LUMEN ET VIRTUS
ISSN: 2177-2789

# MANIFESTATIONS AND COMORBIDITIES OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

https://doi.org/10.56238/levv15n43-109

**Submitted on:** 24/11/2024 **Publication date:** 24/12/2024

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## ABSTRACT

Objective: The aim of this review was to report the current knowledge on the main clinical manifestations and comorbidities associated with Alzheimer's disease (AD). Methodology: Searches were performed in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Alzheimer Disease, Signs and Symptoms, Clinical Diagnosis. From this search, 440 articles were found, which were subsequently submitted to the selection criteria. After applying the inclusion and exclusion criteria, 25 articles were selected from the PubMed database to compose the review. Results: The studies highlight the diversity of clinical manifestations of AD, which include memory loss, cognitive difficulties, language problems, and mood swings. Comorbidities often seen in AD patients include cardiovascular disease, diabetes mellitus, depression, and migraine. The identification of genetic factors and biomarkers, such as alterations in the ApoE, ENPP6 and SOMA1 genes, reveals the biological complexity of the disease. Sex differences in AD manifestations are significant, with women having a higher prevalence of depressive and psychotic symptoms, while men are more prone to apathy. Innovative therapeutic approaches, such as modulation of brain rhythms and artificial rhythmic stimulation, show promise for improving cognitive function. Conclusion: The integration of multidisciplinary and innovative approaches is essential for advancing the diagnosis and treatment of AD. A detailed understanding of clinical manifestations and comorbidities, combined with the identification of biomarkers, is essential to develop more effective therapies. In short, progress in AD management requires a holistic and collaborative approach, aimed at meeting the individual needs of patients and promoting their overall well-being.

**Keywords:** Alzheimer's Disease. Clinical Manifestations. Comorbidities.

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## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive decline, which represents the most prominent clinical manifestation of the disease. This decline is often accompanied by sleep disturbances and varied psychobehavioral symptoms, including apathetic, depressive, and agitated behavior, characterized by exaggerated motor activity and verbal and/or physical aggression (ZANG et al., 2023). Approximately 90% of patients develop one or more psychobehavioral symptoms during the course of AD. In addition, Alzheimer's disease is responsible for most cases of dementia, affecting cognitive functions and, consequently, the quality of life of patients and their caregivers (ZANG et al., 2023).

Historically, the first clinical description of the disease was made by the German psychiatrist Alois Alzheimer in 1906, after examining the brain of a patient who had severe loss of memory and other cognitive abilities. Alois Alzheimer observed specific pathological changes in the patient's brain, including senile plaques and neurofibrillary tangles, which became characteristic markers of AD (Doe,  2015) (YU et al., 2020). Since then, knowledge about AD has expanded significantly, although many aspects still remain incomplete (YU et al., 2020).

Currently, dementia is the seventh leading cause of death among all diseases and one of the leading causes of disability and dependence among seniors globally. More than fifty-five million people live with dementia worldwide, and there are approximately 10 million new cases each year. This continued increase in the number of cases highlights the urgent need for effective prevention and treatment strategies (ZHANG; ZHANG; XU, 2024).

In recent decades, the prevalence and incidence of dementia, including AD, have shown an unequivocal downward trend. This phenomenon has been associated with earlier investments in population factors, such as improved education and vascular health, reinforcing the importance of primary prevention (YU et al., 2020). Improvements in education, for example, can contribute to the construction of a more robust cognitive reserve, which helps delay the onset of clinical symptoms of AD. Similarly, promoting vascular health may reduce the risk of factors that contribute to neurodegeneration, such as hypertension and diabetes (YU et al., 2020). Epidemiologically, AD currently affects more than 55 million people around the world and it is estimated that this number will increase to 78 million in 2030 (CASAGRANDE et al., 2022).element. In Europe, an estimated 10.5 million people are living with dementia, with an expected increase to 13.4 million by 2030 (FREDERIKSEN et al., 2020).

