteine, resulting from a missense mutation (Mizuno et al., 2020) in 1 of the 34 EGFR domains of the Notch3 protein (Cho et al., 2022). Cases of both duplication and deletion have been observed, affecting the quantity of cysteine in the amino acid chain. Each EGFR is expected to contain six cysteines, likely participating in the formation of disulfide bridges. Altering the cysteine count to an odd number may result in the development of abnormal disulfide bridges, leading to aggregation of the Notch extracellular domain (NECD) (Mizuno et al., 2020).

Descriptions exist for more than 200 mutations that contribute to the CADASIL disease phenotype (Cho et al., 2022). Approximately 98% of mutations manifest within exons 2-23, though occurrences have been verified across all exons. Furthermore, the severity of

the disease is contingent on the mutation's specific location within the gene (Ferrante et al., 2019). In their study, Rutten et al. (2019) demonstrated that individuals with a mutation in EGFr 1-6 faced a stroke risk 12 years earlier, had a shorter lifespan and exhibited a larger volume of white matter hyperintensities compared to those with a mutation in EGFr 7-34 (Rutten et al., 2019).

3.3 Dementia with Lewy bodies

DLB relies on specific genetic factors that elevate the risk of disease, primarily involving the *GBA* gene, *APOE* gene, and *SNCA* gene. Studies conducted by Chia et al. in 2021 and by Guo et al. in 2022 further established a correlation between heightened morbidity in individuals with dementia who harbor mutations in the *BIN1*, *TMEM175* (Chia et al., 2021), *APOC1*, *CLU*, *FBXL19*, and *MAPT* genes (Guo et al., 2022).

The *GBA* gene is responsible for encoding the lysosomal enzyme glucocerebrosidase (GCase), and the deficiency or absence of this enzyme likely hampers the degradation of α-synuclein, a protein encoded by the *SNCA* gene. The breakdown of α-synuclein protein is crucial in the formation of Lewy body deposits and Lewy neurites. The extent of GCase dysfunction varies depending on the genetic variant of the *GBA* gene, leading to different levels of association with disease phenotypes. Notably, the most frequently encountered pathogenic variants include p.E326K, p.T369M, p.N370S and p.L444P. The prevalence of these variants varies across different ethnic populations (Blauwendraat et al., 2020). Aggregation tests utilizing genes across the entire genome identified *GBA* gene mutations as particularly crucial in the pathogenic process of DLB. Additionally, Chia et al. demonstrated that greater polygenic risk correlated with more severe dementia symptoms in individuals at risk (P=0.009) (Chia et al., 2021). Insufficient production of the product encoded by the *BIN1* gene, known as bridge integrator 1, contributes to elevated Aβ production by reducing lysosomal degradation of the β-site APP precursor protein-cleaving enzyme 1 (BACE1).

When the *TMEM175* gene product, a transmembrane potassium channel, is deficient, it leads to impaired lysosomal function. This deficiency impairs the clearance of autophagosomes through lysosomes, diminishes the respiratory capacity of mitochondria and contributes to increased deposition of phosphorylated α-synuclein (Chia et al., 2021).

In their large-scale multi-trait association analysis, Guo et al. compared the entire genetic etiology of DLB, AD and Parkinson's disease (PD). Their findings revealed that the most substantial genetic correlation was evident between DLB and AD (rg=0.6603; p=0.0010). The correlation rate was slightly reduced between DLB and PD (rg=0.6352; p=0.0007), and it reached the lowest level between AD and PD (rg=0.2136; p=0.0130) (Guo et al., 2022).

3.4 Frontotemporal dementia

FTD represents another form of dementia, with approximately 1/3 of cases being familial and inherited in an autosomal dominant manner. Mutations in three genes are primarily involved in the pathogenesis of this type of dementia: *GRN*, *MAPT*, and *C9orf72* (Swift et al., 2021). It is important to note that not everyone with family members carrying mutations in these genes is diagnosed with FTD. Furthermore, each subtype of FTD is influenced by different genes with varying frequencies; for instance, the behavioral variant of frontotemporal dementia is predominantly caused by a mutation in the *GRN* gene (Rohrer et al., 2009).

The progranulin gene (*GRN*) consists of 13 exons, with Yu et al. identifying 58 variants, of which 24 were found to be pathogenic. Typically, these pathogenic variants involve a nonsense mutation or a shift in the reading frame, leading to the premature emergence of a stop codon. Consequently, the mRNA undergoes degradation, resulting in the absence of the *GRN* gene expression product. The researchers concluded that FTD is caused by gene haploinsufficiency (Yu et al., 2010).

