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ALZHEIMER'S DISEASE - THE ROLE OF NEUROPSYCHOLOGY. SUMMARY OF RECOMMENDATIONS FOR INTERVENTION AND NOTES ON FUTURE PERSPECTIVES

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Abstract: Alzheimer's disease is a chronic and progressive neurodegenerative condition that affects the brain, causing a gradual deterioration in cognitive functions, memory and the ability to carry out daily activities. It is the most common form of dementia worldwide. Although an area of ongoing research, the field of Alzheimer's disease and dementia has begun to move towards a precision medicine framework where it is essential to identify and describe the different biological and cognitive phenotypes of Alzheimer's disease as well as the driving factors. associated risk and resilience.
Neuropsychology plays an important role in this process by identifying individuals at risk of future cognitive decline in the earliest clinical stages and by framing potentially modifiable risk factors.
In this work, based on a literature review, a synthesis of the main characteristics of the disease, its diagnosis and prognosis as well as the role of neuropsychology and recommended therapy is carried out.
Keywords: Alzheimer's disease; Dementia, Neuropsychology.

BRIEF CHARACTERIZATION OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) [1]is a brain disease that slowly destroys memory and thinking ability and, eventually, the ability to perform the simplest tasks. People with Alzheimer's also experience changes in behavior and personality. The symptoms of Alzheimer's disease - changes in thinking, memory, reasoning and behavior - are known as dementia. This is why Alzheimer's disease is sometimes referred to as "dementia." Other diseases and conditions can also cause dementia, with Alzheimer's disease being the most common cause of dementia in older adults. (Alzheimer's, 2023) (alzheimers.gov, 2023).

Alzheimer's disease is a type of brain disease, just as coronary artery disease is a type of heart disease. It is caused by damage to nerve cells (neurons) in the brain. The neurons in the brain are essential for thinking, walking, speaking and all human activity(Braak & Tredici, 2011) (Breijyeh & Karaman, 2020).

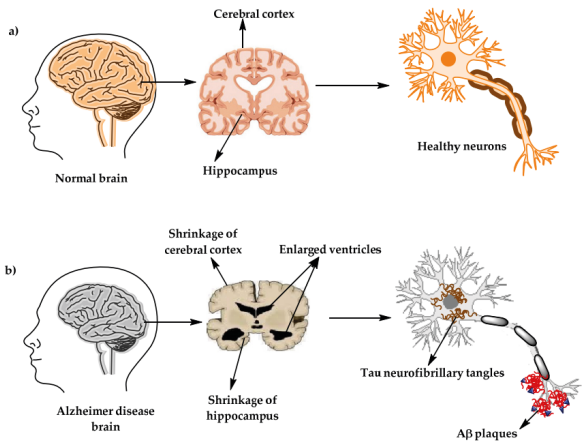

Fig. 1 - The physiological structure of the brain and neurons in (a) a healthy brain and (b) a brain with Alzheimer's disease (AD)
Zeinab Breijyeh and Rafik Karaman

In Alzheimer's disease, the damaged neurons are primarily responsible for memory, language and thinking. Logically, as a result, the first symptoms tend to be problems with memory, language and thinking. Although these symptoms are new to the affected individual, the brain changes that cause them are thought to have begun 20 years or more before symptoms began (Braak & Tredici, 2011).

Alzheimer's disease is not a normal part of aging. It is the result of complex changes in the

1. "On November 3, 1906, a clinical psychiatrist and neuroanatomist, Alois Alzheimer, reported "A peculiar process of severe disease of the cerebral cortex" at the 37th Meeting of Psychiatrists of Southwest Germany in Tubingen. He described a 50-year-old woman who had been followed since her admission for paranoia, progressive sleep and memory disturbances, aggression and confusion, until her death 5 years later." Hanns Hippius & Gabriele Neundörfer (2003) The discovery of Alzheimer's disease, Dialogues in Clinical Neuroscience, 5:1, 101-108, DOI: 10.31887/DCNS.2003.5.1/ hhippius.

brain that begin years before symptoms appear and that lead to the loss of brain cells and their connections. It is essential to distinguish the process of identifying and diagnosing AD (i.e., the disease itself) from dementia, the latter being a clinical manifestation of the neuropathological process of AD. Although AD and dementia are often discussed together, they in fact refer to distinct concepts, assessment methods, diagnostic criteria, and implications for research and clinical practice (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022, p. 11).

Alzheimer's disease is characterized by the abnormal accumulation of proteins in the brain, including beta-amyloid plaques and tau protein tangles (Zhou, Miranda-Saksena, & & Saksena, 2013). These changes in the brain impair communication between nerve cells and eventually lead to the death of those cells.

