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Review Article

Alzheimer's Disease and the Main Aspects - Literature Review

André Eduardo de Almeida Franzoi[1]*, Bruno Bagatin de Souza Moreira[1], Felipe Ibiapina dos Reis[2], Marcus Vinícius Magno Gonçalves[2], Wladimir Kummer de Paula[3], Flávio Dinis Ribas[3] and Osvaldo José Moreira do Nascimento[4]

[1]Medical Student, University of the Region of Joinville, Joinville, Brazil

[2]Professor of Neurology, University of the Region of Joinville, Joinville, Brazil

[3]Neurologist at Dona Helena Hospital, Joinville, Brazil

[4]Professor of Neurology, Fluminense Federal University, Rio de Janeiro, Brazil

***Corresponding Author:** André Eduardo de Almeida Franzoi, Medical Student, University of the Region of Joinville, Joinville, Brazil.

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Abstract

Objectives: To demonstrate the main aspects of the disease.

Methods: The bibliographic research was developed in databases (PubMed/MEDLINE, Scielo/LILACS and UptoDate) from 1980 to 2018, selecting the most relevant articles in a non-systematic way.

Results: The selection of articles considered those most relevant according to the scope of the proposed theme, and non - systematically included 83 articles as content for the literature review of the narrative type. The main topics were sequenced in: pathophysiology, diagnosis, pharmacological and non-pharmacological treatment.

Conclusions: Alzheimer's disease has a pathophysiology not yet elucidated, but with consistent hypotheses (such as cholinergic and amyloid cascade, forming a complex of reactions that generate progressive damage to nervous tissue for those with the disease). Research into new drug agents that may slow or even block the course of the disease is a challenge for many neuroscientists.

Keywords: *Alzheimer's Disease; Neurocognitive Deficits; microRNAs; Pathophysiology*

Introduction

Alzheimer's disease (AD) is the most frequent neurodegenerative disease associated with age, with cognitive and neuropsychiatric alterations that result in progressive deficiency and eventual incapacitation [1,2].

In 2006, the prevalence of AD was 26 million in the world, and by 2050, it is estimated that this disease will affect 1 in every 85 people, overall [3].

In general, the first clinical aspect is the recent memory deficiency, however, the remote memories are preserved until a certain stage of the disease. In addition to the difficulties of attention and verbal fluency, other cognitive functions deteriorate as the disease progresses, among them the ability to perform calculations, visuospatial abilities and the ability to use common objects. The degree of alertness and lucidity of the carrier are not affected until the disease is advanced. Muscle contractures are an almost universal feature in the advanced stages of the disease, however, motor weakness is not observed [4].

These symptoms are often accompanied by behavioral disorders such as aggressiveness, hallucinations, hyperactivity, irritability, and depression. Mood disorders affect a relevant portion of individuals who develop Alzheimer's disease, at least at some point in the evolution of the dementia syndrome [5].

Depressive symptoms are observed in up to 50% of patients, whereas depressive disorders affect around 10 to 20% of cases [6,7].

Symptoms and clinical signs such as apathy, slowing (gait or speech), loss of concentration, weight loss, insomnia and restlessness may be present in this insane syndrome [8].

Statistically, there is a high growth forecast for the diagnoses of the disease, especially in continents where the prevalence of the elderly population tends to increase a lot in relation to the present days. A population of over 65 million individuals with the disease is currently estimated and by 2050 this figure may exceed 115 million [9,10].

America is the continent with the highest prevalence of disease prevalence, with more than 500%, by 2050. Therefore, it is a disease of extreme relevance not only current but also future for Brazil [9].

The economic impact of dementia is enormous, with a total cost estimated at more than 600 billion dollars in 2010 worldwide. In the United Kingdom, for example, the estimated annual expenditure with an Alzheimer's disease patient is estimated at between 29,000 and 57,000 euros [10,11].

Therefore, the study of Alzheimer's disease is extremely important both for the cases already registered and for the diagnosis of new cases that will be computed. Within this, the article in question proposed the revision of a reliable database with the objective of solidifying the understanding of the pathophysiological mechanisms already known and those still proposed for the disease, as well as the drugs, the diagnosis and the treatment related to it, In order to generate an objective source of knowledge on the subject and highlight the new research focuses that seek to improve the treatment of Alzheimer's disease.