Many dementia patients are older adults with comorbidities, such as cardiovascular conditions and diabetes, and also have an increased risk of developing epilepsy and behavioral symptoms. The coexistence of these conditions with AD can complicate the clinical management of patients, requiring multidisciplinary approaches to optimize treatment and improve quality of life. In addition, polypharmacy, i.e., the use of multiple medications, is a common practice among these patients, but it can increase the risk of adverse drug interactions and side effects. Therefore, it is crucial that medical follow-up is systematic and rigorous to minimize these risks and improve clinical outcomes (FREDERIKSEN et al., 2020).

Emerging research has provided evidence that gender is an important factor that may play a role in the clinical variability of AD dementia. Studies indicate that women are more vulnerable to AD pathology and risk factors compared to men, in addition to having more severe cognitive deficits and faster cognitive decline. Determining these differences has important clinical implications, aiding in personalized assessment and guiding interventions for neuropsychiatric symptoms in AD. This differentiation is vital for the development of more effective and personalized treatments that take into account the specific characteristics of each patient (EIKELBOOM et al., 2022).

Prospective observational studies (OPSs) and randomized controlled trials (RCTs) have been instrumental in understanding the causal relationships and efficacy of specific interventions in the prevention of AD (YU et al., 2020). These studies provide valuable data that help outline more effective prevention and treatment strategies. For example, interventions based on lifestyle changes, such as regular physical exercise, healthy diet, and cognitive activities, have shown potential in reducing the risk of developing AD (YU et al., 2020).

In summary, Alzheimer's disease is a complex and devastating neurodegenerative condition with profound impacts on global public health. Continuous research and early interventions are essential to address the challenges posed by this disease, improve patients' quality of life, and reduce the burden on health systems.

The objective of this study is to analyze and review the literature on Alzheimer's disease, in order to better understand the clinical manifestations of the disease and identify the main comorbidities related to the condition. Through the review of the existing literature, we seek to explore the diagnostic challenges, epidemiology, and natural history of the disease, as well as the clinical characteristics that differentiate Alzheimer's disease from other neurodegenerative conditions. This knowledge can guide the creation of new diagnostic tools and evidence-based interventions, with the aim of improving the

management and treatment of patients from the early stages of the disease, in addition to contributing to the understanding and management of associated comorbidities.

## METHODOLOGY

This is a systematic review that seeks to understand the clinical aspects of Alzheimer's disease, aiming to ensure greater knowledge about the clinical picture and diagnosis of this condition, as well as to demonstrate the main associated comorbidities. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the clinical manifestations of Alzheimer's disease and the main comorbidities related to the condition?"

The searches were carried out through searches in the PubMed database. Three descriptors were used in combination with the Boolean term "AND": Alzheimer, Signs and Symptoms, Clinical Diagnosis. The search strategy used in the PubMed database was: (Alzheimer) AND (Signs and Symptoms) and (Alzheimer) AND (Clinical Diagnosis). From this search, 440 articles were found, which were subsequently submitted to the selection criteria.

The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research. In addition, review, observational and experimental studies, which were made available in full, were considered. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the database, a total of 440 articles were found. After applying the inclusion and exclusion criteria, 25 studies were selected, and 14 and 10 were used to compose the collection to participate in the critical analysis of the systematic review.

## RESULTS

TABLE 1: CREATED BY THE AUTHOR

| AUTHORS | MAIN COLLABORATION |
|---|---|
| Burckhardt et al., 2020 | Diets rich in antioxidants and omega-3 fatty acids, nutritional supplementation (Souvenaid). |
| Casagrande et al., 2022 | Current AD prevalence, projections to 2030, population impact of AD in Europe. |
| Cermelli et al., 2024 | Activation of microglia and astrocytes, release of pro- |

