Lost Memory: What is New in the Science of Alzheimer's Disease and How it Relates to Neuroplasticity, Biochemistry, Biophysics and Genetics

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ABSTRACT

During a long time, scientists believed that the brain was immutable, which means that, after its development in childhood, the brain would stay the same during the entire life of the human being, which would only change once it started to deteriorate. With the revolutionary discovery that the brain can change itself and adapt under certain circumstances cause a complete change in the way that neuroscientists treated and searched neurodegenerative diseases, especially Alzheimer. This article's purpose is to bring a greater comprehension of everything that science knows and doesn't, about Alzheimer's disease, bringing its epidemiology, risk factors, main causes, the best treatments e list all of this with neuroplasticity, biochemistry, biophysics and genetics.

INTRODUCTION

A woman arrives at a German hospital with her husband. He claimed that she was having difficulty reading, speaking and, especially, remembering simple things and naming everyday objects. Alois Alzheimer was Auguste D's doctor. At first, he thought that she suffered from a natural aging process, which occurs in every human being. However, when talking to the lady, he realized that something was very wrong. The medical notes show what happened:

What is your name?
Auguste.
Last name?
Auguste.
And her husband's name?
Auguste, I think.
Your husband?
Oh, my husband.
Are you married?
With Auguste.
How long have you been here?
Three weeks (NIEMEYER, 2020, p. 227).

After studying the woman's case extensively, Dr. Alzheimer concluded that:

Within the cell, which appears to be normal, one or several fibrils can be distinguished [...]. Distributed in the entire cortex, but especially numerous in the superficial layers of the cortex, there are tiny foci that are caused by the deposit of a special substance in the cortex (NIEMEYER, 2020, p.229).

His observations were not immediately accepted, considering that the current scenario at the time employed the dispute between two ideas: psychoanalysis and those who believed that neurological diseases had an anatomical basis, as Alzheimer thought. However, psychoanalytic thoughts stood out – which was evidenced in a congress that had featured names such as Carl Jung and Sigmund Freud, in which the genius of the German psychiatrist was left aside. Only years later it was realized that Alzheimer's was right and the pathology that bears his name came to be feared, since it deprives the human being of the ability to produce meaning.

1. The characterization of the disease, its epidemiology, biochemistry and biophysics

1.1 Amyloid Beta and Tau proteins

Alzheimer's disease is classified as dementia. Etymologically, the word Dementia comes from the Latin, de + mens, which means “without mind”. The word points to the understanding of it as a syndrome that affects the brain leading to the total or partial loss of cognitive skills and abilities, such as language, memory and thinking. It is not something only suffered by the elderly, - although in these individuals, dementia appears as a combination of pathologies such as Alzheimer's, atherosclerosis and Lewis body pathology - and the number of demented people has been increasing over time. Two other characteristics are important for the definition of the term dementia. The first: that the cognitive impairment is so severe that it can cause problems in personal and social relationships; the second is memory impairment. Based on this, the National Institute of Neurological and Communicative Problems and Strokes (NINCDS) diagnoses Alzheimer's disease (ROSSOR, et. al., 2010).

In the case of AD (English for Alzheimer's disease), Paulo Niemeyer Filho classified it as:

[...] the result of a progressive neurodegenerative disease, which is manifested by a marked impairment of recent memory, language, thinking, behavior, the ability to perform daily tasks and which, in an advanced stage, will also limit movements, usually leading to death from infectious complications, similar to a bedridden patient (NIEMEYER, 2020, p. 229).

Even though neurodegenerative diseases are classified primarily “on the basis of a protein accumulation and anatomic vulnerability, they share processes such as neuronal dysfunction and/or death (apoptosis), proteotoxic stress, and their concomitant abnormalities in the ubiquitin-proteosomal and autophagosomal/lysosomal systems, oxidative stress, programmed cell death and neuroinflammation” (DUGGER, DICKSON, 2017, p.1).

Despite the severity, “many cases seem to have a slow evolution, it may take twenty to thirty years for symptoms to manifest. It is believed that, in the initial phase, there is a compensation of the brain, but from a certain level of neuronal loss, the manifestations of the disease begin to emerge” (NIEMEYER, 2020, p.231).

The disease still fits into the so-called frontotemporal dementia (FTD) which are those that affect the temporal and frontal lobes of both hemispheres, and 15%-20% of diagnoses of dementia syndromes are of this nature (DE PAULA; GUIMARÃES; FORLENZA , 2009).

Therefore, Alzheimer's disease is “characterized by an abnormal accumulation of neuritic plaques (immunoreactive dystrophic neuritis TAU, the most common and significant in AD) and neurofibrillary tangles” (KUMAR, et. al., 2021, p.1). The disease is divided into three phases. In the first, there are no symptoms, but there are chemical and anatomical changes observed on PET (Positron Emission Tomography) and on cerebrospinal fluid (biological fluid related to the central nervous system and meninges); in the second phase, there is a small cognitive deficit. Former US President Ronald Reagan was diagnosed with AD at this stage. In the last phase, the patient has advanced cognitive loss and disability (NIEMEYER, 2020).

