The immune system in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized as a progressive and chronic disorder that leads to the destruction of cholinergic neurons. AD was studied by Alois Alzheimer, a psychiatrist and neuroanatomist, who reported the pathology as amyloidal fibrillar deposits located in the walls of blood vessels, associated with a variety of different types of senile plaques, accumulation of abnormal filaments of tau protein and consequent formation of neurofibrillary tangles (NFT), neuronal and synaptic loss, glial activation, and inflammation (Castellani et al., 2010). This article aimed to address the role of the immune system in the pathogenesis of Alzheimer's disease. This is a literature review article carried out from 2002 to 2023. The databases for search were National Library of Medicine (PUBMED), Scientific Electronic Library Online (SCIELO) and Google Scholar, using the following descriptors Neuroinflammation, Glial Cells, Amyloid Beta Peptide and Tau Protein. Innate immunity cells such as microglia and astrocytes are found close to senile plaques, evidencing the participation of elements of the immune system in neuroinflammation and neurodegeneration, consequently contributing to the progression of AD. Therefore, it is concluded that a better understanding of the action of the immune system in the disease is essential for the establishment of possible prevention and control measures.

Keywords: Neuroinflammation, Glial Cells, Amyloid Beta Peptide and Tau Protein.

LIST OF ABBREVIATIONS AND ACRONYMS

APCs - ApoE - Apolipoprotein E Antigen-Presenting Cells
ApoE2 - Apolipoprotein E2 ApoE3 - Apolipoprotein E3 ApoE4 - Apolipoprotein E4
APP - Amyloid precursor protein ATP - Adenosine triphosphate
Aβ – amyloid beta peptide
BHE – Blood-Brain Barrier DA - Alzheimer's Disease
DAMPs - Molecular Patterns Associated with Damage DAP12 - Protein Tyrosine Kinase
GFAP - acid fibrillary glial protein
GSDMD – Gasdermin D Pore Forming IG - Imunoglobulin
IL-18 - Interleucine 18 IL-10 - Interleucine 10 IL-12 - Interleucine 12 IL-13 - Interleucine 13 IL-1β - Interleucine 1β IL-4 - Interleucine 4
IL-6 - Interleucine 6
ITAM – Tyrosine Cytosolic Immunoreceptor
M-CSF - Macrophage Colony-Stimulating Factor MHC - Major Histocompatibility Complex

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NFT - NK Neurofibrillary Tangle – Natural Killer Cells NLRP3 – NLRP3 P2X7R Inflammasome – Purinergic Receptor
P3 - Non-amyloidogenic peptide
PAMPs - Molecular Patterns Associated with Pathogens
PRRs - Pattern Recognition Receptors PSEN1 - Presenilin 1
PSEN2 - Surprise 2
RAGE - Receptor for Advanced Glycation End Products SKY – Spleen Tyrosine Kinase
CNS – Central Nervous System
SRAGE - TLR Receptor for Advanced Soluble Glycation End Products - Toll-Like Receptors
TNF-α - Tumor Necrosis Factor Alpha
TREM2 - Trigger receptor expressed on myeloid cells 2

INTRODUCTION

According to the Ministry of Health (MS), Alzheimer's disease is a progressive neurodegenerative disorder that compromises neuronal activity, causing changes associated with aging (Brazil, Ministry of Health).

The global number of people living with dementia more than doubled between 1990 and 2016, mainly due to increasing ageing and population growth. In 2016, the global number of individuals living with dementia was 43.8 million, up from 20.2 million in 1990 (GBD, 2016).

Alzheimer's disease (AD) was identified in 1906, when the German psychiatrist and neuroanatomist Alois Alzheimer first described pathological findings characteristic of the disease: senile plaques derived from the accumulation of amyloid beta protein (Aβ) and neurofibrillary tangle (NFT), which are alterations of tau protein. Growing evidence suggests that the multifactorial pathophysiological mechanisms of AD are not restricted to the neuronal compartment, as a relevant role has been attributed to the close interactions of immune mechanisms within the brain (Burgaletto et al., 2020).