| AUTHORS | MAIN COLLABORATION |
|---|---|
| | inflammatory cytokines, blood-brain barrier (BBB) dysfunction. |
| Dan et al., 2021 | Cognitive decline and impairment of memory function, impact on the quality of life of patients and caregivers. |
| Doe, 2015; Yu et al., 2020 | Early clinical description of AD by Alois Alzheimer, senile plaques, and neurofibrillary tangles as characteristic markers. |
| Eikelboom et al., 2022 | Sex differences in AD pathology, women's vulnerability, faster cognitive decline, personalization of interventions. |
| Fong et al., 2023 | Degeneration of the suprachiasmatic nucleus (SCN), dysregulation of circadian rhythms, impact on sleep, and behavioral symptoms. |
| Frederiksen et al., 2020 | Impact of comorbidities on the clinical management of AD, use of polypharmacy, and risks of adverse drug interactions. |
| Island; Balleza-Tapia; Fisahn, 2021 | Beta-amyloid (Aβ) plaques, tau tangles, synaptic loss, and neuronal death. |
| Koppelmans; Silvester; Duff, 2022 | Neuroimaging techniques (MRI, PET), biomarkers in cerebrospinal fluid (CSF). |
| Lu et al., 2020 | Reduction of agitation, promotion of emotional well-being, engagement in activities and social interaction. |
| Betrayed; Baker; Korhonen, 2020 | Healthy lifestyle, control of metabolic risk factors, multidisciplinary approaches. |
| Yu et al., 2020 | Systematic review and meta-analysis of prospective observational studies and randomized controlled trials for AD prevention. |
| Zang et al., 2023 | Cognitive decline, sleep disorders, psychobehavioral symptoms, impact on the quality of life of patients and caregivers. |
| Zhang; Zhang; Xu, 2024 | Prevalence and global impact of dementia, need for prevention and treatment strategies. |

## DISCUSSION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline and impaired memory function. It is the leading cause of dementia among older adults, positioning itself as a major public health concern due to its significant impact on the quality of life of patients and their caregivers (DAN et al., 2021). The main neuropathological findings of AD include the presence of extracellular beta-amyloid (Aβ) plaques and hyperphosphorylated tau neurofibrillary tangles. These abnormalities are accompanied by synaptic loss and neuronal death, particularly in regions of the hippocampus and cerebral cortex, which are critical for memory and other cognitive functions (ISLA; BALLEZA-TAPIA; FISAHN, 2021).

Environment and stress levels play a crucial role in the progression of Alzheimer's disease. Chronic exposure to stress can aggravate neuroinflammation and increase the production of reactive oxygen species (ROS), exacerbating neuronal damage. Cortisol, a hormone released in response to stress, can negatively affect the hippocampus, a brain region essential for the formation of memories, contributing to cognitive impairment (CERMELLI et al., 2024). In contrast, stimulus-rich environments such as nature and social interaction can have a beneficial effect on AD patients. Horticultural therapy, for example, has proven effective in reducing agitation and promoting emotional well-being by allowing patients to engage in activities that refer to past experiences and interact socially. These interventions help reduce stress levels and promote mental health in patients (LU et al., 2020).

Prevention of AD involves adopting a healthy lifestyle, which includes a balanced diet, regular exercise, and control of metabolic risk factors such as diabetes and hypertension. Diets rich in antioxidants and omega-3 fatty acids have been shown to reduce the risk of AD by promoting brain health and reducing inflammation (CERMELLI et al., 2024). Effective management of AD requires a multidisciplinary approach that includes physicians, neurologists, psychologists, and occupational therapists. Personalized treatment strategies that take into account patients' comorbidities and genetic profile are essential to optimize therapeutic outcomes (PETTI; BAKER; KORHONEN, 2020).