Methods

A bibliographic search was performed in reliable databases (PubMed/MEDLINE, Scielo/LILACS and UptoDate) from 1980 to 2018, using the descriptors "Alzheimer's disease", "neurocognitive deficits", "microRNAs", "pathophysiology" and combinations thereof.

Results

The selection of articles considered those most relevant according to the scope of the proposed theme, and non - systematically included 83 articles as content for the literature review of the narrative type. The main topics were sequenced in: pathophysiology, diagnosis, pharmacological and non-pharmacological treatment.

Discussion

Pathophysiology

Alzheimer's disease (AD) is characterized by the great synaptic loss and neuronal death observed in the brain regions responsible for cognitive functions, especially the cerebral cortex, the hippocampus, the entorhinal cortex and the ventral striatum [12].

The histopathological features of the brain of patients with Alzheimer's disease include amyloid fibrillary deposits around the walls of blood vessels associated with different types of senile plaques, accumulation of abnormal filaments of tau protein, with subsequent formation of neurofibrillary tails (NFT), Neuronal and synaptic loss, as well as glial activation and inflammation [12].

Within this, two main hypotheses have been proposed in order to elucidate the etiology of the disease. According to the amyloid cascade hypothesis, neurodegeneration begins with the proteolytic cleavage of the amyloid precursor protein (APP) and results in the production, aggregation and deposition of β-amyloid (Aβ) substance and senile plaques [13].

As for the cholinergic hypothesis, the dysfunction of the cholinergic system is sufficient to produce a memory deficiency [14].

Brains of patients with Alzheimer's disease showed degeneration of cholinergic neurons, and the enzymes choline acetyltransferase and acetylcholinesterase had their activities reduced in the cerebral cortex [15].

The enzyme phospholipase A2 (PLA2) contributes to the release of arachidonic acid from the phospholipid membranes, which is fundamental in the synthesis of the main mediators of the inflammatory response. As phosphatidylcholine is one of the substrates of PLA2, reducing the activity of this enzyme could produce a decline in the catabolism of phosphatidylcholine, reducing choline to the synthesis of acetylcholine, further contributing to cholinergic deficiency in Alzheimer's disease [16,17].

Therefore, the reduction of PLA2 activity in patients with this disease may be directly related to the severity of dementia and the degree of cognitive impairment [16].

Treatment with antipsychotic drugs results in an increase in plasma PLA 2 concentration, but in brains of patients with Alzheimer's disease, the presence of reduced levels of this enzyme [16,18].

Another study demonstrated that the alteration of acetylcholinesterase activity in the frontal and parietal cortex was related to the onset of dementia, the amount of senile plaques and NFT, and to early death after autopsy in brains of Alzheimer's disease patients [19].

The hypothesis of the amyloid cascade has been supported by genetic studies with cases of the familial form of Alzheimer's disease, in which mutations in both the expression of genes for the production of APP and in the presenilins (PS) have shown an increase in the synthesis of β- amyloid [13].

However, while the study of cases of familial Alzheimer's disease has shown to be significant for understanding this form of the disease, the reasons for the neuronal vulnerability of sporadic cases of Alzheimer's disease remain unknown [20].

Researchers have investigated levels of Aβ42 and Aβ40 (related to β-amyloid substance), which are possibly linked to the synthesis of senile plaques in patients with AD, aiming to develop disease-specific biomarkers, however, there was no significant difference between patients with AD and the control group on the expression profile of these peptides [21].

In addition, there are hypotheses that suggest a deregulation of the glutamatergic pathway in AD, and the activation of NMDA receptors is more difficult due to the lower efficiency of the binding of magnesium to its site in the glutamatergic receptor in question. Negative levels of this neurotransmitter are a crucial neurotoxicity factor and would be important in neurodegeneration within this dementia (with greater loss of glutamatergic neurons in the cerebral cortex and hippocampus) [22].

In general, 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 changes compared to senile and NFT plaques [23].

Regarding senile plaques, when substance Aβ is in high concentrations, insoluble amyloid fibers are formed in the brain, which can lead to aggregation of zinc and copper, thus aggravating neuronal toxicity [24,25].