The most common form of Alzheimer's disease is so-called sporadic Alzheimer's disease - this means that the disease has no specific family connection and often begins after the age of 60. Another form of Alzheimer's disease is hereditary, or "familial," and accounts for less than 5% of all Alzheimer's cases (APACS, 2015). This form of Alzheimer's disease is called Familial Alzheimer's Disease (FAD), also known as early-onset dementia (Alzheimer Society of Canada, 2018).

The underlying cause of the pathological changes in Alzheimer's disease (Aβ, NFTs and synaptic loss) is still unknown. Several hypotheses have been proposed as the cause of Alzheimer's disease, but two of them are believed to be the main cause:

1. some believe that a deficiency in cholinergic function is a critical risk factor for AD,
2. while others suggest that alteration in the production of amyloidβ-amyloid protein is the main initiating factor (Alzheimer Society of Canada, 2018).

However, there is currently no accepted theory to explain the pathogenesis of AD.

If we think of dementia as a tree; Dementia is the trunk of the tree and the branches are the various forms of dementia that extend from the trunk, each with its own set of leaves representing the signs and symptoms. Each branch is slightly different from each other, but they still belong to the same tree.

Four different types of dementia are identified: Alzheimer's Disease (AD), Vascular Dementia (VD), Lewy Body Dementia (LBD) and Frontotemporal Dementia (FTD). These types of dementia share similar symptoms, but there are differences in the number of cases, signs and treatments for each of them. (Alzheimer Society of Canada, 2018) (NIH N. I.) (ADI, 2015). The following infographic helps to understand the types mentioned above and presents an overview of the disease:

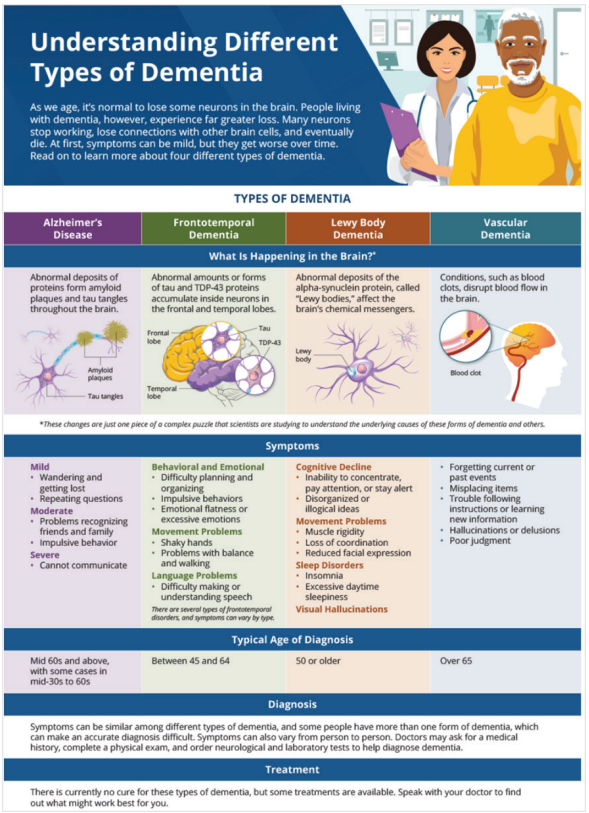

Fig. 2 – Understanding the different types of dementia. National Institutions of Health

Some of the most common features and symptoms of Alzheimer's disease include(Alzheimer's, 2023) (NIH N. I.):

- Cognitive Decline: The most striking symptom is the progressive decline in cognition, including memory loss, difficulty reasoning, solving problems and making decisions.
- Behavioral and Personality Changes: Many people with Alzheimer's experience changes in their behavior and personality. This may include agitation, irritability, confusion, depression, anxiety, and changes in judgment.
- Temporal and Spatial Disorientation: People with Alzheimer's can become disoriented in time (they don't know what day or year it is) and in space (they don't know where they are).
- Language Difficulties: Difficulty finding words, expressing thoughts, and understanding language may occur as the disease progresses.
- Difficulty Performing Daily Tasks: As the disease progresses, daily activities, such as dressing, bathing and preparing food, become challenging.
- Orientation Difficulties: People with Alzheimer's may have difficulty recognizing close family and friends.
- Loss of Motor Skills: Motor coordination and motor skills may be impaired as the disease progresses.
- Sleep Changes: Sleep disorders, such as insomnia or excessive daytime sleepiness, are common.
- Hallucinations and Delusions: Some Alzheimer's patients may experience hallucinations (seeing or hearing things that are not present) and delusions (false, irrational beliefs).
- Loss of Autonomy: As the disease progresses, patients often lose the ability to care for themselves and require assistance with daily activities.
- Changes in the Brain: At the brain level, Alzheimer's disease is characterized by beta-amyloid plaques and tau protein tangles, which interfere with the normal functions of brain cells.