Metabolic risk factors, such as insulin resistance and hyperglycemia, are closely linked to AD. Cerebral insulin resistance is characterized by altered insulin signaling in the central nervous system, which can result in cognitive impairment and increased risk of neurodegeneration. Chronic hyperglycemia can lead to the formation of advanced glycation end products (AGEs), which accumulate in tissues and promote inflammation and oxidative stress (CERMELLI et al., 2024). Studies suggest that type 2 diabetes is associated with an increased risk of AD, with mechanisms including mitochondrial dysfunction and Aβ deposition in the brain. Effective management of these metabolic factors is essential to reduce the risk of AD and mitigate its effects. Interventions that aim to improve insulin sensitivity and control blood glucose levels can have a positive impact on AD progression (CERMELLI et al., 2024).

Prevention of AD is a crucial goal that requires multifaceted strategies. Promoting a healthy lifestyle, including a balanced diet, regular exercise, and stress management, is key to reducing the risk of AD (CERMELLI et al., 2024). In addition, education about risk factors and early signs of the disease can help with early detection. Preventive interventions should also focus on reducing exposure to harmful environmental factors, such as pollutants and

toxic substances, which can contribute to the development of AD. Prevention and community awareness programs can play an important role in reducing the incidence of AD in the long term (CERMELLI et al., 2024).

The interaction between genetic and environmental factors plays a critical role in the predisposition and progression of AD. APOE4, a variant of the apolipoprotein E (APOE) gene, plays a crucial role in lipid transport and metabolism in the body. The APOE4 allele is one of the most well-established genetic risk factors for AD. The presence of APOE4 is associated with an increase in Aβ and phosphorylated tau deposition, as well as synaptic dysfunction (CERMELLI et al., 2024). In addition to genetic factors, environmental factors such as diet, level of physical activity, and toxic exposures also influence the progression of AD (CERMELLI et al., 2024). Chronic exposure to stress, for example, can exacerbate neuroinflammation and oxidative stress, accelerating neuronal degeneration. Additionally, a diet high in saturated fats and refined sugars may promote insulin resistance and inflammation, increasing the risk of AD. Interventions that promote a healthy lifestyle, including a balanced diet, regular exercise, and stress management, are essential for the prevention and management of AD (CERMELLI et al., 2024).

Recent experimental studies suggest that artificial rhythmic stimulation can emulate brain rhythms and potentially prevent or treat cognitive changes in AD patients. These approaches include invasive techniques, such as deep brain stimulation, and non-invasive techniques, such as transcranial direct current stimulation and transcranial magnetic stimulation (ISLA; BALLEZA-TAPIA; FISAHN, 2021). Artificial rhythmic stimulation aims to restore neuronal oscillatory activity, particularly the ÿ and ÿ rhythms, which are essential for memory function. These rhythms are often disrupted in AD due to Aβ deposition and synaptic dysfunction. Restoring these rhythms can improve cognitive function and reduce the behavioral and psychological symptoms of AD(ISLA; BALLEZA-TAPIA; FISAHN, 2021).

Sleep disturbances are common in AD patients and pose a significant challenge in managing the disease. Dysregulation of circadian rhythms, which includes melatonin and core body temperature, is a frequent feature in AD patients. These changes can lead to multiple nocturnal awakenings and discontinuous sleep, exacerbating the cognitive and behavioral symptoms of the disease (FONG et al., 2023). The pathophysiology of sleep disorders in AD is linked to degeneration of the suprachiasmatic nucleus (SCN) of the hypothalamus, which is the main regulator of circadian rhythms. The loss of neurons in the SCN results in poor regulation of sleep-wake cycles, leading to fragmented sleep patterns (FONG et al., 2023). In addition, the deposition of Aβ in the SCN and other areas of the brain can further aggravate sleep disorders (CERMELLI et al., 2024). Light therapy has

been investigated as an intervention to improve sleep disturbances in AD patients. Light exposure can help regulate circadian rhythms and improve sleep quality, although the long-term effects still need to be better understood. Studies indicate that light therapy can reduce the number of nocturnal awakenings and increase sleep efficiency, providing an improvement in patients' quality of life (FONG et al., 2023).