Genetic factors contribute to the pathogenesis of every form of dementia, playing a pivotal role as risk factors. This emphasizes the importance of incorporating genetic studies into dementia diagnoses, particularly for family members of individuals with dementia. In a 2022 study by Ward and colleagues using a multi-gene dementia risk assessment, lifestyle assessment, and

frailty index, it was shown that the occurrence of dementia is influenced by various factors. The study revealed that a high genetic risk of dementia can be mitigated through a healthy lifestyle and maintaining a low frailty index with minimal health deficits. For instance, individuals with both a high genetic risk and a high frailty score were 5.6 times more likely to develop dementia compared to those with a low genetic risk and a low frailty score. Importantly, the study showed that a high frailty score represents a significant increase in dementia risk independent of genetic risk factors, highlighting the frailty score as a key and modifiable risk factor influenced by lifestyle (Ward et al., 2022).

4. Conclusions

Dementia stands as a global public health priority, affecting millions of individuals and posing significant challenges for patients, caregivers, and healthcare systems. The associated societal costs are substantial, emphasizing the urgent need for effective interventions and support systems. Dementia manifests through a range of cognitive, emotional, and behavioral symptoms. Moreover, the pathogenesis of dementia involves numerous biochemical and genetic factors. Early recognition of symptoms and molecular causes is crucial for timely diagnosis and treatment. However, distinct types of dementia, such as AD, DLB, FTD, and, VaD, exhibit unique pathophysiological mechanisms, symptoms, and biochemical and genetic factors. Therefore, a thorough understanding of the molecular factors specific to each dementia type has the potential to significantly reduce diagnosis time and bring clinicians closer to unravelling the precise causes of the challenges posed by aging societies.

Conflict of Interest Statement

The authors declare no conflict of interest.

References:

Aarsland D. (2020) Epidemiology and Pathophysiology of Dementia-Related Psychosis. *The Journal of clinical psychiatry* **81**, AD19038BR1C.

Albai, O., Frandes, M., Timar, R., Roman, D. & Timar, B. (2019) Risk factors for developing dementia in type 2 diabetes mellitus patients with mild cognitive impairment. *Neuropsychiatric Disease and Treatment* **15**, 167-175.

Armstrong, R.A. (2019) Risk factors for Alzheimer's disease. *Folia Neuropathologica* **57**, 87–105.

Arvanitakis, Z., & Bennett D.A. (2019) What Is Dementia? *Journal of the American Medical Association* **322**, 1728.

Arvanitakis, Z., Shah, R.C. & Bennett, D.A. (2019) Diagnosis and Management of Dementia: Review. *Journal of the American Medical Association* **322**, 1589-1599.

Atri, A. (2019) The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. *Medical Clinics of North America* **103**, 263-293.

Basheer, N., Smolek, T., Hassan, I., Liu, F., Iqbal, K., Zilka, N. & Novak, P. (2023) Does Modulation of Tau Hyperphosphorylation Represent a Reasonable Therapeutic Strategy for Alzheimer's Disease? From Preclinical Studies to the Clinical Trials. *Molecular Psychiatry* **28**, 2197–2214.

Bellenguez, C., Küçükali, F., Jansen, I.E., Kleineidam, L., Moreno-Grau, S., Amin, N., Naj, A.C., Campos-Martin, R., Grenier-Boley, B., Andrade, V., Holmans, P.A., Boland, A., Damotte, V., van der Lee, S.J., Costa, M.R., Kuulasmaa, T., Yang, Q., de Rojas, I., Bis, J.C., *et al.* (2022) New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics* **54**, 412-436.

Blauwendraat, C., Reed, X., Krohn, L., Heilbron, K., Bandres-Ciga, S., Tan, M., Gibbs, J.R., Hernandez, D.G., Kumaran, R., Langston, R., Bonet-Ponce, L., Alcalay, R.N., Hassin-Baer, S., Greenbaum, L., Iwaki, H., Leonard, H.L., Grenn, F.P., Ruskey, J.A., Sabir, M., Ahmed, S. *et al.* (2020) Genetic modifiers of risk and age at onset in GBA associated Parkinson's disease and Lewy body dementia. *Brain* **143**, 234-248.

Blennow, K., de Leon, M. J. & Zetterberg, H. (2006) Alzheimer's disease. *The Lancet* **368**, 387–403.