Many years after the discovery of Alzheimer's, and with the development of technology and more modern medical devices, it was noticed that the fibrillar alterations mentioned by the German doctor "are due to the inclusion of an abnormal form of the TAU protein in neurons, forming the tangled described by Alzheimer's, and that the deposits referred by him are beta-amyloid proteins, which form plaques scattered throughout the cortex” (NIEMEYER, 2020, p. 229). These plaques are “spherical microscopic lesions that have an extracellular amyloid beta-peptide core surrounded by enlarged axonal endings” (KUMAR, et al, 2021, p.1). Amyloids “are abnormal fibrils found deposited extracellularly and proteins found in organs and tissues” (RAMBARAM; SERPELLI, 2008, p.1) being insoluble and predominantly formed by a beta sheet structure and by soluble proteins that agglomerate to form them.

Beta-amyloid is derived from a transmembrane (which envelops the entire cell membrane) known as amyloid precursor protein (APP), concentrated in the synaptic zones of neurons. Although there are other members of this same protein family, such as APLP 1 and APLP 2 that are important modulators of glucose and insulin homeostasis, only PPA is capable of generating amyloidogenic fragments (RAMBARAM; SERPELL, 2008).

In the process of cell division, APP is synthesized either by alpha or beta secretases, which are not toxic to neurons, making APP important for processes such as memory, gene transcription and calcium transmission (these last two in the case of intracellular APP). However, if it is synthesized by beta and then secreted by gamma, they generate 42 peptide amino acids, forming beta-amyloid protein which, from its accumulation, forms amyloids (protein fibrils) or plaques that are harmful to neurons; as these fibrils form, they become resistant to degradation.

The gene responsible for the synthesis of APP, chromosome 21 (Trisomy 21), is also the one that suffers the mutation responsible for Down syndrome, which reveals an intrinsic relationship between these two disorders. Studies indicate that individuals with Down syndrome have a 50% increased chance of developing dementia throughout their lives (NIEMEYER, 2020). This usually occurs in the basal forebrain, which interferes with the cholinergic neurotransmission of the hippocampus, compromising the cognitive functions of this structure. In this scenario, asymptomatic individuals are those most at risk, as the accumulation of these proteins occurs “without warning”. Although this is a determining factor in Alzheimer's disease, it is uncertain whether the accumulation of beta-amyloid indicates dementia or neuronal death. Studies have identified dementia patients with senile plaques and individuals who do not have the disease may also have them. Even though this hypothesis, know as amyloid cascade, has been supported by genetic studies, neuronal vulnerability is still unknown (SERENIKI; VITAL, 2008).

The amyloid cascade hypothesis has received support from genetic studies with cases of the familial form of Alzheimer's disease, in which mutations in both APP and presenilins (PS) have shown an increase in the production of Aβ9 substance. However, while the study of cases of familial Alzheimer's disease has been shown to be significant for understanding this form of the pathology, the reasons for the neuronal vulnerability of sporadic cases of Alzheimer's disease remain unknown. Thus, the cholinergic hypothesis, in which synaptic abnormalities could represent the cause of dementia in Alzheimer's disease, admits a better correlation between the pattern and severity of cognitive alterations compared to senile plaques and NFT17 (SERENIKI; VITAL, 2008, p.3).

Another problem caused by excessive extracellular (in the brain parenchyma) aggregation of beta-amyloid protein is the formation of neurofibrillary tangles, neuronal intracytoplasmic structures formed by the accumulation of TAU protein (can aggregate to zinc and copper), which are important for stabilization of axon microtubules and also contribute to intracellular transport in neurons. Nevertheless, the malformation of these proteins generates neurofibrillary tangles (NFTs) that accumulate in neurons, hindering the propagation of action potentials, due to hyperphosphorylation (which may be the result of increased activity of taukinases, undersensitization of their phosphatases,

or both the mechanisms). This prevents intracellular trafficking of neurotrophic proteins and other functional proteins of the TAU protein making it insoluble. TAU is identified in the paired helical filaments that are the main component of neurofibrillary tangles. This accumulation occurs mainly in the substantia nigra, which increases neurotoxicity (DE PAULA; GUIMARÃES; FORLENZA, 2009). This normally occurs in the hippocampus and can spread throughout the cerebral cortex. AD and other neurodegenerative diseases are often associated with “change in the number and shape of dendritic spines (small outgrowths on neuronal dendrites where major postsynaptic components reside) before neuron death.” The gene responsible for decoding this protein is chromosome 17 (17q21), which has 16 exons. Exons are transcribed and introns are not.

AD is considered a secondary taopathy, given the presence of another dominant force, because mutations in the genes that cause AD in APP and in those of presenilin (a family of related multistep transmembrane proteins that function as a part of the gamma secretase of the intermembrane secretase complex) are characterized by primary or initial changes in amyloid metabolism (DUGGER, DICKSON,
2021, p.5).

According to the location of beta-amyloid deposits, there is classification into phases of TAU deposit, with “phase 1 and 2 having plaques restricted to the neocortex and hippocampus, going to the striatum, and to the brainstem and cerebellum in the phase 4” (DUGGER, DICKSON, 2017, p.4).

A study by Anatoly Nikolaev showed that secreted APP acts as a ligand for the death receptor, DR6 (O'BRIEN; WONG, 2011). This happens due to growth factor (GDNF) deprivation.

A study by Kumar and colleagues also suggests that cognitive decline, one of the most notable features of the disease, is most closely linked to a drop in presynaptic bud density in lamina, plaque, III, and IV pyramidal neurons (KUMAR, et al, 2021). However, scientists show that neurofibrillary tangles and neuritic/senile plaques appear in 40%-70% of cases of cognitive impairment. According to Mariana Adriana Sereniki and Maria Vital,

According to the amyloid cascade hypothesis, neurodegeneration in Alzheimer's disease begins with the proteolytic cleavage of the amyloid precursor protein (APP) and results in the production, aggregation and deposition of amyloid beta substance (Aβ) and senile plaques. According to the cholinergic hypothesis, dysfunction of the cholinergic system is sufficient to produce a memory impairment in animal models, which is similar to Alzheimer's disease. Brains of patients with Alzheimer's disease showed degeneration of cholinergic neurons, also occurring a reduction of cholinergic markers, and choline acetyltransferase and acetylcholinesterase had their activity reduced in the cerebral cortex of patients with Alzheimer's disease (SERENIKI; VITAL, 2008, p.3).