The *Alzheimer's Association* [2]reports that Alzheimer's disease is the sixth leading cause of death in the United States. It also highlights that, among the 10 main causes of death, it is the only one that does not have an effective treatment or cure (Rosenzweig, 2022). It is important to highlight that the symptoms of Alzheimer's disease vary from person to person and can progress differently in each case. Alzheimer's disease is progressive and has no cure, but there are treatments available to help alleviate symptoms and improve patients' quality of life (Larson, 2023).

MAIN RISK AND PROTECTIVE FACTORS

AD has been considered a multifactorial disease associated with several risk factors (Figure 2) such as increasing age, genetic factors, head injuries, vascular diseases, infections and environmental factors (heavy metals, trace metals, among others) (Breijyeh & Karaman, 2020).

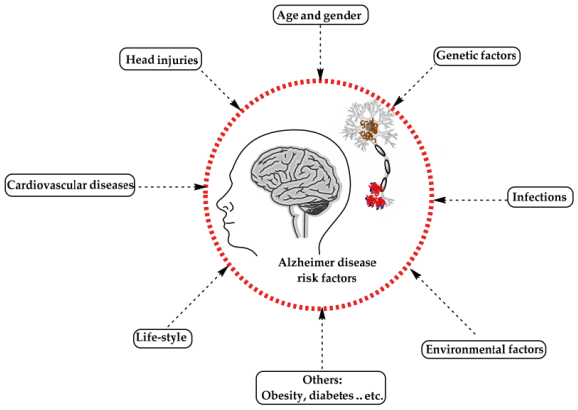

Fig. 3 - Risk factors for Alzheimer's Disease - Zeinab Breijyeh and Rafik Karaman, 2020)

2. Alzheimer's Association. Chicago IL. Website: https://www.alz.org/

Risk factors are aspects of your lifestyle, environment and genetic background that increase the likelihood of contracting a disease, as described in *Alzheimer Society of* Canada. [3]Risk factors, by themselves, are not causes of a disease; on the contrary, risk factors represent a greater probability, but not a certainty, of developing dementia. Likewise, the fact of being little or not at all exposed to risk factors does not necessarily protect a person from developing dementia.(ASC, 2023)

Some risk factors are modifiable, meaning they can be changed. It is estimated that around 40% of dementia cases may be the result of twelve modifiable risk factors (Silva, Lessa, & Araujo, 2021, pp. 10123-24).

"Cardiovascular disease" refers to conditions that affect your heart and blood vessels. Risk factors that appear in both cardiovascular disease and dementia, in particular Alzheimer's disease and vascular dementia, that the individual can control include:

- High blood pressure (hypertension)
- Smoke
- Diabetes
- Lack of physical activity
- Obesity
- Poor diet
- Other risk factors you can control include:
  - Alcohol consumption
  - Low levels of cognitive engagement
  - Depression
  - Traumatic brain injuries
  - Hearing loss
  - Social isolation
  - Atmospheric pollution
  - Food

There are risk factors for dementia that are non-modifiable, meaning they cannot be changed. These include: Age; Sex; Genetics (ASC, 2023).

On the other hand, some habits and mechanisms can help prevent the development of dementia, including AD, such as those indicated in the following figure:

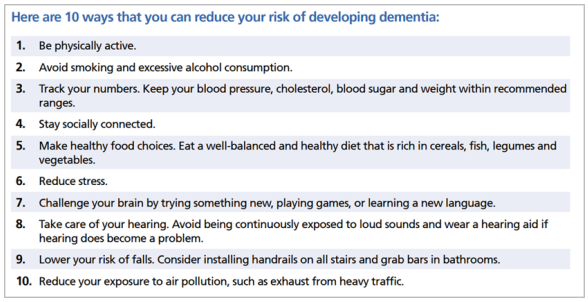

Fig. 4 – Protective mechanisms for Alzheimer's Disease - Alzheimer Society of Canada

In a more graphic way, the following figure illustrates the modifiable risk factors according to The Lancet:

Fig. 5 – 12 modifiable risk factors – The Lancet

3. Alzheimer Society of Canada. Toronto & Ontario. Website: https://alzheimer.ca/en/

PREVALENCE AND INCIDENCE

In 2020, more than 55 million people around the world were registered to be living with dementia. This number will almost double every 20 years, reaching 78 million in 2030 and 139 million in 2050 (WHO, Ageing and health, 2022).

Global estimates of the number of people in the early stages of Alzheimer's disease (AD), including the prodromal and preclinical phases, are lacking, but these are needed to inform policymakers about preventative measures and the planning of future therapies that target the condition. from DA (Gustavsson et al, 2022).