Breijyeh, Z. & Karaman, R. (2020) Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules* **25**, 5789.

Buccellato, F. R., D'Anca, M., Fenoglio, C., Scarpini, E. & Galimberti, D. (2021) Role of Oxidative Damage in Alzheimer's Disease and Neurodegeneration: From Pathogenic Mechanisms to Biomarker Discovery. *Antioxidants* **10**, 1353.

Cerejeira, J., Lagarto, L. & Mukaetova-Ladinska, E.B. (2012) Behavioral and psychological symptoms of dementia. *Frontiers in Neurology* **7**, 73.

Chertkow, H., Feldman, H.H., Jacova, C. & Massoud, F. (2013) Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimer's Research & Therapy* **5**, 2.

Chia, R., Sabir, M.S., Bandres-Ciga, S., Saez-Atienzar, S., Reynolds, R.H. *et al.* (2021) Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nature Genetics* **53**, 294-303

Cho, B.P.H., Harshfield, E.L., Al-Thani, M., Tozer, D.J., Bell, S. & Markus, H.S. (2022) Association of vascular risk factors and genetic factors with penetrance of variants causing monogenic stroke. *JAMA Neurology* **79**, 1303-1311.

Elahi, F.M. & Miller, B.L. (2017) A clinicopathological approach to the diagnosis of dementia. *Nature Reviews Neurology* **13**, 457-476.

Feast, A., Orrell, M., Charlesworth, G., Melunsky, N., Poland, F. & Moniz-Cook, E. (2016) Behavioural and psychological symptoms in dementia and the challenges for family carers: systematic review. *The British Journal of Psychiatry* **208**, 429-434.

Ferrante, E.A., Cudrici, C.D., Boehm, M. (2019) CADASIL: new advances in basic science and clinical perspectives. *Current Opinion in Hematology* **26**, 193-198.

Fink, A., Doblhammer, G. & Tamgüney, G. (2021) Recurring gastrointestinal infections increase the risk of dementia. *Journal of Alzheimer's Disease* **84**, 797-806.

Guo, P., Gong, W., Li, Y., Liu, L., Yan, R., Wang, Y., Zhang, Y. & Yuan, Z. (2022) Pinpointing novel risk loci for Lewy body dementia and the shared genetic etiology with Alzheimer's disease and Parkinson's disease: a large-scale multi-trait association analysis. *BMC Medicine* **20**, 214.

Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S. H., Villemagne, V. L., Aisen, P., Vendruscolo, M., Iwatsubo, T., Masters, C. L., Cho, M., Lannfelt, L., Cummings, J. L. & Vergallo, A. (2021) The Amyloid-β pathway in Alzheimer's disease. *Molecular Psychiatry* **26**, 5481–5503.

Husebo, B.S., Achterberg, W. & Flo, E. (2016) Identifying and managing pain in people with Alzheimer's disease and other types of dementia: A systematic review. *CNS Drugs* **30**, 481-497.

Institute for Health Metrics and Evaluation (2021) Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Reference Life Table. Seattle, United States of America.

Jack, C. R., Jr, Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M. & Sperling, R. (2018) NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* **14**, 535–562.

Jansen, C., Parchi, P., Capellari, S., Vermeij, A. J., Corrado, P., Baas, F., Strammiello, R., van Gool, W. A., van Swieten, J. C. & Rozemuller, A. J. (2010) Prion protein amyloidosis with divergent phenotype associated with two novel nonsense mutations in PRNP. *Acta Neuropathologica* **119**, 189–197.

Jellinger, K.A. (2022) Recent update on the heterogeneity of the Alzheimer's disease spectrum. *Journal of Neural Transmission* **129**, 1-24.

Jerónimo-Santos, A., Vaz, S. H., Parreira, S., Rapaz-Lérias, S., Caetano, A. P., Buée-Scherrer, V., Castrén, E., Valente, C. A., Blum, D., Sebastião, A. M. & Diógenes, M. J. (2015) Dysregulation of TrkB receptors and BDNF function by amyloid-β peptide is mediated by calpain. *Cerebral cortex* **25**, 3107–3121.

Jorde, L.B., Carey, J.C. & Bamshad, M.J. (2014) Medical genetics. Fourth Edition. Elsevier Urban & Partner.

Kao, Y. C., Ho, P. C., Tu, Y. K., Jou, I. M. & Tsai, K. J. (2020) Lipids and Alzheimer's disease. *International Journal of Molecular Sciences* **21**, 1505.