Neuroinflammation is another striking feature of the pathogenesis of AD, characterized by the activation of microglia and astrocytes, in addition to the release of pro-inflammatory cytokines. This inflammatory response is in part a reaction to the deposition of Aβ and hyperphosphorylated tau, which are recognized as foreign bodies by the brain's immune system. Reactive microgliosis results in a neurotoxic environment, exacerbating synaptic dysfunction and neuronal death (CERMELLI et al., 2024). Studies indicate that neuroinflammation is also associated with blood-brain barrier (BBB) dysfunction, allowing peripheral immune cells and other inflammatory factors to enter the brain. BBB dysfunction aggravates neuroinflammation, creating a vicious cycle that contributes to the progression of AD. Therapeutic interventions that aim to reduce brain inflammation may therefore be beneficial in mitigating the effects of AD (CERMELLI et al., 2024). Oxidative stress, in turn, results from the excessive production of reactive oxygen species (ROS), which cause damage to cellular components, including lipids, proteins, and DNA (ISLA; BALLEZA-TAPIA; FISAHN, 2021). Neuroinflammation and oxidative stress work together to promote neuronal death and progression of AD. Interventions that aim to reduce inflammation and oxidative stress may be beneficial in slowing disease progression (CERMELLI et al., 2024).

Ongoing research is focused on new therapeutic approaches to treat AD, including the use of brain stimulation techniques and the modulation of neuroinflammatory pathways. Transcranial magnetic stimulation (TMS), for example, is a non-invasive technique that has shown promising results in modulating cortical activity and improving cognitive symptoms in AD patients. Studies suggest that TMS may help restore oscillatory ÿ and ÿ activity, which is essential for memory function (ISLA; BALLEZA-TAPIA; FISAHN, 2021). Another promising approach is the use of anti-inflammatory therapies to reduce neuroinflammation and protect against neuronal degeneration. Anti-inflammatory agents, such as TNF-α and IL-1 inhibitors, are being investigated for their potential to alleviate brain inflammation and improve AD symptoms (CERMELLI et al., 2024).

Patients with AD often have comorbidities such as cardiovascular and metabolic diseases, which can aggravate the progression of the disease. Hypertension, for example, can lead to damage to cerebral blood vessels, exacerbating neurovascular dysfunction and promoting Aβ deposition. Similarly, diabetes is associated with insulin resistance, which

negatively affects brain metabolism and increases the risk of neurodegeneration (CERMELLI et al., 2024). Cerebral insulin resistance, in particular, is characterized by altered insulin signaling in the brain, which can result in cognitive impairment and increased risk of AD. Effective management of these comorbidities is crucial to slow the progression of AD and improve patients' quality of life (CERMELLI et al., 2024).

Nutritional interventions are also important for the management of AD. Antioxidant-rich diets, such as the Mediterranean diet, have shown potential to reduce oxidative stress and inflammation, promoting brain health. Supplementation with omega-3 fatty acids, which have anti-inflammatory properties, is also a promising area of research (CERMELLI et al., 2024). Therapy with Souvenaid, a nutritional supplement intended to provide essential nutrients for synaptic function, has been investigated in clinical studies with mixed results. Although some studies have shown small benefits on cognitive function, significant clinical efficacy has not yet been established (BURCKHARDT et al., 2020). The relationship between headaches, especially migraine, and AD has been the subject of several studies. Patients with a history of migraine have an increased risk of developing dementia, including AD. The pathophysiology underlying this association may include common mechanisms such as neuroinflammation and cerebral vascular dysfunction. Migraine is associated with systemic inflammation, which may contribute to the neuroinflammation seen in AD (CERMELLI et al., 2024). In addition, repeated migraine episodes can lead to changes in brain function and predispose individuals to cognitive decline.