Further explaining memory loss, according to the amyloid cascade hypothesis, the authors state:

In most cells, phospholipase A2 (PLA2) contributes to the release of arachidonic acid from phospholipid membranes, which is a fundamental step in the synthesis of the main mediators of the inflammatory response. As phosphatidylcholine is one of the substrates of PLA2, reduced activity of this enzyme could produce a decline in phosphatidylcholine catabolism, reducing choline for acetylcholine synthesis, further contributing to cholinergic deficiency in Alzheimer's disease. In the brains of patients with Alzheimer's disease, the reduction in acetylcholinesterase activity in the frontal and parietal cortex was related to the onset of dementia, the amount of senile plaques and NFT and the early death of these patients. Thus, the reduction in PLA2 activity in patients with Alzheimer's disease is directly related to the severity of dementia and the degree of cognitive impairment (SERENIKI; VITAL, 2008, p.3).

NFTs follow a hierarchical phase division proposed by Braak and Braak:

In the six stages of Braak NFT, stage I begins in the transentorhinal cortex, followed by the hippocampus and limbic cortex (stages II-III) and multimodal association cortices (stages IV-V), with the primary cortices being the last affected (stage VI). A recent review of this schema suggests that tau pathology in subcortical areas, such as the locus

coeruleus in the pons, may precede medial temporal lobe pathology (Braak et al. 2011). Although AD has both NFTs and amyloid deposits, some elderly people only have NFTs. This process is termed "age-related primary tauopathy" (PART), with most cases having early stages of Braak NFT I-IV (DUGGER; DICKSON, 2017, p.5).

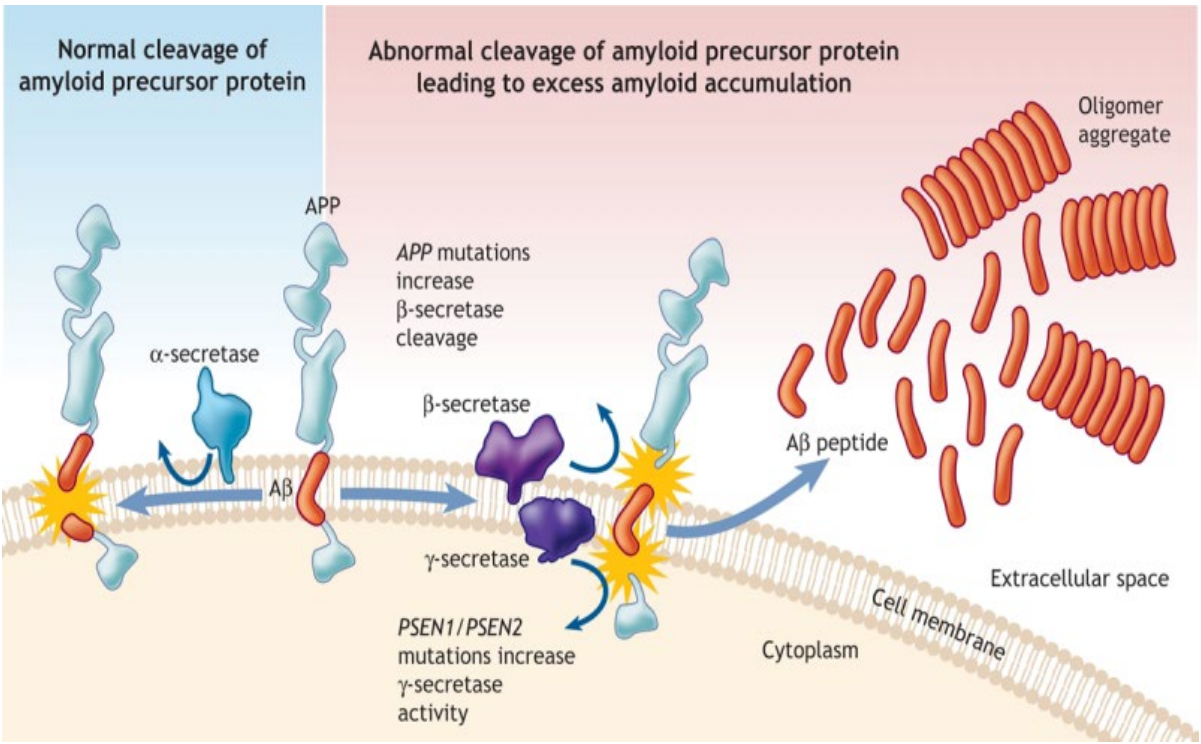


Figure 1 – Amyloid beta protein formation process. Source: Friesen, Woolridge (2021)

1.2 Differences between early-onset and late-developing Alzheimer's

The term "early onset" refers to the development of neurodegenerative diseases before age 65. There are two main aspects that involve this condition. The first is the exponential increase in the number of individuals who have it, affecting young adults in the most productive years of their lives, especially between 30 and 40 years of age. The second involves the fact that dementia occurs mainly in the elderly, causing early-onset Alzheimer's to be underestimated, misunderstood, undiagnosed, and treated incorrectly. Furthermore, Alzheimer's disease is the most common EOD (English for Early-Onset-Dementia) in both late and early nature (VEIRA, et. al., 2013). Some studies even suggest that Alzheimer's is more deadly.