Khan, S., Barve, K.H., & Kumar, M.S. (2020) Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. *Current Neuropharmacology* **18**, 1106–1125.

Kim, B., Noh, G.O. & Kim, K. (2021) Behavioural and psychological symptoms of dementia in patients with Alzheimer's disease and family caregiver burden: a path analysis. *BioMed Central Geriatrics* **21**, 160.

Kuo, C.Y., Stachiv, I. & Nikolai, T. (2020) Association of late life depression, (non-) modifiable risk and protective factors with dementia and Alzheimer's disease: Literature review on current evidences, preventive interventions and possible future trends in prevention and treatment of dementia. *International Journal of Environmental Research and Public Health* **17**, 7475.

Lei, S., Li, X., Zhao, H., Zhenzhen, F., Chun, L., Xie, Y. & Jiansheng, L. (2022) Risk of dementia or cognitive impairment in sepsis survivals: a systematic review and meta-analysis. *Frontiers in Aging Neuroscience* **14**, 839472.

Martens, Y.A., Zhao, N., Liu, C.C., Kanekiyo, T., Yang, A.J., Goate, A.M., Holtzman, D.M. & Bu, G. (2022) ApoE Cascade Hypothesis in the pathogenesis of Alzheimer's disease and related dementias. *Neuron* **110**, 1304-1317.

McGrowder, D. A., Miller, F., Vaz, K., Nwokocha, C., Wilson-Clarke, C., Anderson-Cross, M., Brown, J., Anderson-Jackson, L., Williams, L., Latore, L., Thompson, R. & Alexander-Lindo, R. (2021) Cerebrospinal fluid biomarkers of Alzheimer's disease: Current evidence and future perspectives. *Brain Sciences* **11**, 215.

Mizuno, T., Mizuta, I., Watanabe-Hosomi, A., Mukai, M. & Koizumi T. (2020) Clinical and genetic aspects of CADASIL. *Frontiers in Aging Neuroscience* **12**, 91.

Moloney, C. M., Lowe, V. J. & Murray, M. E. (2021) Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. *Alzheimer's & Dementia* **17**, 1554–1574.

Mulder, C., Verwey, N.A., van der Flier, Wiesje, M., Bouwman Femke, H., Kok, A., van Elk, Evert, J., Scheltens, P. & Blankenstein, M.A. (2010) Amyloid-β(1–42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. *Clinical Chemistry* **56**, 248–253.

Olufunmilayo, E. O., Gerke-Duncan, M. B. & Holsinger, R.M.D. (2023). Oxidative stress and antioxidants in neurodegenerative disorders. *Antioxidants* **12**, 517.

Pasieka, A., Panek, D., Szałaj, N., Espargaró, A., Więckowska, A., Malawska, B., Sabaté, R. & Bajda, M. (2021) Dual inhibitors of amyloid-β and tau aggregation with amyloid-β disaggregating properties: Extended *In cellulo*, *In silico*, and kinetic studies of multifunctional anti-Alzheimer's agents. *ACS Chemical Neuroscience* **12**, 2057–2068.

Patterson, C., Feightner, J.W., Garcia, A., Hsiung, G.Y., MacKnight, C. & Sadovnick, A.D. (2008) Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. *Canadian Medical Association Journal* **178**, 548-556.

Paulson, H.L. & Igo, I. (2011) Genetics of dementia. *Thieme Medical Publishers* **31**, 449-460.

Pemberton, H.G., Collij, L.E., Heeman, F., Bollack, A., Shekari, M., Salvadó, G., Alves, I.L., Garcia, D.V., Battle, M., Buckley, C., Stephens, A.W., Bullich, S., Garibotto, V., Barkhof, F., Gispert, J.D., Farrar, G. & AMYPAD consortium. (2022) Quantification of amyloid PET for future clinical use: A state-of-the-art review. *European Journal of Nuclear Medicine and Molecular Imaging* **49**, 3508–3528.

Piekut, T., Hurła, M., Banaszek, N., Szejn, P., Dorszewska, J., Kozubski, W., & Prendecki, M. (2022) Infectious agents and Alzheimer's disease. *Journal of Integrative Neuroscience*, **21,** 73.

Prendecki, M., Kowalska, M., Łagan-Jędrzejczyk, U., Piekut, T., Krokos, A., Kozubski, W. & Dorszewska, J. (2020) Genetic factors related to the immune system in subjects at risk of developing Alzheimer's disease. *Journal of Integrative Neuroscience*, **19**, 359–371.