The global number of people with dementia, prodromal AD and preclinical AD was estimated at 32, 69 and 315 million, respectively. Altogether, they constituted 416 million across the AD continuum, i.e. 22% of all people aged 50 and over (Gustavsson et al, 2022).

The prevalence of AD clinical dementia increases with age and appears to be higher in women than in men(Hendriks, Peetoom, Bakker,, & al., 2021) (Cao, Tan, XU, & al., 2020). This female preponderance is not confirmed in all studies (Jack, Therneau, Weigand, & al., 2019)and may be stronger in Europe and North America than in Asia (Gustavsson et al, 2022).

There is geographic variation in the prevalence of overall dementia, even when controlling for age and sex (ADI, 2015). However, the evidence supporting this geographic variation in people with AD dementia is weak at best. It is known that the majority of individuals with Alzheimer's disease dementia are women, which is also confirmed by estimates that two-thirds of people with Aβ-positive Alzheimer's disease dementia are women. In Europe, the estimated number of women is almost double the number of men with AD, while the differences in other regions, such as the United States, are smaller; A better understanding of these regional effects is needed (Gustavsson et al, 2022).

We know that people around the world are living longer. Currently, most people can expect to live to age sixty or beyond. All countries in the world are experiencing growth in both the number and proportion of elderly people in the population. By 2030, 1 in 6 people in the world will be 60 years of age or older. At that time, the percentage of the population aged 60 and over will increase from 1 billion in 2020 to 1.4 billion (WHO, Ageing and health, 2022).

By 2050, the world population of people aged 60 and over will double (2.1 billion). The number of people aged 80 and over is expected to triple between 2020 and 2050, reaching 426 million (WHO, Dementia, 2021). Therefore, as our societies age, the number of people living with dementia worldwide is expected to increase from 55 million in 2019 to 139 million in 2050. In this sense, the costs associated with dementia are also expected to more than double from 1.3 trillion dollars per year in 2019 to 2.8 trillion dollars by 2030 (World Alzheimer Report, 2023).

In Portugal, as there is no epidemiological study to date that portrays the real situation of the problem, we can take as a reference data from Alzheimer Europe, which points to more than 193,500 people with dementia (Alzheimer Europe, 2019). In 2018, the year the study refers to, the percentage of dementia cases in Portugal was 1.8% - around 193,516 cases. Alzheimer Europe projections say that in 2025 it will be 2.29% and 3.82% in 2050 (Soares, 2020).

At EU level, it is estimated that there are more than 7.8 million people with dementia, a reduction compared to previous estimates. Furthermore, the Alzheimer Europe study indicates that women are much more affected

by dementia than men. In Portugal, there are more than 133 thousand female patients and 59.9 thousand male patients. At European level, the ratio is 6.65 million women to 3.13 million men (Soares, 2020).

DIAGNOSIS

There is currently no cure for AD, and it continues to have a devastating impact on families, communities and healthcare systems around the world. Finding an effective treatment for AD has been challenging, in part, because there is still much to learn about the neurobiology of the aging brain, including the factors that increase the risk of neurodegeneration and lead to the development of AD dementia. To address this knowledge gap, significant efforts have been made by researchers, clinicians, and policymakers to improve understanding of AD and other neurodegenerative diseases that result in cognitive impairment at the end of life. Since cognitive dysfunction and decline are central components of AD dementia, neuropsychologists have played a central role in improving the understanding of AD and its clinical manifestations for decades (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022).

According to Wehane et. al, (2022), it is essential to distinguish the process of identification and diagnosis of AD (i.e., the disease itself) from the dementia process of AD, the latter being a clinical manifestation of the neuropathological process of AD. Although AD and dementia are often discussed together, they in fact refer to distinct concepts with different assessment methods, diagnostic criteria, and implications for research and clinical practice.

AD is a neurodegenerative disease with a characteristic histopathology. It therefore requires a neuropathological diagnosis which, at this point, can only be confirmed *post-mortem* through a brain autopsy. In contrast, AD dementia can be assessed and diagnosed clinically throughout life and specifically refers to a pattern of clinical signs and symptoms that are commonly associated with AD pathology once this disease progresses sufficiently to cause cognitive dysfunction. (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022).

Alzheimer's disease progresses clinically through several stages: preclinical, mild (sometimes called the early stage), moderate and severe (sometimes called the late stage). (NIH N. I.).

Cognitive symptoms such as forgetfulness - or concern from family members - encourage patients to establish first contact with a primary care doctor. This doctor plays a decisive role in the patient's diagnosis process. The first diagnostic step, already accessible in primary care, is the patient's clinical history (their own or by proxy), complemented by a cognitive screening test and a physical examination. These clinical examinations can determine, in most cases, whether a cognitive deficit or dementia is present (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022).