Immunity is the defense mechanism against foreign substances and pathogens that invade the body and is characterized by the ability to recognize antigens that can cause some damage to the systems. The immune response is divided into two stages: the first corresponds to innate immunity, which is present in the body from birth, where it is not necessary to be exposed to an invader to obtain the immune response, being responsible for the body's first line of defense, and the second represents adaptive immunity, which is developed if it comes into contact with the invading agent. Innate immunity, when it is dysregulated, affects beta-amyloid protein and tau protein, which in excess are neurotoxic, favoring neurodegeneration (Edin et al., 2022).

According to the Brazilian Alzheimer's Association - Abraz (2020), Alzheimer's disease is an incurable disease that worsens over time, but it can and should be treated. Almost all of its victims are elderly, however, AD has as a preponderant characteristic the existence of two forms, the familial and the idiopathic. About 5% of cases are familial and usually related to specific genetic mutations, which will lead to early onset (before 65 years of age). Hereditary AD is mainly caused by genetic mutations encoding the amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2), which are essential for Aβ production, suggesting a critical role of Aβ in the development of the disease (Raulin et al., 2022). The idiopathic subtype, on the other hand, corresponds to another portion of cases, and is mainly associated with age, presenting late onset (after 65 years of age). AD involves a series of symptoms, starting with episodic memory loss and reaching deterioration in memory, behavior, and movement execution, altering cognitive function (Machado et al., 2020).

Therefore, in this context, the objective of this study is to present a brief literature review on the participation of immune mechanisms in the pathophysiology of AD.

METHODOLOGY

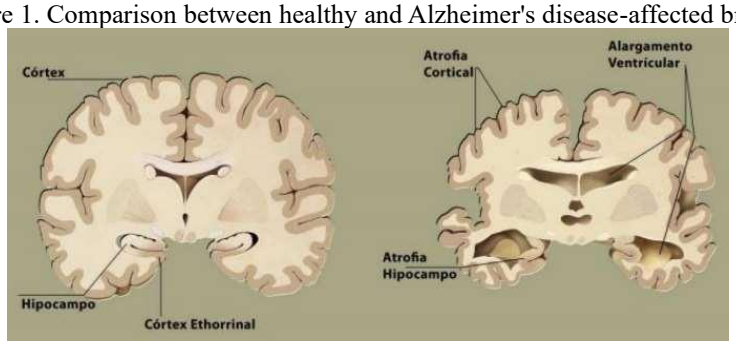
To conduct this bibliographic search, searches were carried out in scientific articles published in Portuguese, English and Spanish, indexed between the year 2002 and 2023, from databases of the National Library of Medicine (PUBMED), Scientific Electronic Library Online (SCIELO) and Google Scholar. To screen these materials, the following search terms were applied: "immune system and Alzheimer's", "neuroinflammation and Alzheimer's", "Alzheimer's disease", "microglia and astrocytes". Studies dated before 2002 and studies in languages other than Portuguese, English and Spanish were discarded, and the World Health Organization (WHO) database and the Mystery of Health (MS) were used to select statistical data.

DEVELOPMENT

ALZHEIMER'S DISEASE

Alzheimer's is a proteinopathy that affects the brain, being macroscopically characterized by brain atrophy with neural death, while the cerebral ventricles undergo a considerable enlargement. Microscopically, two characteristic lesions occur: accumulations of Aβ, with senile plaques appearing in the cerebral cortex (more precisely in the frontal and temporal lobes) and hippocampus, and NFTs caused by deposits of hyperphosphorylated tau protein that starts in the limbic region and radiates to the cortex, causing a progressive neurodegenerative disorder with neuroinflammation (Souza et al., 2021; Edin et al., 2022).

Figure 1. Comparison between healthy and Alzheimer's disease-affected brains.



Cast iron: SOUZA, Elizabeth Scatolino de et al., 2021.

Glial cells have different functions, including the defense of the central nervous system (CNS), which includes the participation of astrocytes and microglia. Astrocytes and microglia help in the restoration and protection of neuronal tissue during infections and inflammatory processes, are characteristically found close to senile plaques, evidencing the participation of elements of the immune system in the disease and leading to inflammatory and degenerative conditions (Machado et al., 2020).