Some studies have shown the correlation between metals and cellular biology of APP and the neurodegeneration of the disease. Within this, metals such as copper, zinc and iron have been found in amyloid deposits of brains of Alzheimer's disease carriers. In addition, studies have shown that zinc and copper chelators were able to solubilize these Aβ fibers in tissue samples from patients with Alzheimer's disease [26-28].

Another neuropathological characteristic of Alzheimer's disease, the NFT, consists of helical filaments derived from the hyperphosphorylation of the Tau protein cytoskeleton. The hypothesis of these proteins and NFT, suggested that the function of Tau protein (important for the stabilization of neuronal microtubules) was impaired and that with neurodegeneration, normal microtubules were gradually replaced by NFT [29,30].

The group of neuronal cell bodies known as the basal Meynert nucleus (nbM) or cholinergic nucleus is also related to the disease. It has been established that cholinergic neuronal loss in nbM is related to cognitive decline in dementia disorders, such as Alzheimer's disease. However, its pathological significance was first recognized by Lewy in a series of patients with "agitating paralysis" (clinical picture now known as Parkinson's disease), where severe neuronal degeneration and intraneuronal tangles [31].

The reason for the large variation between studies may be related to variance of disease severity, however, one of the main causes is that neuronal loss is not homogeneous throughout the nbM. Studies that have divided the nbM regions (in anterior, posterior and intermediate nbM) indicate a regional susceptibility to neuronal loss in Alzheimer's disease, with a caudorospheric gradient of neuronal loss and the posterior sector being the most affected [31].

As already mentioned, an exponential increase in the number of patients with memory disorders and cognition, mainly of Alzheimer's disease, is estimated. Unfortunately, the current context is the absence of really effective treatments and this means that there is a huge need to develop new therapies to achieve a more effective treatment of the disease in question.

However, new media have been investigated to identify early AD, among them, biomarkers known as micro-RNA (small circulating or intracellular non-encoded RNA particles) that are screened in blood or CSF.

The miRNA is a type of non-coding RNA, which acts in an endogenous way, regulating the gene expression through the process of binding to the messenger RNA, which prevents its reading and the subsequent production of the protein that would be decoded. Dysregulation of miRNA is a process involved in various diseases. It is believed that approximately 60% of the genes encoding human proteins are regulated by miRNA [32,33].

This action of the active miRNA is one of the forms of epigenetic action, a process that occurs through the mediation of two known principal mechanisms, DNA methylation and histone compaction, both of which arise from modifications associated with the environment (such as tobacco, which can cause Epigenetic changes in various diseases, including tumors) [34-37].

Recent studies have demonstrated the expression of subregulated microRNAs (miRNA) in AD cases, such as miRNA-31, miRNA-93, miRNA-143 and miRNA-146a [38].

One study demonstrated the increased expression of nine miRNAs in the peripheral blood mononuclear cells of patients with AD. Subsequently, researchers found that miR-137, miR-181c, miR-9 and miR-29 were subregulated in the serum of patients with the disease [38].

Researchers examined postmortem CSF and found that expression levels of 60 miRNAs were significantly different between patients with AD and normal controls. However, the identification of these miRNAs in the CSF is still a challenge. In the same study, miR-146a was significantly decreased in the CSF of patients with AD and a low level of 146a was associated with disease progression [38].

In the hippocampus, five miRNAs (miR-370, miR-328, miR-15a, miR-138 and miR-132) were identified as dysregulated in patients with the disease, suggesting that expression levels of deregulated miRNAs may contribute to the pathophysiology of AD. In addition, variations in the expression of miRNAs in different brain regions may represent specific pathologic patterns, which may be useful in characterizing specific miRNAs as biomarkers at diagnosis. Most of the existing studies examined the miRNAs in the hippocampus or the cerebral cortex in the postmortem setting and obtaining living tissue through biopsy would be a challenge with great potential [38].

Diagnosis

The clinical diagnosis of Alzheimer's disease is based on the observation of the compatible clinical picture and the exclusion of other causes of dementia due to both laboratory and neuroimaging tests. Computed tomography and magnetic resonance imaging reveal atrophy of the cerebral cortex and hippocampus, resulting in a probable diagnosis of the disease. As a possibility, monitoring of the evolution of the patient's clinical condition is also feasible, however, for definitive diagnosis, anatomopathological examinations [39].