An important clinical distinction is a full syndrome of dementia (i.e., cognitive impairment severe enough to impair daily activities) *versus* mild cognitive impairment (MCI - *Mild Cognitive Impairment*), for example, deficit in one or more cognitive domains with maintenance of cognitive function. global and daily activities) *versus* subjective cognitive decline (i.e., cognitive complaints without impairment of cognitive tests). Both MCI and subjective cognitive decline are recognized as risk states for developing dementia, but most countries do not approve specific pharmacological treatments outside of clinical trials (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022).

The etiological diagnosis of MCI or a dementia syndrome will normally be made by a specialist. Diagnosis requires in-depth neuropsychological and neurological examinations, basic laboratory tests, and structural brain imaging by magnetic resonance imaging or computed tomography. Other diagnostic tests may include biomarkers from PET brain imaging, cerebrospinal fluid (CSF), and (in the future) peripheral blood. Etiological diagnosis is challenging, as autopsy studies show that comorbidities of two or more neurodegenerative proteinopathies are common (Werhane, Sheppard, Pagulayan, Bondi, & Delano-Wood, 2022).

Early-onset Alzheimer's disease (EAD) is defined as onset before age 65. Differences in the neuropsychological profile between EAD and late-onset Alzheimer's disease (LAD) remain unclear (Yoash-Gantz, 2010).

Three possible diagnostic errors in early-onset dementia were discussed by (Mendez, 2006). Although EAD is the predominant cause of early-onset dementia, there are numerous other causes. On the other hand, the traditional model of LAD is characterized by prominent memory difficulties and word finding problems, but EAD may have predominant cognitive deficits in addition to memory loss. Finally, EAD may present greater neuropsychiatric than cognitive deficits (Yoash-Gantz, 2010).

Several studies have observed different progression rates for EAD and LAD. These studies found a greater rate of decline in EAD than in LAD(Jacobs, et al., 1994) (Kono, Kuzuya, Yamamoto, & Endo, 1994) (Seltzer & Sherwin, 1983). In 2002, it was reported that disease progression in EAD is sometimes faster than in LAD (Greicius, Geschwind, & Miller, 2002). Alzheimer's disease is currently recognized as a continuous process that progresses from an initial asymptomatic phase, through a prodromal symptomatic phase, mild cognitive impairment (MCI) and, finally, mild, moderate and severe dementia.

Consensus on the clinical diagnosis of Alzheimer's disease was achieved in 1984 with the development of the NINCDS-ADRDA criteria (McKhann, et al., 1984)and these criteria continue to be applied in the diagnosis of both EAD and LAD.

The NINCDS-ADRDA criteria (Dubois & al, 2007)for Alzheimer's disease specify eight cognitive domains that may be affected in Alzheimer's disease: memory, language, perceptive abilities, attention, constructive abilities, orientation, problem solving, and functional abilities.

These criteria, which have been universally adopted, have been extremely useful and have survived intact, without modification, for more than a quarter of a century. However, in the intervening 27 years, there have been important advances in our understanding of AD, our ability to detect the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease (Jack & et.al, 2011).

Alzheimer's disease is diagnosed based on a clinical evaluation that takes into account symptoms, medical history, brain imaging tests and, in some cases, genetic testing. It is essential to seek medical advice if Alzheimer's is suspected to obtain an accurate diagnosis and develop an appropriate treatment plan (Tahami Monfared & al., 2023).

Several genes have been linked to Alzheimer's disease, but more research is needed. Researchers have discovered a number of genes that are linked to Alzheimer's disease. Some genes increase the likelihood of contracting the disease, called risk genes. Others guarantee the onset of the disease, called deterministic genes. Deterministic genes are rare. However, genes are only one part of what is involved in the development of

Alzheimer's disease.(Mayo Cinic, 2023) (NIH, 2023).

As previously mentioned, the most common type of Alzheimer's disease usually begins after the age of 65 and is called late-onset Alzheimer's disease. The most common gene linked to late-onset Alzheimer's disease is a risk gene called apolipoprotein E (APOE). (Mayo Cinic, 2023) (NIH, 2023).

APOE has three common forms:

- APOE e2. The least common. Reduces the risk of Alzheimer's.
- APOE e4. This gene is a little more common. Increases the risk of Alzheimer's. And it is associated with a worse form of the disease.
- APOE e3. This most common gene does not appear to affect Alzheimer's risk.