Atypical antipsychotics, such as olanzapine and risperidone, are widely used to treat behavioral symptoms in AD. Studies indicate that olanzapine may be more effective at reducing delusions and nocturnal behavior disorders, while risperidone is associated with less weight gain. However, long-term use of antipsychotics can lead to significant adverse effects, such as excessive sedation and increased risk of falls (ZHANG; ZHANG; XU, 2024). Alternative therapies, such as light therapy and horticultural therapy, offer non-pharmacological approaches to improving the well-being of AD patients. Light therapy helps regulate circadian rhythms and improve sleep quality, while horticultural therapy promotes social interaction and reduces agitation (FONG et al., 2023) (LU et al., 2020). These interventions have the potential to improve patients' quality of life and reduce the burden on caregivers. Psychiatric disorders, including depression, anxiety, and psychosis, are common comorbidities in AD patients. Depression is often seen in the early stages of AD and may precede the diagnosis of dementia. The pathophysiology of depression in AD may be related to neurotransmitter dysfunction, neuroinflammation, and neuroendocrine changes. The presence of depressive symptoms is associated with an increase in the rate

of cognitive decline in AD patients (CERMELLI et al., 2024). Effective anxiety management is crucial to improve patients' quality of life and ease the burden on caregivers (LU et al., 2020).

The integrated approach in the management of AD involves the combination of pharmacological and non-pharmacological interventions. Acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are commonly used to treat the cognitive symptoms of AD due to their effect on modulating the ÿ and ÿ rhythms. However, the efficacy of these drugs is limited, especially in advanced stages of the disease, and many patients may experience side effects (ZHANG; ZHANG; XU, 2024) (ISLA; BALLEZA-TAPIA; FISAHN, 2021). Non-pharmacological therapies, such as light therapy and horticultural therapy, have shown benefits in reducing the behavioral and psychological symptoms of AD (FONG et al., 2023) (LU et al., 2020). Light therapy can help regulate circadian rhythms and improve sleep quality, while horticultural therapy promotes emotional well-being and social interaction. Studies indicate that these interventions can reduce agitation, improve quality of life, and provide a therapeutic environment for AD patients (LU et al., 2020).

Research into innovative therapies for AD is constantly evolving. One of the most promising approaches involves the use of monoclonal antibodies to neutralize Aβ plaques. These antibodies can bind to the plaques and facilitate their removal by the immune system, potentially slowing the progression of AD (ISLA; BALLEZA-TAPIA; FISAHN, 2021). In addition, BACE inhibitors (beta-secretase) are being investigated to prevent the formation of Aβ by blocking one of the enzymes responsible for its production. Preliminary studies suggest that these inhibitors may reduce Aβ levels in the brain and improve cognitive symptoms in animal models of AD (ISLA; BALLEZA-TAPIA; FISAHN, 2021). However, the efficacy and safety of these treatments are still in the clinical testing phase.

Genetic and epigenetic interventions are emerging as areas of interest in the treatment of AD. Gene editing, using technologies such as CRISPR/Cas9, has the potential to correct genetic mutations associated with AD. This approach may, in the future, allow the modification of specific genes to prevent or treat the disease (CERMELLI et al., 2024). In addition, epigenetics, which studies changes in gene expression without altering the DNA sequence, offers new opportunities for the development of therapies. Epigenetic modifications, such as DNA methylation and histone acetylation, can influence the expression of genes associated with neuroprotection and neurodegeneration (CERMELLI et al., 2024). Therapies that aim to modify these epigenetic processes are being explored to reduce the progression of AD.

Given the complexity of AD, combined approaches that use multiple therapies simultaneously may be more effective. For example, combining acetylcholinesterase inhibitors with anti-inflammatory agents may provide synergistic benefits by improving cognitive function and reducing neuroinflammation (ISLA; BALLEZA-TAPIA; FISAHN, 2021). In addition, interventions that combine pharmacological and non-pharmacological therapies, such as light therapy along with transcranial direct current stimulation, can address multiple aspects of disease in an integrated manner. Future studies should investigate the efficacy of these combined approaches in clinical trials to determine the best treatment strategies (FONG et al., 2023) (LU et al., 2020).