Therefore, the efficacy in the confirmation of the diagnosis becomes high when imaging tests are used together with the clinical findings of the disease [39].

Analysis of cerebrospinal fluid may reveal the detection of elevated levels of abnormal components in the cerebrospinal fluid, such as β-amyloid substance, Tau protein, and phosphorylated Tau protein. Again, this type of laboratory analysis added to the neurological imaging tests gives a greater accuracy to the diagnosis [40].

It is now known that polymorphisms in the apolipoprotein E (apoE) gene are important risk factors for the development of Alzheimer's disease [41].

The gene located in the long arm of chromosome 19 is the encoder of the production of this glycoprotein, which plays a fundamental role for the catabolism of components rich in triglycerides in the human body [41].

In humans, identification of the E4 variant allele, as the most common genetic risk factor for the late onset of Alzheimer's disease, suggests that cholesterol may play a direct role in its pathogenesis. However, the mere presence of the apoE E4 allele is not sufficient to cause the disease, i.e. this allele only increases the risk of the individual developing the syndrome [41].

Thus, the classical identification of the disease is still widely used, which is performed in two steps. First, we analyze cognitive changes in the patient (such as altered memory that interferes with their life habits). Then, other possible diseases related to the insane process are eliminated [39].

Currently, the biomarkers validated for the diagnosis of AD are: (1) low β-amyloid-42 levels in the cerebrospinal fluid and/or high amyloid marker retention on positron emission tomography (PET), indicating cerebral amyloidosis; (2) elevated levels of CSF tau protein, indicating neuronal injury; (3) temporoparietal pattern of 18F-fluorodeoxyglucose absorption reduction in PET, indicating cerebral hypometabolism, and (4) patterns of cerebral atrophy in nuclear magnetic resonance, indicating neurodegeneration. Studies of functional encephalic connectivity through functional magnetic resonance imaging or rsfMRI in AD still have low statistical evidence. Recent meta-analysis quantified and strengthened the scientific evidence for the use of rsfMRI as a potential biomarker for the earlier diagnosis of AD [42,43].

In advanced cases of this dementia, identification of the clinical picture may be more rapid (since the signs and symptoms tend to be more severe), especially: marked memory deficits (such as aprosopagnosia), minimal verbal skills, inability to travel Independent, inability to do any daily routine activity and urinary and fecal incontinence [44,45].

A study published in early 2017 aimed to find a more economical and less invasive way for the diagnosis of early AD than via CSF or via positron emission by PET scanning. That surpassed the current basic model (which compares age, sex and APOE genotype). However, the authors conclude that there is evidence of serological testing to be slightly more accurate than the baseline test, but that larger sample sizes and greater knowledge of alleles involved in Alzheimer's risk are needed [46].

Another diagnostic complement can occur with the evaluation of the thickness of the retina in patients with the disease. A recent study has confirmed the relationship of decreased retinal thickness (assessed by optical coherence tomography) of patients with neurodegenerative diseases, such as Alzheimer's disease, compared to healthy individuals of the same age [47].

Finally, researchers sought to understand the association of cortical thickening and a possible diagnosis of early dementia, but did not obtain relevant statistical data in their study [48].

Pharmacological Treatment

Currently, a well-studied strategy for the treatment of Alzheimer's disease has been to block the proteolytic machinery, which produces the substance Aβ. This strategy may be accompanied by the reduction of APP formation or inhibition of APP proteolysis for the formation of Aβ [30].

Inhibition of β and γ-secretase pathways (amyloidogenic pathways of proteolytic cleavage of APP) and stimulation of the α-secretase pathway have been the most promising strategies for neuroprotection in Alzheimer's disease within this research focus [30].

Even so, current therapy for Alzheimer's disease is far from satisfactory. However, studies have already contributed greatly to treatment and it is well known that the use of acetylcholinesterase (AChE) inhibitors has already demonstrated symptomatic efficacy and reduced disease progression. Such medications produced some improvement in approximately 35% of patients with mild to moderate Alzheimer's disease [49].