Rohrer, J.D., Guerreiro, R., Vandrovcova, J., Uphill, J., Reiman, D., Beck, J., Isaacs, A.M., Authier, A., Ferrari, R., Fox, N.C., Mackenzie, I.R.A., Warren, J.D., Silva, R de., Holton, J., Revesz, T., Hardy, J., Mead, S. & Rossor, M.N. (2009) The heritability and genetics of frontotemporal lobar degeneration. *Neurology* **73**, 1451-1456.

Rutten, J.W., Van Eijsden, B.J., Duering, M., Jouvent, E., Opherk, C., Pantoni, L., Federico, A., Dichgans, M., Markus, H.S. *et al.* (2019) The effect of NOTCH3 pathogenic variant position on CADASIL disease severity: NOTCH3 EGFr 1-6 pathogenic variant are associated with a more severe phenotype and lower survival compared with EGFr 7-34 pathogenic variant. *Genetics in Medicine* **21**, 676-682.

Schneider, J.A. (2022) Neuropathology of dementia disorders. *Continuum (Minneapolis, Minn)* **28**, 834–851.

Schoonenboom, N.S., Reesink, F.E., Verwey, N.A., Kester, M.I., Teunissen, C.E., van de Ven, P.M., Pijnenburg, Y.A., Blankenstein, M.A., Rozemuller, A.J., Scheltens, P. & van der Flier, W.M. (2012) Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology* **78**, 47–54.

Swift, I.J., Sogorb-Esteve, A., Heller, C., Synofzik, M., Otto, M., Graff, C., Galimberti, D., Todd, E., Heslegrave, A.J., van der Ende, E.L., Van Swieten, J.C., Zetterberg, H. & Rohrer, J.D. (2021) Fluid biomarkers in frontotemporal dementia: past, present and future. *Journal of Neurology, Neurosurgery & Psychiatry* **92**, 204-215.

Verwey, N.A., Maartje, I., Van Der Flier, Wiesje, M., Veerhuis, R., Berkhof, H., Twaalfhoven, H., Blankenstein, Marinus A., Scheltens, P. & Pijnenburg, Y.A.L. (2010) Additional value of CSF amyloid-B40 levels in the differentiation between FTLD and control subjects. *Journal of Alzheimer's Disease* **20**, 445–452.

Ward, D.D., Ranson, J.M., Wallace, L.M.K., Llewellyn, D.J. & Rockwood, K. (2022) Frailty, lifestyle, genetics and dementia risk. *Journal of Neurology, Neurosurgery & Psychiatry* **93**, 343-350.

Wimo, A., Seeher, K., Cataldi, R., Cyhlarova, E., Dielemann, J.L., Frisell, O., Guerchet, M., Jönsson, L., Malaha, A.K., Nichols, E., Pedroza, P., Prince, M., Knapp, M. & Dua, T. (2023) The worldwide costs of dementia in 2019. *Alzheimer's & Dementia* **19**, 2865–2873.

World Health Organization (2021) The top 10 causes of death 2021. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

World Health Organization (2023) Fact sheets of dementia 2023. https://www.who.int/news-room/fact-sheets/detail/dementia

Yu, C.E., Bird, T.D., Bekris, L.M., Montine, T.J., Leverenz, J.B., Steinbart, E., Galloway, N.M., Feldman, H., Woltjer, R., Miller, C.A., Wood, E.M., Grossman, M., McCluskey, L., Clark, C.M., Neumann, M., Danek, A., Galasko, D.R., Arnold, S.E., Chen-Plotkin, A., Karydas, A., Miller, B.L., Trojanowski, J.Q., Lee, V.M., Schellenberg, G.D. & Van Deerlin, V.M. (2010) The spectrum of mutations in progranulin: a collaborative study screening 545 cases of neurodegeneration. *Archives of Neurology* **67**, 161-170.

Zhang, X.X., Tian, Y., Wang, Z.T., Ma, Y.H., Tan, L., & Yu, J.T. (2021). The epidemiology of Alzheimer's disease modifiable risk factors and prevention. *Journal of Prevention of Alzheimer's Disease* **8**, 313–321.

Zheng, H., & Koo, E.H. (2011) Biology and pathophysiology of the amyloid precursor protein. *Molecular Neurodegeneration* **6**, 27.