The genetic risk factor for AD is the polymorphism in the apolipoprotein E (apoE) gene, which is the main transporter of cholesterol and other lipids to neurons in the CNS. There are 3 apoE alleles in humans, the first being the apoE2 allele, where studies suggest this is the least common and is believed to reduce the genetic risk of AD by almost half. The second is the apoE3 allele, which is the most common and neutral for the disease. And the third and most important is the apoE4 allele, which is a risk factor for AD (Raulin et al., 2022; Fernández-Calle et al., 2022)

Glial cells, more specifically astrocytes, are the main producers of ApoE in the CNS, however, activated microglia can also produce in specific circumstances. ApoE has been identified as an Aβ-binding protein that affects β-amyloid deposition of a specific dosage and isoform form: apoE4>apoE3>apoE2 (Shi et al., 2018). ApoE4 exacerbates Aβ accumulation in the form of senile plaques, tau-mediated pathogenesis, and glial activation by increasing the production of pro-inflammatory cytokines. Regardless of Aβ, apoE4 triggers inflammatory cascades that cause neurovascular dysfunction, including disruption of the blood-brain barrier (BBB), leakage of toxic blood-derived proteins into the brain, and reduction in the length of small vessels (Liu et al., 2013). Therefore, carriers of the apoE4 gene may be subject to aberrant immune responses to pathological development, which may ultimately lead to detrimental effects on responses to injury and cognitive deficits. Thus, targeting apoE-mediated inflammatory responses can attenuate AD pathologies and neurodegeneration (Raulin et al., 2022).

PATHOGENESIS OF ALZHEIMER'S DISEASE

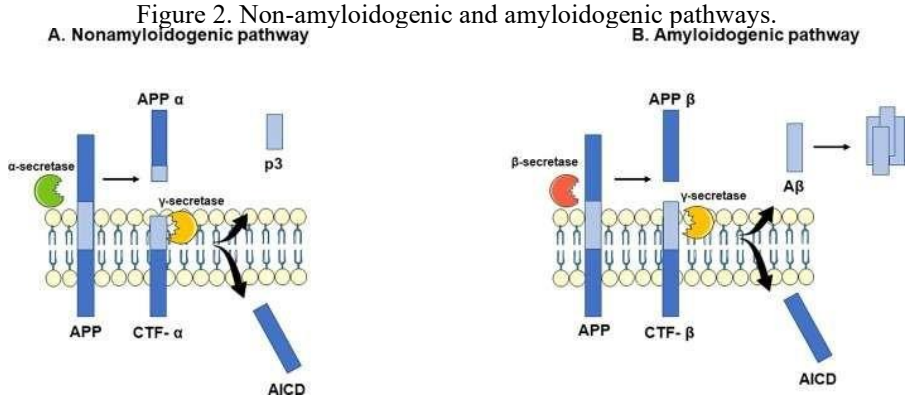
According to Monteiro et al (2023), despite the studies and knowledge acquired on cellular, molecular, and biochemical issues, the true etiology and pathogenesis of AD remain unknown. Despite the lack of knowledge, some pathological findings in patients are very similar, with the main pathological features being those caused by the accumulation of protein Aβ (causing the formation of deformed senile plaques in the CNS), the accumulation of Tau protein (forming NFTs), neural loss and gliosis. However, small amounts of amyloid protein do not cause the disease, and are also found in healthy brains.

Peptid β-Amyloid

The Aβ protein is a natural product of the metabolism of APP. APP represents one of the most abundant proteins in the CNS. It is metabolized by two distinct pathways: the non-amyloidogenic and amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by α-secretase and γ-secretase enzymes resulting in the production of an APP fragment called p3, classified as a non-amyloidogenic peptide, with no pathological effects. In the amyloidogenic pathway, the enzyme β-secretase and γ-secretase are involved, generating Aβ peptides, which, due to their aggregation

capacity, give rise to the amyloid plaques characteristic of the disease (Monteiro et al., 2023). The Aβ peptides released after cleavage accumulate in oligomeric aggregates, which are considered the most toxic form of the Aβ peptide, playing a crucial role in the pathogenesis of AD. They interact with neurons and glial cells leading to activation of inflammatory cascades, oxidative stress, dysregulation of calcium metabolism and tau phosphorylation, and induction of neuronal apoptosis. Under normal conditions, the APP protein is metabolized in a non-amyloidogenic pathway and there is a balance between production and its clearance in the CNS, however, under pathological conditions, there is a metabolic change that favors cleavage in the amyloidogenic pathway of APP, which together with the reduction of clearance, leads to the accumulation of Aβ in the brain. These plaques disrupt cellular communication and can cause microglial activation and inflammation (De Paula et al., 2009).