As stated earlier, EOAD (English for Early-Onset-Alzheimer-Dementia, also called Familial Alzheimer's because it is mainly genetically based) represents a much smaller percentage of the total AD diagnoses. A study by Peter Panegyres and Huei-Yang Chen showed that, in a total of 3,747 patients with Alzheimer's, 16.4% were individuals with EOAD and, of that total, 45% were male, as shown in the following table.

Table 1

The demographics of the study population: late-onset and early onset of Alzheimer's disease

		All (n=3747)		LOAD (n=3133)		EOAD (n=614)			
		N	%	N	%	N	%	Chi-square	*p*-value
Gender	Male	1672	44.6	1385	44.2	287	46.7	χ^2=1.36	0.25
Race	While	3467	92.5	2913	93.0	554	90.2	χ^2=14.8	0.002
	Asian	173	4.6	143	4.6	30	4.9		
	Black	45	1.2	36	1.2	9	1.5		
	Others*	62	1.7	41	1.3	21	3.4		
Parental/Sibling AD	Yes	1147	30.6	973	31.1	174	28.3	χ^2=1.79	0.18
First degree relative AD	Yes	2510	67.0	2157	68.9	353	57.5	χ^2=29.94	<0.0001

*Including native American Indians, Alaskans and Hawaiians.

Figure 2: Incidence of EOAD and LOAD. Source: Panegyres; Cheng (2013)

EOAD presents different biochemical and genetic characteristics and forms of treatment when compared to LOAD (English for Late-Onset-Alzheimer-Disease). In a study by Panegyres and Cheng, an increased presence of CRP (C-Reactive Protein), creatinine and BUN was observed in patients with LOAD.

However, older patients are at an increased risk of infection in general, including urine and periodontal disease. It is possible that the increase in CRP is a consequence of the increased burden of infection in the elderly and is not implicated in the pathophysiology of AD. In addition, some studies suggest that CRP may decrease in AD after elevations in middle age. It cannot be disregarded that in patients with LOAD that, compared to EOAD, inflammatory mechanisms may be more important (PANEGYRES; CHENG, 2013, p.7)

Both BUN and creatinine indicate kidney health. This is relevant for understanding AD and for differentiating between EOAD and LOAD.

Renal impairment is associated with vascular aging and vascular complications as a result of accelerated atherosclerosis. Patients with chronic kidney disease are at increased risk of stroke. The significantly impaired renal function in the LOAD group in our study may just be a consequence of age; however, renal dysfunction can promote cerebrovascular pathology and AD in the elderly. In addition, patients with end-stage renal disease who receive peritoneal dialysis have excessive white hyperintensity as a result of ischemic disease of small vessels of the brain, which can trigger pro-inflammatory and endothelial reactions resulting in AD; this mechanistic pathway may not be relevant in younger patients (PAGERYNE, CHENG, 2013, p.7).

Based on the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS – COG), it was found that patients with EOAD show a greater and faster cognitive decline, with greater cortical atrophy, hypoperfusion and hypometabolism, and "particularly in the parietal and lateral temporal cortices, and relatively larger medial temporal lesions in late-onset Alzheimer's disease" (RABINOVICI, et. al., 2010, p.2). There are differences in the way cognitive decline manifests itself. In EOAD, there is a "greater loss of attention, language, visual-spatial, and executive functions" (RABINOVICI, et. al., 2010, p.1), while in LOAD, episodic memory, that is, of autobiographical movements , is more affected. The authors also state that the pathological mechanisms behind this phenomenon are still not fully understood by the scientific community.

Regarding genetics, which will be discussed in greater depth later, only a minority percentage (1-5%) of patients have mutations that lead to an autosomal dominance (which appears in several generations of a family) in the development of EOAD from a rapid and efficient accumulation of amyloid betas. There are also known sporadic DPOAE variations, with a greater chance of carrying the Apolipoprotein E ε4 allele – ApoE4 - (protein that binds lipids), which is related to the rapid deposition of beta-amyloid (KOK, et. al., 2009).

Young adult patients with AD also have more diffuse and severe deficits in acetylcholine (the first neurotransmitter discovered, related to sleep, memory and learning) and norepinephrine, (also called noradrenaline), is a hormone produced by the adrenal glands that helps coordination of brain functions such as memory and attention), reflecting further degeneration of Meynert's nucleus and locus coeruleus. This fact, that neurodegeneration and the ensuing cognitive decline impairment occur mainly in EOAD, shows a greater amount of "cognitive reserve" in these patients. "Cognitive reserve" is understood as the brain's ability to store, for a long time, the discoveries and learnings achieved during the individual's life and resilience to injuries (BIRD, et. al., 1983).

Another difference is the fact that patients with EOAD suffer the worst in the final stages of the disease, while those with LOAD lose their lives in the early stages. Furthermore, for those "older people" becomes more complicated to treat and diagnose, since cognitive decline and other symptoms related to Alzheimer's are common in other pathologies faced by people of this age, such as "depression, medication side effects, thyroid disorders, vitamin deficiencies, excessive alcohol intake, hydrocephalus or brain tumors, causes that should be investigated, as they are reversible if treated" (NIEMEYER, 2020. P.233).