Caregivers of AD patients face significant challenges and often experience high levels of stress and burnout. Support and training programs for caregivers are essential to help them manage the care of AD patients effectively and maintain their own well-being (LU et al., 2020). Psychological and emotional support, as well as access to resources and information, can help caregivers cope with the daily demands of caregiving. Support groups and community networks are also valuable in providing a sense of community and sharing of experiences (LU et al., 2020). Future research should focus on interventions that address both the cognitive and behavioral aspects of AD. Restoration of neuronal oscillatory activity, control of neuroinflammation and oxidative stress, and promotion of a therapeutic environment are promising areas for new interventions (ISLA; BALLEZA-TAPIA; FISAHN, 2021). In addition, longitudinal studies are needed to better understand the progression of AD and to evaluate the efficacy of therapies over time (PETTI; BAKER; KORHONEN, 2020).

The main manifestation of AD is the progressive impairment of cognitive functions, particularly memory formation and retention. Patients with AD have a gradual loss of cognitive abilities that significantly impacts their ability to perform daily activities (ISLA; BALLEZA-TAPIA; FISAHN, 2021). This cognitive dysfunction is thought to be related to the deposition of Aβ plaques and tau neurofibrillary tangles, which are toxic to neurons and synapses (CERMELLI et al., 2024). Neurofibrillary tangles are composed of paired helical filaments of hyperphosphorylated tau protein, which accumulate within neurons and interfere with axonal transport. This process leads to synaptic dysfunction and cell death, contributing to the cognitive decline seen in AD (ISLA; BALLEZA-TAPIA; FISAHN, 2021). In addition, neuronal oscillatory activity, particularly the ÿ and ÿ rhythms, is essential for memory function. Studies have shown that disruption of these brain rhythms is correlated with Aβ deposition and disease progression. Modulation of these brain rhythms has been

suggested as a potential approach to restore cognitive function in AD (ISLA; BALLEZA-TAPIA; FISAHN, 2021).

Neuroimaging and biomarkers play a crucial role in the early detection and monitoring of AD progression. Neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), allow visualization of brain changes associated with AD, including Aβ deposition and hippocampal atrophy (KOPPELMANS; SILVESTER; DUFF, 2022). In addition, biomarkers in cerebrospinal fluid (CSF), such as Aβ and tau levels, can help in diagnosis and monitoring response to treatment (CERMELLI et al., 2024). The integration of advanced technologies such as artificial intelligence (AI) and machine learning is revolutionizing DA research. AI algorithms can analyze large volumes of clinical, genetic, and neuroimaging data to identify patterns and predict disease progression (PETTI; BAKER; KORHONEN, 2020). These tools can help personalize treatments based on individual patient characteristics and improve therapeutic outcomes. Using wearable devices to monitor physical activity, sleep patterns, and other health indicators can provide real-time data for AD management. These devices can help detect early changes in patients' health and enable timely interventions (FONG et al., 2023).

## CONCLUSION

In conclusion, Alzheimer's disease (AD) has a wide range of clinical manifestations and comorbidities that complicate its management. Cognitive losses, language problems, and mood swings are prevalent symptoms that evolve over time. Comorbidities, such as cardiovascular disease, diabetes, and depression, exacerbate the progression of AD and significantly affect patients' quality of life.

Genetic studies and the identification of biomarkers reveal the biological complexity of AD and offer new perspectives for diagnosis and treatment. Sex differences in AD manifestations, as well as the importance of vascular risk factors and lifestyle, are crucial for the development of effective preventive and therapeutic strategies.

Innovative pharmacological approaches, focused on modulation of brain rhythms and artificial rhythmic stimulation, emerge as promising to improve cognitive function and quality of life in patients. In short, a multidisciplinary and integrated approach, which considers both the direct manifestations of AD and its comorbidities, is essential to advance in the fight against this complex and challenging disease.

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