Acetylcholinesterase inhibitors are a symptomatic treatment for Alzheimer's disease (examples are tacrine, rivastigmine, donepezil and galantamine). Such drugs inhibit the degradation enzymes of the neurotransmitter acetylcholine (enzymes acetylcholinesterase and butyrylcholinesterase), increasing the action of acetylcholine on the activation on the nicotinic and muscarinic receptors in the brain [50].

Rivastigmine is widely used in the treatment of Alzheimer's disease, being able to inhibit the enzyme acetylcholinesterase and butyrylcholinesterase, being very effective in increasing the cerebral levels of acetylcholine. However, this drug caused several adverse cholinergic effects (such as adverse gastrointestinal side effects) when the dose was abruptly elevated [39].

It should be noted that this drug had adverse gastrointestinal effects also associated with weight gain [50].

Another selective acetylcholinesterase inhibitor, donepezil, was tested experimentally and after chronic treatment for one year and demonstrated a 38% reduction in functional decline in patients with Alzheimer's disease when compared to the placebo group [51].

Tacrine is a first generation inhibitor and was the first reversible acetylcholinesterase inhibitor to be used in the treatment of Alzheimer's disease. However, this drug presented important forms of toxicity and is no longer used in clinical practice [52].

Experimentally, tacrine showed hepatotoxicity, leading to increased hepatic transaminases, resulting in drug-induced hepatitis and causing withdrawal of medication in many patients. Unfortunately, more than 90% of the cases involving drug-induced hepatitis in Alzheimer's disease occurred within the first twelve weeks of treatment with tacrine [52].

Recently, studies have emphasized the synthesis of tacrine congeners, which were more potent and selective than the original drug [53].

Galantamine is also an anticholinesterase used in the treatment of Alzheimer's disease. This drug is capable of inhibiting acetylcholinesterase and also modulating allosteric nicotinic receptors. Furthermore, there is evidence that galantamine improves brain perfusion and cerebral glucose metabolism (which would be associated with a gain in cognitive stabilization in the clinical setting) [54,55].

The clinical significance of nicotinic modulation in the treatment of Alzheimer's disease has not yet been elucidated. Presynaptic nicotinic receptors control the release of neurotransmitters, which are important for memory and mood. In this sense, the blockade of nicotinic receptors has been shown to impair cognition. Furthermore, studies have shown that the binding of galantamine to nicotinic receptor subtypes improves cognitive function and memory [52,56].

In addition to the gains during treatment, it is possible that these acetylcholinesterase enzyme inhibitors may induce an increase in the production of this enzyme after discontinuation of pharmacological treatment [57].

NMDA receptors are a subtype of glutamate receptors that are involved in regulating synaptic neuroplasticity and the intracellular influx of calcium, playing an important role in memory and learning. NMDA receptors contribute to the intracellular Ca2+ homeostasis and modulate the oxygen supply to the peripheral tissues. Any alteration of the activity of this receptor by an agonist or antagonist causes an alteration of the ion flow through the channel. Therefore, uncontrolled activation of the receptor results in a transient accumulation of intracellular Ca^{2+} inducing cellular contraction and alteration in intracellular pH [58].

Memantine (3,5-dimethyladamantan-1-amine) is an NMDA receptor antagonist clinically used for the treatment of moderate to severe AD. This drug is thought to function by preferentially blocking reversibly open NMDA channels. Several randomized studies have been conducted to determine the efficacy of memantine in AD. Memantine monotherapy significantly improves various aspects of the disease such as behavior, activities of daily living and global function. However, there is limited evidence that its use inhibits the progression of neurodegeneration in patients with AD [59,60].

Another suggested therapy is the use of the neurotrophic factor derived from the brain, which stimulates the growth of the parasympathetic ganglion, substantia nigra, hippocampus and motor neurons in the central nervous system. However, this therapy still requires more scientific elucidation [30].

There is also interest in the use of polyphenolic antioxidants in order to reverse age-related decline and cognitive and motor deficits in patients with Alzheimer's disease [30].

An *in vitro* and *in vivo* study with 2,4-dinitrophenol and 3-nitrophenol demonstrated that these nitrophenols were able to inhibit amyloid aggregation, as well as disintegrating the already formed amyloid fibers. There was still protection against Aβ-induced toxicity (in tests with cultures of hippocampal neurons) [61].