As genetic research advances, researchers are finding links between late-onset Alzheimer's disease and a number of other genes. Examples include:

- ABCA7. This gene appears to be linked to an increased risk of Alzheimer's disease. Researchers suspect it may be related to the gene's role in how the body uses cholesterol.
- CLU. This gene helps the brain eliminate a protein called beta-amyloid. Research suggests that an imbalance in the production and elimination of beta-amyloid is fundamental to the onset of Alzheimer's disease.
- CR1. An insufficient amount of the protein produced by this gene can cause chronic swelling and irritation, called inflammation, in the brain. Inflammation is another possible factor in the development of Alzheimer's disease.
- PICALM. This gene is linked to the way nerve cells in the brain, called neurons, communicate with each other. The way they relate to each other is important for their proper functioning and the formation of memories.
- PLD3. Scientists don't know much about PLD3's role in the brain. But it has recently been linked to a significantly higher risk of Alzheimer's disease.
- TRAIN2. This gene affects how the brain reacts to swelling and irritation, called inflammation. Rare changes in this gene are associated with an increased risk of Alzheimer's disease.
- SORL1. Some forms of SORL1 on chromosome 11 appear to be linked to Alzheimer's disease.

Researchers continue to learn more about Alzheimer's disease. Knowing more about how the disease works could lead to new ways to prevent and treat it. As with APOE, these genes are risk factors, not causes. In other words, having one of these altered genes may increase your risk of Alzheimer's, but not everyone who has an altered gene will get Alzheimer's disease.(Mayo Cinic, 2023) (NIH, 2023).

Most experts do not routinely recommend genetic testing for late-onset Alzheimer's disease. However, in some cases of early-onset Alzheimer's disease, genetic testing may be helpful.

Typically, healthcare providers do not test for APOE genes. The results cannot fully predict who will get Alzheimer's disease, and typically, healthcare professionals can diagnose Alzheimer's disease without the use of genetic testing.

However, for certain treatments, called anti-amyloid therapies, it is important to test for APOE genotype. Testing for genetic changes that have been linked to early-onset Alzheimer's disease may be helpful for someone who has symptoms or for someone who has a family history of early-onset disease. Genetic testing for early-onset Alzheimer's disease could also affect current and future drug trials and help with family planning(Mayo Cinic, 2023) (NIH, 2023).

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In summary, regarding the phases and evolution of the disease, they can be listed as follows:

- Preclinical phase: there is a mild brain change;
- Mild cognitive impairment (MLD): there are clinical symptoms of memory problems, without impairment of daily activity;
- Dementia (final stage of the disease) changes in memory and other cognitive functions:
  - Emotional dependence
  - Forgetfulness
  - Confusion
  - Vegetative state (confinement, coma, mutism, intubation...).

In terms of diagnosis, the following procedures stand out:

- Study of clinical history
- Personal/family background
- Neurological examination
- Neuropsychological examination
- MCDT'S (clinical analyses, brain imaging...) and Biomarkers
- Genetic testing

ROLE OF NEUROPSYCHOLOGY

Over the last 30 years, neuropsychological assessment has played a central role in the characterization of dementia associated with Alzheimer's disease (AD), identifying the earliest cognitive and behavioral symptoms and contributing to the tracking and identification of the developmental stage of the disease.(Flicker, Bartus, Crook, & Ferris, 1984) (Morris, et al., 1989) (Storandt & Hill, 1989) (Storandt M. , 1991, pp. 100-101) (Welsh, Butters, Hughes, Mohs, & Heyman, 1992) (Albert M. , 1996) (Salmon & Bondi, 2009).

As research has increasingly focused on the early stages of the disease, it has become clear that biological markers of AD may precede cognitive and behavioral symptoms by years. It has also become clear that the early symptoms of Alzheimer's disease represent selection by the disease of specific, "large-scale" neuroanatomical networks, with clinical deficits consistent with the anatomical site of impact.(Weintraub & Mesulam, With or without FUS, it is the anatomy that dictates the dementia phenotype, 1993, 1996, 2009) (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). In the usual case, AD pathology is initially selective for the limbic regions that serve episodic memory, which leads to a limited memory deficit in the early stages of the disease.(Braak & Braak, Neuropathological staging of Alzheimer-related changes, 1991) (Jack, et al., 1997). Only when the pathology progresses to other neocortical regions over time do additional cognitive symptoms emerge and the full dementia syndrome becomes apparent.(Braak & Braak, Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis, 1996) (Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2000).

These findings led to a review of the investigational diagnostic criteria established for AD dementia since 1984 (McKhann, et al., 1984), as already mentioned. The new criteria not only define AD dementia (McKhann & al., 2011), but also incorporate a fuller spectrum of cognitive aging, including an intermediate phase of mild cognitive impairment (MCI) that precedes dementia (Albert & et.al, 2011).