Figure 2. Non-amyloidogenic and amyloidogenic pathways.



Fonte: Monteiro, Ana R de et al., 2023.

Proteína year

Tau is the protein responsible for the formation of neurofibrillary tangles, and this formation is the second pathological feature of AD. Its function is to facilitate the polymerization of tubulin in the cell to form microtubules, an important component of the neural cytoskeleton. In addition to microtubules, two other constituents are neurofilaments and microfilaments. All are part of the neuronal infrastructure and participate in functions such as the axonal transport of organelles (mitochondria, lysosomes, endoplasmic reticulum) and other substances, as well as the maintenance of the structural integrity of the neuron (Gra Menendez et al., 2002).

In Alzheimer's disease, tau proteins undergo post-translational modifications, which lead to a decrease in their interaction with microtubules, such as hyperphosphorylation. The hyperphosphorylation of the protein decreases its affinity for microtubules, causing their destabilization, which makes the protein more prone to aggregation. Hyperphosphorylation is caused by increased kinase activity and decreased phosphatases. Like the Aβ peptide, phosphorylated tau aggregates to form oligomers that later mature into paired helical and straight filaments. Therefore, tau hyperphosphorylation leads to the loss of its inherent functions, culminating in impairments in

microtubule assembly, axonal trafficking and dendritic structure, loss of synapses, neuronal death, and, eventually, dementia (Monteiro et al., 2023).

IMMUNE SYSTEM IN ALZHEIMER'S DISEASE

The immune system is responsible for protecting and preventing the body from invaders, and has been conceptually divided into innate and adaptive response. Innate immunity generates rapid responses and is the body's first line of defense, as it is composed of physicochemical barriers, cells such as macrophages, neutrophils, dendritic cells and Natural Killer (NK) cells as the main effector cells of innate immunity. Adaptive immunity, on the other hand, depends on the activation of specialized cells. Although the main cell involved is the lymphocyte and its products, the activation of this system is triggered from antigen-presenting cells (APCs), which present antigens associated with molecules of the major histocompatibility complex (MHC I and MHC II) to the T lymphocytes. develop immunological memory to defend themselves against pathogenic microorganisms (Machado et al., 2020)

The healthy brain is an organ protected by resident immune cells and/or peripheral cell infiltration, however, when in excess, neuroinflammation is a major contributor to the pathogenesis and progression of AD. The term neuroinflammation indicates the presence of an inflammatory response in the CNS with the accumulation of glial cells, specifically astrocytes and microglia, in response to injury. In the early stage of AD, brain immune cells play a neuroprotective role. However, as the disease progresses, glial cells are activated and the production of pro-inflammatory cytokines associated with oxidative stress increases, leading to increased neuroinflammation and neurotoxicity (Al-Ghraiybah et al., 2022). Inflammation in the CNS can occur as a result of cells detecting Aβ or other molecular patterns associated with damage or pathogens (DAMPs or PAMPs). Cells contain several pattern recognition receptors (PRRs), both on the cell surface and in the cytoplasm, which are responsible for recognizing DAMPs and PAMPs; detection can induce inflammatory signaling pathways and immune responses that contribute to the progression and severity of Alzheimer's disease (Rajesh et al., 2022).

Micróglia

Microglia are the cells of the CNS-resident innate immune system and play roles such as first-line defense against pathogens and response to injury. These are cells that carry out phagocytosis, a receptor-mediated process that comprises the recognition, envelopment, and digestion of large extracellular particles, which is vital for CNS development and the maintenance of brain homeostasis after birth (Borst et al., 2021). Microglia can be classified into two opposite phenotypes: neurotoxic and neuroprotective. Type M1 promotes inflammation and produces pro-inflammatory cytokines (IL-

1β, IL-6, IL-12, TNF-α) and type M2 undergoes neuroprotective activation, which is associated with anti-inflammatory function, producing cytokines (IL-10, IL-4, IL-13); (Rajesh et al., 2022; Martins., 2018).