In addition, experiments using microinjections of these nitrophenols have shown that such compounds were able to inhibit amyloid deposition in rat brains [61].

In other experiments, taurine has been shown to protect against glutamate induced excitotoxicity, although mechanisms for such protection have not yet been elucidated [62].

Further research has shown inhibitory properties in Aβ oligomerization. In an *in vitro* study, for example, some components, such as 2-amino-4-chlorophenol and 3-4-dihydroxybenzoic acid, demonstrated antiamyloidogenic activity, inhibiting the formation of Aβ oligomers and reducing the already formed amyloid fibers. In addition, these components completely blocked Aβ-induced neurotoxicity in culture of hippocampal neurons in rats [63,64].

As a complement to some medications, it is important to remember caffeine and its derivatives, with positive therapeutic power in neurodegenerative diseases already demonstrated in many studies. Caffeine is a purine that acts as a competitive antagonist of the neurotransmitter adenosine and has interaction with some enzymes, such as acetylcholinesterase [65].

Concerning agitation, research indicates a favorable therapeutic future for some drugs in Alzheimer's disease, such as citalopram, quinidine, prazosin and some cannabinoids [66].

Most of the knowledge of this treatment comes from the study of individual cases with depressed geriatric patients with absence of dementia. Certain symptoms can commonly be confused with depression. In depression, common complaints are usually added to dysphoria, depressive ideation, and vegetative symptoms [6].

In a meta-analysis published in 2016, the authors concluded that the use of antidepressants is associated with a greater relative risk of developing AD, especially in patients who started using antidepressants before 65 years of age [67].

Tricyclic antidepressants should not be used as the first therapeutic option in patients with Alzheimer's disease. The most important side effects in the elderly include postural hypotension, voiding delay in some cases, constipation, blurred vision and cardiac changes [6].

Harmful effects on cognition may result from their anticholinergic and sedative actions [68].

Monoamine oxidase (MAO) inhibitors, such as phenelzine and tranylcypromine, had few anticholinergic properties, however, their use should be indicated only in cases refractory to other options, postural hypotension (risk of falls and fractures) or seizures Hypertension due to dietary failure [6].

The monitoring of postural hypotension is extremely important and care should be doubled in relation to diet (relationship to tyramine, for example) and drug interaction [6].

Recently, numerous studies have questioned anti-inflammatory therapy, mainly using non-steroidal drugs as a treatment for neuroinflammation caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) and by the formation of free radicals, among Which would be associated with Alzheimer's disease [69].

Within this context, research has observed the use of non-steroidal anti-inflammatory drugs and steroidal glucocorticoids as a complementary treatment option for patients with Alzheimer's disease [70].

In contrast, cilostazol has been experimentally tested in animal guinea pigs and has shown a considerable decrease in Aβ substance formation. This drug is a selective inhibitor of the enzyme phosphodiesterase 3 and has already shown promise in its early clinical trials [71].

Bapineuzumab is a fully humanized monoclonal antibody that, in theory, binds to amyloid proteins in the brain, increasing clearance and decreasing excess formation. However, in practice, its use has not brought benefits and has led to a greater risk of vasogenic cerebral edema. Therefore, the conclusion of the study is that this monoclonal antibody is not recommended for patients with AD [72].

Non-Pharmacological Treatment

Although safe in the treatment of severe depression in the elderly with dementia, there are few studies that relate the therapeutic effects of electroconvulsive therapy (ECT) in patients with Alzheimer's disease [73].

ECT may be effective in selected cases, but should be indicated only for patients who present with severe depression, refractory patients or those who are intolerant to other pharmacological therapies [6,73].

Deep Brain Stimulation (DBS) begins to emerge as a new therapeutic focus. DBS is a neurosurgical procedure, which is the standard of care for many patients with refractoriness in the treatment of Parkinson's disease, dystonia and essential tremor. DBS has been shown to be an effective means to modulate motor activity in interrupted circuits and has been shown to be promising as a modulator of other dysfunctional circuits, including mood and anxiety disorders. As deficits in Alzheimer's disease and other memory and cognition disorders are also beginning to be seen as a result of dysfunction in neural circuits, this dysfunction may be amenable to modulation using deep brain stimulation. Currently, a worldwide innovation may be emerging for the use of DBS in the treatment of this neurodegenerative disease [74].