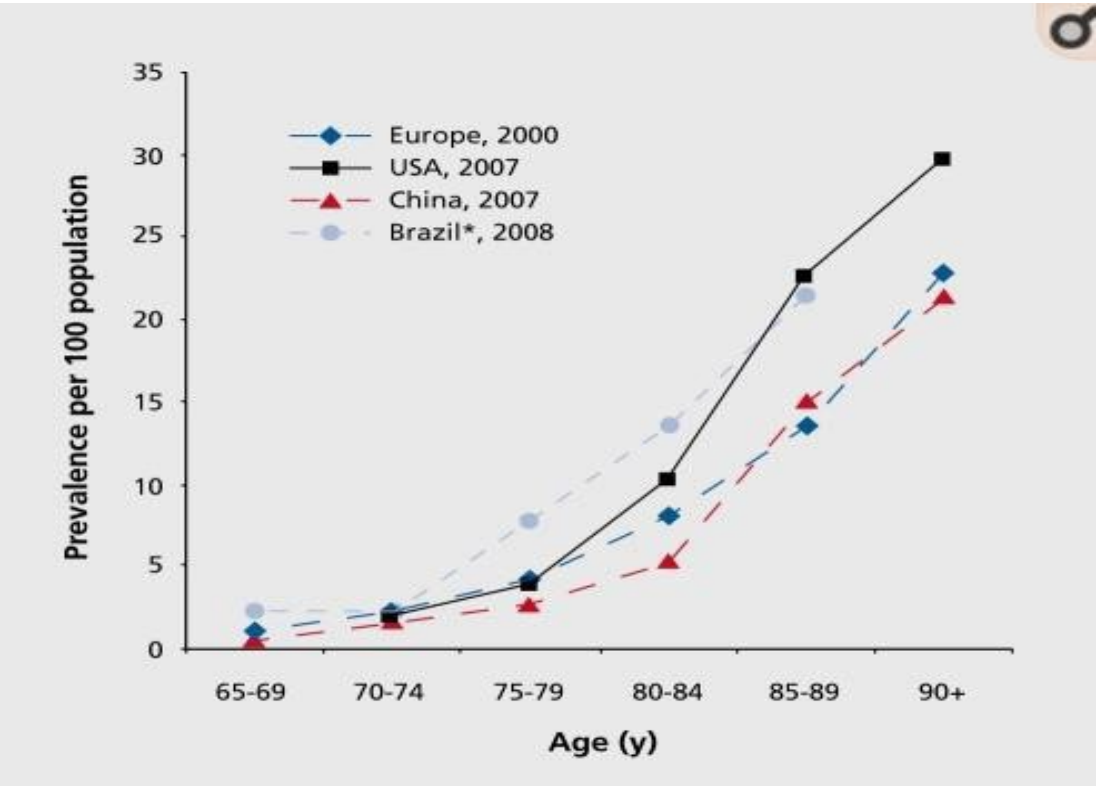
1.3 Epidemiology

At the individual level, AD is one of the main causes of physical deficit and considerable decrease in quality of life (QIU, et. al., 2009). Developing countries are facing a phenomenon that today affects developed countries: the inversion of the age pyramid. That is to say an increase in life expectancy and a decrease in the birth rate and fertility. Therefore, the number of elderly people increases, and the number of young people decreases. According to the UN, the expectation is that the number of elderly people to grow from 420,000,000 in 2000 to 1,000,000,000 in 2030, with an increase in proportion from 7% to 12%. Having experienced this phenomenon for a longer period, developed countries – those that have a high level of economic and social development – are the most affected (QIU, et. al., 2009).

In the United States alone, "one in ten individuals over 65 years of age has Alzheimer's disease, and 81% of these people are over 75 years of age" (NIEMEYER, 2020, p.235). In the US, around 6,000,000 American citizens have also been identified with AD, and this number is expected to grow to 14,000,000 (NIEMEYER, 2020). On a global scale, according to 2009 data, 3.9% of people over 60 years of age had AD. Currently, about 35.6 million people are diagnosed annually and that number could double every 20 years.

Worldwide, the global prevalence of dementia has been estimated to be 3.9% in people over 60 years of age, with the regional prevalence being 1.6% in Africa, 4.0% in China and the Western Pacific regions, 4 .6% in Latin America, 5.4% in Western Europe, and 6.4% in North America. More than 25 million people worldwide are currently affected by dementia, the majority suffering from AD, with around 5 million new cases occurring each year. The number of people with dementia is predicted to double every 20 years. Despite different inclusion criteria, several meta-analyses

and surveys across the country have produced approximately similar age-specific AD prevalence across all regions. Age-specific AD prevalence nearly doubles every 5 years after age 65. Across nations developed, approximately 1 in 10 older people (65+ years) is affected by some degree of dementia, while more than a third of very old people (85+ years) may have symptoms and signs related to dementia. There is a similar pattern of dementia subtypes worldwide, with AD and vascular dementia, the two most common forms of dementia, accounting for 50% to 70% and 15% to 25%, respectively, of all dementia cases. (QIU, et. al., 2009, p.1).



Age-specific prevalence of Alzheimer's disease (per 100 population) across continents and countries. *, prevalence of all types of dementia

Figure 3: Epidemiology of Alzheimer's disease in Europe, USA, China and Brazil. Source: QUI (2009)

The incidence of AD in European countries is such that a study carried out in the year 2015 in the United Kingdom showed that british people over 60 years old feared Alzheimer's disease more than the loss of family and friends, or cancer (NIEMEYER, 2020). In Europe, geographical evidence shows a higher incidence of AD among older people in the northwest. In addition, the rates in North America were higher compared to Europe (QIU; KIVIPELTO; STRAUSS, 2009).