A third, even earlier stage of "preclinical AD" was also identified (Sperling & et.al., 2011). This prodromal period is characterized by the presence of biomarkers, such as brain amyloid and tau deposition, and CSF amyloid, which can be detected in vivo in asymptomatic individuals years before the onset of cognitive decline.(Perrin, Fagan, & Holtzman, 2009) (Jack & et.al, 2010).

Currently, the recommendation of biomarkers to detect AD applies mainly to research. Thus, neuropsychological assessment continues to provide reliable symptom markers of AD that are critical for early diagnosis (Weintraub, Wicklund, & Salmon, 2012).

Neuropsychology has contributed significantly to the characterization of dementia associated with AD neuropathology, to its differentiation from the cognitive changes that accompany normal aging and to its distinction from dementias associated with other types of neuropathology.

The neuropsychological study of AD has advanced our understanding of other diseases that cause dementia, including cortical Lewy body disease, cerebrovascular disease, and FTLD. The earliest neuropsychological symptoms of dementia reflect the neuroanatomical systems that bear the burden of the associated pathology, but the relationship between the symptoms and the underlying disease is less obvious (Weintraub, Wicklund, & Salmon, 2012).

Amnestic dementia is most likely to be associated with AD pathology, but early-onset aphasia, progressive visuospatial deficits, and personality changes may also be associated with AD neuropathology. As dementia progresses from early to late stages, the boundaries of symptom domains become blurred and it is difficult to discern distinct profiles. Thus, neuropsychological profiles are most informative in the early stages (Weintraub, Wicklund, & Salmon, 2012).

The development of fluid and neuroimaging biomarkers will undoubtedly improve diagnosis and ultimately be used to measure treatment effects (Weintraub, Wicklund, & Salmon, 2012).

However, neuropsychological characterization remains essential to understand a patient's individual deficits, so that non-pharmacological interventions can be applied appropriately and so that educational materials for patients and caregivers are appropriately targeted. (Weintraub & Morhardt, Treatment, education and resources for non Alzheimer dementia: One size does not fit all, 2005) (Weintraub, Wicklund, & Salmon, 2012).

Numerous studies have consistently and convincingly demonstrated the diagnostic value of a cross-sectional neuropsychological assessment to distinguish normal cognition from mild cognitive impairment (MCI) and dementia (Schmand, Eikelenboom, & Van Gool, 2011).

However, technological advances allow new approaches to characterize markers of cognitive progression. Digital cognitive testing is a promising direction for repeated neuropsychological assessment. They involve ongoing change through digital assessment tools, which can be used alone or in combination with traditional neuropsychological assessments (Gold & et.al., 2018).

Software-supported tests have the potential to reduce administration and scoring errors, automatically adapt tasks to an individual's ability level (ie, computerized adaptive testing), capture nuanced performance information (ie, response latencies and sequencing), quickly calculate and compare scores, and generate meta-data. Digital assessment tools can also be used to easily capture and characterize speech and language using advanced analytics such as machine learning(Libon, Baliga, Swenson, & Au, 2021) (Thomas, et al., 2020).

Ultimately, combining the predictive power of cognitive data and biomarkers as complementary approaches may be particularly useful for differentiating healthy aging from preclinical AD (Chen, et al., 2016) and people at risk of progression to dementia (Rhodius-Meester, et al., 2018).

However, many of the newer algorithms in development do not include cognitive data (Khan, 2018). This again points to the need for innovative and more sensitive cognitive tools that are easy to administer and repeat as part of a broader multimodal assessment approach.

If the development of new neuropsychological methods for detecting markers of cognitive progression could be accompanied by the analytical and clinical validation of new blood tests for AD pathology, longitudinal studies of the interaction between cognitive function and AD-related brain changes would become more viable (Roos & et.al., 2022).

RECOMMENDATIONS FOR INTERVENTION

Treatment of Alzheimer's disease is usually part of a multidisciplinary approach that may include non-pharmacological therapies, psychological support and long-term care.

Until recently, treatment options for AD dementia were restricted to three approved cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an N-methyl-D-aspartate receptor antagonist (memantine), available commercially. which include the USA, Europe, South Korea and Japan. Clinical trials of cholinesterase inhibitors have demonstrated symptomatic effects in AD and are prescribed to patients in mild to late stages of AD dementia (Hampel, Mesulam, Cuello, & etal., 2018).

Several medications for Alzheimer's disease may be prescribed to help temporarily improve some symptoms (NHS, 2021):

ACETYLCHOLINESTERASE (ACHE) INHIBITORS

These medications increase levels of acetylcholine, a substance in the brain that helps nerve cells communicate with each other. Currently, they can only be prescribed by specialists, such as psychiatrists or neurologists.

Donepezil, galantamine and rivastigmine can be prescribed to people with early or intermediate-stage Alzheimer's disease.

The latest guidelines recommend that these medications must be continued in the most advanced and severe stages of the disease.