In addition to the chemical compounds produced by the pharmaceutical industry, natural products rich in polyphenols (alkaloids and flavonoids, for example), such as green tea, sage and saffron, should be mentioned. This phytotherapy has been used in ancient China for more than 2,000 years for several therapeutic foci and several studies have shown substantial benefits for neuroprotection and decreased amyloid aggregation with the use of several of these natural compounds, suggesting a new complement to treatment of neurodegenerative diseases [75,76].

There are many different types of intervention that may have a beneficial impact on the communicative skills of people with AD. Most of these studies had positive effects. The studies that showed higher levels of evidence were the lexical-semantic interventions and those with integrated language with physical activities [77,78].

There is a group of other types of interventions that yielded positive results: face-name association interventions, approaches that use memory cards during conversation, communicative training of caregivers, Doll therapy and training of communicative instrumental activities. A larger number of studies that explore these interventions and the use of methodology that can assure higher evidence levels may offer better parameters to attest whether or not these approaches are effective. Currently, these are promising options for the treatment of patients with AD [79,80].

A scientific study conducted in 2015 evaluated the use of acupuncture in patients with AD. Ten randomized controlled trials with a total of 585 participants were included in the meta-analysis. Evidence from the pooled results of 3 trials showed that acupuncture plus donepezil was more effective than donepezil alone at improving the Mini Mental State Examination (MMSE) scale score (MD 2.37, 95% CI 1.53 - 3.21). The adverse reactions in acupuncture were described as tolerable and not severe. Acupuncture may also be more effective than drugs at improving AD patients' ability to carry out their daily lives. This review work showed that acupuncture may be beneficial in association with medications used to treat AD. This association may generate clinical cognitive gains to patients [81].

Another alternative to non-pharmacological treatment is vitamin E, which was done a study comparing the results of the mini mental state examination between the groups that used vitamin E, or selegiline, the two together, or the placebo group. The only statistically significant difference was in the placebo group, that the results of the mini mental state examination were higher. Among the other groups there was no relevant statistical difference [82].

In a meta-analysis done in 2017, the authors proposed a possible neuroprotective effect of another substance, a seasoning, curcumin. The study was modeled on the neuroprotective properties of curcumin in cases of depression [83].

Conclusions

Alzheimer's disease has a pathophysiology not fully elucidated yet, but consistent hypotheses already give us a relevant knowledge about the central mechanisms of the disease.

Within the concepts proposed in the scientific scope, it is believed that the cholinergic and amyloid cascade hypotheses form a complex of reactions that often generate the main damages to the nervous tissue for the Alzheimer's disease patients.

Therefore, although many studies have contributed to elucidate the major pathophysiological mechanisms of Alzheimer's disease, selective neuronal loss has not yet been fully understood. In addition, the search for these mechanisms is directly related to the development of new drugs for the treatment of this disease, and the investigation of new drug agents that may delay or even block the evolution of the disease is the goal and challenge for many neuroscientists.

The initiation of AD treatment should occur as early as possible. For this, early and effective diagnosis is essential. Scientific research has refined the complementary tests to diagnose the disease. However, there is no well-established early biomarker. Positive family history and early clinical evaluation are still the basis for the initial investigation of the condition. New scientific research is being developed to provide an increasingly early diagnosis and treatment for this group of patients.

Currently, the pharmacological treatment of the disease has not yet succeeded in halting the progression of neurodegeneration. Multiple combinations and new drugs have already been tested. However, the results are modest. Current drugs slow the progression of neurodegeneration, especially until the moderate phase of the disease.

The association of non-pharmacological therapies in the follow-up of patients with AD was positive with pharmacological therapy. New research with a larger number of patients evaluating non-pharmacological therapies will help to highlight which alternative therapies are actually effective. The choice of non-pharmacological therapy can be individualized for each patient, focusing on their comfort to achieve better therapeutic results.

Therefore, our expectation is that new researches within the pathophysiology, diagnosis and treatment of the disease will lead to a better quality of life with the interruption of neurodegeneration and perhaps even the clinical cure of the disease in the future.

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