The problems caused by the inversion of the age pyramid and the consequent increase in the number of patients diagnosed with AD are not only of an individual nature, that is that they do not affect only individuals with the disease and their respective families, but society and the economy. as a whole. At the individual level, estimates are that those with brain metastasis are at a lower risk of death than those with dementia (QIU; KIVIPELTO; STRAUSS, 2009).

2. Genetics, Epigenetics and Risk Factors

Due to the evolutionary process of homo sapiens, its skull grew abundantly and the female body, responsible for carrying the fetus during its development, showed a decline in the size of the pelvic cavity. In this way, individuals of this species are born “prematurely”, that is, without having completed their total brain development. This eases the process of childbirth. In other species the process occurs differently. A baby horse, for example, is out walking and galloping right after giving birth. A human baby is still dependent on maternal and paternal care for approximately 5 years (HARARI, 2014). This favored the appearance of dementia that is not common in other species, such as autism, for example. The same happens with Alzheimer's disease (NIEMEYER, 2020).

Thus, the conditions and environment experienced by the species in the early stages of progress are determinant in the appearance of neurodegenerative diseases; therefore, changes in the adult brain are determined in the early years of life. (SEIFAN, et. al., 2015). However, the role of genes in this child development is paramount at this stage.

It is important to note that although genetics contribute to the development of Alzheimer's disease, only 1% of Alzheimer's cases result from inherited genetic mutations (NIEMEYER, 2020).

The hypothesis that Down Syndrome and Alzheimer's are somehow related was proposed by Glenner and Wong in 1984, which gave rise to the PPA hypothesis.

Cerebrovascular amyloid protein from an adult Down syndrome case was isolated and purified. Amino acid sequence analysis showed it to be homologous to the Alzheimer's disease β protein. This is the first chemical evidence of a link between Down syndrome and Alzheimer's disease. This suggests that Down syndrome may be a predictable model for Alzheimer's disease. Assuming that the β protein is a human gene product, it also suggests that the genetic defect in Alzheimer's disease is located on chromosome 21 (GLENNER; WONG, 1984, p.1).

In 1990, “Frangione and colleagues reported that sequencing of APP exons 16 and 17, encoding the Aβ domain, revealed the first pathogenic mutation in APP that caused hereditary cerebral hemorrhage with amyloidosis in a Dutch family linked to chromosome 21” (TANZI; BERTRAM, 2005, p.4).

An amyloid protein that precipitates in the cerebral vessel walls of Dutch patients with hereditary cerebral hemorrhage with amyloidosis is similar to the amyloid protein in the vessel walls and senile plaques in the brains of patients with Alzheimer's disease, Down syndrome, and sporadic cerebral amyloid angiopathy. Cloning and sequencing of the two exons encoding the amyloid protein from two patients with this amyloidosis revealed a cytosine to guanine transversion, a mutation that caused a single amino acid substitution (glutamine instead of glutamic acid) at position 22 of the amyloid protein . The mutation may be responsible for the deposition of this amyloid protein in the walls of the cerebral vessels of these patients, leading to cerebral hemorrhages and premature death (FRANGIONE, et. al., 1990, abstract).

This led to the discovery of the first mutation causing EOAD that was, in fact, linked to chromosome 21. However, it was realized that these mutations were only a part of the causes of Alzheimer's EOAD; thus, in 1995, research by LevyLahad and colleagues showed that presenilin 1 and 2 (PSEN1 and PSEN2) “were reported as new genes on chromosomes 14 and 1. Presenilins are serpentine proteins with eight transmembrane domains and large hydrophilic cytoplasmic loops that undergo regulated endoproteolytic cleavage to produce N- and C-terminal fragments To date, a total of 16 rare autosomal dominant mutations have been found in APP, 140 in PSEN1 and 10 in PSEN2” (TANZI; BERTRAM, 2005, p.5). While this is evident, mutations in these genes are rare and not all families that develop DPOAE have them, indicating that other genes must be involved. However, the influence of PSEN1 and PSEN 2 is undeniable.

As not all families with autosomal dominant EOAD have identifiable mutations in PSEN1, PSEN2 or APP, it is likely that there are additional genes that influence the pathophysiology of EOAD. Predictive/presymptomatic testing for autosomal dominant DPOAE is most informative when a mutation has been confirmed in a symptomatic family member. Mutations in PSEN1 and APP are associated with complete penetrance, which means that all individuals with a PSEN1 or APP mutation will develop AD if they live a normal life. In contrast, mutations in PSEN2 show 95% penetrance, which means that not all people with a mutation in PSEN2 will develop AD (GOLDMAN, et. al., 2012, p.3).

In 1990, genetic variations were found on chromosome 19 that contributed to LOAD, although much of its manifestation is due to environmental factors and phenotypic expression. After that, a common polymorphism was found in the genetic coding of apolipoprotein E (APOE), "it is an important cholesterol transporter that helps in the transport of lipids and in the repair of brain injuries" (LIU, et. al., 2013, p. 1). Apolipoprotein E is therefore "in the same chromosomal region associated with increased risk for LOAD" (TANZI; BERTRAM, 2005, p.5). This gene is present in about 15% of the population, therefore, carrying one or two genes is not enough for the disease to manifest.