There is no difference in the effectiveness of each of the 3 different AChE inhibitors, although some people respond better to certain types or have fewer side effects, which can include nausea, vomiting and loss of appetite. Side effects generally improve after 2 weeks of taking the medicine.

MEMANTINE

This medicine is not an AChE inhibitor. It works by blocking the effects of an excessive amount of a chemical in the brain called glutamate. Memantine is used for moderate or severe Alzheimer's disease. It is suitable for people who cannot take or cannot tolerate AChE inhibitors.

It is also suitable for people with severe Alzheimer's disease who are already taking an AChE inhibitor. Side effects may include headaches, dizziness and constipation, but these are usually only temporary.

In the later stages of dementia, a significant number of people will develop what are known as behavioral and psychological symptoms of dementia (BPSD). Symptoms of BPSD may include:

- increased agitation
- anxiety
- ambulation
- aggressiveness
- delusions and hallucinations

These behavioral changes can be very upsetting for both the person with Alzheimer's disease and their caregiver.

RISPERIDONE

If coping strategies don't work, a psychiatrist may prescribe risperidone or haloperidol, antipsychotic medications, for people who demonstrate persistent aggression or extreme distress. These are the only medicines authorized for people with moderate to severe Alzheimer's disease, when there is a risk of harm to themselves or others. Risperidone must be used at the lowest dose and for the shortest time possible, as it has serious side effects. Haloperidol must only be used if other treatments have not helped.

Antidepressants may sometimes be given if depression is suspected as an underlying cause of the anxiety. Other medications may also be recommended to treat specific symptoms of DPBS, but these will be prescribed "off-label" (not specifically authorized for DPBS). It is acceptable for your doctor to do so, but you must provide a reason for using these medications in these circumstances.

Medication for the symptoms of Alzheimer's disease is just one part of caring for a person with dementia.

Other treatments, activities and support – also for the carer – are equally important to help people live well with dementia (NHS, 2021):

COGNITIVE STIMULATION THERAPY

Cognitive stimulation therapy (CST) involves participation in group activities and exercises designed to improve memory and problem-solving skills.

COGNITIVE REHABILITATION

This technique involves working with a trained professional, such as an occupational therapist, and a family member or friend to achieve a personal goal, such as learning to use a cell phone or other daily tasks. Cognitive rehabilitation works by having you use the parts of your brain that are working to help the parts that aren't.

REMINISCENCE AND LIFE HISTORY WORK

Reminiscence work consists of talking about things and events from your past. Typically, it uses props such as photographs, favorite objects or music. Life history work involves a compilation of photographs, notes and memories from your childhood to the present day. It can be a physical book or a digital version.

Sometimes these approaches are combined. There is evidence that they can improve your mood and well-being (NHS, 2021).

In the coming decades, regular, evidence-based updates to existing guidelines for the AD *continuum are needed* to integrate rapidly evolving technological advances and medical scientists and to introduce emerging approaches to managing early disease into clinical practice. This will pave the way for biomarker-guided identification and targeted treatment and the realization of precision medicine for AD.

Finally, we analyze some studies that have been carried out on dementia and neurofeedback techniques. It has been discovered that neurofeedback can be used alone or in collaboration with other treatment modalities. Memory, verbal language and comprehension may improve and neurofeedback, when used in collaboration with cholinesterase inhibitors, may be a potential treatment to stabilize the progressive deterioration of patients with Alzheimer's disease.(Fernández & et.al, 2008) (Luijmes, 2016) (Trambaiolli, Raymundo, M. A., & Falk, 2021).

FINAL CONSIDERATIONS

The imminent changes that make Alzheimer's disease a treatable disease have a profound impact on the patient's entire journey. However, it is necessary to constantly address issues such as how to make healthcare increasingly accessible and ensure the scalability of new diagnostic, prediction and prevention solutions.

On a positive note, the first disease-modifying treatments for AD are beginning to appear, showing that we are rapidly moving into a new era. Furthermore, knowledge of lifestyles that can contribute to reducing the effect of the disease can somehow reduce the risk of contracting the disease; as well as the production and dissemination of information on modifiable risks.

In scientific terms, the next step is to understand how we can move towards a future of personalized medicine for AD, a future that will include technical and neuroscientific innovations. Combining this context with an increasingly earlier diagnosis must allow a better quality of life for the patient.

From a challenge perspective, it is necessary to find answers to ethical dilemmas, socioeconomic consequences and personal considerations. These are aspects that society as a whole will have to debate and implement.

Providing information to patients and their families about what to expect from the patient's journey in terms of diagnostic testing, information about the disease and disease trajectory, and information about different types of prevention strategies is critical to working towards providing care designed for each patient individually.

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