Under resting conditions, microglia are characterized by a branching morphology and a weak antigen presentation activity, however, activated microglia have an amoeboid-like morphology and a high antigen presentation activity, leading to interactions with peripheral immune cells (Borst et al., 2021). In the early stages of AD, activated microglia play a positive role in the elimination of Aβ by phagocytosis. However, after prolonged exposure, its efficiency to eliminate Aβ is reduced and begins to negatively affect the brain, leading to the accumulation of Aβ, which subsequently forms extracellular plaques that continuously stimulate microglial activation. This aggressive status of microglia creates a chronic neuroinflammatory environment and exacerbates neuronal and synaptic loss (Al-Ghraiybah et al., 2022).

Microglia Activation Receptors

TREM2

The triggering receptor expressed in myeloid cells 2 (TREM2) is a transmembrane protein expressed in the microglial cell, being responsible for the regulation of innate immunity in the CNS from the recognition of several molecules. This protein plays a neuroprotective role against AD, because in addition to being a receptor responsible for inducing the anti-inflammatory response, it also provides the migration of microglia to settle around amyloid plaques, which helps in the phagocytosis of amyloid debris, hinders the formation of oligomeric aggregates and prevents axonal dystrophy. Studies indicate that mutations in the coding of TREM2 promote the loss of microglial function and decrease of phagocytic capacity, so that the mutation most associated with AD is TREM2 R47H. From the stimulation of TREM2, the interaction with the protein tyrosine kinase (DAP12) occurs, which contains an activation motif based on tyrosine cytosolic immunoreceptor (ITAM) that after phosphorylation, recruits the spleen tyrosine kinase (SYK). The activation of SYK initiates a signaling cascade that promotes cellular anabolic metabolism, proliferation, and phagocytosis, however, in cases of R47H mutation, this interaction is impaired, decreasing phagocytosis (Nícholas Dias., 2020 and Shi Y., 2018). Mutations or deficiency of the gene encoding TREM2 prevent the migration and recruitment of microglia, hindering its circumdation in senile plaques, allowing access to the brain parenchyma, promoting axonal dystrophy, neuronal death, and increased neurotoxicity (Nícholas Dias., 2020)

Of P2s7

The purinergic receptor (P2X7R) is expressed in astrocytes, microglia, oligodendrocytes, and neurons and its regulation in microglial cells contributes to neuroinflammation. In pathological conditions, adenosine triphosphate (ATP), a high-energy molecule, is capable of causing morphological changes, which favor the activation of microglial cells and peripheral immune cells, triggering the participation of the purinergic receptor in the cell signaling mechanism. Dead cells release ATP molecules, which bind to P2X7 receptors and promote the assembly of the NLRP3 inflammasome, which induces IL-1β secretion, worsening inflammation, inducing cell death that promotes the release of more ATP, stimulating microglial cells and recruiting peripheral immune cells. The involvement of several cytokines increases the inflammatory scenario and activates pro-apoptotic cascades, culminating in cell death. (Francistiová et al., 2020; Oliveira et al., 2021; Martin et al., 2019). Regarding AD, Aβ peptides trigger immune cells by releasing more ATP, which activates P2X7 receptors, causing the release of inflammatory cytokines and increasing neuroinflammation (Al-Ghraiybah et al., 2022).

NLRP3 Inflammasome

Inflammasome is a multiprotein complex that mediates inflammation. In response to some cellular damage, the NLRP3 inflammasome is a component of the innate immune system that acts on the activation of inflammatory caspase-1 and the secretion of pro-inflammatory cytokines IL-1β and IL-18, resulting in an exacerbated inflammatory response (Al-Ghraiybah et al., 2022; Kelley et al., 2019; Barczuk et al., 2022).

Currently, there is an activation model of the NLRP3 inflammasome, which is a route of two signals, the *priming signal* (signal 1) and the activation signal (signal 2). In the priming model, microbial components or endogenous cytokines initiate the NLRP3 inflammasome by provided signals; in the activation model, there may be several stimuli for its activation, such as extracellular ATP, particulate matter, and ionic flow (Kelley et al., 2019).