APOE is present in three polymorphic allele genes (when more than one allele occupies the locus of that gene within the population) "ε2, ε3 and ε4 - which have a worldwide frequency of 8.4%, 77.9% and 13.7%, respectively. However, the frequency of the ε4 allele increases dramatically to ~40% in patients with AD" (BU, et al, 2013 p. 2).

Genome-wide association studies have confirmed that the APOE ε4 allele is the strongest genetic risk factor for AD.16, 17 The presence of this allele is associated with increased risk for early-onset AD and LOAD.18, 19 The goal - analysis of clinical and autopsy-based studies demonstrated that, compared to individuals with an ε3 / ε3 genotype, the risk of AD was increased in individuals with one copy of the ε4 allele (ε2 / ε4, OR 2.6; ε3 / ε4, OR 3.2) or two copies (ε4 / ε4, OR 14.9) among Caucasian subjects.10 The APOE ε2 allele has protective effects against AD: the risk of AD in subjects carrying APOE ε2 / ε2 (OR 0.6) or ε2 / ε3 (OR 0.6) are lower than ε3 / ε3.10 In population-based studies, the APOE4-AD association was weaker among African Americans (ε4 / ε4, OR 5.7) and Hispanic (ε4 / ε4, OR 2.2) and was stronger in Japanese (ε4 / ε4, OR 33.1) compared to Caucasian cases (ε4 / ε4, OR 12.5). APOE ε4 is associated with higher prevalence of AD and lower id ade from the beginning. 20 The frequency of AD and the mean age of clinical onset are 91% and 68 years of age in homozygous ε4, 47% and 76 years of age in heterozygotes ε4, and 20% and 84 years in non-carrier ε4, 7, 20 indicating that APOE ε4 confers dramatically increased risk of developing AD with an earlier age of onset in a gene dose-dependent manner (LIU, et. al., 2013, p.5).

APOE, in the central nervous system (CNS), is produced by astrocytes "and transports cholesterol to neurons via ApoE receptors, which are members of the low-density lipoprotein receptor (LDLR) family" (LIU, et al, 2013, p.3). Astrocytes are neural cells found in gray matter. Its functions are to help maintain the ionic balance of extracellular fluids, take up and process neurotransmitters for synaptic abilities, and aid in the formation of new synapses and circuits. Astrocytes also contribute to the formation of the blood-brain barrier and the ventricular barrier of the empedymal brain. In addition to being extremely important in the formation of scars in post-injury necrotic neural tissues.

The presence of this protein is also associated with "increased risk of cerebral amyloid angiopathy and age-related cognitive decline during normal aging" (LIU, et.al., 2013, p.1). Neurodegeneration and neurotoxicity, both hallmarks of AD, occur when APOE binds to cell surfaces in order to "deliver" lipids and the hydrophobic beta amyloid protein.

Epigenetics "is the science that seeks to understand reversible changes in gene expression, that is, the components that can modify how genes are read without altering the nucleotide sequence of DNA. In addition, epigenetic modifications can be transmitted over generations, being inherited at the time of cell division (mitosis), acting in the formation of different phenotypes among individuals" (SANTANA, 2018, p.1).

Alzheimer's disease may be caused by aberrations in methylation (a term that refers to the attachment or replacement of a methyl group on various substrates) and the role played by methylation in being an AD biomarker (LIU; JIAO; SHEN, 2018).

For example, it has been found that some cytokines, particularly those at -207 to approximately -182, in the promoter region of the APP gene are primarily methylated and that their demethylation with age can lead to Aβ deposition in the brain. Microtubule-related tau protein (MAPT) gene methylation can also suppress MAPT expression, which can affect tau protein levels used post mortem brain samples from AD patients and found that BRCA1 expression was significantly upregulated positively, consisting in its hypomethylation. Furthermore, BRCA1 protein levels increased in response to Aβ and became poorly localized in the cytoplasm, both in in vitro cell models and in vivo mouse models. Recently, it was discovered that reducing DNA methylation at the myeloid cell-expressed trigger receptor 2 (TREM2) gene intron 1 caused greater expression of TREM2 mRNA in leukocytes from subjects with AD than in controls (LIU; JIAO; SHEN , 2018, p.5).

Histone deacetylase are crucial enzymes in biological processes that play a very important role in deacetylation, the removal of the acetyl group. One study showed the role of HDAC (histone deacetylase) in Alzheimer's disease.

Class I HDACs, such as HDAC2 and HDAC3, are expressed at much higher levels than other HDACs in memory regions of the brain. A recent study used a mouse model of AD, which deleted the HDAC1 and HDAC2 genes in microglial cells, leading to a decrease in amyloid burden and improvement in cognitive impairment by increasing microglial amyloid phagocytosis. In the CKp25 AD mouse model, they found that elevated levels of HDAC2 epigenetically block expression of neuroplasticity genes during neurodegeneration, and HDAC2 reduces histone acetylation of genes important for learning and memory. In another AD mouse model, HDAC2 was found to be strongly expressed in the hippocampus and prefrontal cortex. Neuron-specific overexpression of HDAC2 led to a decrease in dendritic column density, number of synapses, synaptic plasticity, and memory formation (Levenson et al., 2004; Guan et al., 2009). Under conditions of stress and injury, the level of HDAC2 increases, and this causes a decrease in the expression of genes related to memory and cognition. HDAC3 also plays a vital role in regulating long-term memory formation. HDAC3 deletion in the dorsal hippocampus leads to improved long-term memory for object location (LIU; JIAO; SHEN, 2008, p. 8).

Other factors with long non-coding RNAs also participate in the manifestation of AD.