In AD, the Aβ peptide and NFTs act as a stimulus for the activation of the NLRP3 inflammasome. They are recognized by Toll-like receptors (TLR), inducing inflammation and leading to transcription of pro-IL-β and NLRP3 (Barczuk et al., 2022). After inflammasome activation, caspase-1 is activated and cleaves the cytokines pro IL-1β and pro IL-18. IL-1β induces endothelial cell response by facilitating the infiltration of immune cells into infected or damaged tissues. IL-18 is a cytokine that mediates adaptive immunity. Caspase-1 also triggers the cleavage of pore-forming Gasdermin D (GSDMD) that triggers a pro-inflammatory form of cell death, called pyroptosis (Hanslik et al., 2020; Barczuk et al., 2022).

RAGE

The Receptor for Advanced Glycation End Products (RAG) belongs to the immunoglobulin (Ig) superfamily and is expressed in immune and/or inflammatory cells. There are two predominant isoforms: complete RAGE and soluble RAGE (sRAGE). In full RAGE, signal transduction is initiated after binding of RAGE to its ligand and this interaction causes pathological effects. In sRAGE, the soluble form competes with the full RAGE for ligand binding, thus preventing the interaction of RAGE with its ligands, and for this reason, it is suggested that they are protective against inflammation. Complete RAGE binds to multiple DAMPs and its binding triggers a series of cell signaling events, leading to the production of pro-inflammatory cytokines (IL-6 and TNF-α). Studies have reported increased expression of RAGE in the microglia of AD patients, and its expression level is correlated with disease severity. Overexpression of RAGE causes increased levels of Aβ in the hippocampus and cortex. Due to the accumulation of protein Aβ in the CNS, RAGE facilitates the entry of Aβ from circulating plasma to the brain via the BBB. The interaction of RAGE with Aβ in neurons, microglia, and vascular cells accelerates and amplifies harmful effects on neuronal and synaptic function (Yan et al., 2012; Paudel et al., 2020; Al-Ghraiybah et al., 2022).

Astrocytes

Astrocytes are the most common glial cells in the brain. They can respond to noxious stimuli with proliferation, migration, hypertrophy and increased production of glial fibrillary acidic protein (GFAP), which is a biomarker of reactive astrogliosis. It has an important role in the maintenance of senile plaque and Aβ clearance, as well as in the secretion and metabolism of neurotransmitters, neuronal support, neuroprotection, acting as a pathway of elimination of neurotoxic wastes and the permeability of the BBB, regulating cerebral blood flow for the functioning of neuronal activity. Studies have noted that reactive astrocytes always lose their supporting role and gain a toxic function in the progression of neurodegenerative diseases (Minter., 2016; Al-Ghraiybah et al., 2022).

In AD, activated astrocytes are divided into 2 groups: A1 and A2. A1s promote inflammation, lose neuroprotective function and synaptogenesis, become phagocytic, and lead to neuronal loss. A2 upregulate neuronal survival, however, the signaling pathways involved in the activation of astrocyte groups A1 and A2 are unclear (Gamage et al., 2020; Li et al., 2019). Reactive astrocytes overexpress GFAP, which, together with Vimentin, acts as the main factor for the formation of the intermediate filaments that make up the cytoskeleton of astrocytes. In addition, they cause an increase in the production of inflammatory cytokines, such as IL-1β, IL-6, TNF-α and macrophage colony-stimulating factor (M-CSF) increasing the neuroinflammatory response, thus initiating neuronal functional impairment (Li et al., 2019; Al-Ghraiybah et al., 2022; Martins., 2018).

Astrocytes eliminate Aβ, however, in AD this ability is reduced, leading to increased Aβ levels and formation of senile plaques. Astrocytes recognize Aβ through receptors, however, according to Li Y et al (2014) it is not known exactly which receptors mediate the uptake of Aβ and oligomeric Aβ in astrocytic cells (Al-Ghraiybah et al., 2022; Li Y et al., 2014). IL-1β and TNF-α are released after detection of Aβ and their long-term exposure can damage the BBB and accumulate peripheral immune cells and neurotoxic compounds in the brain, leading to various CNS damage (Minter et al., 2016). The cytokines produced also promote the activation of astroglia and caspases, which are proteases involved in the initiation and execution of apoptosis, contributing to cell death and also stimulating the synthesis of Aβ, resulting in an increase in oligomers, being considered the most toxic form of the Aβ peptide (Martins., 2018; Al-Ghraiybah et al., 2022).

CONCLUSION

Based on this literature review, it is possible to conclude that Alzheimer's disease is a very complex disease that involves genetic, environmental and idiopathic factors, with aging being one of the risk factors for Alzheimer's. With the increase in life expectancy, a greater number of individuals reach an advanced age in which the manifestations of neurodegenerative diseases are more frequent. The interaction between microglia and astrocytes plays an important role in the pathogenesis of the disease and its progression, evidencing its contribution to neuroinflammation. Activation of these cells activates an immune response that can trigger an increase in Aβ deposits and tau hyperphosphorylation, causing chronic neuroinflammation, leading to ever-increasing levels of neuronal injury, degeneration, and death.

This work aims to contribute to the understanding of the role of the immune system in Alzheimer's disease, offering valuable *insights* for future research and the development of innovative therapeutic approaches.

REFERENCES

1. Abraz. Associação Brasileira de Alzheimer. (2020). Disponível em: http://abraz.org.br/web/sobre-alzheimer/o-que-e-ealzheimer/.

2. Al-Ghraiybah, N. F., Wang, J., Alkhalifa, A. E., Roberts, A. B., Raj, R., Yang, E., & Kaddoumi, A. (2022, September 12). Glial Cell-Mediated Neuroinflammation in Alzheimer's Disease. *International Journal of Molecular Sciences*.

3. Barczuk, J., Siwecka, N., Lusa, W., Rozpędek-Kamińska, W., Kucharska, E., & Majsterek, I. (2022, August 11). Targeting NLRP3-Mediated Neuroinflammation in Alzheimer's Disease Treatment. *International Journal of Molecular Sciences*.

4. Borst, K., Dumas, A. A., & Prinz, M. (2021, October 12). Microglia: Immune and non-immune functions. *Immunity, 54*(10), 2194-2208.

5. Burgaletto, C., Munafò, A., Di Benedetto, G., et al. (2020). O sistema imunológico na trilha da doença de Alzheimer. *Journal of Neuroinflammation, 17*, 298.

6. Brasil. Ministério da Saúde. (Acesso em: 13 set. 2023). Disponível em: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/a/alzheimer.

7. Castellani, R. J., Rolston, R. K., & Smith, M. A. (2010, September). Alzheimer disease. *Disease Monthly, 56*(9), 484-546.

8. De Paula, V. J. R., Guimarães, F. M., Diniz, B. S., & Forlenza, O. V. (2009, Jul-Sep). Neurobiological pathways to Alzheimer's disease: Amyloid-beta, TAU protein or both? *Dementia and Neuropsychology, 3*(3), 188-194.

9. Dias, N. C. (2020). Imunomodulação na progressão da doença de Alzheimer. Monografia (Graduação em Biomedicina), Faculdade de Ciências da Educação e da Saúde, Centro Universitário de Brasília.

10. Edin, N., & Babicz, C. (2022). A ação do sistema imunológico no Alzheimer: uma revisão. *Visão Acadêmica, 23*.

11. Gra Menendez, S., Padron Perez, N., & Llibre Rodriguez, J. de Jesús. (2002). Péptido beta amiloide, proteína Tau y enfermedad de Alzheimer. *Revista Cubana de Investigaciones Biomédicas, 21*(4), 253-261.

12. Fernández-Calle, R., Konings, S. C., Frontiñán-Rubio, J., García-Revilla, J., Camprubí-Ferrer, L., Svensson, M., ... Deierborg, T. (2022, September 24). APOE in the bullseye of neurodegenerative diseases: impact of the APOE genotype in Alzheimer's disease pathology and brain diseases. *Molecular Neurodegeneration, 17*(1), 62.

13. Francistiová, L., Bianchi, C., Di Lauro, C., Sebastián-Serrano, Á., de Diego-García, L., Kobolák, J., ... Díaz-Hernández, M. (2020, June 3). The Role of P2X7 Receptor in Alzheimer's Disease. *Frontiers in Molecular Neuroscience*.