3. Neuroplasticity

Unlike other diseases, Alzheimer's cannot be reproduced in the laboratory. This means that scientists cannot reproduce what happens in the human brain during AD in an animal guinea pig as is done with diabetes, for instance. This has made research into the treatment and diagnosis of AD very difficult. In addition, the localizationist view that the brain is immutable (a theory that was reinforced with Broca's discovery) made neuroscientists limit the search for a cure. Currently, there is no effective medication against Alzheimer's.

However, the concept of neuroplasticity has gained strength over time and can have a great influence on AD. Michel Merzenich and Jon Kaas showed that:

“the elaborate neuronal circuits that define mammalian and primate brains exhibit a process of self-adaptation that extends throughout life. Our brain changes, both anatomically and functionally, in response to everything we interact with, whether during learning new skills, when relevant changes occur in our body or during our social engagements. Neuroscientists call this property neuronal plasticity” (NICOLELIS, 2020, p.79).

Neuroplasticity “is both a substrate of learning and memory and a mediator of responses to neuronal wear and tear (compensatory plasticity). It is a continuous process in reaction to neuronal activity and neuronal injury, death and genesis, which involves the modulation of structural and functional processes of axons, dendrites and synapses” (TETER; ASHFORD, 2002, p.3). Among some processes that occur in plasticity, we can mention “the production of neurons from neural progenitor cells, the growth of axons and dendrites and the formation and reorganization of synapses” (CHENG; HOU; MATTSON, 2010, p.2). According to the Canadian psychoanalyst Norman Doidge, there are 4 types of plasticity: expansion of the brain map, sensory redistribution, compensatory strategy and activation of mirror areas (DOIDGE, 2007).

[..] the number and distribution of synapses that one neuron establishes with another can be fundamentally altered as a result of learning a new task or as part of the recovery process initiated when damage to our body – or to the brain. Even in adult animals, individual neurons can give rise to new synapses, which will lead to increased connectivity established with some or all of the other brain cells with which these neurons communicate. In the opposite direction, neurons can 'reabsorb' part of their synapses and thus reduce their connectivity with other cells. The magnitude of the influence of each of these synapses, made with other neurons, can also be modified upwards or downwards, according to the contingencies to which the brain is exposed. Essentially, a new stimulus can lead to changes in the delicate microstructure and function of the hundreds of trillions of synaptic connections through which tens of billions of cortex neurons communicate (NICOLELIS, 2020. P.79).

Neuroplasticity occurs in 4 main steps: correction of general cellular function of neurons and glia, neurostimulation, neuromodulation, reticular activation system and neurorelaxation (DOIDGE, 2016). A greater “dynamicity” of synapses during development, molecular adhesion and the action of glia and astrocytes are essential for neuroplasticity, while other aspects such as age decrease this process (TETER; ASHFORD, 2002).

In Alzheimer's, the way the disease spreads impair neuroplasticity:

AD pathology affects CNS regions involved in higher brain functions that are synaptic (structurally and functionally) plastic and involved in the acquisition of new epigenetic information. The limbic system has perhaps the greatest potential for neuroplasticity compared to other parts of the cerebral cortex (indicated by high-level expression of GAP43, particularly in the entorhinal-hippocampal pathway. Plasticity-related dendritic remodeling (length and branching) is most extensive in the limbic and paralimbic (entorhinal-hippocampal) regions, less in association cortices and undetectable in sensory and primary motor areas. Increased burden of neuroplasticity throughout life and chronic upregulation of cellular activities related to plasticity of the limbic system may increase its vulnerability to NFT formation. Degeneration in limbic structures could then spread to adjacent limbic and paralimbic neurons in reciprocally connected association cortices to increase their plasticity burden. This would induce reactive synaptogenesis to replace the synapses originally provided by the degenerating axons of n NFT-bearing neurons and induce dendritic remodeling to receive synapses at once idle with dendritic trees of adjacent degenerating neurons. If these reactive neurons cannot respond to the challenge of this increased plasticity burden due to barriers to plasticity, they may also be subjected to similar τ events and subsequent NFT formation with disruption of the cytoskeleton (TETER; ASHFORD, 2002, p.5).

One of the essential processes for synaptic organization is cholinergic neurotransmission. In AD, there is a loss of cholinergic input to the hippocampus. “Cortical cholinergic depletion in AD arises from the loss of neurons that project from Meynert's nucleus basalis, a limbic structure that retains high plasticity in late adulthood and contains some of the first neurons to show NFT pathology” (TETER; ASHFORD, 2002), p.7).

Plasticity acts mainly in regions that take a long time to mature, and these are precisely the most vulnerable to AD. Even though plasticity allows change, it can also strengthen it and make it more difficult. Therefore, AD-affected brains share an evolutionary basis.

The differential susceptibility of specific AD regions and neurons may be related to the degree of retained capacity for plastic remodeling In vivo, rates of synaptogenesis decline with developmental age and there is recapitulation of developmental gene expression responses in injury and adult aging, including AD (TETER; ASHFORD, 2002, p.8).

Conclusion

Therefore, the brain's ability to adapt to circumstances is undeniable. In Alzheimer's disease, this is no different. Although the nature of the disease is still very uncertain, we can conclude that the individual's entire life is decisive for the manifestation of this disease, even if science does not know how. The revolutionary discovery that the brain is changeable and that genetic factors are also changeable (epigenetics) could lead to a possible effective treatment for Alzheimer's disease; however, this will only be a fruit of the distant future.

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